# Effects of missed anti-tuberculosis therapy doses on treatment outcome: a multi-center cohort study

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## Summary

**Background** Tuberculosis (TB) remains a leading cause of infectious disease mortality globally. Although directly observed therapy (DOT) has been widely implemented to improve adherence, nonadherence continues to compromise treatment success rates, especially in real-world settings. Therefore, this study aims to assess the impact of missed doses on TB treatment outcomes.

**Methods** Prospective study that followed adults with drug-sensitive TB for two years after TB treatment initiation at five clinical centers of the RePORT-Brazil cohort between June 2015 and June 2019. Participants not in DOT or followed for less than 30 days were excluded. Nonadherence was defined as the percentage of missed doses relative to the prescribed regimen, monitored daily through DOT. The primary composite outcome comprised treatment failure, disease recurrence, drug resistance, death, or loss to follow-up (LTFU) after 30 days of treatment. Associations were assessed with multivariable logistic regression.

**Findings** Among the 578 participants analyzed, 218 (37·7%) experienced unfavorable outcomes. Overall, 23% of participants missed more than 10% of prescribed doses, and this group had an 81·2% likelihood of experiencing unfavorable outcomes, compared to only 21·6% among those with complete adherence. A significant association was observed between the percentage of missed doses and unfavorable outcomes (adjusted OR: 1·11, 95% CI: 1·07–1·14, p-value < 0·0001).

**Interpretation** Even minor nonadherence in TB treatment was associated with an increased risk of unfavorable outcomes, highlighting the role of adherence in successful TB care.

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**Keywords:** Tuberculosis; Adherence; Treatment; Compliance; Unfavorable treatment outcome

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**Translation:** For the Portuguese translation of the abstract see Supplementary Materials section.

## Research in context

### Evidence before this study

A review was conducted between January and August 2024 in PubMed, Web of Science, Embase, and Google Scholar using terms such as "Tuberculosis", "Adherence", "Nonadherence", "Compliance", "Unfavorable Treatment Outcome", "Adverse Treatment Outcome", "Treatment". The review targeted studies assessing the impact of adherence on treatment success through observational or interventional designs. The pooled evidence consistently shows that nonadherence significantly increases the risk of unfavorable outcomes, including relapse and drug resistance. However, most of the available studies relied on secondary analyses of clinical trial data, limiting their relevance to real-world settings where adherence patterns are more complex and multifaceted.

### Added value of this study

This study extends previous research by employing a prospective, multicenter design within diverse regions of Brazil, thereby addressing the limitations of prior studies focused on clinical trial populations. It captures real-world adherence rates and demonstrates that even minimal nonadherence, as low as 2·8% of prescribed doses, can significantly increase the risk of unfavorable outcomes, and that even under Directly Observed Therapy, adherence remains a significant challenge, with 23% of the study population missing more than 10% of their prescribed treatment.

### Implications of all the available evidence

Early detection of nonadherence and timely interventions are critical for improving treatment outcomes. This study emphasizes the importance of routine adherence monitoring throughout the treatment period. This understanding suggests a need for improved programs that prioritize patient-centered care, integrating community engagement, socioeconomic support, and digital tools into adherence strategies, shaping future research directions and informing policy development for a more effective and equitable response to TB management.

## Introduction

Despite the availability of curative treatment, tuberculosis (TB) has regained its position as the deadliest infectious disease worldwide. Until 2022, the global treatment success rate had consistently fallen short of the 90% target established by the END TB Strategy for 2025, underscoring the ongoing challenge in achieving optimal TB control.[1] A major obstacle to treatment success is the prolonged treatment duration, often requiring 6–9 months of daily medication intake, which makes patient adherence critical yet vulnerable.

Improving adherence has been a primary focus of the World Health Organization (WHO) since the 1990s, leading to the recommendation of Directly Observed Therapy (DOT) as an adjunct measure to enhance treatment compliance. DOT aims to ensure that patients take their medications under supervision, reducing the likelihood of missed doses. However, even with DOT implementation, nonadherence remains prevalent in many settings, with missed doses continuing to compromise treatment outcomes.[2–4]

Previous studies have examined the association between adherence and treatment outcomes, often employing a composite measure of negative outcomes, such as death, emerging resistance, disease recurrence, and loss to follow-up (LTFU).[5–7] While these studies provide valuable insights, they were largely based on secondary analyses of randomized clinical trials, which may not fully reflect the complexities of real-world settings.

Given the expected challenges in real-world contexts, this study was designed to assess the impact of missed doses on patient outcomes through a multicentre prospective observational cohort with two years of follow-up from the time of TB treatment initiation, providing an opportunity to better understand how nonadherence influences treatment success in a diverse patient population.

## Methods

### Study design

Prospective multicentre cohort study conducted at clinical sites in the RePORT-Brazil network (www.reportbrazil.org), which adheres to an international protocol harmonized with other cohorts in high-burden tuberculosis countries, including India, South Africa, China, and others. The study sites include one in Salvador, (Instituto Brasileiro para Investigação da Tuberculose), three in Rio de Janeiro (Instituto Nacional de Infectologia Evandro Chagas, Clínica de Saúde Rinaldo Delmare, Secretaria de Saúde de Duque de Caxias), and one in Manaus (Fundação Medicina Tropical Doutor Heitor Vieira Dourado). Participants enrollment occurred between June 2015 and June 2019, with DOT monitoring implemented in the RePORT-Brazil cohort starting in August 2017.

### Participants

This study included all adult participants with drug-sensitive TB, confirmed by culture and baseline drug susceptibility testing (DST). Participants who were not managed under DOT or who had less than 30 days of follow-up, to ensure adequate assessment of treatment adherence and outcomes. All eligible participants within the defined period were included in the analysis.

The study protocol and cohort profile have been described in detail previously, and the RePORT-Brazil cohort has been validated as representative of TB cases reported in the Brazilian national surveillance system (SINAN).[8]

### Procedures

Sociodemographic and clinical data were collected at three key points: TB treatment initiation, 2 months after initiation, and at treatment completion. Participants self-identified their sex and race following the five official categories used by the Brazilian Institute of Geography and Statistics. For analytic purposes, this variable was dichotomized as "White" vs. "Non-white", following prior tuberculosis research in Brazil. Additional follow-up was conducted via phone calls every six months, up to 24 months from enrollment. Moreover, culture samples and drug sensitivity testing are done in baseline, end of month 1 and 2 and at treatment completion.

Standard anti-TB therapy consisted of isoniazid, rifampin, pyrazinamide, and ethambutol for the first two months (intensive phase), followed by isoniazid and rifampin for additional four months (maintenance phase). In Brazil, these medications are commonly administered as fixed-dose combination tablets. Alternative treatment regimens, either through therapy extension or substitution of first-line drugs, could be prescribed based on clinical judgment, mainly in cases of extrapulmonary disease, comorbidities, or drug intolerance, in alignment with national TB treatment guidelines.[9]

Treatment adherence was monitored daily via DOT and compiled into monthly summaries. Each study site assigned a staff member fully dedicated to supervising DOT during regular business days. Medication intake on weekends and holidays was assessed retrospectively on the next DOT session. Participants could transition between different DOT strategies throughout treatment, reflecting the flexible, real-world nature of care delivery. Four DOT strategies were implemented: (i) In-person, with supervision at a healthcare facility; (ii) Telephone-based, with daily contact to confirm medication intake; (iii) Virtual, using photos or videos; and (iv) Family Supervision, where a trained household member recorded medication intake using a DOT card, reviewed during clinical follow-up. Nonadherence was defined as the percentage of prescribed doses missed over the full course of treatment, calculated by dividing the number of missed doses by the total number of prescribed doses on a given treatment day. For participants who discontinued treatment, all remaining doses after discontinuation were counted as missed.

For this study, favorable outcome was defined as clinical or bacteriological cure, as per national TB treatment guidelines.[9] The primary outcome was defined as a composite unfavorable outcome, encompassing treatment failure, disease recurrence, development of drug resistance, TB-related or non-TB-related death, or LTFU occurring after the first 30 days of treatment. LTFU was defined as a treatment interruption lasting more than 30 consecutive days, with no further contact despite repeated follow-up attempts. While we acknowledge that LTFU may have distinct clinical and epidemiological implications compared to other unfavorable outcomes, its inclusion in the primary composite was intentional. This choice aimed to reflect the real-world complexity of treatment adherence, which is often shaped by patient preferences, systemic barriers, and access to care. Our analysis captures a broad spectrum of nonadherence, ranging from abrupt discontinuation with minimal missed doses to progressively declining adherence, highlighting the multiple pathways through which treatment may be prematurely interrupted. Additionally, a secondary outcome, referred to as the biological outcome, included treatment failure, disease recurrence, drug resistance, and death, excluding LTFU. The exclusion of LTFU from the biological outcome aimed to isolating them from factors related to patient retention in care.

### Statistical analysis

Categorical variables were summarized as frequencies and percentages, while continuous variables were reported as medians with interquartile ranges (IQR). Differences between groups were evaluated using the Mann–Whitney *U* test for continuous variables, and either Fisher's exact test or the chi-square test for categorical variables, as appropriate. To assess the impact of nonadherence on clinical outcomes, a binary logistic regression model was employed, adjusting for established risk factors identified in prior studies, including age, sex, region of residence, smoking status, alcohol and drug use, history of TB, diabetes, body mass index (BMI), cavitation on chest x-ray, positive smear results, percentage of missed doses, hemoglobin levels, and HIV status.[10,11] Potential non-linearity of the percentage of missed doses was explored by replacing the linear term with a restricted cubic-spline function containing knots at the 5th, 27·5th, 50th, 72·5th, and 95th percentiles of the exposure distribution, and comparing the spline model with the linear specification using a likelihood-ratio test and the Akaike Information Criterion (AIC).

Model performance was evaluated by estimating discriminatory capacity using the Area Under the Receiver Operating Characteristic (ROC) curve, while calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test. To explore the relationship between nonadherence and predicted outcomes further, a Locally Estimated Scatterplot Smoothing (LOESS) curve was applied, providing a non-linear visualization of how changes in the percentage of missed doses were

associated with predicted probabilities of unfavorable outcomes. Statistical significance was defined as a two-tailed p-value of less than 0·05. All analyses were conducted using RStudio (version 4·3·3) and GraphPad Prism (version 8·4·2).

### Ethical considerations

The study was conducted according to the principles in the Declaration of Helsinki. The RePORT-Brazil protocol was approved by the institutional review boards at each study site and at Vanderbilt University Medical Center. Participation in RePORT-Brazil was voluntary, and written informed consent was obtained from all participants.

### Role of the funding source

The study's funders had no role in the study design, data collection, management, analysis, interpretation, or writing of the report.

## Results

There were 968 participants enrolled in the study. After applying the exclusion criteria, 578 remained in the analysis (Fig. 1). A detailed description of patients' characteristics regarding to screening to cohort inclusion and inclusion in the analysis are provided in Supplementary Tables S1 and S2, respectively. The study population had a median age of 35 years (IQR: 25·0–47·0) and was mostly male (390; 67%). Regarding socioeconomic status, 176 (30·8%) participants lived in slums, and 187 (33·1%) reported having no household income. The participants were mostly symptomatic at admission, with 545 (94·3%) individuals presenting cough, while 454 (82·0%) participants reported no comorbidities. Additionally, 18 (3·1%) participants received non-first line treatment medications. Adherence to prescribed therapy was generally high, with participants missing a median of 0·28% (IQR: 0·0%–7·58%) of doses (Table 1).

In this analysis, 288 (49·8%) participants completed TB treatment without missing any doses. Of those, 61 (21·2%) had an unfavorable outcome (Fig. 2). In contrast, 157 participants (27·2%) missed up to 10% of their prescribed doses, with 49 (31·2%) having unfavorable outcomes. Notably, 133 participants (23·0%) missed more than 10% of prescribed doses, with 108 (81·2%) experiencing unfavorable outcomes. The distribution of participants per DOT strategy is represented in eFigure S1.

The heatmap in Fig. 2 illustrates the distribution of missed doses across treatment phases, stratified by outcomes. It identifies two primary nonadherence patterns: discontinuation, where participants ceased treatment entirely, and suboptimal implementation, characterized by intermittent missed doses. 290 (50·2%) participants missed doses intermittently, while 173 (29·9%) permanently discontinued treatment. Adherence was generally high during the intensive phase, regardless of outcomes. However, as treatment shifted into the maintenance phase (months 3–6), a progressive increase in missed doses was observed, especially among participants with unfavorable outcomes (Fig. 2).

When comparing outcomes, 218 (37·7%) participants experienced unfavorable outcomes after two years of follow-up. Those with unfavorable outcomes had a median age of 34·0 years (IQR: 24·0–44·0) compared to 37·0 years (IQR: 26·0–49·0) in the favorable outcome group ($p = 0·05$). There was a higher proportion of males among those with unfavorable outcomes (74·3% vs. 63·3%; $p = 0·01$). Participants with unfavorable outcomes had a higher prevalence of weight loss (94·5% vs. 88·0%; $p = 0·02$) and fatigue (89·0% vs. 76·1%; $p < 0·01$) at baseline. In addition, current smoking was significantly more common among those who subsequently had an unfavorable outcomes (27·5% vs. 18·3%; $p < 0·01$), as was current alcohol use (49·1% vs. 41·7%; $p = 0·01$), and drug use (21·1% vs. 8·9%; $p < 0·01$). Notably, participants with unfavorable outcomes also missed a higher percentage of prescribed therapy. Differences in baseline characteristics according to outcome are presented in Supplementary Table S4.

After adjusting for potential confounders, the percentage of missed prescribed therapy (adjusted OR [aOR]: 1·11, 95% CI: 1·07–1.14, $p < 0·0001$) was significantly associated with unfavorable outcomes. Also, current alcohol use (aOR: 2·52, 95% CI: 1·11–5·67, $p = 0·03$) was associated with unfavorable outcomes, while serum hemoglobin levels had an inverse association (aOR: 0·81, 95% CI: 0·71–0·92, $p < 0·01$) (Fig. 3A). The model had an AUC of 0·84 (95% CI: 0·81–0·87, p-value < 0·001), and a Hosmer–Lemeshow test p-value of 0·189 (Fig. 3B), with an intercept and slope in the calibration plot of 0·03 and 0·90 respectively (eFigure S2). Replacing the linear term for missed doses with a five-knot restricted cubic spline did not improve fit ($p = 0·21$; difference in AIC = +1·4). When nonadherence was stratified by treatment phase, missed doses during both the intensive and maintenance phases showed similar magnitudes of association with unfavorable outcomes (Supplementary Table S5).

The association between missed doses and the predicted risk of unfavorable outcomes, was estimated by the logistic model. It was observed that participants with complete adherence had a 21·6% probability of unfavorable outcomes (Fig. 3C). A 10% absolute increase in the predicted risk (to 31·6%) was observed when participants missed just 2·8% of the prescribed treatment. As the percentage of missed doses increased, the predicted risk of unfavorable outcome rose sharply. However, once the percentage of missed doses exceeded 50%, the risk curve plateaued, with the risk of unfavorable outcomes approaching 100%.

### Secondary analysis

When LTFU was excluded, 405 participants remained in the analysis, with 45 (12·5%) having unfavorable biological outcomes. The distribution of clinical and sociodemographic characteristics was consistent with the primary analysis and is presented in Supplementary Table S1. In this secondary analysis, the only variables associated with unfavorable outcomes were serum hemoglobin levels (aOR: 0·75, 95% CI: 0·58–0·98, p-value = 0·04) and the percentage of missed doses (aOR: 1·08, 95% CI: 1·03–1·14, p-value < 0·01) (eFigure S4A). The model maintained good discriminatory capacity, with an AUC of 0·87 (95% CI: 0·81–0·93, p-value < 0·01), and calibration, with Hosmer–Lemeshow p-value of 0·82 (eFigure S4B).

In this subgroup, 235 (58·0%) participants adhered completely to treatment, with 8 (3·5%) having unfavorable biological outcomes. Conversely, 47 (11·6%) individuals missed more than 10% of the prescribed treatment, with 22 (46·8%) experiencing unfavorable outcomes. eFigure S3 illustrates the distribution of missed doses during treatment. Plotting the predicted probability of unfavorable biological outcomes against the percentage of missed treatment, as estimated by the regression model, showed that missing 6·25% of treatment corresponded to a 10% absolute increase in the risk of poor biological outcomes (eFigure S4C).

## Discussion

This study assessed the impact of nonadherence on TB treatment outcomes within a real-world, multicentre cohort with a two-year follow-up. Our findings revealed a clear dose-response relationship between nonadherence and unfavorable treatment outcomes, underscoring the significant role of adherence in achieving successful TB treatment. Notably, even minimal nonadherence, such as missing only 2·8% of prescribed doses, increased the predicted risk of unfavorable outcomes by 10%.

These results align with previous research that highlights the role of adherence throughout the treatment course. For example, Fox et al. found that missing as few as four treatment days in a month increased the risk of poor outcomes by 61%, supporting our observation that even small deviations in adherence can have significant consequences.[6] Moreover, Imperial et al. demonstrated that nonadherence exceeding 10% of prescribed doses is associated with a sharp increase in the risk of treatment failure, a threshold that matches our findings.[5]

Unlike many previous studies that relied primarily on secondary analyses of randomized clinical trials, the RePORT-Brazil cohort is broadly representative of TB cases across Brazil.[8] This study reflects the complexities of real-world adherence patterns, offering a more realistic view of patient behavior in routine clinical practice.

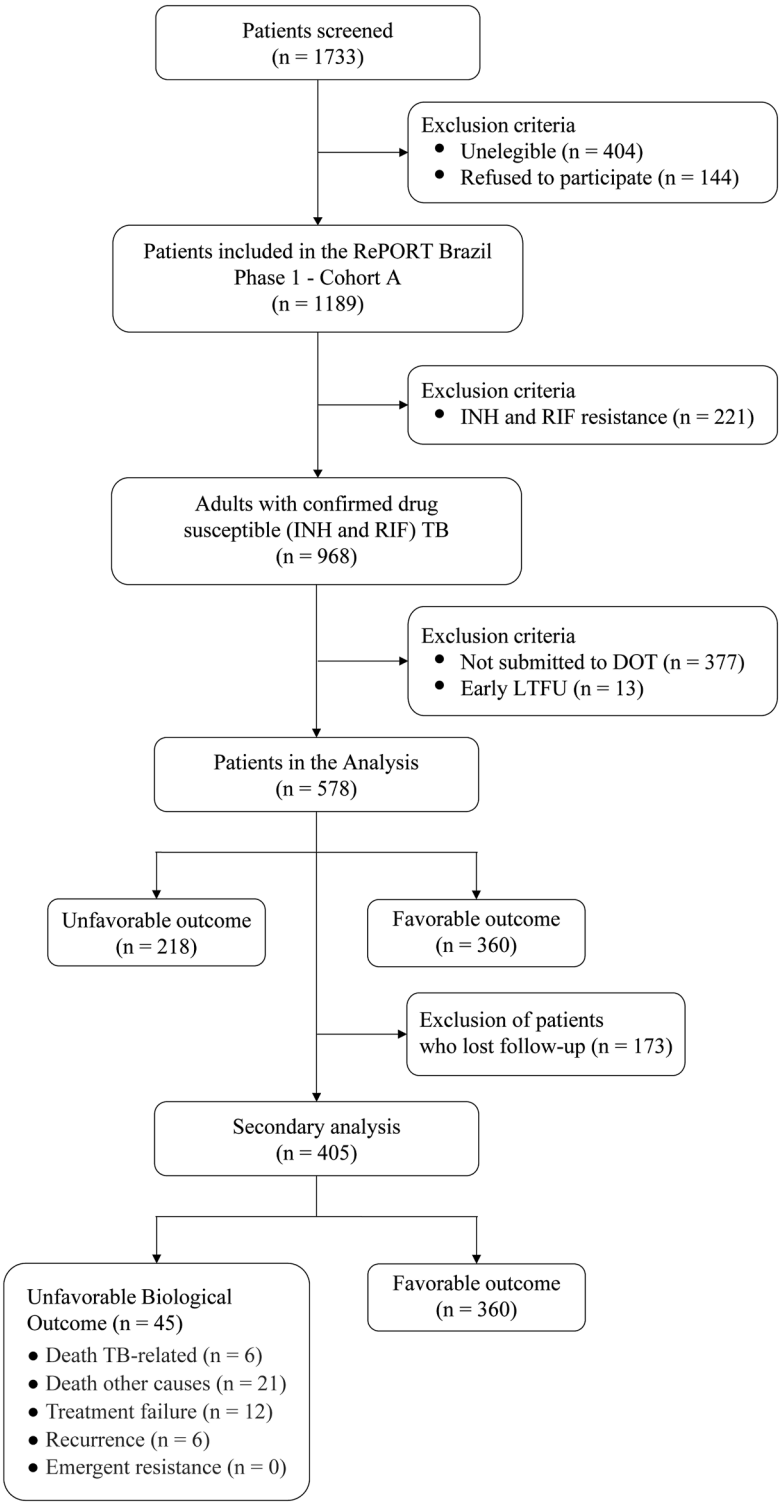


*Fig. 1:* **Flowchart of the study.**

However, despite the use of DOT, adherence remains a significant challenge, as 23% of the study population missed more than 10% of their prescribed therapy,

| Characteristics | Study population (n = 578) | Favorable outcome (n = 360) | Unfavorable outcome (n = 218) | p-value |
|---|---|---|---|---|
| Percentage of missed prescribed therapy, median [IQR] | 0·28 [0·00; 7·58] | 0·00 [0·00; 1·05] | 8·99 [0·00; 34·4] | <0·01 |
| Intensive phase, median [IQR] | 0·00 [0·00; 1·64] | 0·00 [0·00; 0·00] | 0·00 [0·00; 5·00] | <0·01 |
| Maintenance phase, median [IQR] | 0·00 [0·00; 5·83] | 0·00 [0·00; 0·82] | 6·25 [0·00; 43·6] | <0·01 |
| Symptoms, No. (%) | | | | |
| Cough | 545 (94·3) | 342 (95·0) | 203 (93·1) | 0·45 |
| Fever | 446 (77·2) | 269 (74·7) | 177 (81·2) | 0·09 |
| Weight loss | 522 (90·5) | 316 (88·0) | 206 (94·5) | 0·02 |
| Fatigue | 468 (81·0) | 274 (76·1) | 194 (89·0) | <0·01 |
| Night sweats | 387 (67·0) | 244 (67·8) | 143 (65·6) | 0·65 |
| Chest pain | 385 (66·7) | 236 (65·7) | 149 (68·3) | 0·58 |
| Age, median [IQR], years | 35·0 [25·0; 47·0] | 37·0 [26·0; 49·0] | 34·0 [24·0; 44·0] | 0·05 |
| Sex, No. (%), male | 390 (67·5) | 228 (63·3) | 162 (74·3) | 0·01 |
| Region of enrollment, No. (%) | | | | <0·01 |
| Rio de Janeiro | 246 (42·6) | 179 (49·7) | 67 (30·9) | |
| Manaus | 195 (33·8) | 76 (21·1) | 119 (54·8) | |
| Salvador | 136 (23·6) | 105 (29·2) | 31 (14·3) | |
| Live in Slums, No. (%) | 176 (30·8) | 137 (38·4) | 39 (18·2) | <0·01 |
| Marriage status, No. (%) | | | | 0·11 |
| Never married | 227 (39·4) | 128 (35·8) | 99 (45·4) | |
| Married | 234 (40·6) | 155 (43·3) | 79 (36·2) | |
| Divorced | 92 (16·0) | 60 (16·8) | 32 (14·7) | |
| Widowed | 22 (3·82) | 15 (4·19) | 7 (3·21) | |
| Not applied | 1 (0·17) | 0 (0·00) | 1 (0·46) | |
| Race, No. (%) | | | | 0·04 |
| White | 106 (18·4) | 78 (21·7) | 28 (12·8) | |
| Black | 147 (25·5) | 92 (25·6) | 55 (25·2) | |
| Yellow | 12 (2·08) | 6 (1·67) | 6 (2·75) | |
| Brown | 312 (54·1) | 183 (51·0) | 129 (59·2) | |
| Household income higher than minimum wage, No. (%) | 164 (29·0) | 111 (31·6) | 53 (24·8) | |
| Smoking, No. (%) | | | | <0·01 |
| Never | 272 (47·1) | 200 (55·6) | 72 (33·0) | |
| Current | 126 (21·8) | 66 (18·3) | 60 (27·5) | |
| Previous | 180 (31·1) | 94 (26·1) | 86 (39·4) | |
| Secondary smoking, No. (%) | 197 (34·1) | 117 (32·6) | 80 (36·7) | 0·36 |
| Alcohol, No. (%) use | | | | <0·01 |
| Never | 101 (17·5) | 85 (23·6) | 16 (7·34) | |
| Current | 257 (44·5) | 150 (41·7) | 107 (49·1) | |
| Previous | 220 (38·1) | 125 (34·7) | 95 (43·6) | |
| Drug use, No. (%) | | | | <0·01 |
| Never | 367 (63·5) | 270 (75·0) | 97 (44·5) | |
| Current | 78 (13·5) | 32 (8·89) | 46 (21·1) | |
| Previous | 133 (23·0) | 58 (16·1) | 75 (34·4) | |
| History of TB, No. (%) | 85 (14·9) | 52 (14·6) | 33 (15·3) | 0·93 |
| Comorbidities, No. (%) | | | | |
| Cancer | 4 (0·69) | 3 (0·83) | 1 (0·46) | 1·00 |
| Diabetes | 57 (9·86) | 36 (10·0) | 21 (9·63) | 1·00 |
| COPD | 4 (0·69) | 2 (0·56) | 2 (0·92) | 0·64 |
| Kidney disease | 4 (0·69) | 1 (0·28) | 3 (1·38) | 0·15 |
| Arterial hypertension | 45 (7·79) | 31 (8·61) | 14 (6·42) | 0·43 |
| HIV | 124 (21·5) | 68 (31·2) | 56 (15·6) | <0·01 |
| No comorbidity | 454 (78·5) | 273 (75·8) | 181 (83·0) | 0·05 |
| BMI, median [IQR], Kg/cm$^2$ | 20·1 [18·2; 22·3] | 20·4 [18·6; 22·9] | 19·5 [17·6; 21·6] | 0·01 |
| Cavitations on x-ray, No. (%) | 249 (43·1) | 171 (47·5) | 78 (35·8) | 0·01 |
| Positive smear result, No. (%) | 474 (82·0) | 288 (80·0) | 186 (85·3) | 0·13 |
| Time in the study, median [IQR], days | 732 [715; 743] | 735 [727; 744] | 328 [190; 740] | <0·01 |
| Serum hemoglobin levels, median [IQR], g/dL | 12·1 [10·7; 13·3] | 12·4 [11·4; 13·5] | 11·3 [9·54; 13·0] | <0·01 |

Baseline characteristics of the study population categorized by favorable and unfavorable outcomes. Continuous variables are expressed as medians with interquartile ranges (IQR), while categorical variables are shown as absolute numbers and percentages. The p-values indicate statistical comparisons between the two outcome groups, using the Mann–Whitney *U* test for continuous variables and either the chi-square or Fisher's exact test for categorical variables, as appropriate.

***Table 1:*** **Clinical characteristics of participants with tuberculosis stratified by treatment outcomes.**

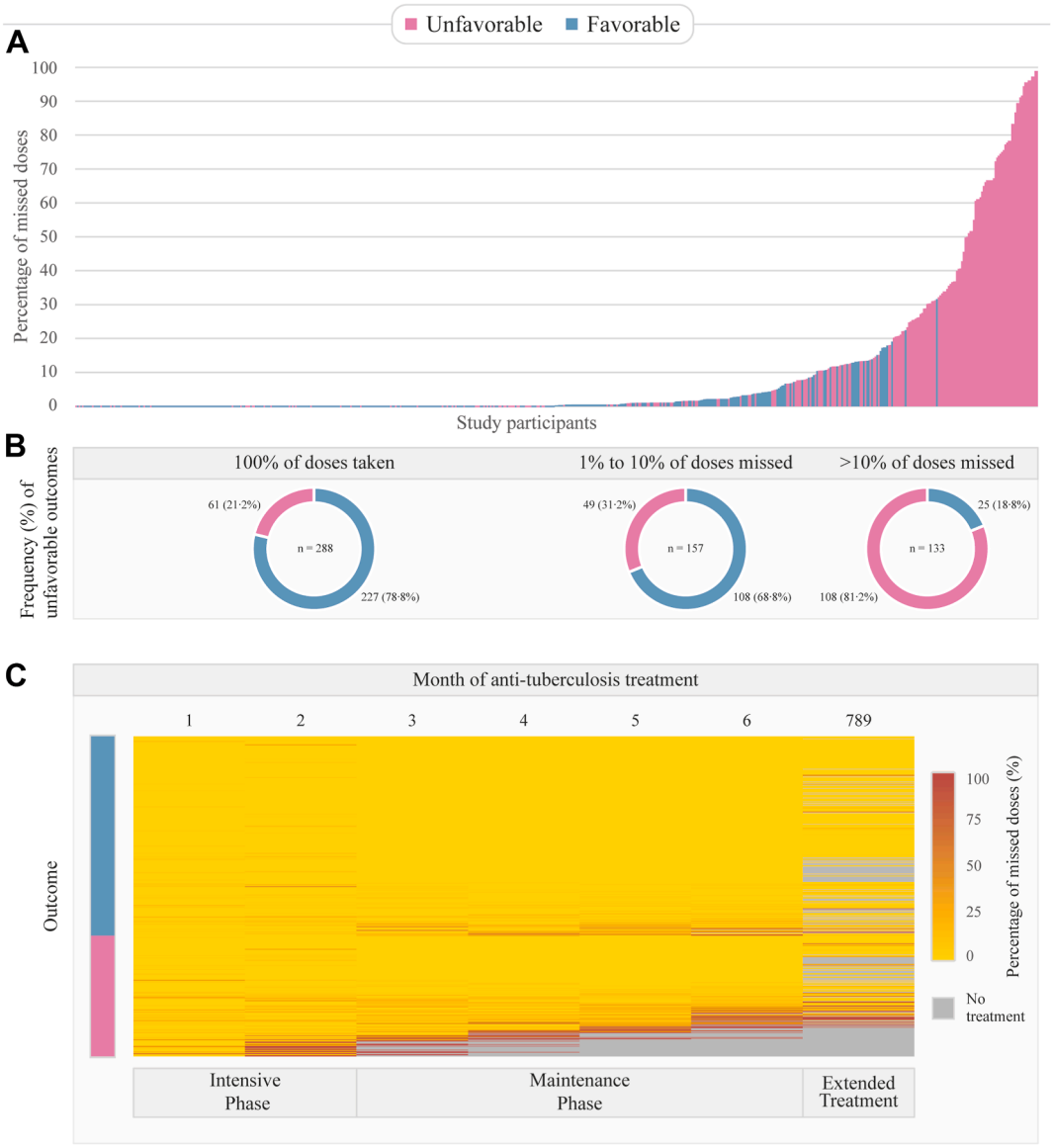


***Fig. 2:* Distribution of missed doses and their relationship with treatment outcomes across phases of tuberculosis treatment.** (A) Distribution of missed doses as a percentage of the prescribed therapy, stratified by favorable and unfavorable outcomes. (B) Proportion of unfavorable outcomes stratified by adherence levels total adherence, adherence above 90%, and nonadherence [missing more than 10% of prescribed doses]. (C) Heatmap of missed doses over months, divided into the intensive (months 1–2), maintenance (months 3–6), and extended phases of treatment. Warmer colors indicate higher percentages of missed doses. Gray areas represent months in which no doses were taken, which may reflect either complete treatment discontinuation or completion of the prescribed regimen.

indicating that existing adherence support measures may be insufficient.

The rapid increase in the predicted probability of unfavorable outcomes, characterized by the accumulation of missed doses, emphasizes that there is limited "forgiveness" for missed treatment and that minor deviations can compromise treatment success. On the contrary, this study highlights that early detection and support for at-risk patients must be prioritized to prevent rapid declines in adherence which could result in treatment failure. This is particularly important as the need for retreatment places a significant economic burden on the healthcare system and can have catastrophic cost to patients.[12]

To mitigate the impact of nonadherence, several public health interventions could be valuable. Campaigns aimed at raising awareness about the importance of adherence could reduce stigma and

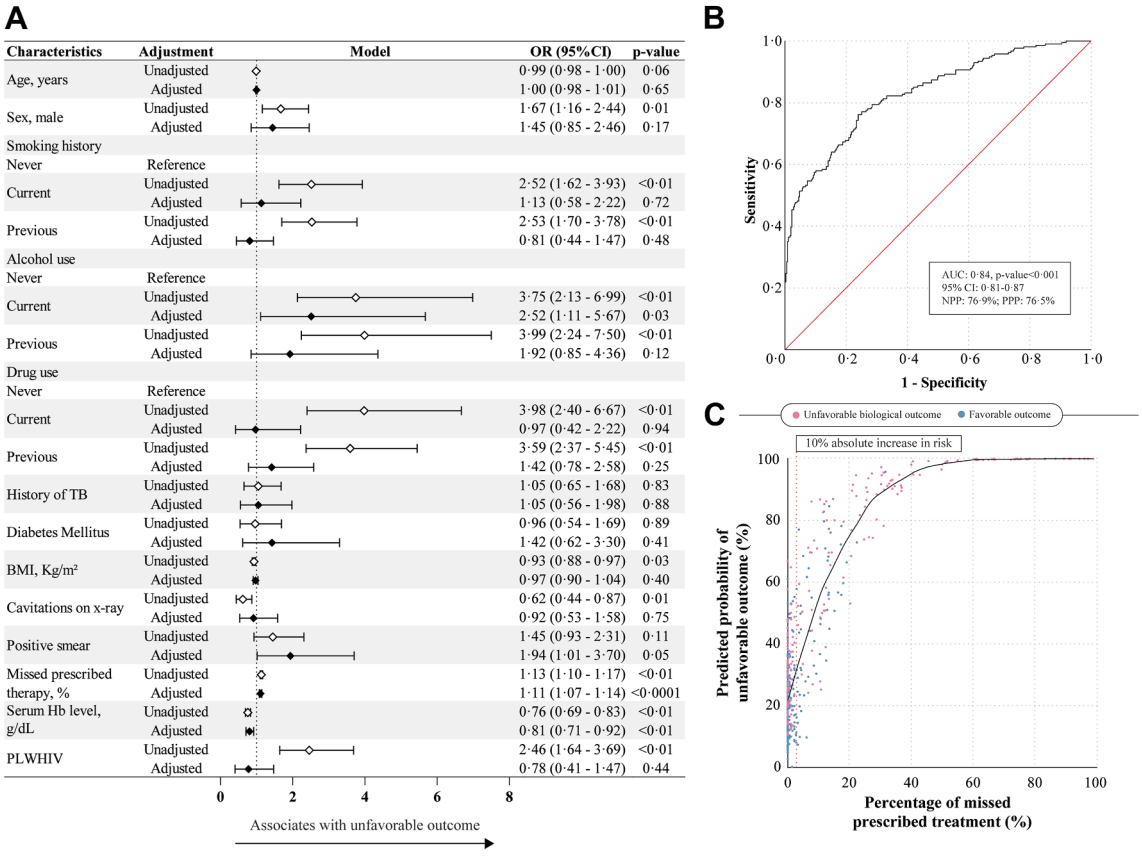


***Fig. 3:* Associations between patient's characteristics and unfavorable treatment outcomes**. (A) Binary logistic regression model assessing the association between patient's characteristics and unfavorable treatment outcomes. Odds ratios (OR) with 95% confidence intervals (CI) are presented for both unadjusted (white) and adjusted (black) models. The vertical dotted line represents an OR of 1, indicating no effect. Abbreviations: Tuberculosis (TB), Body Mass Index (BMI), People Living with HIV (PLWHIV). (B) Receiver operating characteristic (ROC) curve of the multivariable model, with an area under the curve (AUC) indicating strong discrimination. (C) Scatterplot of the predicted probability of unfavorable outcomes for each participant, plotted against their percentage of missed prescribed doses. Pink and blue dots represent participants with unfavorable and favorable outcomes, respectively. The black curve represents a locally weighted scatterplot smoothing (LOWESS) line, which visually illustrates the relationship between missed doses and predicted risk. A reference line illustrates a 10% absolute increase in risk for context.

misinformation, particularly among vulnerable populations.[13,14] Incorporating family members or peer support systems into adherence plans could also foster a more supportive environment for patients.[15] Given the socio-economic challenges many patients face, conditional cash transfers could also provide financial incentives for treatment adherence.[16]

Furthermore, predictive models could be developed and integrated into electronic health records to identify patients at high risk of nonadherence, enabling more targeted interventions throughout the treatment course and better resource allocation.[17] Real-time adherence monitoring using electronic tools, such as mobile health applications or electronic medication event monitoring systems, while more costly, could facilitate timely interventions, allowing healthcare providers to address nonadherence before it escalates to treatment failure.[18–20] Moreover, the implementation of shorter TB regimens, which are currently under evaluation in clinical trials, could reduce treatment fatigue and improve overall adherence.[5,21]

Demographic and clinical challenges also play a critical role in TB treatment outcomes. Socioeconomic barriers, such as living in slums and lack of income, are well-documented contributors to nonadherence and poor outcomes, particularly among vulnerable populations.[22,23] These barriers underscore the need to integrate adherence support with broader social services, including mental health care and substance use counseling, as recommended by recent TB guidelines.[21,24,25] Additionally, clinical factors such as anemia, which has been previously demonstrated in RePORT-Brazil to be a predictor of unfavorable TB treatment outcomes, may further exacerbate these challenges.[26,27]

Improving adherence has significant public health implications, as it can enhance treatment success rates, reduce *Mycobacterium tuberculosis* transmission, and prevent the development of drug-resistant TB. The findings of this study emphasize the need for early detection of nonadherence and continuous support throughout the treatment duration, particularly during the maintenance phase when adherence tends to decline.

This study had several limitations. First, adherence data for weekends and holidays were collected retrospectively, which may have led to inaccuracies and underreporting of these missed doses. Second, different DOT strategies could have been used by the same patient within a given month, reflecting the pragmatic and adaptive nature of real-world TB care. While this flexibility aligns with the operational complexities of TB treatment delivery, it also complicates accurate assessment of adherence. Certain modalities, particularly telephone-based and family-supervised DOT, are more susceptible to reporting bias, such as socially desirable responses, where medication intake is reported despite non-consumption.[28] This may reduce the precision of the estimated attributable risk of each missed dose. Moreover, the variability and overlap of DOT limited our ability to establish robust associations with any single DOT modality. Third, in cases of suboptimal DOT implementation, we were unable to distinguish between clustered (i.e., consecutive) and sporadic missed doses, which may differ in their impact on treatment outcomes. Our dataset did not support this level of granularity. Additionally, participants not monitored under DOT were excluded from this analysis, limiting the generalizability of our findings to populations receiving TB treatment without DOT. Although it is worth noting that this is the first study to assess the impact of variable adherence from a pragmatic perspective within real-world TB care, the use of a nationally representative and internationally harmonized cohort strengthens the external validity of our findings and underscores their relevance to global TB elimination efforts.

## Conclusion

Despite strategies such as DOT, adherence challenges persist. This study demonstrated the critical role of adherence in TB treatment, revealing that even minimal nonadherence significantly increased the risk of unfavorable outcomes. The findings underscore the limited tolerance for missed doses in TB care, emphasizing that early detection of nonadherence and targeted interventions are essential to prevent treatment failure.

### Contributors

Conceptualization: IBBF and BBA. Access to raw data: CS. Data verification: IBBF and CS. Data curation: IBBF, RCM, MAP, and CS. Investigation: IBBF, RCM, VCR, ALK, MCS, GA, AT, TRS, and BBA. Formal analysis: RCM and IBBF. Funding acquisition: VCR, ALK, MCS, TRS, and BBA. Methodology: IBBF and BBA. Project administration: CS, MCS, TRS, and BBA. Resources: IBBF, TRS, and BBA. Software: IBBF and BBA. Supervision: AT, GA, MAP, and BBA. Writing—original draft: IBBF, RCM, and BBA. Writing, review and editing: All authors. All authors have read and agreed to the submitted version of the manuscript.

### Data sharing statement

Data dictionaries and study protocol are available at https://reportbrazil.org. Study data will be shared to researchers whose propose use of data has been approved by Report-Brazil. De-identified individual participant data will be made available to researchers upon reasonable request. Requests should include a methodologically sound proposal and will be subject to approval by the RePORT-Brazil steering committee. Data will be accessible for analyses that align with the original study objectives and purposes deemed appropriate by the committee. To request access, please access https://reportbrazil.org/collaborate-with-us/.

### Declaration of interests

We declare no competing interests.

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### Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2025.101162.

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