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HIV and Tuberculosis in Atlanta, GA: Antiretroviral Therapy Uptake and Factors Associated with Unfavorable Outcomes

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Abstract

HIV and Tuberculosis in Atlanta, GA: Antiretroviral Therapy Uptake and Factors Associated with Unfavorable Outcomes

By Destani J. Bizune

Background: We investigated antiretroviral therapy (ART) uptake and the association of HIV and unfavorable treatment outcomes among patients with culture-confirmed tuberculosis at Grady Memorial Hospital (GMH), a safety net hospital in Atlanta, GA.

Methods: Retrospective cohort study of patients with culture-confirmed TB admitted to GMH from 2008-15. We compared baseline characteristics between HIV-positive and negative patients. Factors associated with unfavorable outcomes during TB treatment were analyzed using multivariate logistic regression.

Results: Among 271 patients, 95 (35%) were HIV-positive; 23 (24%) of whom were newly diagnosed at the time of TB diagnosis. The 72 patients with known HIV were diagnosed a median of 6 years prior to developing TB, and only 11 (15%) were receiving ART at presentation. Most HIV patients (67%) had a baseline CD4 count ≤ 200 cells/mm^3. Fifty-six (67%) of eligible HIV-infected patients were started on ART after TB diagnosis and median days from TB treatment to ART initiation was 81 days (IQR 34 - 118). Most patients were male (75%), black (81%), and median age was 47 years. Almost half the patients (44%) had a history of homelessness. Patients with HIV were more likely to have disseminated disease and complications during treatment, including a higher rate of isoniazid resistance, extrapulmonary involvement, adverse side effects, and hospital readmissions. Overall, 36 (14%) patients died during TB treatment, 17 (47%) of whom were HIV-positive. While the death rate was higher in HIV (19%) vs. non-HIV (11%) TB patients, the difference was non-significant (p = 0.26). In multivariate analysis, disseminated and CNS disease were associated with unfavorable outcome while HIV was not (aOR 1.31, 95% CI 0.63 – 2.74, p = 0.47).

Conclusions: The majority of patients with TB/HIV co-infection in this cohort had known HIV infection before TB diagnosis and were not receiving ART. Additionally, a substantial proportion of co-infected patients did not start ART within a recommended time period. There was no significant association with HIV infection and mortality, but HIV-infected patients had more complications during treatment and higher rates of disseminated disease. Interventions to increase linkage to HIV care are needed and could contribute to TB control in Atlanta.

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INTRODUCTION

Since the early 1990s, the association of human immunodeficiency virus (HIV) and tuberculosis (TB) has been recognized as a "deadly syndemic," in that the infections act synergistically and exacerbate the negative sequelae of both diseases. [1, 2] The World Health Organization (WHO) estimates that in 2015 there were 10.4 million new cases of tuberculosis, with 1.2 million (11%) of these cases occurring in persons living with HIV/AIDS. There were 1.4 million TB-related deaths, and additional 0.4 million deaths occurring among people with TB/HIV co-infection. TB is one of the leading 10 causes of death worldwide. [3]

Once infected with the bacteria *M. tuberculosis*, the lifetime risk of progressing from latent infection to active TB disease is approximately 5-10% for a healthy individual and approximately 10% per year for an HIV-infected person. [1] Infection with HIV leads to a chronic state of immune inactivation and inflammation, impairing the body's ability to respond to infections including *M. tuberculosis*. HIV infection is the most significant risk factor for progressing from latent TB infection to active disease and active TB disease is the leading cause of death for HIV-infected persons. [1, 4] TB disease has been positively correlated with increased HIV viral replication and a higher risk of infection with other opportunistic infections (OIs). [1, 4, 5] Most studies on patients with TB/HIV coinfection have found a higher risk of mortality and other unfavorable treatment outcomes compared to infection with TB or HIV alone; [6-10] however, there are contrasting data showing no association of HIV on clinical outcomes among patients with TB. [11]

The Southeastern region of the United States including the state of Georgia has a disproportionately high burden of both TB and HIV infection when compared to other US regions. [12, 13] Georgia has the 7th highest TB case rate and the 5th highest HIV/AIDS

diagnosis rate among the 50 states. [12] In 2015, 9% of all TB cases in Georgia had a positive HIV test, compared to 6% of all TB cases nationally. To our knowledge, there are very few studies examining the impact of TB/HIV co-infection on TB treatment outcomes in the United States or other high-resource settings. [7, 14] Given the impact of HIV on TB mortality seen worldwide, our aim is to study this association in a cohort of patients in the Atlanta area with high rates of active TB disease and TB/HIV co-infection. [15]

The main aims of our study were to assess the impact of HIV infection on treatment outcomes of patients with tuberculosis and to assess the rate of antiretroviral therapy (ART) uptake during TB treatment. Our secondary aims included evaluating the effect of HIV infection on additional clinical outcomes including rates of adverse events, TB drug interruptions, hospitalization data, and overall TB treatment duration. Our overall goal was to identify the challenges in providing care to TB/HIV co-infected patients and to provide data that will help improve the management of patients with TB/HIV in Atlanta, Georgia and other similar settings.

STUDY POPULATION AND METHODS

Study Design and Setting: A retrospective cohort study design was utilized. Eligible study participants included all adults (≥ 18 years) treated for culture-confirmed pulmonary or extrapulmonary TB at Grady Memorial Hospital (GMH) during the period January 1, 2008 and October 31, 2015. GMH is a 1,000 bed safety net hospital for underserved communities in the Atlanta-metropolitan area and served as the primary treatment center for patients involved in an outbreak of isoniazid (INH) resistant TB at shelters for people experiencing homelessness, most of whom were included in our study cohort. [16] Following national and state recommendations all of our study participants had HIV testing performed. Patients

treated for active TB without culture or molecular confirmation of disease were deemed clinical cases and excluded from the study. Additionally, patients with confirmed TB and no baseline drug susceptibility testing (DST) results or with missing treatment outcomes were excluded. Following discharge from the hospital, all patients were referred to a local county health department for further TB care and management. The Institutional Review Boards (IRB) of Emory University and the state of Georgia approved this study. The study also received approval to conduct research from the Grady Research Oversight Committee.

Laboratory Testing: All pulmonary TB suspects presenting for care at GMH had a minimum of two sputum samples sent for solid and liquid acid-fast bacillus (AFB) culture to the GMH microbiology laboratory. Non-pulmonary TB suspects have samples sent at the discretion of their treatment team. For all cultures positive for *M. tuberculosis*, isolates were sent to the Georgia Public Health Laboratory (GHPL), where DST for rifampin (RIF), isoniazid (INH), and ethambutol (ETH) was performed using Mycobacterial Growth Indicator Tube (MGIT) 960. Pyrazinamide (PZA) was not added to this panel until 2015 and thus most of our patients did not have DST testing for PZA. Drug resistance was defined per CDC guidelines. Samples with any drug resistance detected at the GHPL lab were sent to the CDC for confirmation and further testing. INH and RIF resistance were defined as *M. tuberculosis* isolates with growth at an INH concentration of ≥ 0.2 μg/ml and an RIF concentration ≥ 1 μg/ml using the indirect proportion method on agar. [17] Cases with INH resistance and RIF susceptibility were defined as having INH mono-resistance. State protocols mandate that all TB patients be offered HIV testing; all patients in this cohort had a HIV serologic test performed.

Data Management: Data were abstracted from paper medical charts and electronic medical records at GMH, county health department TB clinics, and the Georgia State Electronic Notifiable Surveillance System (SENDSS) using a standardized case report form. Data were entered into online and HIPPA compliant REDCap database, a secure web application for building and managing online databases. [18] Data collected included information on demographics, medical history, TB treatment course, culture results, and final treatment outcomes.

Study Definitions: Disseminated TB disease was defined as having either a blood culture positive for *M. tuberculosis* or the presence of miliary TB based on chest radiology results. Meningeal (CNS) TB disease was defined as having a positive cerebrospinal fluid (CSF) culture or nucleic acid amplification test for *M. tuberculosis* or CSF profile and/or symptoms plus imaging findings consistent with meningeal disease. Recurrent TB was defined as having a second episode of the same strain of active TB within two years of completing treatment for their initial episode of active TB. An abnormal chest X-ray (CXR) was defined by the presence of an infiltrate, consolidation, cavitary lesion, pleural effusion, adenopathy, or other abnormalities suggestive of active TB. Final radiology reports were used for recording abnormalities in chest x-rays and computed tomography scans. A high sputum smear is any sputum sample classified as ≥ 3+ AFB by the GMH microbiology laboratory, and indicates a strongly positive result. Drug interruptions were defined as any drug interruption by the treating clinician for drug adverse events. Comorbidities and other patient characteristics such as active tobacco, alcohol, and illicit drug use and a history of homelessness, were defined as reported in the medical record. Diabetes mellitus (DM) was defined by a combination of either self-report, prescribed medications, and/or HgA1C ≥

6.5%. Glomerular filtration rate (GFR) was calculated using the Cockcroft-Gault formula. Body mass index (BMI) was calculated using baseline weight and height measurements.

A favorable outcome was defined as a patient who had a treatment outcome of cure as per WHO guidelines. [19] An unfavorable outcome consists of any patient who died or was lost to follow-up during TB therapy or had recurrent disease after treatment completion. Cause of death was determined by death certificate, treating clinician, or other infectious disease physician.

Data analysis: All data analysis was performed using SAS, 9.4 (SAS Institute Inc., Cary, NC). Selected baseline characteristics of the study participants according to HIV status were compared using either a Fisher's exact or chi-square tests for categorical variables, and either a nonparametric Wilcoxon/Mann-Whitney or two sample t-test for continuous variables. Differences in clinical outcomes such as adverse side effects leading to a drug interruption, the number of hospital readmissions, cause of death, and treatment duration were also tested using a Fisher's exact, chi-square, Wilcoxon/Mann-Whitney, or two-sample t-test. In regards to the analysis of treatment outcomes, the primary exposure of interest was HIV co-infection and the primary outcome of interest was an unfavorable outcome (death, lost to follow-up, or TB recurrence) that occurred between TB diagnosis and the end of TB treatment. Patients who were transferred (n= 6) or were still on treatment (n = 1) as of March 2017 were excluded from the final model. Logistic regression models were used to estimate the association of HIV status and unfavorable outcome. An alternative model comparing HIV-positive patients stratified by CD4 count ($\leq$ 50 cells/mm^3 and > 50 cells/mm^3) to HIV-negative patients as the main exposure was also created. Missing baseline weight and height data were imputed with study cohort medians based on gender.

Race and country of origin were dichotomized into black/non-black and US-born/non-US-born for the univariate and multivariate analyses. Covariates were selected for inclusion in the final model based on previous literature, biologic plausibility, and using the purposeful selection strategy. [20] The purposeful selection strategy determined initial variables for including in the final model as those having a p value <0.10 in univariate analysis. Collinearity and statistical interaction were assessed between the primary exposure and all covariates of interest included in the final model. Confounding between the primary exposure and covariates was assessed using the all-possible subsets method and the 20% change in estimate approach. A two sided p value of < .05 was considered significant for all analyses.

RESULTS

A total of 361 patients were treated for active TB at GMH during the study period (figure 1), among which 271 had culture confirmed TB and were included in our study cohort. The median age of patients was 47 years and the majority of patients were male (75%), black (81%), and US-born (72%). Ninety-five (35%) patients were HIV-positive. Almost half had a self-reported history of homelessness (43%), and there were high rates of active tobacco (55%), alcohol (51%), and illicit drug (25%) use. The rates of hepatitis C antibody positivity and diabetes were 12% and 15%, respectively. There were 52 patients (19%) with a glomerular filtration rate < 60 ml/min and 66 patients with an albumin serum level less than 2.5 gm/dl. For further cohort characteristics, see Table 1.

TB clinical characteristics: Twenty-five (9%) and 39 (15%) patients had a history of previous active TB and LTBI, respectively, and close to half (44%) had a positive tuberculin skin test

(TST) or interferon gamma release assay (IGRA) (table 1). Of the 248 pulmonary TB cases, 177 were smear positive (71%) and 126 (51%) had an acid fast bacilli (AFB) sputum smear with a high burden of bacilli (≥ 3+). Ninety-one (34%) patients had extrapulmonary involvement, including 30 (11%) with disseminated TB and 12 (4%) with meningeal TB (table 2). The baseline median measurements for BMI was 21 kg/m^2, hemoglobin 11.3 gm/dL, and GFR 86 mL/min. There were 222 (82%) patients with an abnormal chest x-ray at baseline with the most common abnormality being either the presence of bilateral or multilobar disease in 180 (66%) patients. Less common radiological abnormalities included the presence of cavitary disease in 101 (37%) patients and miliary disease in 19 (7%) patients. *Patients with HIV co-infection*: Among the 95 patients with HIV infection, the majority (n = 72, 76%) had already been diagnosed with HIV for a median time of 6 years (table 2). Over half (67%) of all HIV-infected patients presented with a CD4 count less than 200 cells/mm^3, including 33 patients (40%) with a CD4 count less than 50 cells/mm^3. There were 11 (15%) patients on antiretroviral treatment (ART) at the time of TB diagnosis and only 4 (4%) patients had an undetectable viral load. In regards to initiation of ART during TB treatment, a total of 56 (68%) eligible patients were started on ART during TB therapy (excluding patients who died at index admission, had meningeal TB, or were already on ART at TB diagnosis). The median time to ART initiation was 81 days for the entire cohort, including 62 days for patients with a CD4 count ≤ 50 cells/mm^3, and 89 for those with a CD4 count > 50 cells/mm^3.

In comparing characteristics between patients with and without HIV infection, both groups had similar age and gender profiles while patients with HIV infection had a higher proportion of illicit drug use (39 % vs. 18%, $p < 0.01$) use as compared to patients without HIV. Co-infected patients had a higher hepatitis C antibody positivity rate (18% vs. 8%, p <

0.01) and were more likely to have INH-resistant TB (34% vs. 19%, $p < 0.01$) compared to patients without HIV. In contrast, patients with HIV had a lower prevalence of diabetes (10% vs. 18%, $p = 0.06$) and a lower baseline hemoglobin ($p < 0.01$) as compared to patients without HIV. Co-infected patients were less likely to have an abnormal CXR ($p = 0.01$) including cavitary disease, ($p < 0.01$), but were more likely to have miliary disease ($p = 0.03$). Patients with HIV had twice the proportion of extrapulmonary involvement (50% vs. 25%, $p < 0.01$), and had higher prevalence rates of disseminated (21% vs. 6%, $p < 0.01$) and meningeal TB (8% vs. 2%, $p = 0.03$) as compared to patients without HIV. See Table 1 for further comparisons between patients with and without HIV infection.

Treatment course: Of patients with an index hospital admission, median stay was 9 days (table 4). Ninety-two (34%) patients had at least one hospital readmission during TB treatment (table 2) with over half (53%) of the readmissions being directly related to their active TB disease. Fifty-six (21%) patients experienced an adverse side effect leading to a drug interruption (table 3).

While there was no significant difference in the days of initial or subsequent hospitalizations, patients with HIV infection were more likely to have had at least one hospital readmission as compared to patients without HIV (46% vs. 22%, $p < 0.01$). Patients with HIV also had a higher rate of experiencing a drug interruption due to a side effect (33% vs. 14%, $p < 0.01$) (table 4) compared to patients without HIV. They were also more likely to have a higher number of drugs interrupted ($p < 0.01$) and to have INH, RIF, and PZA interruptions ($p < 0.01$). Patients with HIV experienced more drug-induced hepatoxicity and rash, but were less likely to have a neuropathy attributed to INH.

The median treatment duration for the overall cohort was 9 months, with over half (58%) completing treatment within 7-12 moths (table 3). Those with HIV co-infection were treated a median of 1 month longer than those without (10 months vs. 9 months, $p < 0.01$). HIV-positive patients were less likely to complete in under 7 months (20% vs. 38%) and more likely to have treatment duration last over 12 months (13% vs. 8%, $p < 0.01$).

Treatment Outcomes: Seventeen (6%) patients died at index hospital admission. Of the remaining patients, 214 (81%) were cured, while 36 (14%) patients died during treatment, 10 (4%) were lost to follow-up, 3 (1%) had recurrent disease, and 1 (0.4%) is still on treatment. The majority of deaths (69%) were due to active TB disease. HIV-infected patients had a higher proportion of deaths at index hospital admission (9% vs. 5%, $p = 0.27$), deaths over the entire treatment course (19% vs. 11%, $p = 0.26$), and TB-disease related deaths (82% vs. 58%, $p = 0.13$),

In univariate analysis, patients with HIV infection had an increased odds of having an unfavorable outcome (OR = 1.75, 95% CI 0.93 – 3.01, $p = 0.08$); however, the association was not significant. Patients with an albumin < 2.5 gm/dl, hemoglobin < 10 gm/dl, or GFR < 60 ml/min at baseline were all more likely to have an unfavorable outcome in univariate analyses ($p < 0.05$). Additional covariates that were significantly associated with an unfavorable outcome in univariate analysis included the presence of a negative TST or IGRA result, concomitant extrapulmonary TB, having disseminated or meningeal TB, and the presence of bilateral or multilobar disease on chest radiology ($p < 0.1$). See table 6 for complete univariate analysis results.

When controlling for potential confounders in multivariate analysis, there remained no significant difference in treatment outcomes among patients with HIV infection as

compared to patients without HIV infection (adjusted OR=1.31, 95%, 0.63-2.74). Additionally, there was no significant interaction between HIV and the other covariates included in the final multivariate model. The covariates that were significantly associated with an unfavorable outcome included having an albumin <2.5 gm/dl (aOR = 2.83, 95%, 1.41-5.71) or glomerular filtration rate < 60 ml/min (aOR = 3.23, 95%, 1.49-7.01) at baseline, and the presence of disseminated or meningeal TB (aOR = 2.84, 95%, 1.18-6.80).

An alternative analysis was performed using HIV stratified by CD4 count (≤ 50 cells/mm^3 and > 50 cells/mm^3) as the main exposure variable (supplemental table 1). In univariate analysis, patients with a CD4 count ≤ 50 cells/mm^3 had almost 3-times the odds of an unfavorable outcome (OR = 2.93, 95% CI 1.33 – 6.45, p = 0.01) while patients with a CD4 count > 50 cells/mm^3 had no significant association with an unfavorable outcome (OR = 1.11, 95% CI 0.48 – 2.53, p = 0.30) as compared to HIV negative patients. The association seen among patients with a low CD4 count did not remain significant after adjusting for potential confounders in multivariate analysis.

DISCUSSION

While we found no significant difference in overall TB treatment outcomes among patients with and without HIV infection, our results are notable in regards to the high rate of HIV co-infection and the complicated treatment course experienced by patients with active TB and HIV infection. Slightly over one third (35%) of our cohort had HIV infection, which is a rate much higher than has been reported in both the state (9%) and U.S. (6%) and is similar to the rate of HIV infection among patients with TB found in many Sub-Saharan

231 African countries such as Nigeria (23%) or Cameroon (38%).[6, 12, 21] Given the majority of
232 the patients with HIV infection knew about their diagnosis for many years and were not in
233 care, our findings are an important reminder of the public health impact of untreated HIV.
234 In regards to treatment course, we found that treatment was longer and characterized by
235 higher rates of drug interruptions and hospital readmissions among patients with HIV as
236 compared to patients without. We also observed an increased overall mortality rate when
237 compared to the national average of 0.2 per 100,000. [12] Our results highlight the
238 complexities of care for patients with HIV and TB and the high level of clinical expertise
239 and resources needed to manage such patients. We also found that HIV is associated with
240 disseminated forms of TB disease, which were associated with higher rates of mortality.
241 This has important implications in the work up of patients infected with HIV and TB.

242 Our high rate of HIV infection (35%) among patients with active TB was striking.
243 The nature of the HIV epidemic in the South and in particular Atlanta, as well as cohort
244 characteristics helps to explain this high coinfection rate. Our cohort consisted primarily of
245 US-born, black men, many of whom had experienced homelessness and were active illicit
246 drug users. The Southern U.S. has a history of poorer overall health when compared to
247 other regions and has been disproportionately impacted by the HIV epidemic. [13, 22] In 2009,
248 49% of all HIV infections in the U.S. were diagnosed in the South and the city of Atlanta
249 has one of the highest diagnosis rates of any metropolitan area in the country. [13] African
250 Americans, especially those who reside in the Southern states, have been found to have
251 suboptimal retention in care and worse HIV outcomes than other racial/ethnic groups. [13, 23]
252 Long-term linkage to care studies conducted in Atlanta demonstrated that fewer blacks
253 achieved continuous retention over three years when compared to whites. [24] These inferior
254 health outcomes are the result of a convergence of cultural, political, and economical

disenfranchisement, marked by restrictive circumstances such as stricter Medicaid income eligibility, HIV-related stigma, and high unemployment rates. [25] Georgia, like many other Southern states, chose not to expand Medicaid under the Affordable Care Act, effectively curbing the potential for increased access to HIV care for low-income residents. Georgia also has one of the highest rates of TB incidence in the country, in part fueled by the high prevalence of HIV. The rate of HIV infection among patients with TB in Atlanta is one of the highest in the U.S. and much higher than that found in California which has the highest prevalence of TB in the U.S. and attributed 14% of its TB cases to HIV infection. [14] Most of the TB cases in Georgia occur among African American patients many with a history of homelessness, both of which the CDC identifies as high-risk groups for infection with HIV and TB. [12] This study highlights the dearth of linkage to adequate care among high-risk groups in the Southern U.S. More interventions are needed to increase the rates of linkage and retention into care for HIV-infected persons, particularly high-risk groups living in the Southern US.

While there was a trend towards unfavorable outcomes among patients with HIV, especially those with a CD4 count less than 50 cells/mm^3 as compared to patients without HIV, the differences were not statistically different. This is in contrast to multiple studies performed in settings outside of the U.S. that have found a significant association between HIV infection and mortality among patients with active TB. [6, 8, 9, 26] However, these studies were conducted in resource poor and/or rural settings. When compared to urban settings, patients treated in rural areas have experienced higher mortality rates. [6] Our patients were treated at an urban hospital located in a high-resource setting, which could explain why HIV-positive patients have similar overall treatment outcomes to patients without HIV. One study conducted during our study period in the state of Georgia developed a model

279 demonstrating significant association between HIV co-infection and death during TB
280 treatment. [27] However, this was a state-wide cohort that included rural patients, which
281 could account for the increase in mortality associations.

282 HIV co-infected patients in our cohort experienced more complicated treatment
283 courses. HIV-infected persons had higher proportions of hospital readmissions, adverse
284 side effects leading to drug interruptions, and more treatment interruption due to adverse
285 effects. They had poorer tolerance to TB medications, and had a higher rate of drug related
286 hepatotoxicity and rash. They were less likely to have an abnormal CXR or cavitary disease,
287 but more likely to have miliary disease. Patients with HIV were diagnosed with higher rates
288 of extrapulmonary involvement, including disseminated and meningeal TB, both of which
289 are associated to an increased risk of mortality and other unfavorable outcomes. Co-infected
290 patients also had a higher prevalence of INH resistance, the most common form of TB drug
291 resistance. [15]

292 HIV infected persons experience higher rates of extrapulmonary involvement,
293 including disseminated, meningeal, and miliary TB, all of which are associated with higher
294 rates of mortality. [1, 28] Miliary can be fatal in 25-30% of adults, and researchers in the state
295 of Texas found that patients with meningeal TB died at almost 3-times the rate of those
296 without. [29, 30] Another study conducted among patients treated at GMH determined that
297 extrapulmonary, disseminated, and meningeal TB were correlated with poor treatment
298 prognosis, a cause for concern given that HIV co-infected patients in this study had higher
299 rates of all types of extrapulmonary involvement. [31] TB-drug resistance can complicate both
300 HIV and TB therapies by increasing TB treatment duration and increasing the risk of
301 negative interactions with HIV medication, and MDR-TB can reduce survival probability by

over 50%. [32] Additionally, a Nigerian study demonstrated that HIV positivity increased the rate of developing an adverse drug event by almost two-fold. [33] These correlations could account for lack of linkage and retention to HIV care observed in Southern U.S. populations and addressing them could improve overall health of both HIV and TB infected persons, since linking persons to HIV care through ART can reduce TB-related incidence and mortality. [34] To date, this is the only study that examines the entire treatment course, from diagnosis to outcome, among co-infected patients in the U.S., and our results illustrate the increased rate of complications faced by these HIV and TB co-infected patients.

Our study results show that many patients infected with HIV do not initiate ART during TB treatment or do not start within the periods recommended by the CDC and WHO. [35, 36] While it is recommended that patients without meningeal TB initiate ART within two weeks of TB therapy if the CD4 $\geq$ 50 cells/mm^3 and within 8 weeks if the CD4 $>$ 50 cells/mm^3, our median time to ART initiation among eligible patients was close to 3 months (81 days). Given that earlier initiation of ART has been shown to improve TB treatment outcomes among co-infected patients, it is important to better understand the reasons for delay and also whether not starting ART during TB treatment leads to worse long term outcomes. [32]

To our knowledge, this is one of few studies examining the effect of HIV on TB treatment outcomes conducted in the United States after the availability of ART and the only study investigating a variety of clinical complications over the entire treatment course. [14, 27, 30] The vast majority of the literature on TB/HIV co-infection and treatment outcomes is concentrated outside of the US in low-income countries. Additionally, every patient in our cohort had documented HIV serology. We were also able to collect a wide array of

variables, such as CD4 counts and radiologic features, as well as some variables that are often overlooked in literature, such as adverse side effects and hospital readmissions.

This study has some limitations. Given the retrospective nature of the study the presence of many variables were dependent on patient self-report and inclusion in the medical record. This may leave some variables, such as illicit drug use, subject to misclassification bias, as some patients may be reticent to disclose this information to their medical provider; however, we abstracted data from multiple providers over the course of treatment, increasing our chances of collecting complete information. We did not collect socioeconomic information, such as income, employment status, or educational attainment and were unable to analyze or adjust for these variables. However, some variables, such as history of homelessness, can serve as a proxy for socioeconomic status. Also, given that GMH is a public hospital and serves a large number of patients who are either uninsured or Medicaid/Medicare recipients, we expect our cohort was homogenous with respect to certain markers of socioeconomic status. [37]

CONCLUSION

We found that HIV infection has a profound and varied impact on the clinical presentation and treatment course of patients with active TB disease. HIV infection was associated with disseminated forms of active TB disease which were associated with higher mortality. Additionally, when looking at less studied clinical measures, we found that HIV infection was associated with a more complicated TB treatment course marked by increased drug interruptions, hospital readmissions and longer treatment duration. Most importantly, to help prevent TB infection among patients with HIV infection our study cohort is a stark

reminder that we need to better engage patients with HIV into care after diagnosis and initiate and maintain them on ART.

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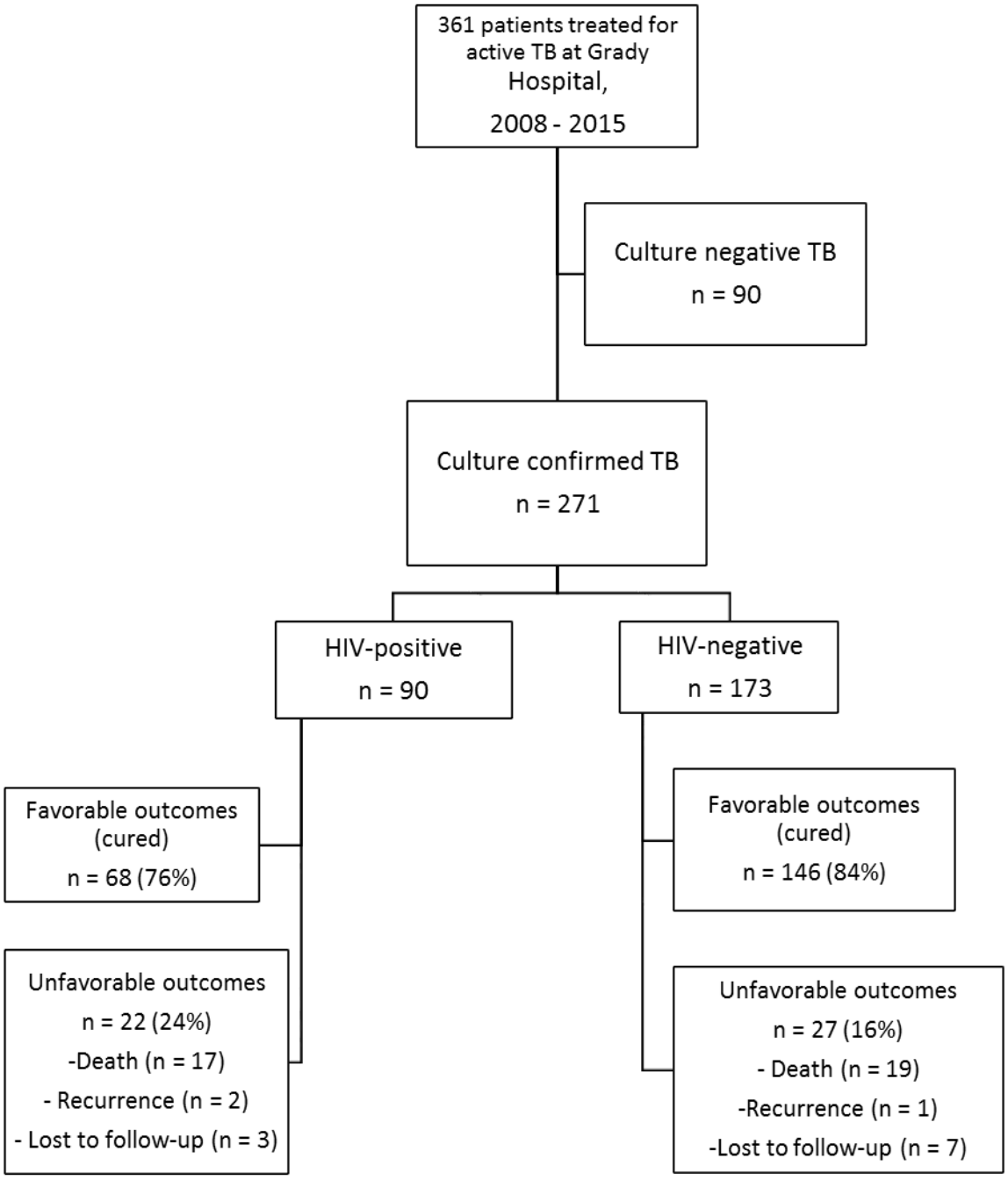
461 ***Figure 1. Study Cohort Flow Diagram***



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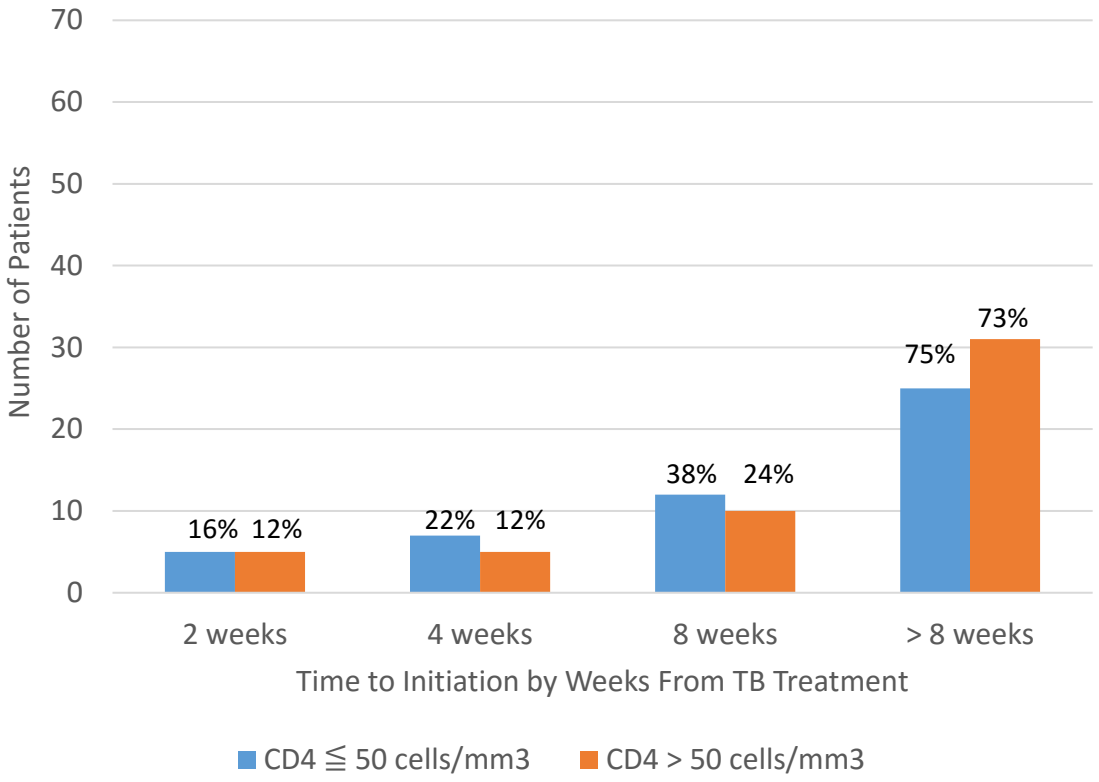
463 Abbreviations: TB, tuberculosis; HIV, human immunodeficiency virus

464 [a]Excludes transfers (n =5)

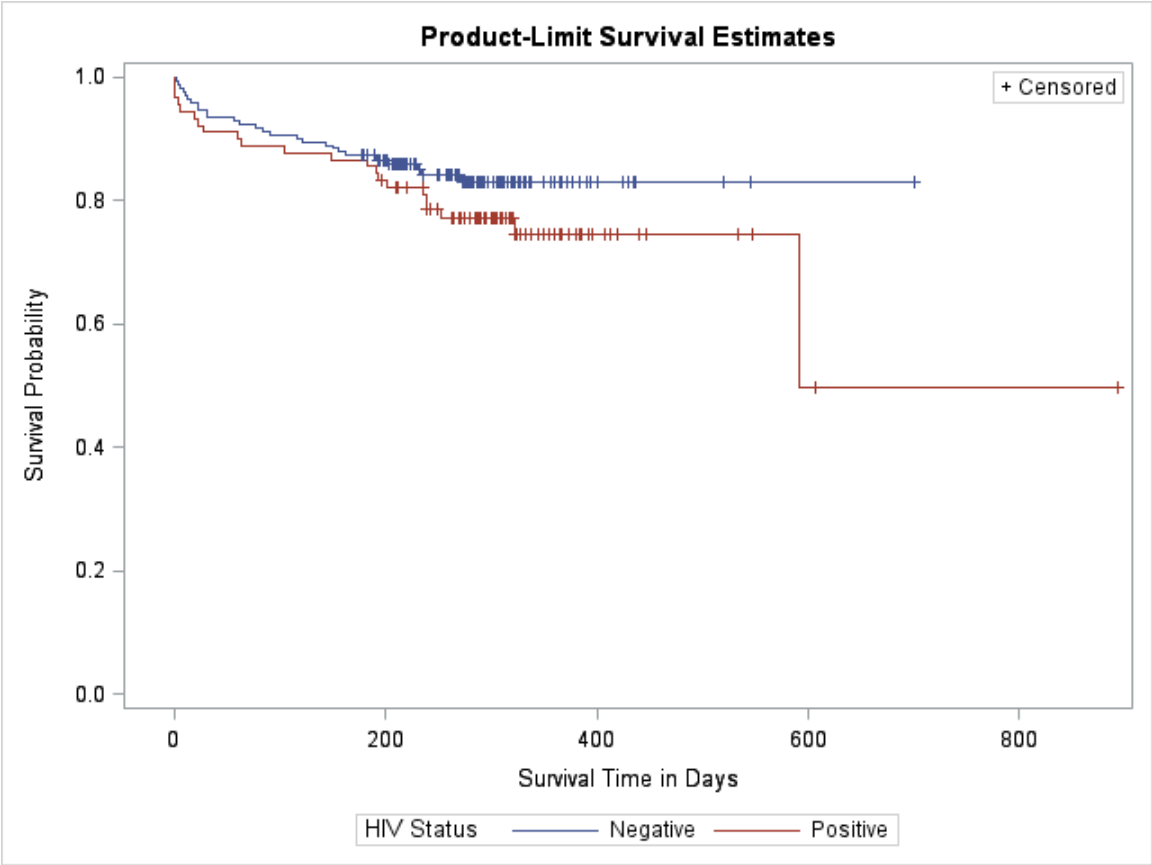
465 [b]Excludes transfer (n = 2) and patients still on treatment (n = 1)

Figure 2. Cumulative Percent and Frequency of Patient ART Initiation during TB treatment, by CD4 Count



Abbreviations: HIV, human immunodeficiency virus; TB, tuberculosis; ART, antiretroviral therapy

Figure 3. Unadjusted Survival Probability Stratified by HIV Status



491 ***Table 1. Baseline Characteristics of Patients with Culture-Confirmed Tuberculosis by***
492 ***HIV Status***

Characteristic	**HIV-Positive n = 95 (%)**	**HIV-Negative n = 176 (%)**	**Total n = 271 (%)**	***p* value**
Age, median (IQR), y	46 (39 – 51)	48 (38 – 57)	47 (38 – 55)	0.11
Male	67 (71)	137 (78)	204 (75)	0.18
Race				0.28
Black	80 (84)	140 (80)	220 (81)	
White	3 (3)	8 (5)	9 (4)	
Hispanic	10 (11)	15 (9)	25 (9)	
Asian	2 (2)	13 (7)	15 (6)	
Country of birth				0.84
USA	68 (72)	126 (72)	194 (72)	
Mexico	7 (7)	10 (6)	17 (6)	
Other[a]	20 (21)	40 (23)	60 (21)	
Hepatitis C antibody				**< 0.01**
Positive	17 (18)	14 (8)	31 (12)	
Negative	74 (78)	111 (64)	185 (69)	
Unknown	4 (4)	49 (28)	53 (20)	
Diabetes	9 (10)	32 (18)	41 (15)	**0.06**
History of homelessness	48 (51)	69 (39)	117 (43)	0.16
History of incarceration	37 (39)	76 (43)	113 (42)	0.50
Tobacco use	56 (59)	94 (53)	150 (55)	0.38
Alcohol use	48 (51)	90 (51)	138 (51)	0.92

Illicit drug use	37 (39)	31 (18)	68 (25)	**< 0.01**
TB Characteristics				
Index BMI, median (IQR), kg/m^2	21 (19 – 24)	21 (19 – 25)	20.9 (19 – 24)	0.27
Index BMI (< 18.5 kg/m^2)	17 (18)	39 (22)	56 (21)	0.41
Albumin (< 2.5 gm/dl)	25 (26)	41 (23)	66 (24)	0.58
Hemoglobin, median (IQR), gm/dl	10 (10 – 12)	12 (10 – 13)	11 (10 – 13)	**< 0.01**
GFR (ml/min), median (IQR)	79 (63 – 105)	92 (73 – 120)	86 (67 – 115)	**0.04**
GFR (< 60 ml/min)	24 (25)	28 (16)	52 (19)	0.06
Previous active TB	9 (10)	16 (9)	25 (9)	0.92
History of LTBI	18 (19)	21 (12)	39 (15)	0.12
INH mono-resistance	31 (34)	32 (19)	63 (24)	**<0.01**
MDR	1 (1)	0 (0)	1 (0.4)	0.35
Sputum smear positive (n = 248)	63 (69)	114 (73)	177 (71)	0.57
Sputum smear positive ≥3+ (n = 248)	43 (47)	83 (53)	126 (51)	0.39
TST or IGRA				0.18
Positive	35 (37))	85 (48)	120 (44)	
Negative	27 (28)	38 (22)	65 (24)	
Not done/unknown	33 (35)	53 (30)	86 (32)	
Radiologic Features				
Abnormal CXR	69 (73)	153 (87)	222 (82)	**0.01**
Cavitary disease[b]	12 (13)	89 (51)	101 (37)	**< 0.01**

Miliary disease[b]	11 (12)	8 (5)	19 (7)	**0.03**
Bilateral or multilobar disease[b]	57 (60)	123 (70)	180 (66)	0.10
Sites of TB Disease				
Any extrapulmonary involvement	47 (50)	44 (25)	91 (34)	**< 0.01**
Only extrapulmonary TB	4 (4)	19 (11)	23 (9)	**0.06**
Disseminated TB	20 (21)	10 (6)	30 (11)	**< 0.01**
Meningeal TB	8 (8)	4 (2)	12 (4)	**0.03**

Abbreviations: HIV, human immunodeficiency virus; BMI, body mass index; LTBI. Latent tuberculosis infection; GFR, glomerular filtration rate; INH, isoniazid; MDR, multidrug-resistance; TST, tuberculin skin test; IGRA, interferon gamma release assay; CXR, chest x-ray

[a]Other countries – Bangladesh, Bhurma, Bhutan, Eritrea, Ehtioppia, Germany, Guatemala, Guinea, Guyana, Haiti, Honduras, India, Jamaica, Kenya, Liberia, Mali, Nigeria, Peru, Russia, Somalia, Sudan, Thailand, Uganda, Uzbekistan, Vietnam, Zambia

[b]Diagnosed via chest x-ray or chest CT scan

T*able 2. Characteristics of Patients Co-infected with HIV*

Characteristic	Total n = 95 (%)
New HIV diagnosis	23 (24)
Prior HIV diagnosis	72 (76)
On ART[b] at time of TB diagnosis	11 (15)
Years since diagnosis, median (IQR)	6 (2-12)
Baseline CD4 count	
CD4 ≤ 50 cells/mm^3	33 (40)
Undetectable VL at Baseline	4 (4)
ART Initiation (N= 82)[a,b]	
Did not start ART during TB therapy	11 (13)
Started ART during TB therapy	56 (68)
Median days to ART Initiation	81 (34-118)
If CD4 ≤ 50 cells/mm^3	62 (23 – 95)
If CD4 > 50 cells/mm^3	89 (62 – 149)

Abbreviations: HIV, human immunodeficiency virus; ART, antiretroviral therapy; VL, viral load

[a]Excludes patients who died at index admission (n = 5) and with meningeal/CNS TB (n = 5), or both (n = 3)

[b]Includes patients with missing ART information (n = 4)

529 ***Table 3. Adverse Side Effects during TB Treatment by HIV Status***

Characteristic	HIV-Positive n = 95 N (%)	HIV-Negative n = 176 N (%)	Total n = 271 N (%)	*p* value
Any adverse effect leading to a drug interruption	31 (33)	25 (14)	56 (21)	**< 0.01**
Number of drugs interrupted due to an adverse effect				**< 0.01**
0	64 (67)	151 (86)	215 (79)	
1	8 (8)	12 (7)	20 (7)	
≥ 2	23 (24)	13 (7)	36 (13)	
Interruptions due to adverse side effects by drug				
Rifamycin (n = 262)	21 (22)	13 (7)	34 (13)	**< 0.01**
Isoniazid (n = 261)	22 (24)	16 (10)	38 (15)	**< 0.01**
Pyrazinamide (n = 258)	17 (19)	13 (8)	30 (12)	**< 0.01**
Ethambutol (n = 256)	8 (9)	12 (7)	20 (8)	0.68
Levofloxacin (n = 39)	2 (11)	0 (0)	2 (5)	0.23
Moxifloxacin (n = 37)	3 (3)	1 (0.6)	4 (2)	**0.13**
Adverse side effect characteristics				
Hepatotoxicity	16 (17)	9 (5)	25 (9)	**< 0.01**
Neuropathy	8 (9)	10 (15)	18 (7)	**0.08**
Rash	9 (10)	5 (3)	14 (5)	**< 0.01**
Gastrointestinal issues	2 (2)	1 (0.6)	3 (1)	0.64
Other	10 (11)	6 (4)	16 (6)	**0.01**

530 Abbreviations: TB, tuberculosis; HIV, human immunodeficiency virus

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532 ***Table 4. Complexities during treatment and treatment outcomes by HIV[a] status***

Characteristic	HIV-Positive n = 95 N (%)	HIV-Negative n = 176 N (%)	Total n = 271 N (%)	*p* value
Days in hospital for index admission, median (IQR) (n = 260)	9 (6 – 15)	8 (5 – 14)	9 (6 – 15)	0.15
Culture conversion (n = 241)	81 (91)	139 (92)	220 (91)	0.91
Days to culture conversion, median (IQR) (n = 216)	21 (9 – 35)	35 (17 – 59)	30 (12 – 53)	**< 0.01**
Culture conversion within 28 days	58 (63)	70 (45)	128 (53)	**0.02**
Number of hospital readmissions				**< 0.01**
0	49 (53)	130 (78)	179 (69)	
1	22 (24)	21 (12.7)	43 (17)	
≥ 2	21 (22)	15 (9)	36 (13)	
Days in hospital for readmission, median (IQR)				
First readmission (n = 79)	8 (4 - 12)	6 (4 – 12)	6 (4 - 12)	0.73
Second readmission (n = 35)	9 (4 – 23)	5 (2 – 23)	9 (3 – 23)	0.84
Third readmission (n = 13)	5 (4 – 8)	3 (2 – 9)	4 (4 – 8)	0.33
Reason for first 3 readmissions				0.35
TB-disease related	21 (58)	17 (47)	38 (53)	

Other	15 (42)	19 (53)	34 (47)	
Treatment duration, median (IQR), months (n = 246)[a]	10 (7 – 11)	9 (6 – 10)	9 (6 – 10)	**< 0.01**
Treatment duration by months (n = 246)[a]				**< 0.01**
< 7	16 (20)	63 (38)	79 (32)	
7 – 12	55 (67)	89 (54)	144 (58)	
> 12	11 (13)	13 (8)	24 (10)	
TB Treatment Outcomes[b]				0.26
Cured	68 (76)	146 (84)	214 (81)	
Death	17 (19)	19 (11)	36 (14)	
On treatment	0 (0)	1 (0.6)	1 (0.4)	
Lost to follow-up	3 (3)	7 (4)	10 (3)	
Recurrence	2 (2)	1 (0.6)	3 (1)	
Cause of death				**0.13**
TB disease related	14 (82)	11 (58)	24 (69)	
Other	3 (18)	8 (42)	11 (32)	
Death during index hospital admission	8 (9)	9 (5)	17 (6)	

Abbreviations: HIV, human immunodeficiency virus; BMI, body mass index; LTBI. Latent tuberculosis infection; GFR, glomerular filtration rate; INH, isoniazid; MDR, multidrug-resistance; TST, tuberculin skin test; IGRA, interferon gamma release assay; CXR, chest x-ray

[a]Excludes patients who died at index admission and patients with meningeal/CNS TB

[b]Excludes patients who transferred-out

541 ***Table 5. Baseline Patient Characteristics by Treatment Outcome Status***

Characteristic	**Unfavorable Outcome[a] N = 49** (%)	**Favorable Outcome[b] N = 214** (%)	**Total[c] n = 263** (%)	***p* value**
HIV Positive	22 (45)	68 (32)	90 (34)	**0.08**
Age, median (IQR), y	49 (42 – 56)	47 (38 – 54)	47 (38 – 55)	0.41
Male	37 (76)	161 (75)	198 (75)	0.97
Race				**0.17**
Black	43 (88)	170 (79)	213 (81)	
White	3 (6)	8 (4)	11 (4)	
Hispanic	3 (6)	22 (10)	25 (9)	
Asian	0 (0)	14 (7)	14 (5)	
Country of birth				0.24
USA	39 (80)	152 (71)	191 (73)	
Mexico	4 (8)	13 (6)	17 (7)	
Other[d]	6 (12)	49 (23)	55 (21)	
History of homelessness	24 (49)	92 (43)	116 (44)	0.63
Hepatitis C antibody positive	6 (12)	25 (12)	31 (12)	0.99
Diabetes	8 (16)	32 (15)	40 (15)	0.81
Tobacco use	28 (57)	122 (57)	150 (57)	0.99
Alcohol use	25 (51)	111 (52)	136 (52)	0.91
Illicit drug use	14 (39)	53 (25)	67 (25)	0.58
TB Characteristics				
Index BMI, median (IQR), kg/m^2	21 (19 – 23)	21 (19 – 25)	21 (19 – 24)	0.45
Index BMI < 18.5, kg/m^2	11 (23)	44 (21)	55 (21)	0.77
Albumin (< 2.5 gm/dl)	22 (45)	43 (20)	65 (25)	**< 0.01**

Hemoglobin, median (IQR), gm/dl	10 (9 – 11)	12 (10 – 13)	11 (10 – 13)	**< 0.01**
GFR, median (IQR), ml/min	69 (50 – 86)	93 (74 – 118)	86 (67 – 115)	**<0.01**
Previous active TB	5 (10)	20 (9)	25 (10)	0.79
History of LTBI	4 (8)	35 (17)	39 (15)	**0.14**
INH mono-resistance	14 (39)	48 (22)	62 (24)	0.36
MDR	1 (2)	0 (0)	1 (0.4)	0.19
Days in hospital for initial admission, median (IQR) (n = 253)	11 (7 – 22)	8 (5 – 12)	8 (6 – 15)	**0.02**
Smear positive (n = 240)	32 (76)	142 (72)	174 (73)	0.56
High grade smear positive (n = 240)	25 (60)	99 (50)	124 (52)	0.26
TST or IGRA				**< 0.01**
Positive	8 (16)	109 (51)	117 (45)	
Negative	14 (29)	49 (23)	63 (24)	
Note done/unknown	27 (55)	56 (26)	83 (32)	
Culture Conversion (n = 233)	19 (49)	194 (100)	213 (91)	**< 0.01**
Days to culture conversion, median (IQR) (n = 210)	8 (0 – 33)	22 (1 – 49)	22 (1 – 47)	0.23
Radiologic Features				
Abnormal CXR	42 (86)	174 (81)	216 (82)	0.74
Cavitary disease[e]	**1**8 (37)	82 (38)	98 (39)	0.84
Miliary disease[e]	3 (6)	14 (7)	17 (7)	0.99
Bilateral or multilobar disease[e]	38 (78)	139 (65)	177 (67)	**0.09**
Extrapulmonary involvement				

Any	23 (47)	64 (30)	87 (33)	**0.02**
Disseminated	8 (16)	20 (9)	28 (11)	**0.15**
Meningeal	8 (16)	4 (2)	12 (5)	**< 0.01**

HIV, human immunodeficiency virus; BMI, body mass index; LTBI. Latent tuberculosis infection; GFR, glomerular filtration rate; INH, isoniazid; MDR, multidrug-resistance; TST, tuberculin skin test; IGRA, interferon gamma release assay; CXR, chest x-ray

[a] Unfavorable treatment outcome was defined as either death, recurrence of tuberculosis, or loss-to follow-up

[b]Cured

[c]Excluded patients who are still on treatment or transferred out

[d]Other countries – Bangladesh, Bhurma, Bhutan, Eritrea, Ehtioppia, Germany, Guatemala, Guinea, Guyana, Haiti, Honduras, India, Jamaica, Kenya, Liberia, Mali, Nigeria, Peru, Russia, Somalia, Sudan, Thailand, Uganda, Uzbekistan, Vietnam, Zambia

[e]Diagnosed via chest x-ray or chest CT scan

567 ***Table 6. Univariate Associations with Unfavorable Outcome[a]***

Characteristic	Univariate OR (95% CI)	*p* value
HIV Positive	**1.75 (0.93 – 3.01)**	**0.08**
Age per year	1.02 (1.0 – 1.05)	**0.08**
Male	1.02 (0.49 – 2.09)	0.97
Black (vs. Non-black)	1.86 (0.74 – 4.64)	0.19
Country of birth (US vs. Non-US)	1.59 (0.75 – 3.38)	0.23
History of homelessness	1.21 (0.64 – 2.29)	0.34
Hepatitis C antibody positive	1.06 (0.40 – 2.78)	0.95
Diabetes	1.11 (0.48 – 2.59)	0.81
Tobacco use	1.01 (0.54 – 1.88)	0.99
Alcohol use	0.97 (0.52 – 1.80)	0.91
Illicit drug use	1.22 (0.61 – 2.43)	0.58
TB Characteristics		
Index BMI, median, g/m^2	1.00 (0.94 – 1.07)	0.94
Index BMI < 18.5 kg/m^2	1.12 (0.53 – 2.36)	0.77
Albumin (< 2.5 gm/dl)	3.24 (1.68 – 6.24)	**< 0.01**
Hemoglobin (< 10 gm/dl)	2.74 (1.43 – 5.26)	**< 0.01**
GFR (< 60 mL/min)	4.40 (2.20 – 8.78)	**< 0.01**
Previous active TB	1.10 (0.39 – 3.10)	0.85
History of LTBI	0.45 (0.15 – 1.33)	0.15
INH mono-resistance	1.38 (0.69 – 2.78)	0.36
Days in hospital for initial admission, median (IQR) n = 253)	1.01 (0.99 – 1.02)	0.25

Smear positive (n = 240)	1.48 (0.70 – 3.16)	0.31
High grade smear positive (n = 240)	1.71 (0.90 – 3.27)	0.10
TST or IGRA		
Negative vs. Positive	3.89 (1.53 – 9.88)	**< 0.01**
Note done/unknown vs. Positive	6.57 (2.80 – 15.40)	0.26
Radiologic Features		
Abnormal CXR	1.21 (0.50 – 2.91)	0.97
Cavitary disease[b]	0.94 (0.49 – 1.78)	0.84
Miliary disease[b]	0.93 (0.26 – 3.38)	0.91
Bilateral or multilobar disease[b]	1.86 (0.90 – 3.86)	**0.09**
Complexities during Treatment		
Any drug interruption due to adverse side effects	1.19 (0.56 – 2.51)	0.66
Any extrapulmonary Involvement		
Any	2.07 (1.10 – 3.90)	**0.02**
Disseminated/meningeal	3.322 (1.56 – 7.07)	**< 0.01**

HIV, human immunodeficiency virus; BMI, body mass index; GFR, glomerular filtration rate; INH, isoniazid; TST, tuberculin skin test; IGRA, interferon gamma release assay; CXR, chest x-ray

[a] Unfavorable treatment outcome was defined as either death, recurrence of tuberculosis, or loss-to follow-up

[b] Diagnosed via chest x-ray or chest CT scan

578 ***Table 7. Adjusted HIV Association with Unfavorable Treatment Outcomes[a]***

Characteristic	Multivariate OR (95% CI)	*p* value
HIV Positive	1.31 (0.63, 2.74)	0.47
Age	1.01 (0.98 – 1.04)	0.37
Albumin (< 2.5 gm/dl)	2.83 (1.41, 5.71)	< 0.01
GFR (< 60 ml/min)	3.23 (1.49, 7.01)	< 0.01
Disseminated or Meningeal Involvement	2.84 (1.18, 6.80)	0.02

HIV, human immunodeficiency virus; GFR, glomerular filtration rate

[a] Unfavorable treatment outcome was defined as either death, recurrence of tuberculosis, or loss-to follow-up

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Supplemental Table 1: Adjusted Association of HIV with Unfavorable Outcome, Stratified by CD4 Count

Characteristic	**Multivariate OR (95% CI)**	**p value**
HIV	1.24 (0.60, 2.57)	0.56
Negative	--	
CD4 ≤ 50	1.77 (0.72 – 4.31)	0.16
CD4 > 50	1.0 (0.36 – 2.25)	0.39
Albumin (< 2.5 gm/dl)	2.78 (1.38, 5.59)	0.0042
GFR (< 60)	3.66 (1.76, 7.60)	0.0005
Disseminated or Meningeal extrapulmonary Involvement	2.83 (1.18, 6.77)	0.0197