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Multimethod analysis of adherence to preventive treatment for tuberculosis: a pragmatic randomized clinical trial

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Abstract

Tuberculosis Preventive Treatment (TPT) can reduce the likelihood of active disease from 1.6% to 0.6% in contacts of infectious cases. In Brazil, four therapeutic regimens for Tuberculosis infection (TBI) are currently in use, with isoniazid (INH) being the predominant regimen. The perspective of study this study is that simplifying the regimen by reducing the number of tablets required per dose could lead to improved adherence to TPT. Therefore, in 2018, the INH 300 mg dosage (one tablet per day) was introduced to improve adherence, since previously, only the 100 mg presentation was available. The present study is a pragmatic randomized clinical trial to assess adherence to treatment with 300 mg INH versus 100 mg INH, which included volunteers aged over 18 years from February 2021 to July 2022. Adherence was measured in three ways: self-reported, treatment persistence and the medication possession ratio (MPR). The results demonstrated that the INH 300 mg group had lower dropout rates and higher adherence to treatment rates, although the difference was not statistically significant. The 300 mg INH group presented greater persistence, indicating a lower probability of abandonment. This study compared two presentations of INH for TPT: a control group, in which three 100 mg tablets were administered, and an intervention group, in which one 300 mg tablet was administered, and revealed several important trends. However, not all of them reached statistical significance. These findings may support the incorporation of new therapeutic strategies in the management of TBI, as well as improve regular follow-up by health professionals for people on TPT, with the aim of optimizing the results of control and elimination programs.

Keywords Tuberculosis infection, Latent tuberculosis infection, Tuberculosis preventive treatment, Treatment adherence, Isoniazid

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Introduction

One quarter of the global population is estimated to be infected with the bacterium *Mycobacterium tuberculosis* (*M.tb*), the causative agent of tuberculosis (TB) [1]. In 2015, the World Health Organization (WHO) defined Tuberculosis infection (TBI) as a state of persistent immune response to stimulation by *M.tb* antigens without evidence of clinical manifestations of TB. Contacts of infectious TB are screened with tuberculin or RD1-based skin test or with an IGRA. Those who have a negative result are unlikely to develop TB disease. Preventive treatment is recommended for those with a positive test, even though a detectable immune response does not necessarily indicate viable *M.tb* organisms. Approximately 5 to 10% of people infected with *M.tb* will develop TB disease during their lifetime, usually in the first five years after infection, and will be able to transmit the bacillus [1–3].

Tuberculosis Preventive Treatment (TPT) can reduce the likelihood of active disease from 1.6% to 0.6% in contacts of infectious cases. To reduce the progression of TBI to TB and reduce the transmission of the disease, this is recommended, which, if used correctly for the appropriate period, can reduce the risk of patients presenting clinical manifestations by 60–90% [4, 5].

In Brazil, four distinct therapeutic regimens are recommended for the treatment of TBI [6]. Isoniazid (INH) is incorporated into three of these regimens, and until 2021, monotherapy with INH was recommended as the first-line treatment. Until 2017, INH was available in the health network exclusively at the 100 mg presentation, necessitating that most individuals treated for TBI ingest three tablets a day on an empty stomach [7]. Therefore, to increase adherence and convenience in treatment, in 2018, 300 mg INH (one tablet per day) became available for people living with HIV [8].

The two presentations of INH (100 mg and 300 mg tablets) have proven bioequivalence; however, they may differ in terms of patient adherence to pharmacotherapy, and the simultaneous offer of these two presentations may present a safety risk owing to the possibility of administration errors by patients [9–11].

The assessment of adherence to medication regimens is crucial to improving medication use and can be facilitated through subjective methodologies, including self-assessment by patients and healthcare professionals, or objective methods, such as pill counting, electronic monitoring and plasma level measurements. The selection of methodology influences the outcomes, suggesting that a multimethod approach may be more effective [12–15].

The aim of this study was to compare adherence, to a single 300 mg isoniazid as a daily tablet with the same dose administered as 3 × 100 mg tablets and use a multimethod approach to assess adherence.

Methods

Study design and participants

This study was a pragmatic, randomized, multicenter, open clinical trial conducted to assess the adherence to and safety of TPT with INH in the form of 300 mg tablets [16]. The protocol was implemented in health units that treat individuals with TB and prescribe treatment for TBI. The study was conducted with the participation of five Brazil centers (Federal District, Paraná, Minas Gerais, Ceará and Espírito Santo) previously selected for convenience from January 2019 to December 2022. The study protocol was conducted in accordance with the 2010 Consolidated Standards for Reporting Trials [16, 17].

The data analyzed in this study concern the follow-up of volunteers from the Brasília-DF center. Individuals receiving treatment at two reference units that provide care for TB patients, who are affiliated with the National Tuberculosis Program (NTP) and were prescribed treatment for TBI in Brasília, Federal District, were invited to participate in the study.

The inclusion criteria for the study were as follows: patients aged > 18 years with an indication for TBI treatment from February 2021 to July 31, 2022, treated at the health units included in the Brasília study center. Individuals whose index case was retreated, multidrug resistant, and extensively drug resistant as well as individuals who were transferred from the original center two or more weeks after starting treatment and individuals in the prison system were excluded from the study.

Procedures

All the participants were informed about the research procedures and expressed their free and unrestricted willingness to participate in the study by signing the protocol's informed consent form. The treatment recommended by the Brazilian guidelines is guaranteed to participants who do not accept the study protocol or who withdraw from it.

The subjects were allocated to two groups via randomization (1:1) in blocks of 10, using a table of random numbers. The randomization procedure was carried out via Studio R. The study was conducted as an open-label trial because the intervention and control tablets were visually distinguishable. The study intervention entailed the treatment of TBI with the administration of one tablet of INH at 300 mg (INH 300 mg), whereas the control group received a treatment regimen consisting of three tablets of INH at 100 mg (INH 100 mg), in accordance with Brazilian guidelines [16, 18].

Participants in the intervention group received monthly packs of 30 tablets of INH 300 mg, with instructions to take one tablet per day on an empty stomach until the end of treatment (6 or 9 months). The control

group received monthly packs of 90 tablets of 100 mg INH with instructions to take three tablets together on an empty stomach every day until the end of treatment (6 or 9 months), as provided by the Brazilian Ministry of Health.

The researchers conducted interviews with all participating centers via standardized questionnaires, which contained information regarding the use of medications and adverse effects. The study researchers developed the questionnaires used based on the forms proposed in the Protocol for surveillance of latent *Mycobacterium tuberculosis* infection and published (Supplementary Material 2) [16]. These interviews were carried out at baseline at the start of treatment and at follow-up during the TBI treatment period of 6–12 months, as established by the Brazilian protocol [16, 19]. Drug dispensations were recorded according to the service routine in the electronic system *Sistema Nacional de Gestão da Assistência Farmacêutica* (Hórus - National System of Pharmaceutical Services Management) of the Brazilian Ministry of Health.

All the data collected during the interviews were stored in the project database, which is hosted on the REDCap platform (redcap_v13.1.25) of the Federal University of Espírito Santo.

Variables

The following sociodemographic and clinical variables of the study participants were analyzed: age (completed age); sex; skin color/race (white, black, mixed race); formal education (years of schooling); marital status; and preexisting medical conditions and comorbidities: contact with tuberculosis, HIV, diabetes, alcoholism, smoking and mental illness.

The primary outcome variable of interest was treatment adherence. The second variable of interest in the outcome were treatment dropout, was defined as the participant who did not receive dispensation for at least 90 days after starting INH, whether consecutive or not [12, 19]. Treatment adherence was measured via three different methods: (i) self-reports, (ii) dispensation records and (iii) plasma monitoring.

The initial assessment of treatment adherence was self-reported by the volunteers from the two data collection centers in the Federal District during the participants' first follow-up interview through inquiries regarding users' behavior in relation to medication use, adapted from the Morisky-Green Adherence Scale (MGL) [20]. To categorize the self-reported adherence outcome variable, the participants were classified as adherent (score of 4) or nonadherent (score between 0 and 3).

The second measure of adherence was treatment persistence, measured by electronic records of medication dispensed to subjects treated at one of the study center's

reference units. For each dispensation, the date of receipt of the medication was extracted, and the number of tablets dispensed was adjusted according to the prescribed dose and regimen. In the case of dispensations of larger quantities of medication, both the time and the number of tablets were adjusted to the appropriate period.

Treatment persistence was calculated via the method of the estimated level of persistence for those who had completed treatment [12]. In this method, persistence time is defined as the length of time in days from the first dispensation to the discontinuation of therapy (absence of a dispensation of medication within 7 days or more, after the days of the previous dispensation have elapsed).

The medication possession ratio (MPR) was also calculated from the ratio between the total number of days of medication supply in six months (180 days) or nine months (270 days), depending on the prescribed treatment regimen. Thus, the numerator corresponds to the total number of days of drug supply recorded in the system, regardless of whether there were intervals between dispensations in the period [12].

The third methodological strategy for measuring adherence involved direct measurement through plasma monitoring of the volunteers. For the determination and quantification of INH, three 10 mL blood samples were taken, separated by a 20-minute interval were collected in Heparinized tubes on at least one follow-up visit, and the time elapsed between the last dose taken by the volunteer and the collection was noted.

The chromatographic runs were carried out on a UHPLC-MS/MS system-Qtrap 6500 (Sciex) (Supplementary Material 1). The limit of quantification (LOQ) was established at 1 mg/mL for both INHs, and concentrations ranging from 3 to 6 mg/mL were considered to be within the therapeutic range.

The direct adherence was estimated via visual analysis of the concentration versus time graphs and the drug elimination constant (k), which was obtained from the slope of the concentration versus time line derived from the plasma concentrations of each participant in the study. Participants were classified as nonadherent if their plasma concentrations were lower than expected for the time at which the samples were collected and if their plasma concentrations were estimated from the k values and the equation of the straight line for the time preceding the blood samples. The expected plasma concentrations were derived from data sources referenced in the literature [21].

Statistical analysis

For the sample calculation, we used an expected abandonment reduction rate is expected to be around 11%. With a power of 80% to detect differences, a 5% significance level, using Pearson's chi-square test, two-sided, about

478 individuals would be needed for all six research centers, that is, 79 volunteers per center [16].

The data were analyzed via RStudio statistical software version 2022.12.0. To describe the study population, the absolute and relative frequencies of the categorical variables and medians with interquartile ranges (IQRs) for the numerical variables were calculated. To compare the intervention and control groups with the primary outcome of adherence, bivariate analysis (crude) and logistic regression (adjusted) were performed, with the treatment group variables (INH300 and INH100) and the dose adopted (180 and 270 doses) as predictors. With respect to adherence, missing data were addressed by imputing the mean adherence via self-reports. The measure of association adopted was the odds ratio (OR), with the 95% confidence interval (95% CI) being calculated to supplement the findings.

To analyze treatment persistence, a descriptive analysis of the means and standard deviations (SDs) of continuous variables was performed. In addition, the survival analysis model was constructed via the Kaplan–Meier estimator and Cox regression to obtain the probability of a discontinuation curve.

Ethics approval and consent to participate

The study protocol was registered and approved by the Research Ethics Committee of the Foundation for Teaching and Research in Health Sciences of the State Health Secretariat of the Federal District (FEPECS/SES/DF) (opinion n° 4,589,430), by the National Research Ethics Committee (CONEP) under the number 88226218.0.3008.5553. The individuals are informed about the study and the possibility of refusing and withdrawing at any time without interfering with their regular treatment. They are invited to participate in the investigation and give signing the informed consent form to be included in the study. The protocol was registered in the Brazilian Registry of Clinical Trials (REBEC) under the code RBR-2wsdt6 (<http://ensaiosclinicos.gov.br/rg/RBR-2wsdt6/>).

Results

Among the 71 subjects included in the study, 35 (49.3%) were allocated to the intervention group and underwent TPT with 1 tablet of 300 mg INH, whereas 36 (50.7%) were allocated to the control group, which underwent TPT with 3 tablets of 100 mg INH (Fig. 1). The majority of the subjects in the intervention group were male, single, mixed-race, with more than eight years of schooling and a mean age of 44 years. With respect to their clinical characteristics, 16 (57.1%) were individuals living with HIV, 11 (45.8%) were receiving long-term corticosteroid therapy, 13 (44.8%) had an autoimmune disease, 29 (50.0%) had pulmonary tuberculosis contacts, and none

reported alcoholism. With respect to the therapeutic regimen, 20 (47.6%) participants underwent TPT with 180 doses, whereas 16 (55.2%) received 270 doses (Table 1).

Self-reported treatment adherence

The data from 67 study volunteers were analyzed in relation to their adherence behavior reported according to the MGL scale. The results, presented in Table 2, indicate that 16 (53.3%) of the individuals who used 100 mg INH abandoned treatment, whereas in the group that used 300 mg INH, 10 (33.3%) individuals did so. The findings suggest a discrepancy in the probability of discontinuation among the two INH presentations, with the INH 300 mg regimen, administered in one tablet per day, reducing the chance of abandonment by 35% (see Table 2), although it was not possible to show a statistically significant difference.

With respect to treatment adherence, 36 (67.9%) of the volunteers exhibited adherence, 15 (65.2%) of whom were administered 100 mg INH, and 21 (70.0%) of whom were administered 300 mg INH. The absolute data indicated a trend in the chance of adherence among participants who received INH300, but there was no significant difference.

Treatment persistence

The electronic dispensing records of 47 volunteers who were followed up at the outpatient unit of the University Hospital of Brasilia were analyzed. The analysis of the probability of abandoning the treatment curve (Fig. 2) demonstrated that during the follow-up period, the probability of abandonment in the intervention group (INH300) was lower than that in the control group (INH100), although the difference was not statistically significant (log rank $p = 0.008$).

For persistence, 21 (44.7%) of the participants who had completed the treatment were included in the analysis, of which 14 (66.7%) were part of the INH300 group and 7 (33.3%) were in the INH100 group, with a longer persistence time in days in the intervention group (224(σ 36)) than in the control group (183(σ 74)). With respect to the MPR, both groups presented values higher than 1.0 (INH 300–1,19; INH100–1,04), indicative of an oversupply.

Direct measurement of treatment adherence

The data from 31 volunteers were analyzed, with 15 (48.4%) from the intervention group (INH300) and 16 (51.6%) from the control group (INH100) having at least one blood sample taken during follow-up. For the majority of the study participants, blood samples were collected three times at each visit, with a minimum interval of 20 min between each collection. As illustrated in the scatter plots (Fig. 3), which include the INH concentration measurements of all participants in each group, the INH concentrations observed among nonadherents

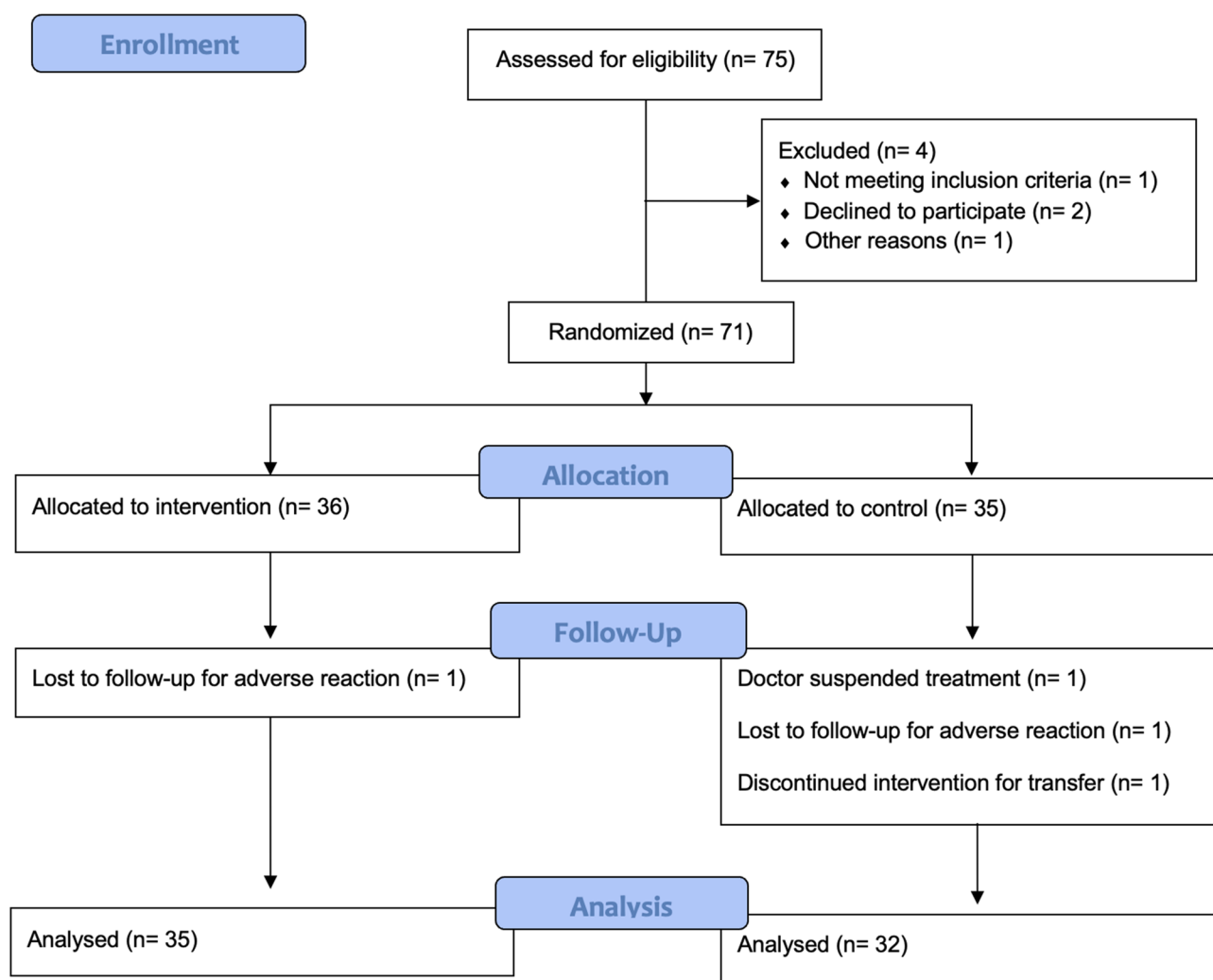


Fig. 1 Consort flow chart

approximate the quantification limit of 1 mg/L. Accordingly, one participant (6.7%) in the INH300 group and 3 (18.8%) in the INH100 group exhibited nonadherence, whereas the remaining 14 (93.3%) and 13 (81.3%) demonstrated adherence, respectively.

A comparison of the direct and indirect methods revealed that 4 (12.9%) volunteers were considered adherent by monitoring but showed nonadherent behavior according to self-reports. A further 3 (9.7%) participants exhibited nonadherence to both methods, whereas a significant proportion of 20 (64.5%) demonstrated adherence to both self-reports and plasma monitoring. However, for four participants (12.9%), no comparison could be made due to the absence of results from the self-report analysis.

Discussion

The majority of the subjects who used INH300 were more adherent to TPT and exhibited a reduced probability of treatment abandonment. This group demonstrated higher persistence levels, indicating a lower probability of treatment discontinuation. Importantly, TPT is recognized as one of the main preventive measures against TB. Global goals to end the TB epidemic will require investments in effective TB prevention interventions [22]. INH300 has demonstrated efficacy in reducing dropout and enhancing treatment persistence, and its integration into TPT therapeutic regimens corroborates effective measures to curtail the disease burden.

Adherence to treatment is essential for individuals to maintain a sustained and persistent response to tuberculosis prevention, thereby preventing the development of the active form of the disease. Health professionals must support and inform patients properly and respect their choices [23, 24].

Table 1 Sociodemographic characteristics of the volunteers included in the clinical trial in Brasília-DF (n = 71)

Sociodemographic variables	Total	INH 300 ^a	INH 100 ^b
	n(%)	n(%)	n(%)
Sex			
Male	37 (52.1)	19 (52.8)	18 (51.4)
Female	34 (47.9)	17 (47.2)	17 (48.6)
Age			
Median	44	44	45
Interquartile range	41–48	39–49	39–50
Race/color			
Mixed-race	41 (57.7)	19 (52.8)	22 (62.9)
White	18 (25.4)	7 (19.4)	11 (31.4)
Black	11 (15.5)	9 (25.0)	2 (5.7)
Others	1 (1.4)	1 (2.8)	-
Years of study			
> 8 years	58 (81.7)	28 (77.8)	30 (85.7)
5–8 years	7 (9.9)	4 (11.1)	3 (8.6)
1–4 years	5 (7.0)	3 (8.3)	2 (5.7)
No study	1 (1.4)	1 (2.8)	-
Marital status			
Single	39 (54.9)	19 (52.8)	20 (57.1)
Married	15 (21.1)	4 (11.1)	11 (31.4)
Separated/Divorced	11 (15.5)	10 (27.8)	1 (2.9)
Widowed	4 (5.6)	2 (5.6)	2 (5.7)
Stable union	2 (2.8)	1 (2.7)	1 (2.9)
Contact with pulmonary tuberculosis	58 (81.7)	29 (80.6)	29 (82.9)
Autoimmune disease	29 (40.8)	13 (36.1)	16 (45.7)
HIV	28 (39.4)	16 (44.4)	12 (34.3)
Prolonged use of corticosteroids	24 (33.8)	11 (30.6)	13 (37.1)
Depression	19 (26.8)	8 (22.2)	11 (31.4)
Use of TNF-alpha inhibitors	15 (21.1)	6 (16.7)	9 (25.7)
Smoking	11 (15.5)	6 (16.7)	5 (14.3)
Diabetes Mellitus	6 (8.5)	3 (8.3)	3 (8.6)
Renal insufficiency	2 (2.8)	1 (2.8)	1 (2.9)
Liver disease	2 (2.8)	1 (2.8)	1 (2.9)
Viral Hepatitis B/C; Transplantation and Neoplasia	3 (4.2)	-	3 (8.6)
Doses of the therapeutic regimen			
180 doses	42 (59.2)	20 (55.6)	22 (62.9)
270 doses	29 (40.8)	16 (44.4)	13 (37.1)

Source: Prepared by the authors

^a Isoniazid 300 mg^b Isoniazid 100 mg

Despite the extensive measurement and discussion of treatment adherence in the literature, this remains a significant challenge for individuals, patients and health systems. Knowing the magnitude of treatment adherence is one of the most significant strategies for improving this aspect of medication use [13, 15].

Adherence can be measured via indirect (subjective) or direct (objective) methods. Method selection can influence outcomes, and an approach that integrates multiple

measurement methods may offer a more comprehensive explanation of the phenomenon [13, 14].

The adherence rates from both the intervention and control groups observed in this study correspond to the TPT completion rates documented in the extant literature, which range from 40% to 80% [25–27]. Adherence to preventive treatment for tuberculosis is typically assessed by treatment completion, which is defined as the fulfillment of a specified number of doses within the timeframe stipulated by national protocols [28–31]. However, other behavioral aspects related to medication use during this period may reveal new and effective strategies for understanding and proposing better interventions to avoid abandonment and discontinuation of treatment.

Treatment persistence is defined as continuity in following a prescribed therapeutic regimen over time, plays a crucial role in adherence to treatment, and its evaluation is a key element associated with the effectiveness of drug treatments, which are most widely evaluated for the treatment of chronic diseases [32–34]. Although studies have demonstrated that high persistence is linked to achieving therapeutic goals [35–37], this is the first study in the context of tuberculosis to utilize this measure to assess treatment discontinuation by individuals receiving TPT.

The analysis revealed a tendency for volunteers who received INH 300 mg to abandon treatment less frequently, in accordance with self-reports, electronic records of dispensations and plasma monitoring. Additionally, we observed the effect of the intervention on treatment time, with volunteers in the intervention group demonstrating a longer time before abandoning treatment than did those in the control group.

Treatment abandonment has been demonstrated to have a direct effect on TB control, leading to consequences at both the individual and public health levels. Treatment abandonment significantly increases the risk of developing active tuberculosis, especially in the initial years following initial infection [38, 39]. Thus, the probability of community transmission also increases, and the economic repercussions are notable, as treatments for active TB are more expensive and prolonged, requiring a greater allocation of resources from health systems [1]. In addition, treatment interruption can lead to the development of drug-resistant strains of *Mycobacterium tuberculosis*, further complicating efforts to control TB [40, 41].

In both presentations (INH300 and INH100), an MPR of more than one was observed, indicating an oversupply of medicine. This practice involves the supply of medicines in quantities that exceed the therapeutic and/or prescribed needs of the patients. Treatments involving certain types of medication, such as antibiotics, opioids

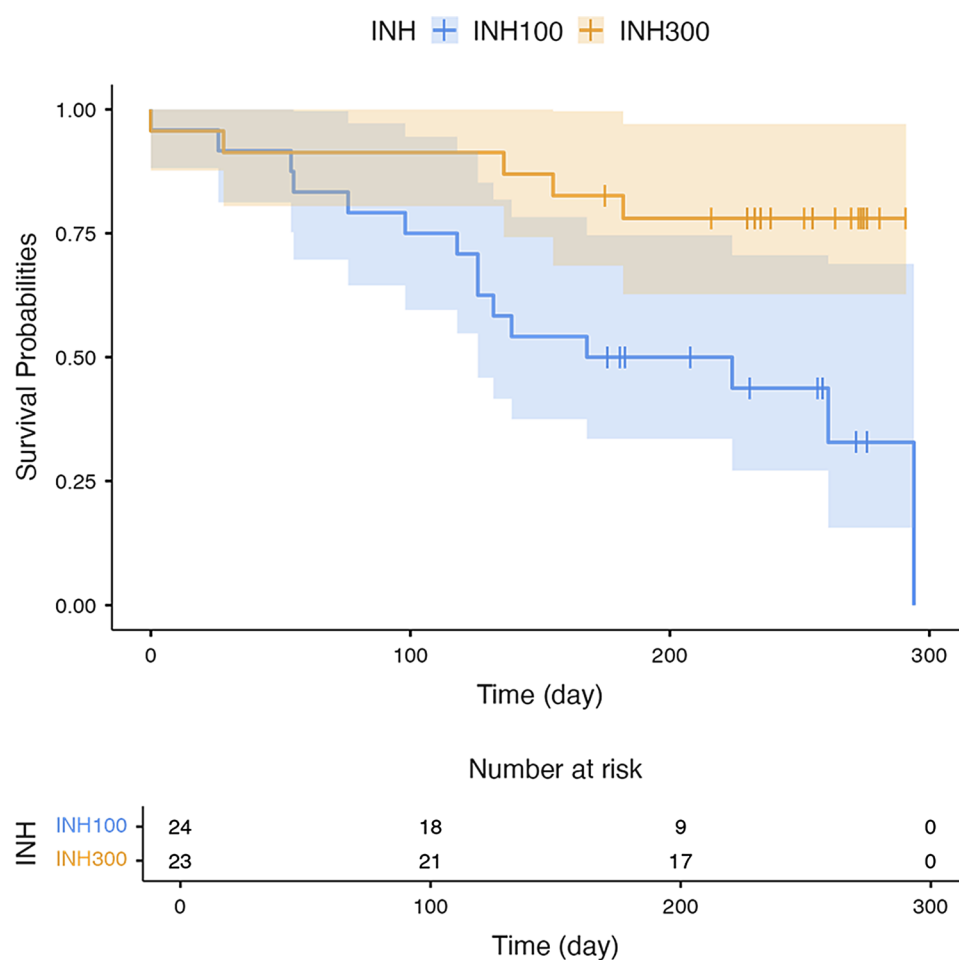
Table 2 Distribution and estimates of the effects of the use of 300 mg INH on abandonment and adherence to preventive tuberculosis treatment

Treatment Scheme	Frequency		Gross Analysis*		Adjusted Analysis** ^a	
	Yes n (%)	No n (%)	OR (95%CI)	p-value	OR (95%CI)	p-value
Abandonment of treatment						
INH 100 mg 3 cp (n = 30)	16 (53.3)	14 (46.7)				
INH 300 mg 1 cp (n = 30)	10 (33.3)	20 (66.7)	0,40 (0,15 a 1,10)	0,147	0,35 (0,12 a 1,05)	0,094
Total	26 (43.3)	34 (56.7)				
Treatment Adherence						
INH 100 mg 3 cp.(n = 23)	15 (65.2)	8 (34.8)				
INH 300 mg 1 cp.(n = 30)	21 (70.0)	9 (30.0)	1,70 (0,64 a 4,48)	0,824	1,72 (0,64 a 4,58)	0,771
Total	36 (67.9)	17 (32.1)				

Source: Prepared by the authors

* bivariate analysis

** regression

^a Model adjusted for the number of treatment doses (180 or 270 doses)**Fig. 2** Dropout probability curve (in days) for treatment with 100 mg INH and 300 mg INH for TBI during the follow-up period (n = 47)

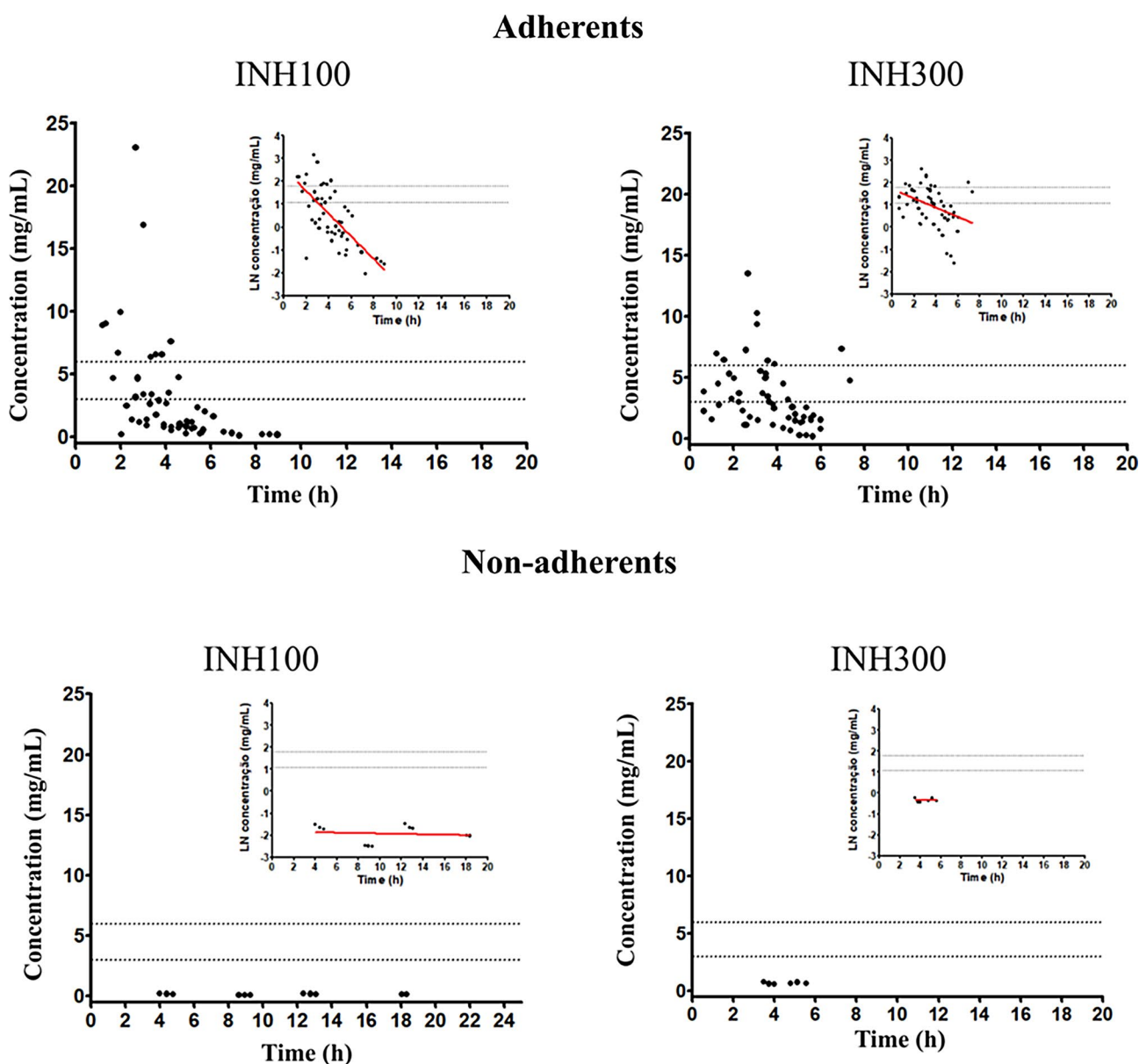


Fig. 3 Direct measurement of adherence via plasma monitoring ($n=31$)

and benzodiazepines, are at risk of harm to patients [41, 42].

However, when TPT is utilized, the occurrence of oversupply is justified by advancements in dispensing in certain circumstances. This is because 100 mg INH is available in a 20-tablet blister pack and is not fractionated to align with the precise number of monthly tablets. It is further recommended that, in cases of forgetfulness regarding medication administration, pills not taken during treatment should be administered at the end of the treatment, given that the primary concern is the total number of doses administered, not merely the duration of treatment [19].

There has been limited research on the assessment of patient treatment adherence using different measurement methods simultaneously, including plasma drug levels [43–45]. The present study is pioneering in its approach, as it is the first to measure adherence to TPT and TB treatment via both indirect and direct methods. The findings from these diverse approaches yielded similar results, as indicated by the absolute measures. Compared with the control group (INH100), the intervention group (INH300) exhibited better adherence and lower rates of treatment abandonment; however, this difference was not statistically significant.

Furthermore, a discrepancy was observed in the adherence outcomes of some volunteers across different

measures; these volunteers exhibited adherence in plasma monitoring but nonadherence in self-reports. These differences can be partially attributed to the variability in the time interval after the administration of the dose at which the samples were collected. This was due to the difficulty in scheduling visits at a time that was convenient for all participants. At each visit, we collected a total of three blood samples, with a minimum separation of 20 min, and ideally, at least eight samples at approximately 30 min, 1, 2, 3, 4, 6, 8 and 10 h, to ascertain the complete pharmacokinetic curve, as well as pharmacokinetic parameters such as the area under the curve, volume of distribution, clearance and metabolic profile. In addition, the nonadherent behavior of the participants at the time of the self-reported interview and blood samples were not taken on the same day. Another hypothesis could be related to the limitations of the direct method [45, 46].

Despite being regarded as the closest to real adherence, this method merely reflects the adherence profile on the day of collection, whereas self-reporting reflects a period of days or months. Biochemical methods, like other methods, have limitations [45, 46]. These limitations may be related to interindividual pharmacokinetic variations. Therefore, we propose that future studies employ a synchronized approach, integrating the collection of blood samples for plasma concentration monitoring of INH and adherence interviews at the same time and multiple times during treatment.

A plethora of care services for individuals with tuberculosis and TBI have adversely affected human resources, structure and care flows [47], as the study was conducted partly during the course of the COVID-19 pandemic in Brazil, which hindered the recruitment of study participants and led to a reduction in sampling power, representing one limitation of the study. The findings of this study indicate a tendency toward the impact of INH300 administration on the probability of reducing abandonment and enhancing treatment adherence. We believe that subsequent studies with larger sample sizes will demonstrate this tendency, with significant differences.

TPTs have the potential to produce clinical, humanistic and economic gains for the population and health systems. Investments in the diagnosis and prevention of tuberculosis have been demonstrated to engender substantial advancements in public health, concurrently generating economic advantages for countries; it is estimated that for every dollar invested, there is a return of up to 39 dollars [48]. Consequently, investing in preventive treatments that favor adherence and therapeutic convenience is a strategy that has the potential to contribute to health and economic gains.

In addition, the multimethod approach employed in study—combining self-reported adherence, medication

dispensing records, and plasma drug concentration monitoring—could be similarly applied to evaluate adherence to the short-course rifapentine and isoniazid regimen (3HP). This approach would provide comprehensive insights into patient behavior, allowing assessment of adherence patterns, persistence, and potential barriers in the context of shorter preventive treatment regimens.

Conclusion

This comparative study of two presentations of INH for TPT by direct and indirect methods of measuring adherence, with the control using three 100 mg tablets and the intervention using one 300 mg tablet, revealed some important trends, although they were not statistically significant. The group that received 300 mg INH presented a lower dropout rate and enhanced treatment adherence, suggesting that a single 300 mg dose might be more effective in maintaining treatment adherence than three 100 mg tablets. Additionally, the probability of sustaining treatment was greater in the intervention group than in the control group, suggesting a potential advantage of this approach in promoting treatment continuity. These findings may contribute to the incorporation of new therapeutic strategies in the management of TBI and the enhancement of routine follow-up by healthcare professionals for individuals on TPT, with the aim of optimizing the results of TB control and elimination programs.

Abbreviations

CI	Confidence interval
INH	Isoniazid
IQRs	Interquartile ranges
LOQ	Limit of quantification
TBI	Tuberculosis infection
MGL	Morisky-Green Adherence Scale
MPR	Medication possession ratio
M.tb	Mycobacterium tuberculosis
OR	Odds ratio
SD	Standard deviation
TB	Tuberculosis
TPT	Tuberculosis preventive treatment
WHO	World Health Organization

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12879-026-13069-0>.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Author contributions

BMCSA conceived and designed the study, analyzed and interpreted the patient data, and was a major contributor to the writing of the manuscript. WNA conceived and designed the study and analyzed and interpreted the data. IRZ analysis and interpretation of data. IFM analysis and interpretation of data for plasma monitoring, MCSV conception and design of the study, general review, JPC conception and design of the study, general review, TNP conception and design of the study, general review, LRLP interpretation of data and general review, ADOF interpretation of data and general review, ELNM conception and design of the study, general review, NULT conception and design of the study, analysis and interpretation of data and final approval of the version to be submitted. All the authors read and approved the final manuscript.

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Data availability

The data that support the findings of this study are not openly available for reasons of sensitivity and are available from the corresponding author upon reasonable request. The data are stored in controlled access data at the Laboratory of Evidence and Pharmaceutical Studies.

Declarations

Ethics approval and consent to participate

The study protocol was reviewed and approved by the Research Ethics Committee of the Foundation for Education and Research in Health Sciences of the State Secretariat of Health of the Federal District (FEPECS/SES/DF) through Opinion no. 4.589.430 and by the National Commission for Research Ethics (CONEP) under number 88226218.0.3008.5553. Clinical Trial Registry: the protocol is registered in the Brazilian Registry of Clinical Trials (REBEC) under the code RBR-2wsdt6 (UTN code: U1111-1215-3100) (<http://ensaiosclinicos.gov.br/rg/RBR-2wsdt6/>), registration date in October 9, 2018.

Consent for publication

The authors declare that they have no individual person's data in any form (including any individual details, images or videos).

Competing interests

The authors declare no competing interests.

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