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# Long-Term Protective Effect of Tuberculosis Preventive Therapy in a Medium/High Tuberculosis Incidence Setting

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***Background.*** The duration of the protective effect of tuberculosis preventive therapy (TPT) is controversial. Some studies have found that the protective effect of TPT is lost after cessation of therapy among people with human immunodeficiency virus (HIV) in settings with very high tuberculosis incidence, but others have found long-term protection in low-incidence settings.

***Methods.*** We estimated the incidence rate (IR) of new tuberculosis disease for up to 12 years after randomization to 4 months of rifampin or 9 months of isoniazid, among 991 Brazilian participants in a TPT trial in the state of Rio de Janeiro, with an incidence of 68.6/100 000 population in 2022. The adjusted hazard ratios (aHRs) of independent variables for incident tuberculosis were calculated.

***Results.*** The overall tuberculosis IR was 1.7 (95% confidence interval [CI], 1.01– 2.7) per 1000 person-years (PY). The tuberculosis IR was higher among those who did not complete TPT than in those who did (2.9 [95% CI, 1.3–5.6] vs 1.1 [.4–2.3] per 1000 PY; IR ratio, 2.7 [1.0–7.2]). The tuberculosis IR was higher within 28 months after randomization (IR, 3.5 [95% CI, 1.6–6.6] vs 1.1 [.5–2.1] per 1000 PY between 28 and 143 months; IR ratio, 3.1 [1.2–8.2]). Treatment noncompletion was the only variable associated with incident tuberculosis (aHR, 3.2 [95% CI, 1.1–9.7]).

***Conclusions.*** In a mostly HIV-noninfected population, a complete course of TPT conferred long-term protection against tuberculosis.

**Keywords.** *Mycobacterium tuberculosis*; isoniazid; rifampicin; Brazil; latent tuberculosis infection.

Tuberculosis preventive therapy (TPT) is a key component of the End TB Strategy led by the World Health Organization [1]. Although immunosuppressed patients are the population with the highest individual risk for tuberculosis disease, contacts of index persons with pulmonary tuberculosis are the largest population now targeted for TPT [2]. Systematic reviews have shown the efficacy of TPT for preventing tuberculosis in people with human immunodeficiency virus (HIV; PWH) [3] and other populations [4]. Studies have found long-term reduction of death following TPT in PWH [5–11], but the duration of the TPT protection for tuberculosis incidence in high-risk populations has found conflicting results in long-term follow-up of randomized controlled trials (RCTs).

In Botswana, which had a tuberculosis incidence rate (IR) during the study period of 593/100 000 population, the incidence of tuberculosis and deaths from tuberculosis were substantially lower in PWH assigned to 36 months of isoniazid than in those who were assigned to a 6-month isoniazid regimen [8]. However, in a long-term follow-up analysis, the protective effect of 36 months of isoniazid was lost soon after discontinuation of TPT [12]. Likewise, in South Africa, a setting with an even higher incidence (3000/100 000 miners in the study period), the RCT that compared 6 months of isoniazid, 3 months of isoniazid and rifapentine (12 weekly doses; 3HP), and indefinite isoniazid in PWH suggested that the protection was significantly higher during therapy than after [13]. However, in Rio de Janeiro city, Brazil, a setting with a lower incidence (93/100 000 population [14]), protection for up to 7 years was reported in tuberculin skin test–positive PWH participants in the THRio RCT [9]. In the Temprano study, conducted in Côte d'Ivoire, where the tuberculosis IR is 159/100 000 population, a 6-month course of isoniazid reduced the mortality rate in PWH by 37%, and the benefits were sustained for up to 6 years of follow-up [6].

The long-term protective effect of TPT in contacts was suggested in a study conducted in Alaska in the 1950s and 1960s; protection from isoniazid was maintained for up to 19 years [15]. In Vitória, Brazil, a city with an IR of 34.4/100 000 population , observational data suggested that the protective effect of TPT with isoniazid in contacts was sustained for up to 7.9 years [16].

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In low-incidence settings, such as the United States and Canada, an RCT of treated contacts showed a decline in the risk of tuberculosis for ≥5 years after diagnosis in the index patient [17]. The current study evaluated the long-term (up to 12-year) protective effect of TPT on the Brazilian participants in 2 RCTs [18, 19] comparing the efficacy and safety of 4 months of rifampicin (4R) versus 9 months of isoniazid (9H). The objective was to verify whether TPT protection is sustained in the long term in a setting with an upper-moderate incidence of tuberculosis.

## METHODS

### Setting and Study Design

In Brazil, a middle-income country with an overall tuberculosis IR of 35/100 000 population, national guidelines recommend TPT for contacts of all ages with a positive tuberculosis infection test result and a normal chest radiograph. The IR of tuberculosis in Rio de Janeiro in 2009 was 93/100 000 [14]. In recent years, the IRs per 100 000 people (year) in the city of Rio de Janeiro were: 90.6 (2012), 86.0 (2013), 82.6 (2014), 83.8 (2015), 90.0 (2016), 91.9 (2017), 97.2 (2018), 107.4 (2019), 95.3 (2020), and 104.1 (2021) [20].

The current analysis is a long-term follow-up of 2 noninferiority RCTs using reported incident episodes of tuberculosis as the outcome. Both RCTs compared adherence, safety, and effectiveness for 4R versus 9H for prevention of tuberculosis, carried out between 2009 and 2014 in adults [19] and between 2011 and 2014 in children [18]. Participants with a positive tuberculin skin test result and TPT indication according to the country's guidelines were randomized to undergo daily, self-administered treatment with 4R or 9H. Adherence was checked by dose counts during monthly appointments on presentation of pill cartridges. Treatment completion was defined as having taken ≥80% of prescribed doses in 120% of the time. This means a minimum of 96 doses of rifampicin in a maximum of 146 days or a minimum of 216 doses of isoniazid in a maximum of 324 days. Incident tuberculosis episodes were ascertained by trimestral phone calls until 28 months after randomization for each study participant (active follow-up).

One RCT included 844 children (0–17 years of age) without HIV infection from 7 countries [18]. The other included 6012 adults (aged ≥18 years) from 9 countries; 70% were close contacts of a person with confirmed pulmonary tuberculosis, 4% were PWH, and the rest had other risk factors for tuberculosis disease reactivation [19]. In the pediatric trial, there were only 2 incident episodes of tuberculosis, in participants in arm 9H, and no serious adverse events in either arm. Completion was significantly higher with 4R compared with 9H in children (adjusted risk difference, 13.6 percentage points [95% confidence interval (CI), 7.9–19.3]). In the adult trial, there were 17 incident episodes of tuberculosis, 8 in the 4R arm, 4R was noninferior to 9H with regard to efficacy, and 4R was safer than 9H (adjusted difference, 3.0 percentage points lower rate of severe adverse events [95% CI, −4.1 to −2.0]). Completion was better with 4R (adjusted difference, 15.1 percentage points [95% CI, 12.7–17.4]). The median number of doses taken among those who did not complete treatment was 30 (interquartile range [IQR], 22– 60) in the 4R arm and 84 (33–122) in the 9H arm, corresponding to 25% and 31% of the prescribed doses, respectively. The detailed methods, procedures and results of the trials are reported elsewhere [18, 19].

Of these participants, 1006 (888 adults and 118 children) were enrolled from 6 research centers in the city of Rio de Janeiro, Brazil, and are included in this report of long-term follow-up. Most participants in Brazil (86%) were contacts of patients with tuberculosis. Incident tuberculosis was searched from the Brazil national tuberculosis reporting system over a period of 12 years, from 2009 to 2021.

### Outcomes, Exposure Variables and Data Source

The Notifiable Diseases Information System (SINAN) contains demographic information, laboratory and radiological results, history of previous tuberculosis episodes, and form of tuberculosis (pulmonary, extrapulmonary, or both). Tuberculosis notification is mandatory in Brazil, and the databank is considered good quality [21 (ie, data are complete and accurate).

The outcome was incident tuberculosis (any clinical form, clinically diagnosed or bacteriologically confirmed) reported during the randomization period until the SINAN searches were carried out, through October 25, 2021, using the name, sex, and birthdate of the participant, excluding duplicate reports in both searches. In case of discrepancies in dates, the first identified date was used.

The following data were extracted from the RCT: sex, age, HIV status, other immunosuppressive conditions, use of illicit drugs, initial radiograph, previous diagnosis of tuberculosis infection, TPT completion, and type of contact (casual, close). Close contact was defined as contact for ≥4 hours per week for ≥1 week with a person with active pulmonary tuberculosis. Casual contacts were those with <4 hours of contact per week. Immunosuppressive conditions included diabetes, renal failure, therapy with tumor necrosis factor α inhibitors, and anti–transplant rejection therapy. The following variables were extracted from SINAN: clinical form of tuberculosis, method of diagnosis (clinical or confirmed), and residential address. We calculated the IR of tuberculosis in the neighborhood of residence based on the number of tuberculosis episodes per estimated population for the year 2020 [22–24].

### Statistical Analyses

We calculated the IR and 95% CIs per 1000 person-years (PY) of newly diagnosed tuberculosis in the first 28 months after randomization, in the subsequent years, and for the entire observation period (0–143 months). We estimated the IR ratio (IRR)

**Table 1. Characteristics of Participants in 2 Randomized Controlled Trials by Diagnosis of Tuberculosis During the Study Period[a]**

| Characteristic[b] | Participants, No. (%) (N = 991) | |
|---|---|---|
| | With Tuberculosis (n = 16) | Without Tuberculosis (n = 975) |
| Treatment completed | | |
| No (<80% doses) | 9 (56) | 314 (32) |
| Yes (≥80% doses) | 7 (44) | 661 (68) |
| Sex | | |
| Male | 9 (56) | 535 (55) |
| Female | 7 (44) | 440 (45) |
| Age group | | |
| <18 y | 3 (19) | 115 (12) |
| ≥18 y | 13 (81) | 860 (88) |
| HIV status | | |
| Positive | 5 (31) | 110 (11) |
| Negative | 11 (69) | 213 (22) |
| Unknown | 0 (0) | 652 (67) |
| Tuberculosis contact | | |
| No contact | 4 (25) | 134 (14) |
| Casual (<4 h/wk) | 2 (12) | 74 (7) |
| Close (≥4 h/wk) | 10 (63) | 767 (79) |
| Illicit drug use | | |
| No | 2 (12) | 19 (2) |
| Yes | 14 (88) | 956 (98) |
| Smoking status | | |
| Never smoked | 9 (56) | 667 (68) |
| Current smoker | 4 (25) | 146 (15) |
| Former smoker | 3 (19) | 162 (17) |
| Immunosuppressive drugs | 1 (6) | 102 (10) |
| Abnormal chest radiograph | 4 (24) | 136 (14) |
| Previous diagnosis of tuberculosis infection | | |
| Yes | 1(6) | 6 (0.6) |
| No | 15 (94) | 964 (99) |
| Unknown | 0 (0) | 5 (0.5) |

Abbreviation: HIV, immunodeficiency virus.

[a]Data extracted from 2 randomized controlled trials and the Notifiable Diseases Information System (SINAN).

[b]Age group and other characteristics, such as HIV or smoking habits, correspond to the moment of randomization. The HIV status of participants with tuberculosis diagnosis was confirmed (unchanged) at the date of diagnosis.

and its 95% CI of (1) those who completed versus did not complete TPT (both regimens combined) and (2) the 4R versus 9H arms among those who completed TPT.

The effect of TPT completion on incident tuberculosis was estimated based on the adjusted hazard ratio (aHR) in a Cox regression model. The estimate was adjusted for HIV status, type of contact (close or casual), use of illicit drugs, smoking, immunosuppressive conditions, chest radiography, previous diagnosis of tuberculosis infection, TPT completion, age, and sex.

We constructed cumulative risk graphs (complement of the of the Kaplan-Meier graphs) for fully completed versus noncompleted TPT. The log-rank test was used to verify whether there was a statistically significant difference between the treatment completeness curves. We considered the overall time interval between the date of randomization and the date of the tuberculosis or censorship outcome (ie, the final date of the search on SINAN). To convert total days into years, we considered a year as 365.25 days. All analyses were conducted using R 4.2.2 software (R Core Team; 2022).

### Ethical Considerations

This is a long follow-up among the Brazilian participants of a multicenter study, originally approved by the McGill University Health Centre Ethical Review Board (OCC 2009-100; 24 July 2009). The original informed consent included consent to use nominal information to match to tuberculosis notification data in Brazil. The current study was approved by the Institutional Review Board of Centro Universitario Fluminense in Campos, Rio de Janeiro, on 4 October 2021 (no. 5.018.418).

## RESULTS

Of the 1006 participants, 15 names could not be retrieved. Thus, the sample for the current study includes 991 participants. Among them, 16 had tuberculosis diagnosed within the study period (2009–2021): 8 during the 28-month period and 8 after 28 months. The median time (IQR) to diagnosis of tuberculosis was 27 (14.75–48.75) months. The characteristics of those who developed tuberculosis compared with those who did not is displayed in Table 1.

The median follow-up (IQR) was 9.6 (9–10) years per person. The overall tuberculosis incidence was 1.7 (95% CI, 1.01–2.7) per 1000 PY. The incidence was higher in the first 28 months after randomization than during later follow-up: 3.5 (95% CI, 1.6–6.6) per 1000 PY in the first 28 months after randomization and 1.1 (.5–2.1) per 1000 PY thereafter (IRR, 3.1 [1.2–8.2]).

The IR of tuberculosis among those who did not complete the TPT was 2.9 (95% CI, 1.3–5.6) versus 1.1/1000 PY (.4–2.3) per 1000 PY in those who completed it (IRR, 2.7 [1.00–7.2]). The IRR was also higher in the first 28 months after randomization in this group (uncompleted TPT) (IRR, 3.5 (95% CI, .8–14.5) vs 2.1 (.5–8.3) thereafter (Table 2). The curves in Figure 1 show the protection conferred by completion of TPT (log-rank test; $P = .04$) and the slowdown in the number of tuberculosis episodes after the first 2 years, irrespective of TPT completion.

Table 3 displays the IR and IRR of incident tuberculosis disease among those who completed TPT, by regimen. There was no difference between regimens (4R vs 9H). The risk of incident tuberculosis was 3.3-fold higher in people who did not complete TPT (aHR, 3.2 [CI 95%, 1.1–9.7]; $P = .04$) (Table 4). This was the only independent variable associated with incident tuberculosis.

All 8 participants in whom tuberculosis developed in the late period were at higher risk of reexposure (in prison or living in a

**Table 2. Tuberculosis Incidence Rates Among Participants Who Completed Tuberculosis Preventive Therapy Versus Those Who Did Not**

| | TPT Not Completed (n = 323) | | TPT Completed (n = 668) | | |
|---|---|---|---|---|---|
| Time After Randomization, mo | No. With Tuberculosis/PY | IR/1000 PY (95% CI) | No. With Tuberculosis/PY | IR/1000 PY (95% CI) | IRR (95% CI) |
| 0 to ≤28 (Active follow-up[a]) | 5/747 | 6.7 (2.2–15.6) | 3/1556 | 1.9 (.4–5.6) | 3.5 (.8–14.5) |
| >28 to 143 (After active follow-up[a]) | 4/2302 | 1.7 (.5–4.4) | 4/4801 | 0.8 (.2–2.1) | 2.1 (.5–8.3) |
| 0–143 (Overall) | 9/3049 | 2.9 (1.3–5.6) | 7/6357 | 1.1 (.4–2.3) | 2.7 (1.00–7.2) |

Abbreviations: CI, confidence interval; IR, incidence rate; IRR, IR ratio (TPT not completed/TPT completed); PY, person-years of follow-up; TPT, tuberculosis preventive therapy.

[a]"Active follow-up" refers to the active period of follow-up of participants during the original randomized controlled trials, from randomization to 28 months; "after active follow-up" indicates the subsequent period, during which tuberculosis notifications were identified in the Notifiable Diseases Information System (SINAN), a database of mandatory notifications for tuberculosis in Brazil.

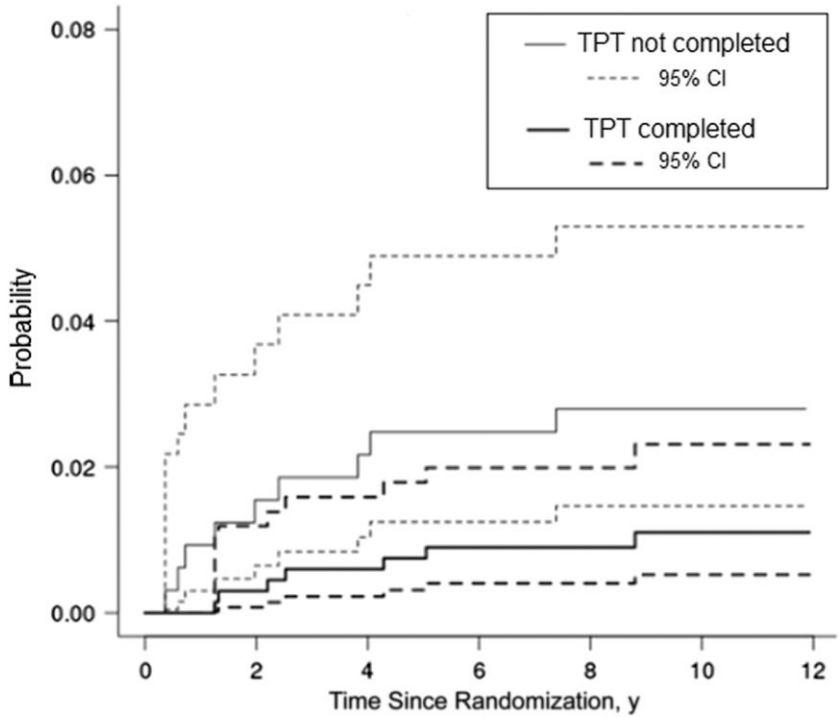


**Figure 1.** Cumulative incidence in participants who completed or did not complete tuberculosis preventive therapy (TPT), with 95% confidence intervals (CIs) ($P = .04$).

**Table 3. Tuberculosis Incidence Rate by Regimen Among Participants Who Completed Treatment (n = 668)**

| | 4R Regimen (n = 363) | | 9H Regimen (n = 305) | | |
|---|---|---|---|---|---|
| Time After Randomization, mo | No. With Tuberculosis/PY | IR/1000 PY (95% CI) | No. With Tuberculosis/PY | IR/1000 PY (95% CI) | IRR (95% CI) |
| 0 to ≤28 (Active follow-up[a]) | 0.1/847 | 0.1 (.0–4.6) | 3.1/709 | 4.4 (.9–12.6) | 0.03 (.0–14.7) |
| >28 to 143 (After active follow-up[a]) | 1/2625 | 0.4 (.0–2.1) | 3/2176 | 1.4 (.3–4.0) | 0.3 (.0–2.7) |
| 0–143 (overall) | 1/3472 | 0.3 (.0–1.6) | 6/2885 | 2.1 (.8–4.5) | 0.1 (.0–1.1) |

Abbreviations: 4R, 4 months of rifampicin; 9H, 9 months of isoniazid; CI, confidence interval; IR, incidence rate; PY, person-years; IRR, IR ratio (4R/9H).

[a]"Active follow-up" refers to the active period of follow-up of participants during the original randomized controlled trials, from randomization to 28 months; "after active follow-up" indicates the subsequent period, during which tuberculosis notifications were identified in the Notifiable Diseases Information System (SINAN), a database of mandatory notifications for tuberculosis in Brazil.

**Table 4. Cox Proportional Hazards Regression Model for Tuberculosis Incidence**

| Characteristic | HR (CI 95%) | aHR (CI 95%) |
|---|---|---|
| TPT completed | | |
| Yes | Reference | Reference |
| No | 2.7 (1.00–7.2) | 3.2 (1.1–9.7) |
| Tuberculosis contact | | |
| None | Reference | Reference |
| Casual (<4 h/wk) | 0.9 (.2–4.9) | 1.3 (.2–10.4) |
| Close (≥4 h/wk) | 0.4 (.1–1.4) | 0.4 (.1–3.2) |
| Previous diagnosis of tuberculosis infection | | |
| No/unknown | Reference | Reference |
| Yes | 9.9 (1.3–75.4) | 8.2 (.7–100.2) |
| Abnormal chest radiograph | | |
| No | Reference | Reference |
| Yes | 2.0 (.7–6.3) | 2.7 (.7–9.9) |
| Age[a] (mean [SD], 36.1 [16.6] y) | 1.00 (.9–1.02) | 1.00 (.9–1.0) |
| Sex | | |
| Male | Reference | Reference |
| Female | 0.6 (.2–1.7) | 0.9 (.3–2.4) |
| Immunosuppressive drugs | | |
| No | Reference | Reference |
| Yes | 0.6 (.1–4.3) | 0.4 (.0–4.8) |
| HIV status[b] | | |
| Negative/unknown | Reference | Reference |
| Positive | 3.5 (1.2–10.0) | 1.7 (.3–11.0) |
| Illicit drug use | | |
| No | Reference | Reference |
| Yes | 7.2 (1.6–31.6) | 4.7 (.8–26.0) |
| Smoking status | | |
| Never | Reference | Reference |
| Current | 2.0 (.6–6.5) | 1.5 (.4–5.5) |
| Former smoker | 1.4 (.4–5.0) | 1.3 (.3–5.7) |

Abbreviations: aHR, adjusted hazard ratio (multivariable); CI, confidence interval; HR, hazard ratio (univariable); SD, standard deviation; TPT, tuberculosis preventive therapy.

[a]Age includes all ages of participants.

[b]The HIV status of participants with tuberculosis diagnosis was confirmed (unchanged) at the date of diagnosis.

high-incidence neighborhood) or higher risk of progression (immunosuppression; Table 5), although the Cox regression model did not show risk factors significantly associated with any variable for the late period only (data not shown). In addition, 4 of them had not completed TPT; the proportions of doses taken were 58%, 77%, 58%, and 11% (Table 5). No participant developed tuberculosis while on TPT.

## DISCUSSION

In the current long-term follow-up in 2 RCTs comparing 2 therapeutic regimens, we confirmed that treatment completion was associated with long-term protection against tuberculosis. The overall risk of developing tuberculosis was almost 3-fold higher (IRR, 2.7) in those who did not complete treatment. The risk was also 3-fold higher (IRR, 3.5) within the first 28 months after randomization. There were few episodes over time, after the first 2 years of follow-up. The higher risk of progression to disease in the first 2 years after exposure is well established in both children [25] and adults [26]. These findings suggest that, unlike in PWH in very high-incidence settings [12, 13], the effects of TPT completion in our population were sustained, and additional courses or prolonged TPT were not necessary for long-term protection [6, 9].

A higher risk of progression to tuberculosis was reported after the end of 36-month TPT in the observational follow-up of PWH participants in the BOTUSA [12] clinical trial and in those in the shorter treatment arms during the clinical trial in South African [13], compared with those randomized to indefinite isoniazid. However, in the WHIP3TB Study, annual treatment of PWH using antiretroviral therapy with the short 3HP TPT regimen for 2 years did not confer additional protection for PWH compared with 3HP once [27], suggesting that repeated TPT courses are not beneficial.

Individual tuberculosis absolute risk is known to be lower among contacts than among immunocompromised subjects [2]. In our study, most participants were HIV negative; their main indication for TPT was contact with a person with bacteriologically confirmed pulmonary tuberculosis. In the same setting, PWH also had long-term protection, up to 7 years after TPT [9]. Participants who developed late tuberculosis had a high risk of either reinfection or progression to disease. Despite the small number of incident episodes overall, these findings, taken together, suggest that a single course of TPT confers sufficient protection against past exposure to *Mycobacterium tuberculosis* for most people with indications for TPT.

TPT completion was associated with protection against tuberculosis, regardless of regimen. Because treatment completion is an observational variable, and risk behaviors could be associated with both treatment completion and the main outcome (tuberculosis disease), we analyzed possible confounders in a multivariate model. We could not identify any variable associated with progression to tuberculosis apart from treatment completion, although the number of incident tuberculosis episodes is small, limiting power. A surprising finding was the higher aHR in casual contacts than in close contacts, although this difference was not statistically significant and might be a random finding.

Our study has a few limitations. Besides the small numbers of incident tuberculosis episodes and the wide CIs, our analyses rely on the information system. Although tuberculosis notification is mandatory in Brazil, this strategy may not have been sensitive enough to identify all persons with tuberculosis. However, a differential underestimation between subgroups is unlikely. Moreover, in the original studies [18, 19], the information system was reliable. Finally, because we did not link the data to the mortality information system, eventual censoring from death is not included.

**Table 5. Details of Participants With Tuberculosis Disease Diagnosed Up to 143 Months After Randomization**

| Participant no. | Time Since Randomization, y | Tuberculosis Contact | Regimen | Completed TPT[a] | Doses Taken, %[b] | HIV+ Status[c] | Smoking Status | Other Condition or Circumstance[c] | Age, y[d] | Sex | Clinical Form[c] | Basis for of Diagnosis[c] | 2020 Neighborhood[e] Tuberculosis Incidence, Cases/ 100 000 Pop |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 0.4 | Close | 9H | No | 0 | No | Current | Alcohol use disorder | 31 | M | P | Positive SSM, positive culture, and suggestive radiographic signs | 214.3 |
| 2 | 0.6 | Close | 4R | No | 52 | No | Former | … | 47 | F | P | Negative SSM and suggestive radiographic signs | 223.6 |
| 3 | 0.7 | No | 4R | No | 73 | Yes | Current | Use of illicit drugs | 47 | M | P | Positive SSM and suggestive radiographic signs | 57.4 |
| 4 | 1.2 | Close | 9H | Yes | 89 | No | Never | … | 42 | M | P | Negative culture and suggestive radiographic signs | 427.6 |
| 5 | 1.2 | Close | 9H | No | 22 | No | Never | … | 35 | F | P | Positive culture and suggestive radiographic signs | … |
| 6 | 1.3 | No | 9H | Yes | 100 | Yes | Former | Stomach cancer | 49 | M | P + EP | Positive SSM and suggestive radiographic signs | 75.7 |
| 7 | 2.0 | Close | 4R | No | 54 | No | Never | … | 24 | M | P | Positive SSM and suggestive radiographic signs | 89.6 |
| 8 | 2.2 | No | 9H | Yes | 100 | No | Never | … | 52 | F | EP | Normal radiograph | 427.6 |
| 9 | 2.4 | Close | 4R | No | 58 | No | Never | … | 16 | M | P | Positive SSM, positive culture, and suggestive radiographic signs | 75.7 |
| 10 | 2.5 | No | 4R | Yes | 100 | Yes | Never | … | 31 | F | P | Radiological sign suggestive of tuberculosis | 69.1 |
| 11 | 3.8 | Close | 9H | No | 77 | No | Never | … | 19 | F | P | Positive culture and suggestive radiographic signs | 282.6 |
| 12 | 4.0 | Close | 4R | No | 58 | Yes | Current | … | 31 | M | P | Positive SSM, culture positive and normal radiography | 112.2 |
| 13 | 4.3 | Casual | 9H | Yes | 100 | No | Never | … | 28 | F | EP | … | 97.4 |
| 14 | 5.0 | Close | 9H | Yes | 100 | No | Former | Rheumatoid arthritis and illicit drug use | 56 | F | P | Positive SSM | 53.8[f] |
| 15 | 7.4 | Casual | 9H | No | 11 | No | Current | Immigrant status and alcohol use disorder | 73 | M | EP | … | 72.0 |
| 16 | 8.8 | Close | 9H | Yes | 100 | No | Never | Prisoner | 22 | M | P | Suggestive radiographic signs | 427.6 |

Abbreviations: 4R, 4 months of rifampicin; 9H, 9 months of isoniazid; EP, extrapulmonary; F, female; HIV+, human immunodeficiency virus–positive; M, male; P, pulmonary; Pop, population. SSM, sputum smear microscopy; TPT, tuberculosis preventive therapy.

[a]Complete TPT defined as ≥96 doses of rifampicin within 146 days or ≥216 doses of isoniazid within 324 days.

[b]Percentage of doses taken proportional to the regimen administered.

[c]Data extracted from the Notifiable Diseases Information System (SINAN).

[d]Age at time of tuberculosis diagnosis.

[e]Neighborhood defined as place of residence.

[f]2019 incidence.

Regardless of these limitations, our findings suggest that the protective effect of a complete course of TPT seems to last in a setting with moderate tuberculosis incidence and a mostly immunocompetent population.

## Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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