

Tuberculosis Treatment Outcomes in Brazil: Different Predictors for Each Type of Unsuccessful Outcome

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Background. Successful tuberculosis (TB) treatment is necessary for disease control. The World Health Organization (WHO) has a target TB treatment success rate of $\geq 90\%$. We assessed whether the different types of unfavorable TB treatment outcome had different predictors.

Methods. Using data from Regional Prospective Observational Research for Tuberculosis-Brazil, we evaluated biological and behavioral factors associated with each component of unsuccessful TB outcomes, recently updated by WHO (death, loss to follow-up [LTFU], and treatment failure). We included culture-confirmed, drug-susceptible, pulmonary TB participants receiving standard treatment in 2015–2019. Multinomial logistic regression models with inverse probability weighting were used to evaluate the distinct determinants of each unsuccessful outcome.

Results. Of 915 participants included, 727 (79%) were successfully treated, 118 (13%) were LTFU, 44 (5%) had treatment failure, and 26 (3%) died. LTFU was associated with current drug-use (adjusted odds ratio [aOR] = 5.3; 95% confidence interval [CI], 3.0–9.4), current tobacco use (aOR = 2.9; 95% CI, 1.7–4.9), and being a person with HIV (PWH) (aOR = 2.0; 95% CI, 1.1–3.5). Treatment failure was associated with PWH (aOR = 2.7; 95% CI, 1.2–6.2) and having diabetes (aOR = 2.2; 95% CI, 1.1–4.4). Death was associated with anemia (aOR = 5.3; 95% CI, 1.4–19.7), diabetes (aOR = 3.1; 95% CI, 1.4–6.7), and PWH (aOR = 3.9; 95% CI, 1.3–11.4). Direct observed therapy was protective for treatment failure (aOR = 0.5; 95% CI, .3–.9) and death (aOR = 0.5; 95% CI, .2–1.0).

Conclusions. The treatment success rate was below the WHO target. Behavioral factors were most associated with LTFU, whereas clinical comorbidities were correlated with treatment failure and death. Because determinants of unsuccessful outcomes are distinct, different intervention strategies may be needed to improve TB outcomes.

Keywords. tuberculosis; treatment; outcomes; loss-to-follow-up; DOT.

Tuberculosis (TB) remains a major public health concern because of its high morbidity and mortality, especially among people with HIV (PWH) [1]. The World Health Organization (WHO) set a target of $\geq 90\%$ TB treatment success rate to reach their goal of a 75% reduction in deaths from TB by 2025 [2]. In 2019, the global treatment success rate for new TB cases was 86%; among PWH, it was 77% [1]. Brazil, which is among

the 30 countries with the highest TB burden [1], had a treatment success rate of 70% in 2019 [3].

Since 2015, a well-characterized multicenter cohort study of newly diagnosed TB cases enrolled pulmonary patients with TB in Brazil: the Regional Prospective Observational Research in Tuberculosis (RePORT)-Brazil [4,5]. A recent study comparing RePORT-Brazil data with the Brazilian national TB registry (SINAN) demonstrated similar characteristics of TB cases and outcomes, though treatment success rates from both data sources were below the WHO target [5].

Most studies examining risk factors for TB treatment outcomes use composite outcomes, in which treatment failure, death, and loss to follow-up (LTFU) are combined as unsuccessful outcomes and compared with successful outcomes [5, 6]. These studies are informative but fail to capture nuances that drive the different components of the “unsuccessful”

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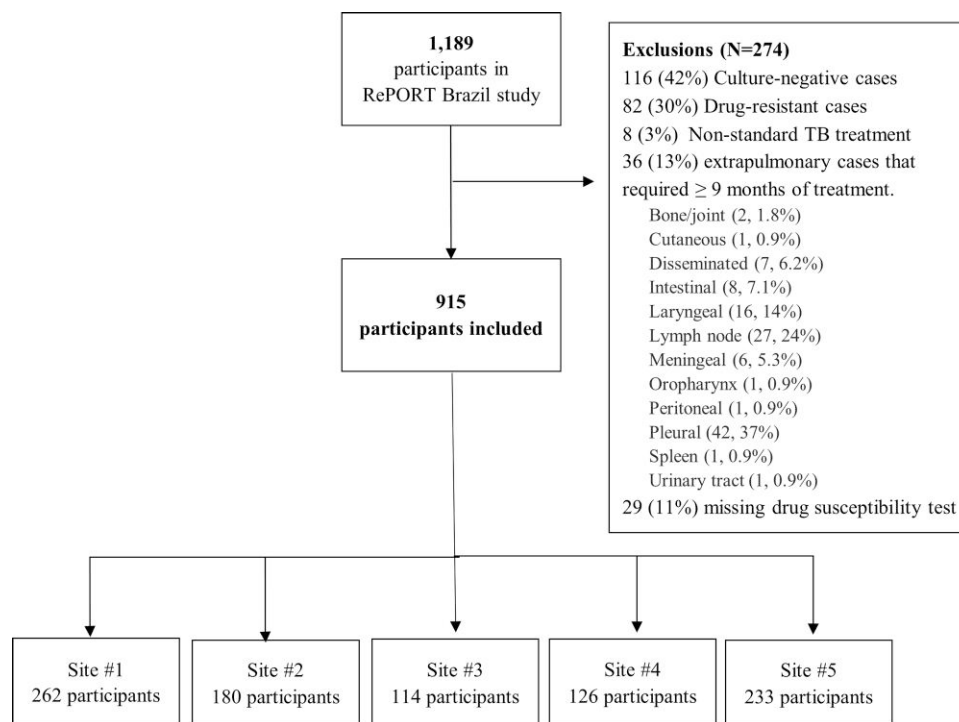


Figure 1. Study cohort.

outcomes, which is necessary to inform treatment and intervention strategies. Because of the large number of study participants enrolled and outcomes observed, RePORT-Brazil is well-positioned to investigate the different determinants of death, failure, and LTFU. In the present study, we evaluated baseline factors associated with the different components of unsuccessful treatment outcomes (treatment failure, death, and LTFU) in a national multicenter cohort of pulmonary TB participants in Brazil.

METHODS

Study Design and Population

From June 2015 through June 2019, individuals with newly diagnosed pulmonary TB were enrolled in the RePORT-Brazil study [4,5] at 5 sites across 3 high TB burden regions in Brazil: 3 sites in the southeast (Rio de Janeiro-Rio de Janeiro), 1 in the northeast (Salvador-Bahia), and 1 in the north (Manaus-Amazonas). The current study included RePORT-Brazil participants with drug-susceptible, culture-confirmed, pulmonary TB, who initiated standard TB treatment (ie, fixed-dose combination of rifampicin, isoniazid, ethambutol, and pyrazinamide for a 2-month intensive phase, followed by 4 months of isoniazid and rifampin in the continuation phase). We excluded participants with resistance to isoniazid and/or rifampin who had concomitant extrapulmonary TB that would require more than 6 months of treatment, and participants who were started on a second-line anti-TB drug regimen (Figure 1). Our study cohort focused on

this group because the standard TB treatment regimen (and duration) reflects the most common TB management in Brazil and globally.

Measurements

Baseline demographic, clinical, and disease severity characteristics were collected, including age, sex, self-reported race, years of education, and monthly income. Participants were considered low income if they reported not having an income or reported making less than Brazil's minimum wage (<R\$1100 per month). In Brazil, race, often referred to as "Race/Skin Color" by the Brazilian Institute of Geography and Statistics, is considered a social construct, and it is believed to influence multiple aspects of individuals' lives. Based on previous research and limited sample size among subgroups of racial categories, categories of White and non-White (including Black, Brown, Asian, and Indian) were used in analysis [7,8]. Diabetes was defined as self-reported history of diabetes or baseline glycated hemoglobin level $\geq 6.5\%$. Anemia was defined as hemoglobin ≤ 13 g/dL for males and ≤ 12 g/dL for females. Body mass index (BMI) was used as a marker of nutritional status, evaluated as a continuous variable and with the following categories: underweight (BMI < 18.5 kg/m²), normal weight (BMI 18.5–25 kg/m²), and overweight (BMI ≥ 25 kg/m²) [9]. Alcohol, tobacco, and drug use were categorized as current, former, or never used, based on self-report. We defined alcohol use based on a score of 2 or higher on the CAGE questionnaire

[10,11]. Drug use included all drugs, such as marijuana, cocaine, crack, ecstasy, injectable drugs, inhaled solvents, oxydone, and cocaine paste base. Sputum smear status at baseline was determined by the Ziehl–Nelson technique. We additionally evaluated presence of cavitation on chest x-ray, whether individuals had a previous TB diagnosis, and considered the prescription (yes/no) of directly observed therapy (DOT).

We considered several HIV-related variables. Baseline CD4 count and viral load were done at the time of TB diagnosis, or up to 6 months before TB diagnosis if not available at TB diagnosis. CD4 count was evaluated as a continuous variable, and categorically, using a cutoff of 200 cells/mL. Viral load was also evaluated as both a continuous variable, and categorically, using a cutoff of <1000 copies/mL to define viral suppression [12]. Prior antiretroviral therapy (ART) use was defined based on exposure to any ART before TB diagnosis; individuals were considered ART-naïve if they had never received ART before TB diagnosis.

For interpretation, we grouped covariates of interest as biological and behavioral factors. Participants' clinical conditions such as being PLHW, having anemia, or diabetes were considered biological conditions, whereas substance use (alcohol, drugs, and tobacco) was considered a behavioral factor. We considered smear positivity and presence of cavitation on chest x-ray at baseline as disease severity markers.

Outcomes were defined according to the recently updated version of TB treatment outcomes proposed by WHO [13]: cure, treatment completion, treatment failure, death from any cause during treatment, and LTFU. Cure and treatment completion were considered successful outcomes. Treatment failure was defined as participants whose TB regimen needed to be terminated or permanently changed to a new regimen or treatment strategy from lack of clinical and/or bacteriological response, adverse drug reactions that resulted in treatment discontinuation, or evidence of acquisition of drug resistance. LTFU consisted of treatment abandonment, lost contact, patient transfers, participant withdrawal, and not evaluated.

Statistical Analysis

Baseline demographic, clinical, and disease severity information were summarized in the full study cohort and stratified by HIV status. Categorical variables were presented as frequencies and percentages, and continuous variables were presented as medians and interquartile ranges (IQR). Only 3% of participants had any missing data. We used multiple imputation with 20 iterations to impute missing data; results were pooled using the Rubin rule [14].

Multinomial logistic regression was used to evaluate the different drivers of LTFU, treatment failure, and death, with successful treatment as the reference outcome category. We evaluated the associations between prespecified baseline covariates of interest and the multinomial outcome in unadjusted,

site-adjusted, and inverse-probability weighted (IPW) models [15–19]. Additional details about construction of the IPW are in [Supplementary Table 1](#).

Additional multinomial logistic regression evaluated unadjusted, site-adjusted, and IPW associations with baseline characteristics and HIV-related factors among PWH. As with the full population analysis, covariates for each propensity score model used to construct the IPW were prespecified based on literature review and clinical relevance ([Supplementary Table 1](#)). Odds ratios and their corresponding 95% confidence intervals (CI) are presented. Exploratory analyses via interaction plots and boxplots were additionally carried out to check whether the relationship between ART use and LTFU was associated with CD4 count or viral load. R version 4.0.2 was used for all analyses.

Ethics

The RePORT-Brazil study was approved by the institutional review board of the Instituto Nacional de Infectologia Evandro Chagas (CAAE: 25102412.3.1001.5262), by the institutional review boards of the other study sites, and Vanderbilt University Medical Center. Written informed consent was obtained from all participants and all clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki.

RESULTS

Among 1189 participants with TB in RePORT-Brazil, 915 met study inclusion criteria ([Figure 1](#)). Overall, the median age of included participants was 35 years (IQR 25–49), most were male (67%, $n = 609$), non-White (80%, $n = 732$), and low income (69%, $n = 629$). PWH represented 19% ($n = 173$) of the study cohort. Additional baseline characteristics of the study population are shown stratified by HIV status ([Table 1](#)), stratified by site ([Supplementary Table 2](#)), and stratified by outcome ([Supplementary Table 3](#)).

TB treatment success was achieved in 79% ($n = 727$) of study participants, including 42% ($n = 385$) cured and 37% ($n = 342$) completed treatment, whereas 21% ($n = 188$) experienced unsuccessful outcomes: 118 (13%) LTFU, 44 (5%) treatment failure, and 26 (3%) death during treatment. LTFU reasons included: treatment abandonment ($n = 77$, 64%), lost contact ($n = 21$, 19%), moved/transferred ($n = 13$, 11%), and withdrawal ($n = 7$, 6%). Treatment failure reasons were bacteriologic evidence of disease (smear or culture positive) at month 5 or later during treatment ($n = 26$, 59%) and regimen modification from adverse reaction or new drug resistance ($n = 18$, 41%).

We evaluated determinants of the different components of unsuccessful outcomes (death, failure, and LTFU) in the full study cohort ([Figure 2](#)). HIV infection was associated with increased odds of each component outcome, though to varying

Table 1. Baseline Characteristics and Outcome in the Study Population, Stratified by HIV-Serology Status

	HIV-seronegative N = 741	PWH N = 173	Total N = 915 ^a
	N (%) or Median [IQR]		
Age	36 [25–50]	35 [28–42]	35 [25–49]
Male	474 (64)	134 (77)	609 (67)
Non-White race	589 (80)	142 (82)	732 (80)
Low income	507 (69)	120 (70)	629 (69)
Diabetes mellitus	173 (24)	40 (23)	215 (24)
Years of education	9 [5–12]	9 [6–12]	9 [6–12]
Anemia	389 (53)	140 (81)	529 (58)
Underweight	204 (27)	49 (28)	253 (28)
Smear positive	635 (86)	116 (67)	753 (82)
X-ray cavitation	423 (57)	37 (22)	460 (50)
Previous TB	106 (14)	32 (19)	139 (15)
Alcohol use			
Never	135 (18)	13 (8)	148 (16)
Former	245 (33)	103 (60)	348 (38)
Current	361 (49)	57 (33)	419 (46)
Tobacco use			
Never	369 (50)	70 (40)	439 (48)
Former	191 (26)	74 (43)	265 (29)
Current	181 (24)	29 (17)	211 (23)
Drug use			
Never	521 (70)	78 (45)	599 (66)
Former	126 (17)	71 (41)	197 (22)
Current	94 (13)	24 (14)	118 (13)
Prescription of DOT	508 (69)	127 (74)	635 (70)
Outcome			
Success	617 (83)	110 (64)	727 (79)
Death	12 (2)	14 (8)	26 (3)
Failure	27 (4)	17 (10)	44 (5)
LTFU	85 (11)	32 (18)	118 (13)

Abbreviations: DOT, directly observed therapy; IQR, interquartile range; LTFU, loss to follow-up; PWH, person with HIV; TB, tuberculosis.

^aIncludes 1 person with missing HIV status.

^bBased on CAGE criteria.

degrees. The strongest associations were seen with death (adjusted odds ratio [aOR] = 3.9; 95% CI, 1.3–11.4) and failure (aOR = 2.7; 95% CI, 1.2–6.2) and to a lesser extent with LTFU (aOR = 2.0; 95% CI, 1.1–3.5). Diabetes was associated with death (aOR = 3.1; 95% CI, 1.4–6.7) and failure (aOR = 2.2; 95% CI, 1.1–4.4), but not LTFU (aOR = 1.4; 95% CI, .8–2.2). Anemia was strongly associated with death during treatment (aOR = 5.3; 95% CI, 1.4–19.7) and moderately associated with LTFU (aOR = 1.7; 95% CI, 1.1–2.6), but not failure (aOR = 1.3; 95% CI, .7–2.6). Being underweight at baseline was associated only with death (aOR = 2.2; 95% CI, 1.0–5.1). Former and current drug use were associated with LTFU (aOR = 2.5; 95% CI, 1.5–4.4 and aOR = 5.3; 95% CI, 3.0–9.4, respectively), but not with death or failure. The same was observed for former and current tobacco use and alcohol use: association with LTFU (aOR = 2.5; 95% CI, 1.5–4.92 aOR = 2.9; 95% CI, 1.7–

4.9, aOR = 1.8; 95% CI, 1.1–2.9, respectively), but none was associated with death or failure. Prescription of DOT at treatment initiation was associated with decreased odds of death (aOR = 0.5; 95% CI, .2–1) and treatment failure (aOR = 0.5; 95% CI, .3–.9), but was not associated with LTFU (Figure 2). Other disease severity markers, such as cavitation on chest x-ray and smear positivity at baseline, were not associated with TB treatment outcomes (Supplementary Table 4).

We additionally evaluated the association between HIV-related factors and outcomes among PWH. Of the 173 PWH in the study, median CD4 count was 134 (IQR: 57–286), median viral load was 28 882 (IQR: 278–216 615), and 58% (n = 93) were ART-naïve (Table 2). In IPW multinomial logistic regression analyses, higher levels of baseline CD4 count were associated with increased odds of LTFU (aOR = 1.2; 95% CI, 1.0–1.4). Being ART-experienced at baseline may have been protective for LTFU, but the association was not statistically significant, perhaps limited by sample size (aOR = 0.40; 95% CI: .1–1.1). None of the HIV-related factors evaluated were associated with death or failure (Figure 3). Full results from unadjusted and site-adjusted multinomial models for the full study cohort and among PWH are in Supplementary Tables 5 and 6, respectively.

In exploratory analyses, an interaction plot and boxplots seem to suggest a possible interaction between CD4 count and prior ART use on LTFU, but the same was not observed among ART-naïve patients. We did not observe an interaction between viral load and prior ART use on LTFU (Supplementary Figure 1 and Figure 2, respectively).

DISCUSSION

In this study, 21% of all participants had an unsuccessful TB treatment outcome, which is far higher than WHO-recommended rate of 10% [2]. The rates of unsuccessful outcomes in our study were slightly better than the national TB treatment outcome rate in Brazil in 2019, but this could be explained in part by our strict inclusion criteria and prospective follow-up. We found that most unsuccessful TB treatment outcomes were due to LTFU, rather than death or treatment failure. Our results indicate that the determinants of death, failure, and LTFU are distinct, suggesting the common convention of grouping together these outcomes into a composite “unsuccessful” outcome may lead to information loss, and inhibit identification of preventive interventions.

Adjusted analyses highlight several factors that are associated with the different components of unsuccessful TB treatment outcomes. Death and treatment failure were largely driven by clinical characteristics, such as being PWH, diabetes, and anemia, whereas starting DOT was protective. LTFU, however, was most strongly associated with behavioral characteristics, such as drug use, tobacco use, and alcohol use, and to a lesser extent

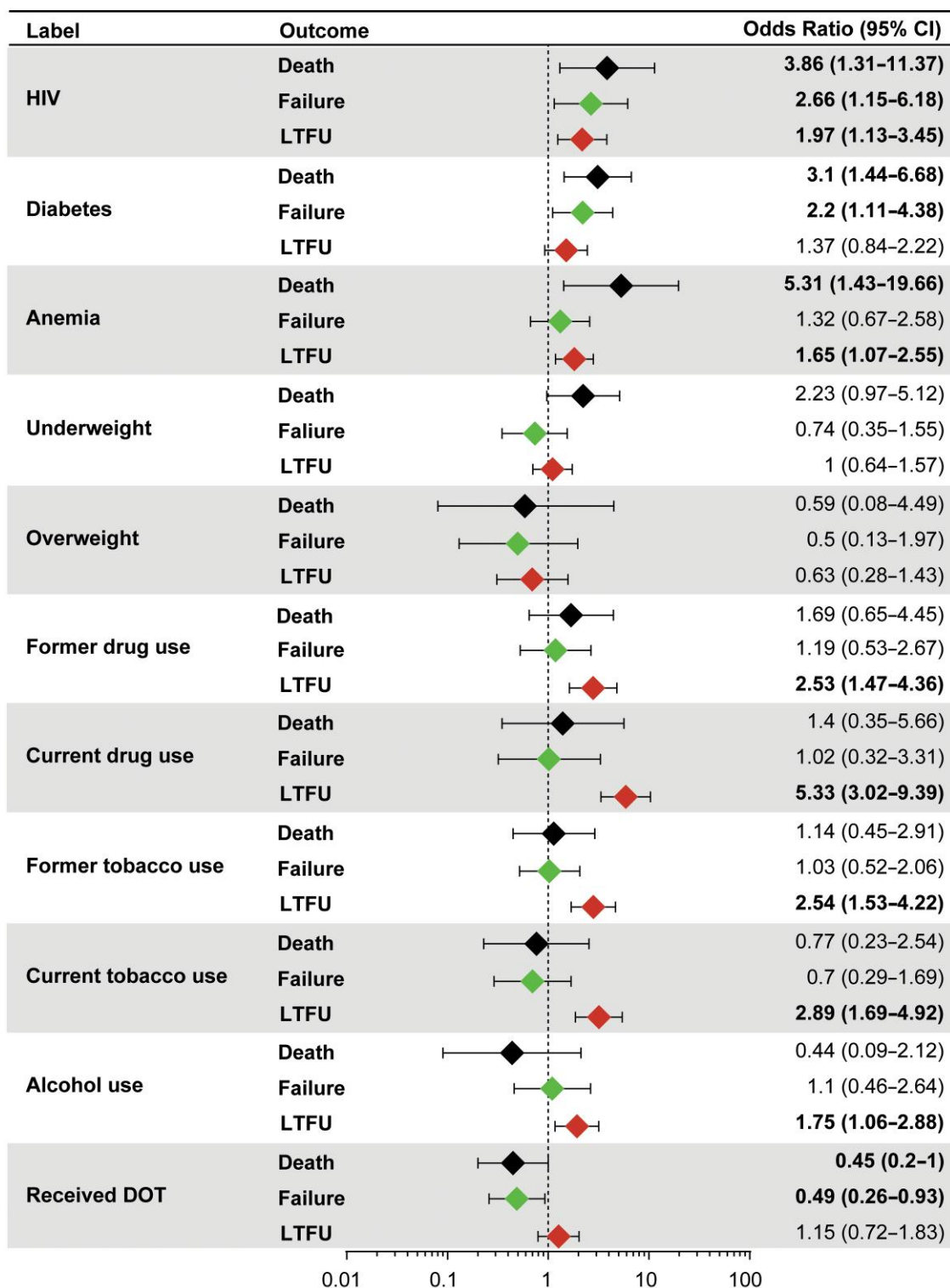


Figure 2. Coefficient plot of inverse probability weighted multinomial logistic regression model of baseline factors associated with the different components of unsuccessful outcomes in tuberculosis (TB) treatment among the full study population (N = 915). Successful outcome (cure and treatment completion, N = 727) was the reference outcome. Statistically significant associations are shown in bold-type font. The adjustment set differed for each baseline parameter analyzed. Confounders were based on prespecified covariates. Additional details about inverse probability weighted multinomial logistic regression model are in [Supplementary Table 1](#).

Table 2. HIV-related Severity Characteristics at Study Baseline Among Persons With HIV (PWH) in the Study (N = 173)

	N (%) or Median [IQR]
CD4 count	134 [57–286]
CD4 < 200 cells	106 (64)
Viral load	28 774 [278–216 615]
Viral load > 1000	112 (69)
ART naïve	93 (58)
Baseline ART regimen (N = 68)	
INSTI	26 (38)
NNRTI	31 (46)
PI	11 (16)

Abbreviations: ART, antiretroviral therapy; DOT, directly observed therapy; INSTI, integrase strand transfer inhibitors; IQR, interquartile range; LTFU, loss to follow-up; NNRTI, non-nucleoside reverse transcriptase inhibitors; PWH, person with HIV; PI, protease inhibitor.

some of the clinical characteristics, such as HIV and anemia. Other disease severity markers, such as smear positivity and cavitation on chest x-ray at baseline, were not associated with TB treatment outcomes.

In all analyses, HIV infection was associated with unsuccessful outcomes, corroborating the already known negative effect of HIV infection on TB treatment outcome [6,20]. Prior ART use may have been slightly protective for LTFU, as evidenced by a strongly protective point estimate, although this was not statistically significant. This result could be explained by the fact that PWH who were on ART were already linked to

healthcare facilities for HIV care and, thus, may be more engaged with the healthcare system and more likely to remain adherent to general treatments. These patients may also have been diagnosed with TB at an earlier stage of infection. Among patients with prior ART use, it seems that higher CD4 cell count at baseline was correlated with LTFU. One possible explanation for this could be that PWH with higher CD4 counts may have had better immunity, overall health status, and felt less sick, leading to lower adherence to treatment and medical appointments.

Overall, our results are in agreement with a recent study of multidrug resistant TB cases in Brazil, which reported that clinical characteristics such as disease severity and HIV infection as factors associated with death and treatment failure, whereas behavioral characteristics, such as drug use and former or current tobacco and alcohol use, were associated with LTFU [21]. Similarly, the study found that prescription of DOT did not influence LTFU. Interestingly, no factors that we examined were protective against LTFU. However, we did not have data on time to clinic, receipt of social or nutritional support, or other socioeconomic factors that may prevent LTFU. Such data are important to evaluate in future studies and may be helpful in designing effective interventions.

Our finding that diabetes was associated with death and treatment failure is consistent with existing literature. Persistent hyperglycemia alters the innate and adaptative response to *Mycobacterium tuberculosis*, leading to increased

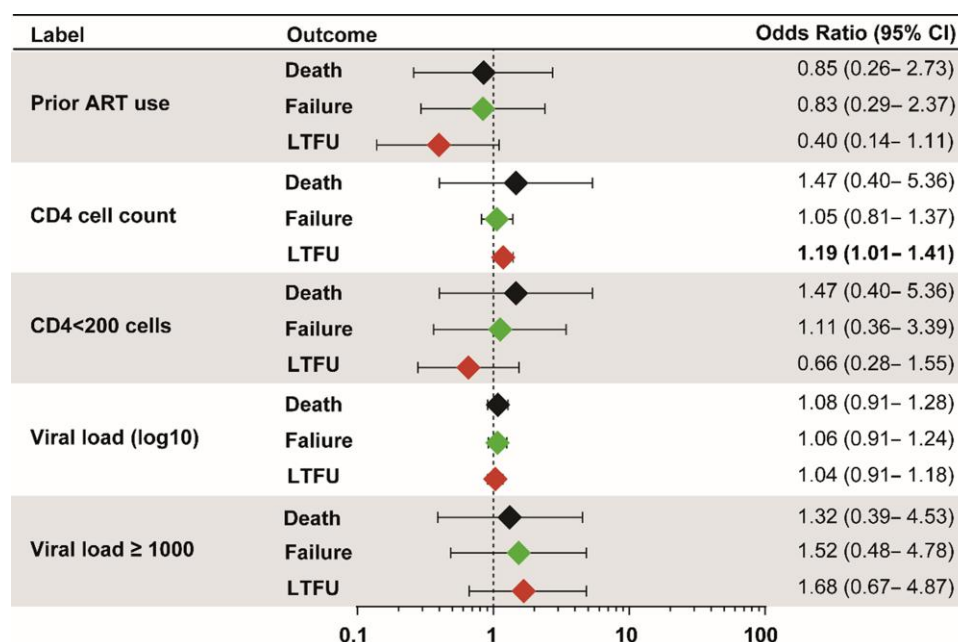


Figure 3. Coefficient plot of inverse probability weighted multinomial logistic regression model of baseline HIV-related factors associated with the different components of unsuccessful outcomes in tuberculosis (TB) treatment among people with HIV (PWH) (N = 173). Successful outcome (cure and treatment completion, N = 110) was the reference outcome. Statistically significant associations are shown in bold-type font. The adjustment set differed for each baseline parameter analyzed. Confounders were based on prespecified covariates. Additional details about inverse probability weighted multinomial logistic regression are in [Supplementary Table 1](#).

rates of smear positivity, more extensive disease, and higher rates of failure, death, and risk of relapse [22]. Our group recently showed that diabetes in TB cases from RePORT-Brazil was associated with substantially higher risk of *M tuberculosis* transmission to close contacts [22]. Furthermore, additional analyses from RePORT-Brazil and SINAN revealed that patients with TB and diabetes were at higher risk of unsuccessful treatment using composite outcomes or death as the main endpoint [23].

Our analysis demonstrated that behavioral factors such as drug use, tobacco use, and alcohol use were more likely to be associated with LTFU. It is known that drug use contributes to worse outcomes in TB treatment; patients who use drugs are more likely to be noncompliant with treatment, and consequently abandon TB treatment [24–27]. Moreover, conditions such as alcohol use, unemployment, homelessness, and malnutrition are often cooccurring, and together are associated with increased risk of unsuccessful TB outcomes [28,29].

Compared with other studies conducted in Brazil and other low- and middle-income countries with similar TB burdens, we found lower rates of mortality and treatment failure [5,30,31]. Interestingly, DOT was protective against both, but not to LTFU. However, we must note that we only evaluated baseline prescriptions of DOT, not adherence or different DOT techniques. Despite robust adjustment for known confounders, residual confounding may in part explain the observed association; it is possible that people who accept DOT remain different from those who do not in terms of their risk for the different outcomes, leading to either over- or underestimation of the association between DOT and each of death, failure, and LTFU. Regardless, DOT is a pillar and a standard of care of TB treatment recommended by WHO and by the Brazilian National TB Program to all TB patients or selected groups with risk factors for nonadherence to improve TB treatment outcomes [32,33]. A study in Brazil found that the Bolsa Familia, which is social support offered by the government to very poor people, was protective against LTFU, but less so against death [34]. Another recent paper from our group using the entire SINAN database demonstrated that DOT was a protective feature against unfavorable treatment outcomes [35]. Taken together with our findings, there is reason to believe that interventions will have different impacts on different outcomes.

This study had limitations. We evaluated only baseline factors and end of TB treatment outcome. We did not consider time-varying covariates, such as adherence or changes in symptoms or clinical characteristics during treatment. Our focus was on baseline, mostly modifiable, covariates because that is when most interventions would be used. Additionally, our outcomes did not include relapse or reinfection. Given the relatively low number of deaths and treatment failures, we were limited in our ability to simultaneously adjust for multiple confounders with

traditional multivariable regression. Because of this, we used stabilized inverse probability weights to adjust for confounding, which enabled confounder adjustment without spending as many degrees of freedom as traditional multivariable modeling [15]. Finally, the study cohort included only participants with culture-confirmed, drug-susceptible, pulmonary TB on standard therapy regimens prescribed for 6 months, so results may not be generalizable to other populations. On the other hand, we highlight that this was a prospective cohort study, with uniform data collection and regular visits; we used the updated WHO definitions for TB treatment outcomes; we considered DOT prescription; and we are not aware of other previous studies in Brazil that have used multinomial logistic regression to evaluate factors associated with the different components of TB treatment outcomes among drug-susceptible TB cases.

In conclusion, our results indicate that baseline factors associated with the different components of unsuccessful TB treatment outcomes are different. Thus, intervention strategies and treatment policies in Brazil need to be uniquely tailored to prevent specific components of unfavorable outcomes. For example, if the goal is to improve retention in care, counseling or social support programs that target behavioral characteristics like drug, alcohol, or tobacco use will likely be of greatest use. If the goal is to prevent deaths and treatment failure, clinical interventions that facilitate improved health related to HIV, diabetes, and anemia will likely be most beneficial.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. F. R. and L. S. P. conceptualized the research question and drafted the initial manuscript. L. S. P. conducted the analysis. V. R. and T. R. S. provided thorough feedback on the research design and analysis interpretation, supervised the analysis, and revised successive drafts of the manuscript. B. A. provided valuable feedback and comments on successive manuscript drafts. G. A. assisted with methodology conceptualization, analysis interpretation and revised successive manuscript drafts. B. A., M. C. S., M. T., A. K., B. D., S. C., T. R. S., V. R., and M. C. F. played pivotal roles in the conceptualization of the RePORT Brazil cohort, project administration, data and funding acquisition, and revised successive drafts of the manuscript. All authors approved the final version of the manuscript.

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