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Completion of tuberculosis preventive treatment with 300 mg vs. 100 mg isoniazid tablets: a pragmatic randomized clinical trial

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Abstract

Background Monotherapy with the drug isoniazid (INH) was for a long time the main therapeutic regimen used for tuberculosis preventive treatment (TPT). Research is progressing into the use of new therapeutic regimens that provide more complete TPT. The objective was to analyze the completion and safety of TPT with the drug INH in the form of 300 mg tablets.

Methods Pragmatic, randomized, non-blinded, multicenter clinical trial conducted in Brazil from January 2019 to December 2022. Subjects over the age of 18 years with an indication for TPT was included and those whose index case of active tuberculosis was in retreatment, multidrug-resistant and extremely resistant, transferred, and people deprived of their liberty was excluded. The intervention was TPT with 1 INH 300 mg tablet and the control group with 3 INH 100 mg tablets. The primary outcome was TPT completion. Pearson's chi-square test was used to analyze the association of TPT completion. The risk of TPT completion was estimated by Poisson regression. The mean treatment effect was calculated. The results were expressed as a risk ratio (RR) with a 95% confidence interval (95%CI).

Results A total of 207 individuals were included, 103 (49.7%) in the intervention group. Seventy-two (69.9%) of the individuals who used INH 300 mg completed TPT. The risk ratio for completing TPT was 1.39 times higher in the group that used the INH 300 mg treatment (RR 1.39, 95%CI 1.08 to 1.79). The mean effect of the intervention was 19% (Coefficient 0.19, 95%CI 0.06 to 0.32). There was no significant difference in adverse events between the groups.

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Conclusion The pragmatic use of INH 300 mg in TPT showed a positive effect on the treatment completion rate and is a safe presentation for use in INH monotherapy regimens.

Trial registration The protocol is registered in the Brazilian Registry of Clinical Trials under the code RBR-2wsdt6 in September 2019 10th.

Keywords Latent tuberculosis, Mycobacterium tuberculosis infections, Preventive treatment of tuberculosis, Isoniazid, Pragmatic clinical trial

Introduction

Tuberculosis (TB) is still a disease with a high global burden. Around 10.8 million people worldwide fell ill with TB in 2023, making it one of the leading causes of death from infectious diseases, with 1.25 million deaths [1]. It is estimated that 25% of the global population is infected with *Mycobacterium tuberculosis*, with 5% to 10% of cases progressing to TB between 2 and 5 years, accounting for an average of 80% of new cases of the disease [2, 3].

Tuberculosis preventive treatment (TPT) is recommended for people at higher risk of progression to the disease and is an important strategy for TB control and elimination [4, 5]. Monotherapy with the drug isoniazid (INH) was for a long time the main therapeutic regimen used for TPT. Research has progressed into the use of new therapeutic regimens that overcome the limitations of INH monotherapy, with the combined therapeutic regimen of rifapentine and INH [6, 7]. However, the number of tablets ingested in a single dose and the duration of the therapeutic regimen is an important factor in the failure to complete TPT [6, 7].

Also associated with non-completion is the occurrence of adverse reactions. One that most lead to changes in the therapeutic regimen is hepatotoxicity which can be caused by INH (20% hepatitis). Characteristics such as age, or the presence of underlying liver disease can increase these liver toxicity rates [6].

In the monotherapy regimens with the INH drug, three 100 mg tablets are used every day for six months, 180 doses (6H), or for nine months, 270 doses (9H) [7]. In the combined therapy regimen of rifapentine and INH (3HP), six 150 mg rifapentine tablets are ingested in a single dose, totaling 900 mg, and nine 100 mg INH tablets, totaling 900 mg, with one single dose per week for 12 weeks [7].

A clinical trial demonstrated the bioequivalence of INH in one 300 mg tablet with three 100 mg tablets [8]. In this sense, the introduction of INH in the 300 mg formulation in therapeutic regimens reduces the number of tablets per dose. However, no clinical studies were found evaluating TPT completion and safety with INH in the 300 mg formulation. Given this scenario, the current study aimed to analyze TPT completion and safety with INH in 300 mg tablets.

Materials and methods

Study design and participants

A pragmatic, randomized, multicenter, open label, unblinded clinical trial to study TPT completion and safety with the drug INH in the form of 300 mg tablets vs. 100 mg tablets [9]. The study protocol was conducted following the guidelines of the 2010 Consolidated Standards for Reporting Trials [9, 10]. The study was conducted in Brazil in 5 centers (Distrito Federal, Paraná, Minas Gerais, Ceará, and Espírito Santo) selected for convenience. The participants recruitment took place from January 2019 20th to December 2022 30th in Health Units that treat TB patients and prescribe and monitor TPT patients.

The eligibility criteria were people over 18 years of age with a prescription for latent tuberculosis infection (LTBI) treatment after consultation at the health units of the aforementioned sites who agreed to participate in the study after reading and signing the informed consent form. According to Brazilian recommendations, people are diagnosed with LTBI based on a positive tuberculin skin test (TST), i.e., induration ≥ 5 mm, or a positive IGRA, followed by a chest X-ray to rule out TB. For People Living with HIV (PLHIV), TPT should be provided if the CD4 + cell count is $< 350/mm^3$, while those with unknown CD4 + count or $\geq 350/mm^3$ should receive TPT only after a positive TST test [7]. Participants whose TB index case was retreatment, multidrug-resistant, and extremely resistant, individuals transferred from the original center after two or more weeks of the start of treatment, and people deprived of liberty were excluded.

Procedures

All participants were instructed about the research procedures and expressed their free and unimpeded willingness to participate in the study by signing the protocol's free consent form. The treatment recommended by the Brazilian guidelines was guaranteed for participants who did not accept the study protocol or withdrew from it.

Participants were allocated into two therapeutic regimen groups for LTBI treatment through the randomization process (1:1) in blocks of 10 by a spreadsheet of random numbers. The randomization procedure was performed by Studio R and was sent by the study

	Entry	Allocation	Post-allocation		Completion
Point in time	$-t_1$	0	t_1	t_2	t_x
ENTRY:					
Eligibility criteria					
	X				
Consent information	X				
Randomization		X			
INTERVENTION:					
Control group three Isoniazid 100mg tablets			←	→	
Intervention group one Isoniazid 300mg tablet			←	→	
EVALUATION:					
Baseline variables	X	X			
Gender					
Weight					
Race/skin color					
Marital status					
Occupation					
Income					
Government benefits					
Alcohol consumption					
Smoking					
Psychoactive substance					
Diabetes					
Kidney failure					
HIV					
Liver disease					
Viral hepatitis					
Silicosis					
Transplant					
Epilepsy					
Use of immunosuppressants					
Neoplasm					
Depression					
Autoimmune disease					
Continuous medication					
Situation of vulnerability					
Therapeutic regimen					
BCG vaccine (Bacilli Calmette - Guérin)					
Chest X-ray					
Interferon Gamma Release Assays (IGRA)					
Tuberculin skin test (TST)					
Contact with tuberculosis patients					
Indication for LTBI treatment					
Interferon Gamma Release Assays (IGRA)					
Outcome variables				X	X
Complete treatment					
Abandonment					
Suspended due to an adverse event					
Active tuberculosis					
Death					
Transfers					
Other variables			X	X	X
Difficulty swallowing the medication					
Difficulty swallowing the medication in the last 30 days					
Forgot to take the medication					
Stopped taking medication when felt unwell					
Headache					
Insomnia					
Euphoria/agitation					
Anxiety					
Dizziness					
Depression					
Visual hallucination					
Auditory hallucination					
Mental confusion					
Psychosis					
Seizures					
Nightmares					
Dizziness					
Toxic encephalopathy					
Nausea					
Vomiting					
Hepatotoxicity					
Joint pain					
Acne on face/trunk					
Jaundice					
Pruritus					
Skin rash					
Bleeding					
Peripheral neuropathy					
Fever					
Changes in liver enzymes					

◀ **Fig. 1** Entry schedule, interventions, and evaluations for the pragmatic randomized clinical trial protocol to assess treatment completion of latent *Mycobacterium tuberculosis* infection with Isoniazid in the 300 mg formulation

coordinator in a sealed envelope to each center. The intervention of the study was LTBI treatment with 1 tablet of INH in the 300 mg formulation (INH 300 mg), while the control group received the LTBI treatment of 3 tablets of INH in the 100 mg (INH 100 mg) formulation according to the Brazilian guidelines [7]. The protocol is not blinded because the intervention is visually different from the control, with 1 tablet in the intervention group and 3 tablets in the control group already made available by the Ministry of Health for the LTBI therapeutic routine.

At baseline, each participant was instructed by the professional responsible for his treatment regarding the use of medications and possible adverse effects. Participants were interviewed at baseline at the start of treatment using the initial questionnaire, standardized for all sites and patients, constructed with the variables described in Fig. 1. At follow-up, the participants were followed up during the LTBI treatment period, which can last from 6 to 12 months, following the Brazilian protocol, and were interviewed in the first month and last month of treatment [7]. All data collected in the interviews were stored in the project's database, which is hosted on the REDCap Platform (redcap_v13.1.25) of the Federal University of Espírito Santo.

Outcomes

The primary analytical variable of interest was treatment completion, determined by the use of 270 doses that could be used between 9 and 12 months and/or 180 doses, which could be used between 6 and 9 months. The duration of treatment was determined by the participant's follow-up service team according to Brazilian guidelines [7]. The TPT was self-administered. The participant's adherence to LTBI treatment was assessed by clinical interview, through self-report, in front of the attending health professional.

There is evidence of greater efficacy of treatment with Isoniazid for LTBI for people who complete at least 80% of the doses, so completion was considered if the volunteer reported taking $\geq 80\%$ of the doses, with 144 or 216 doses of the 180 or 270 prescribed during the follow-up period, respectively. The identification of treatment non-completion was made by participants who remained three months without medication, consecutive or not, suspended due to adverse events, and transferred to the treatment center [11–14].

The secondary outcomes evaluated in the study were the adverse effects, namely: nausea, vomiting, epigastralgia, headache, arthralgia, insomnia, somnolence, nightmare, agitation, visual and/or auditory hallucination, psychosis, mental confusion, appearance of acne, skin itching, rash or hypersensitivity, abnormal bleeding, peripheral neuropathy, jaundice, hepatotoxicity, toxic encephalopathy, effects of the medication itself. These outcomes allowed us to evaluate the safety of INH 300 mg when compared to TPT with three INH 100 mg tablets.

Statistical analysis

All analyses were performed using Stata software version 14.0 (Stata Corp, College Station, TX, USA). Initially, a non-completion reduction rate of 11% was expected. However, during the execution of the protocol, a higher-than-expected non-completion reduction rate was observed. Therefore, the protocol was interrupted with 207 participants. With the reduction rate of 21% in the non-completion found considering a two-tailed test and an alpha error of 5%, we obtained a power of 87%.

To describe the study population, the relative and absolute frequencies of the categorical variables and medians with interquartile range (IQR) of the numerical variables were calculated. To compare the intervention and control groups with the outcome, Pearson's chi-square test was used. Fisher's exact test was used to analyze the occurrence of adverse events in the groups studied.

To ensure the balance and interchangeability of the groups to the study allocation, a propensity score was performed that indicates the conditional probability of receiving the intervention as a function of the observed predictor variables [15–17]. The propensity score was estimated by a *logit* model that included the following predictor variables: age, sex, race/skin color, schooling, HIV infection, and number of TPT doses, 180 doses or 270 doses. These variables were defined a priori by previous studies [11–14, 18–21]. Next, weighting by the propensity score was calculated, using the inverse weighting of the probability of the propensity score [15–17]. Variable balancing was considered when the absolute standardized difference of means was <0.10 and standard deviation and variance ratio between 0.80 and 1.20. [15–17].

Poisson regression models with robust variance were used to examine the association of the intervention with TPT completion rates. The dependent variable was treatment completion, and the independent variable was the intervention, TPT with INH 300 mg. The crude model was first estimated, followed by the adjusted model, which included weighting by the propensity score [15–17]. The results were presented as a risk ratio (RR) with a 95% confidence interval (95% CI).

The mean effect of the intervention on TPT completion was estimated by weighting the propensity score. The result was presented as a coefficient, which is the difference between the effect of TPT with INH 300 mg on TPT completion and TPT with INH 100 mg.

Ethical aspects

The study protocol was reviewed and approved by the Research Ethics Committee of the Health Sciences Center of the Federal University of Espírito Santo through Opinion No. 2.764.103/2018 and by the National Research Ethics Committee under number 88226218.0.1001.5060. The protocol is registered in the Brazilian Registry of Clinical Trials under the code RBR-2wsdt6 (http://ensaiosclinicos.gov.br/rg/RBR-2wsdt6/).

Results

Of the 207 individuals included in the study, 49.7% (103) were allocated to the intervention group and underwent TPT with 1 tablet of INH 300 mg, and 50.3% (104) were allocated to the control group, who underwent TPT with three INH 100 mg tablets (Fig. 2). The sociodemographic and clinical characteristics of the individuals at the beginning of the study are described in Table 1.

In the intervention group, the majority were female, of mixed race/skin color, with more than 8 years of schooling and a median age of 44 years. Among the clinical characteristics, 17.5% (18/103) were PLHIV, 16.5% (17/103) were on long-term use of corticosteroid therapy, 23.3% (24/103) had autoimmune disease, and 44.5% (45/103) had pulmonary TB contacts. Regarding the therapeutic regimen, 67.9% (70/103) underwent TPT with 180 doses and 32.0% (33/103) with 270 doses (Table 1).

Table 2 shows that 69.9% (72/103) of the individuals who used INH 300 mg completed TPT, while in the group that used INH 100 mg, 48% (50/104) completed TPT according to the study's definitions of completion. The risk ratio for TPT completion was 1.45-fold higher in the group that used INH 300 mg treatment vs the group used INH 100 mg treatment (RR 1.45, 95% CI 1.14 to 1.84). In the propensity score-weighted analysis, the risk ratio for TPT was 1.39-fold higher in the group that used INH 300 mg treatment vs the group used INH 100 mg treatment (RR 1.39, 95% CI 1.08 to 1.79). The mean effect of TPT with INH 300 mg, based on propensity score weighting, describes that TPT with INH 300 mg improved the treatment completion rate by 19% (coefficient 0.19, 95% CI 0.06 to 0.32).

There was no significant difference between the intervention and control groups for discontinuing TPT as

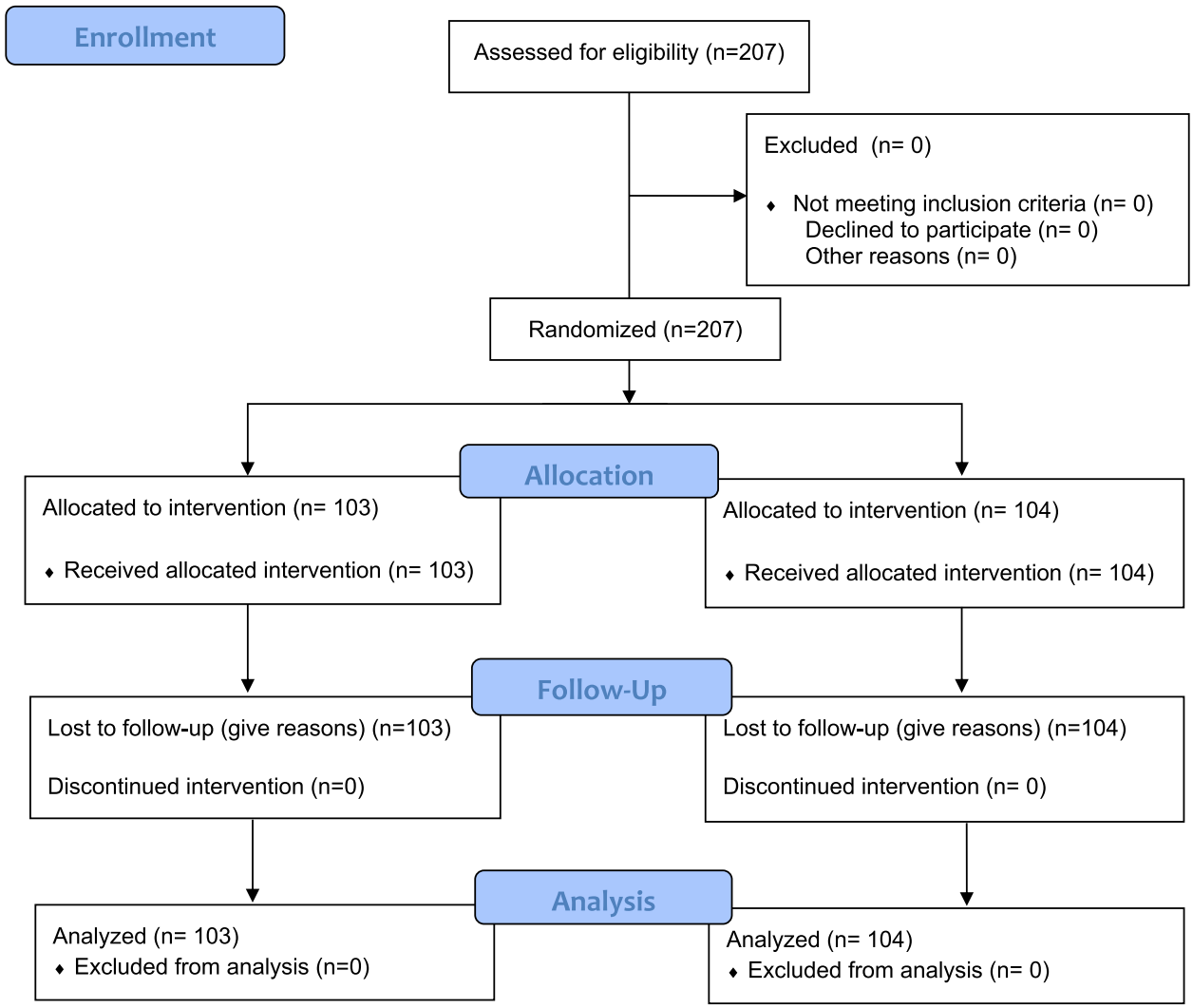

Fig. 2 CONSORT flow diagram

a result of adverse events. In the INH 300 mg group, 7 of the individuals discontinued TPT due to an adverse event, while in the INH 100 mg group, 7 discontinued TPT (6.8% vs 6.7%, $p=1.000$).

Table 3 shows the occurrence of adverse events in TPT with INH 300 mg compared to the INH 100 mg group. There was no significant difference between the groups in the proportion of individuals with adverse events.

Table 1 Clinical and demographic characteristics among people who started tuberculosis preventive treatment with 3 Isoniazid 100 mg tablets and 1 Isoniazid 300 mg tablet

Characteristics	Isoniazid 100 mg 3 tablets (*N* = 104)	Isoniazid 300 mg 1 tablet (*N* = 103)
Sex		
Male	46 (44.23)	46 (44.66)
Female	58 (55.77)	57 (55.34)
Age		
Median	44	43
Interquartile range	29–55	30–57
Race/skin color		
White	27 (25.96)	27 (26.21)
Black	17 (16.35)	27 (26.21)
Brown	60 (57.69)	49 (47.57)
Years of study		
No schooling	6 (5.77)	6 (5.83)
1 to 4 years	13 (12.50)	13 (12.62)
5 to 8 years	12 (11.54)	16 (15.53)
> 8 years	73 (70.19)	68 (66.02)
Receives government benefits	19 (18.45)	20 (19.42)
Smoking	17 (16.35)	18 (17.48)
Alcoholism	4 (3.85)	1 (0.97)
Diabetes Mellitus	14 (13.46)	9 (8.74)
Kidney failure	2 (1.92)	2 (1.94)
HIV/AIDS	14 (13.46)	18 (17.48)
Liver disease	4 (3.85)	3 (2.91)
Viral Hepatitis B/C	2 (1.92)	1 (0.97)
Transplant	1 (0.96)	0 (0.0)
Prolonged use of corticosteroids	20 (19.23)	17 (16.50)
Use of TNF-alpha inhibitors	14 (13.59)	10 (9.71)
Neoplasm	2 (1.92)	0 (0.0)
Depression	19 (18.27)	16 (15.53)
Autoimmune disease	25 (24.04)	24 (23.30)
Contact with pulmonary tuberculosis	49 (49.49)	45 (44.55)
Doses of therapeutic regimen		
180 doses of isoniazid	37 (35.58)	70 (67.96)
270 doses of isoniazid	67 (64.42)	33 (32.04)

However, the INH 300 mg group had a higher frequency of headache (43/90, 47.8%), appearance of acne (17/90, 18.9%), jaundice (10/90, 11.1%), and hepatotoxicity (5/90, 5.6%).

Discussion

The results show a positive effect on TPT completion with one INH 300 mg tablet when compared to TPT with three INH 100 mg tablets. In addition, the occurrence of adverse events was similar between the groups.

It is important to emphasize that the study has limitations. The context of the COVID-19 pandemic in Brazil made it difficult to recruit individuals and contributed to a reduction in sample power. Many care services for patients with TB and LTBI have suffered negative impacts on human resources, structure, and assistance flows [22].

When randomization was applied, a difference was found between the intervention group and the control group regarding the number of doses of the therapeutic regimen. However, the balance of the groups was obtained by weighting the propensity score [15–17].

Another point to highlight is the non-blinding of the study, which may have generated different responses from individuals than what actually occurred and a different evaluation by the evaluator/prescriber of the drug [23]. However, there is no possibility of blinding in the study, because the intervention is visually different from the control one, with 1 tablet in the intervention group and 3 tablets in the control group and depends on the prescription of the healthcare professional. To minimize this, data analyses were performed by a blinded researcher [23]. Self-reported adherence may have led to inaccuracy in the results, as information on treatment compliance may not reflect reality.

Conducting the study in a pragmatic setting, in health units that treat people with TB and LTBI, made it possible not only to evaluate the completion and safety of INH 300 mg in TPT but also its applicability in the routine of health services. To ensure internal validation of the study, we used a real-time data entry platform, with weekly monitoring of randomization, recruitment, and follow-up of individuals enrolled in the study. The number of individuals included in the study ensures extrapolation and external validation of the data to assess the completeness of the TPT. However, the sample size may have affected the extrapolation of the adverse event analyses.

We found TPT completion rates, both in the intervention group and in the control group, which corroborates the rates already described in the literature that can vary from 40 to 80% [19, 20]. Studies have shown that one of the main barriers to TPT completion is the duration of treatment and the number of tablets to be ingested [19, 24, 25]. The Brazilian protocol recommendation for TPT is 5 to 10 mg of INH per kg of patient weight, with a maximum dose of 300 mg, which leads the patient to take 3 tablets per day [7].

The use of INH in the 300 mg formulation decreases the number of tablets to be ingested in the therapeutic regimens of TPT with the ingestion of one tablet per day and allows greater TPT completion. In the 6H regimen, the total reduction is from 540 to 180 tablets, while in the 9H regimen, the reduction is from 810 to 270 tablets [8]. Even with new therapeutic regimens, such as

Table 2 Distribution and estimates of the direct effect of completing tuberculosis preventive treatment with Isoniazid 300 mg

	Tuberculosis preventive treatment		*P* value[a]
	Completed	Did not complete	
Isoniazid 100 mg 3 tablets	50 (48.08)	54 (51.92)	0.001
Isoniazid 300 mg 1 tablet	72 (69.90)	31 (30.10)	
Total	122 (58.94)	85 (41.06)	
Poisson regression			
Unadjusted analysis	RR 1.45 (95%CI, 1.14 to 1.84)		
Adjusted analysis[b]	RR 1.39 (95%CI, 1.08 to 1.79)		
ATE[c]	Coef 0.19 (95%CI, 0.06 to 0.32)		

[a] Pearson's chi-square test

[b] Model weighted by propensity score

[c] Mean treatment effect weighted by propensity score

Coef = difference in effects for 1 Isoniazid 300 mg tablet and 3 Isoniazid 100 mg tablets

Table 3 Distribution of the occurrence of adverse events in tuberculosis preventive treatment with 3 Isoniazid 100 mg tablets and 1 Isoniazid 300 mg tablet

Adverse events	Isoniazid 100 mg 3 tablets (*N* = 82)	Isoniazid 300 mg 1 tablet (*N* = 90)	*P* value[a]
Nausea	23 (28.05)	28 (31.11)	0.739
Vomiting	8 (9.76)	13 (14.44)	0.485
Headache	27 (32.93)	43 (47.78)	0.062
Epigastralgia	24 (29.27)	30 (33.33)	0.623
Arthralgia	22 (26.83)	26 (28.89)	0.865
Insomnia	29 (35.37)	30 (33.33)	0.872
Dizziness	22 (26.83)	28 (31.11)	0.615
Nightmares	9 (10.98)	13 (14.44)	0.648
Agitation	14 (17.07)	23 (25.56)	0.197
Visual and/or auditory hallucinstion	4 (4.88)	6 (6.67)	0.749
Psychosis	3 (3.66)	2 (2.22)	0.670
Mental confusion	6 (7.32)	10 (11.11)	0.441
Appearance of acne	8 (9.76)	17 (18.89)	0.129
Skin itching	15 (18.29)	18 (20.00)	0.847
Exanthema or hypersensitivity	5 (6.10)	2 (2.22)	0.260
Abnormal bleeding	5 (6.10)	3 (3.33)	0.481
Peripheral neuropathy	9 (11.11)	8 (8.89)	0.799
Jaundice	3 (3.66)	10 (11.11)	0.085
Hepatotoxicity	1 (1.22)	5 (5.56)	0.214
Toxic encephalopathy	2 (2.44)	1 (1.11)	0.606

[a] Fisher's exact test

Rifapentine + isoniazid regimen (3HP), which is considered a shortened treatment, lasting 12 to 15 weeks, the number of tablets to be ingested in a single dose is still high [19, 26]. Although the WHO recommends therapeutic regimens with 3 months of rifampicin with INH and 6 months with levofloxacin in its publication of consolidated guidelines on TB in 2024, Brazil has not yet incorporated these regimens into its national strategy [27].

The incorporation of INH in the 300 mg formulation contributes to the reduction of tablets and may have a positive impact on the TPT completion rate. Reducing the number of pills to be taken improves adherence to treatment, especially in the population at higher risk for TB, such as the elderly, PLHIV, and people with immunosuppressive and chronic diseases. These populations already have a high daily pill burden [28, 29].

However, studies are needed to assess the completion of TPT with the 300 mg formulation in specific populations, such as PHI, the elderly, chronic diseases, and immunosuppressed individuals. It was not possible to assess the completion of TPT with the 3HP regimen in this study. Participants were enrolled before the Brazilian health authorities recommended the use of the 3HP regimen. Therefore, studies are needed to assess the completion of TPT with a 3HP regimen using INH in the 300 mg formulation.

The TPT with INH is effective, however, therapeutic regimens with INH present adverse events more frequently [2, 30]. Studies have shown a higher occurrence of adverse events in therapeutic regimens with INH monotherapy when compared to other therapeutic regimens [19, 25, 26, 30–33]. Side effects of INH can include hepatitis, accompanied by fatigue, nausea, decreased appetite, and jaundice, as well as peripheral neuropathy [2]. A study with 6,862 participants comparing daily INH for 9 months (9H) with rifapentine + INH for 3 months (3HP) showed that 1.1% of the patients developed hepatotoxicity, 1.8% in the 9H regimen and 0.4% in the 3HP regimen, a risk four times higher in the INH isolated group, with a higher risk for older people who consumed alcohol, as well as pre-existing liver conditions, which requires closer monitoring in these cases [29–33].

A systematic review with a recent meta-analysis also found advantages in the 3HP regimen compared to the 9H regimen, with lower hepatotoxicity better efficacy, and better treatment completion rates [30, 31]. Nowadays, this is a better therapeutic possibility.

Despite the occurrence of adverse events, INH is considered a safe drug for TPT [30]. In our study, although a higher frequency of headache and acne was found in the intervention group, no significant differences were found in the occurrence of adverse events between the intervention and control groups. Headache and acne are minor adverse events expected with the use of INH, with no indication for treatment interruption [7, 27, 29–33]. The findings of adverse events in our study corroborate those already reported in previous studies [29–33].

Discontinuation of TPT, especially in INH monotherapy, due to an adverse event is expected [19, 20, 24–26]. A retrospective cohort study with data from Brazil's surveillance system that evaluated 39,973 individuals who underwent TPT found a 7.9% TPT discontinuation rate per adverse event [18]. We found TPT discontinuation similar rates per adverse event. Both individuals in the intervention group, INH 300 mg, and the control group, INH 100 mg, showed TPT discontinuation due to adverse events. However, we did not find differences in treatment discontinuation between the groups evaluated. In Brazil, the recommendation is that individuals be followed up with an interval of 30 to 60 days to monitor adverse events [7].

Conclusions

We conclude that the pragmatic use of INH 300 mg in TPT had a positive effect on treatment completion rate, as well as being a safe presentation for use in INH monotherapy regimens. The incorporation of the new presentation into LTBI therapeutic regimens has a potential benefit in reducing the number of tablets ingested in TPT and increasing the TPT completion rate.

Abbreviations

TB	Tuberculosis
TPT	Tuberculosis preventive treatment
INH	Isoniazid
6H	Monotherapy regimen with the isoniazid for six months
9H	Monotherapy regimen with the isoniazid for nine months
3HP	Combined therapy regimen of rifapentine and isoniazid for 12 weeks
LTBI	Latent tuberculosis infection
TST	Tuberculin skin test
PLHIV	People Living with HIV
INH 300 mg	Isoniazid in the 300 mg formulation
INH 100 mg	Isoniazid in the 100 mg formulation
IQR	Interquartile range
RR	Risk ratio
95% CI	95% Confidence interval

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-025-10678-z.

Supplementary Material 1. S1 Checklist. CONSORT 2010 checklist of information to include when reporting a randomised trial.

Supplementary Material 2. S2 File. ReBEC.

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Not applicable.

Clinical trial

The protocol is registered in the Brazilian Registry of Clinical Trials under the code RBR-2wsdt6 (http://ensaiosclinicos.gov.br/rg/RBR-2wsdt6/).

Authors' contributions

JPC, TNP, CMMS and ELNM contributed to the conception, design of the work, acquisition, analysis and interpretation of data. BMCSA, BJPB, WNA and NULT contributed to the conception, design of the work, acquisition and interpretation of data. KCM, ACBCV and SDR contributed to the conception and interpretation of data. All authors drafted the work, substantively revised and approved the submitted version.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. The datasets generated and/or analysed during the current study are not publicly available due Brazilian General Personal Data Protection Law (Law No. 13,709, of 08/14/2018) but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

All participants were instructed about the research procedures and expressed their free and unimpeded willingness to participate in the study by signing the protocol's free consent form.
The study protocol was reviewed and approved by the Research Ethics Committee of the Health Sciences Center of the Federal University of Espírito Santo through Opinion No. 2.764.103/2018 and by the National Research Ethics Committee under number 88226218.0.1001.5060.

Consent for publication

All participants were instructed about the research procedures and expressed their free and unimpeded willingness to participate in the study by signing the protocol's free consent form.

Competing interests

The authors declare no competing interests.

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