

ORIGINAL ARTICLE

Four Months of Rifampin or Nine Months of Isoniazid for Latent Tuberculosis in Adults

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ABSTRACT

BACKGROUND

A 9-month regimen of isoniazid can prevent active tuberculosis in persons with latent tuberculosis infection. However, the regimen has been associated with poor adherence rates and with toxic effects.

METHODS

In an open-label trial conducted in nine countries, we randomly assigned adults with latent tuberculosis infection to receive treatment with a 4-month regimen of rifampin or a 9-month regimen of isoniazid for the prevention of confirmed active tuberculosis within 28 months after randomization. Noninferiority and potential superiority were assessed. Secondary outcomes included clinically diagnosed active tuberculosis, adverse events of grades 3 to 5, and completion of the treatment regimen. Outcomes were adjudicated by independent review panels.

RESULTS

Among the 3443 patients in the rifampin group, confirmed active tuberculosis developed in 4 and clinically diagnosed active tuberculosis developed in 4 during 7732 person-years of follow-up, as compared with 4 and 5 patients, respectively, among 3416 patients in the isoniazid group during 7652 person-years of follow-up. The rate differences (rifampin minus isoniazid) were less than 0.01 cases per 100 person-years (95% confidence interval [CI], -0.14 to 0.16) for confirmed active tuberculosis and less than 0.01 cases per 100 person-years (95% CI, -0.23 to 0.22) for confirmed or clinically diagnosed tuberculosis. The upper boundaries of the 95% confidence interval for the rate differences of the confirmed cases and for the confirmed or clinically diagnosed cases of tuberculosis were less than the prespecified noninferiority margin of 0.75 percentage points in cumulative incidence; the rifampin regimen was not superior to the isoniazid regimen. The difference in the treatment-completion rates was 15.1 percentage points (95% CI, 12.7 to 17.4). The rate differences for adverse events of grade 3 to 5 occurring within 146 days (120% of the 4-month planned duration of the rifampin regimen) were -1.1 percentage points (95% CI, -1.9 to -0.4) for all events and -1.2 percentage points (95% CI, -1.7 to -0.7) for hepatotoxic events.

CONCLUSIONS

The 4-month regimen of rifampin was not inferior to the 9-month regimen of isoniazid for the prevention of active tuberculosis and was associated with a higher rate of treatment completion and better safety. (Funded by the Canadian Institutes of Health Research and the Australian National Health and Medical Research Council; ClinicalTrials.gov number, NCT00931736.)

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TUBERCULOSIS IS A MAJOR GLOBAL HEALTH problem, with an estimated 10.4 million new cases of tuberculosis worldwide in 2015.¹ It has been estimated that one quarter of the global population has latent tuberculosis infection.² There is a growing recognition that, given this enormous reservoir, the treatment of latent tuberculosis infection is a key part of the End TB Strategy^{3,4} and the tuberculosis-elimination plans in high-income countries.⁵

Many authorities, including the World Health Organization (WHO), recommend the treatment of latent tuberculosis infection with isoniazid for 6 or 9 months,⁶⁻⁸ with the longer duration showing evidence of greater protective efficacy.⁹ However, the benefit of treatment with isoniazid is substantially reduced because of poor rates of regimen completion¹⁰ and because of hepatotoxic effects.¹¹ Observational studies¹²⁻¹⁴ have shown superior rates of regimen completion and lower rates of hepatotoxic effects with a 4-month regimen of daily rifampin than with the 9-month regimen of isoniazid. In an earlier trial, a 3-month regimen of daily rifampin was significantly superior to placebo and provided equivalent reduction in the incidence of tuberculosis as the 6-month regimen of isoniazid.¹⁵

We have previously reported the results of two randomized trials in which a 4-month regimen of rifampin was associated with a significantly lower incidence of grade 3 or 4 drug-related adverse events, lower costs, and a higher rate of treatment completion than a 9-month isoniazid regimen.¹⁶⁻¹⁸ In this phase 3 trial, we compared the effectiveness and efficacy of a 4-month regimen of rifampin with a 9-month regimen of isoniazid for the prevention of active tuberculosis.

METHODS

TRIAL DESIGN AND OBJECTIVES

We conducted an open-label, parallel-group, randomized, controlled trial comparing a 4-month regimen of rifampin with a 9-month regimen of isoniazid for the treatment of latent tuberculosis infection in adults. The primary objective was to compare the rates of confirmed active tuberculosis in the two groups among all eligible patients during 28 months after randomization (modified intention-to-treat analysis, defined as the study population remaining after valid and prespecified exclusions after randomization) (see the protocol, available with the full text of this

article at NEJM.org). The secondary objectives were to compare the following in the two groups: the rate of confirmed active tuberculosis plus clinically diagnosed active tuberculosis per 100 person-years; the rate of confirmed or clinically diagnosed tuberculosis per 100 person-years among patients who completed the trial therapy per the protocol; the cumulative incidence of adverse events of grades 3 to 5, overall and those considered by the adjudication panel to be drug-related and occurring throughout the course of therapy or within the maximum time allowed for the completion of the rifampin regimen (120% of 4 months, or 146 days); the percentage of patients in each trial group who completed the trial therapy, which was defined as receipt of at least 80% of the doses; and the rate of drug-resistant active tuberculosis per 100 person-years.

INTERVENTIONS

The control regimen was oral isoniazid at a dose of 5 mg per kilogram of body weight (maximum dose, 300 mg) taken daily for 9 months (270 doses), with vitamin B₆ (pyridoxine) added for adults who were at risk for neuropathy.⁶⁻⁸ The experimental regimen was oral rifampin at a dose of 10 mg per kilogram (maximum dose, 600 mg) taken daily for 4 months (120 doses). The trial drugs were purchased at full cost, unless they were provided free of charge by the local tuberculosis program; no sponsor paid for drugs, in part or in whole.

POPULATION ELIGIBILITY AND RANDOMIZATION

The selected trial sites in Australia, Benin, Brazil, Canada, Ghana, Guinea, Indonesia, Saudi Arabia, and South Korea had extensive experience in previous clinical trials. Trial staff at all the sites received initial training in Good Clinical Practice and trial procedures, and monitoring visits were conducted twice per year (see the Supplementary Appendix, available at NEJM.org).

Adults (18 years of age or older) were enrolled if they had a documented positive tuberculin skin test or interferon- γ -release assay, if they met the criteria for an increased risk of reactivation to active tuberculosis (see the Supplementary Appendix),^{6,8} and if their provider recommended treatment with isoniazid. Before randomization, adults underwent medical evaluation, including radiography of the chest, to rule out active tuberculosis. Testing for the human immunodeficiency



A Quick Take is available at NEJM.org

ciency virus (HIV) was offered to participants who had risk factors for HIV infection. The exclusion criteria were exposure to a patient with active tuberculosis whose isolates were resistant to either trial drug, current or planned pregnancy, the use of medications with potentially serious interactions with either trial drug, history of allergy to either trial drug, or current active tuberculosis. All the eligible patients provided written informed consent.

Randomization was generated centrally, by computer, in blocks of varying length (2 to 8) and stratified according to center with an assignment ratio of 1:1. All the contacts within the same household were assigned to the same trial group if they were all identified within the same week.

ASCERTAINMENT OF ACTIVE TUBERCULOSIS

Follow-up during treatment occurred monthly for the first 2 months and at a minimum of every 8 weeks thereafter. Follow-up after treatment began after the participant completed or discontinued treatment and was conducted by telephone, visits at the health facility, or home visits every 3 months until 28 months after randomization. Hence, the minimum number of total trial-related visits was 11 for participants who had been randomly assigned to the 4-month rifampin regimen and 12 for those who had been randomly assigned to the 9-month isoniazid regimen. Suspected active tuberculosis was investigated according to a standard protocol. The names of all the trial participants who did not complete 28 months of follow-up or who had confirmed or clinically diagnosed active tuberculosis, plus the names of a random 10% sample of participants who completed follow-up, were sent to the local tuberculosis program to ascertain whether any of these participants had been reported as having received a diagnosis of active tuberculosis.

Confirmed tuberculosis was defined as a positive culture for *Mycobacterium tuberculosis* or a finding of caseating granulomas in a biopsy specimen obtained from any site. If there were no culture results, a positive acid-fast smear or a positive nucleic acid amplification test for *M. tuberculosis* complex was considered to be confirmatory. All clinical, radiologic, and microbiologic information of the participants with suspected active tuberculosis, including the response to treatment for active tuberculosis, was reviewed by a

panel of three physicians who had experience regarding tuberculosis. The panel members were unaware of the trial-group assignments and the evaluations of the care providers, and each physician independently judged whether active tuberculosis was probable or unlikely. Clinically diagnosed tuberculosis was defined as a judgment of probable active tuberculosis by at least two of the three physicians.

MEASUREMENT OF TREATMENT COMPLETION

Patients brought all the remaining doses of the trial drug to every visit for pill counts. Treatment completion was defined as receipt of at least 80% of the doses within 12 months for rifampin or within 18 months for isoniazid. This threshold was selected because of evidence that efficacy was greatest if at least 80% of the doses of isoniazid were taken¹⁹ and evidence that the total number of doses taken is the key determinant in the prevention of tuberculosis.²⁰ Treatment completion per protocol was defined as receipt of at least 80% of the recommended doses within the allowed time (146 days for the rifampin regimen and 324 days for the isoniazid regimen).

MEASUREMENT OF SAFETY DURING TREATMENT

At each follow-up visit, participants were questioned about and examined for adverse events. Suspected adverse events were investigated, managed, and reported according to standardized protocols (see Part 2 in the Supplementary Appendix). Information about suspected adverse events was reviewed by a different three-member panel who had expertise in clinical-epidemiologic tuberculosis research; these panel members were also unaware of the trial-group assignments and the judgments of the care providers. Panel members independently judged the severity of adverse events according to published recommendations (for hepatic events²¹ and for all other events²²) and categorized the events as follows: an adverse event that was not related to a trial drug; an adverse event of grade 1 or 2 that was related to a trial drug (not serious); an adverse event of grade 3 or 4 that was related to a trial drug (generally considered to lead to trial-drug discontinuation if related to a trial drug); or a grade 5 event (death) that was related to a trial drug. If opinions differed, the majority opinion was used; if all three opinions differed, the panel members rereviewed the blinded data.

OVERSIGHT

This trial was approved by the Biomedical Clinical Research Ethics Board of the McGill University Health Centre Research Institute and by the responsible ethics review committee at each participating site. All the authors vouch for the accuracy and completeness of the data and analyses presented and for the fidelity of the trial to the protocol.

STATISTICAL ANALYSIS

We originally planned that a sample of 3283 participants in each group would provide the trial with at least 80% power (at an alpha level of 0.05) to detect significantly superior effectiveness of the rifampin regimen as compared with the isoniazid regimen in preventing tuberculosis. For the assessment of tuberculosis prevention, we planned to include the 847 participants from the earlier phase 2 trial because they had been enrolled, undergone randomization, and had been treated and followed according to the same methods. (For details, see the articles by Menzies et al.¹⁷ and Aspler et al.¹⁸) To account for a potential 15% loss to follow-up (on the basis of the results in the phase 2 trial) and clustering within households, we increased enrollment to 6800 participants.

We also prespecified that this number of participants would provide the trial with more than 90% power to declare noninferior efficacy of the 4-month rifampin regimen, with a maximum tolerated difference in cumulative incidence between the two regimens of 0.75 percentage points. This value was based on an expected cumulative incidence of 3% over a 28-month period among untreated close contacts or other high-risk persons,^{7,23-25} a 90% protective efficacy of the 9-month isoniazid regimen,⁹ and a minimum acceptable efficacy of the 4-month rifampin regimen of 65% (which had been achieved with the 6-month isoniazid regimen in previous trials¹⁹ and was widely considered to be sufficiently acceptable for use^{6,8}).

Statistical analyses were directed by the principal investigator and co-investigators, who remained unaware of the trial-group assignments until the analyses had been completed. Differences between groups were tested for significance by Student's *t*-test (if normally distributed) or a Wilcoxon two-sample test (if not normally distributed) or by chi-square analysis for categor-

ical variables. Rates of active tuberculosis were based on person-time of follow-up; patients who were lost to follow-up contributed to person-time until the date of the last contact.

Rate differences and their 95% confidence intervals were estimated with the use of generalized estimating equations to account for clustering in families, on the basis of Poisson distribution, with a log link.²⁶ The differences in the treatment-completion rates and the risk differences for adverse events, with 95% confidence intervals, were calculated with a binomial distribution with an identity link, with the use of generalized estimating equations. If there were no events, risk differences were estimated with the use of the method of Newcombe.²⁷ When superiority was not found, noninferiority with regard to rates of active tuberculosis was assessed by comparing the upper limit of the confidence interval of the rate difference to the prespecified margin.^{28,29}

Interim analyses for safety were performed after 25%, 50%, and 75% of the participants had been enrolled, and the analyses were reviewed by the data and safety monitoring board. Full details of the trial design and analyses are provided in the protocol and the statistical analysis plan. All the analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS**TRIAL PARTICIPANTS**

The treatment-phase results in the 847 participants who were included in the earlier safety (phase 2) trial have been reported previously¹⁷ and are not repeated here. In those participants, only the post-treatment outcomes of active tuberculosis are reported here. In the phase 3 trial, we assessed 16,907 potential participants from October 2009 through December 2014, of whom 6063 underwent randomization (Fig. 1). Of these, 37 participants were excluded after randomization because they were close contacts of patients with active tuberculosis that was caused by isolates resistant to isoniazid or rifampin and 14 withdrew consent, which left 6012 adults in the modified intention-to-treat analysis. Of these, 5744 participants (95.5%) completed 28 months of follow-up after treatment. Of the 847 participants who had been in the safety trial, 614 (72.5%) completed follow-up after treatment.

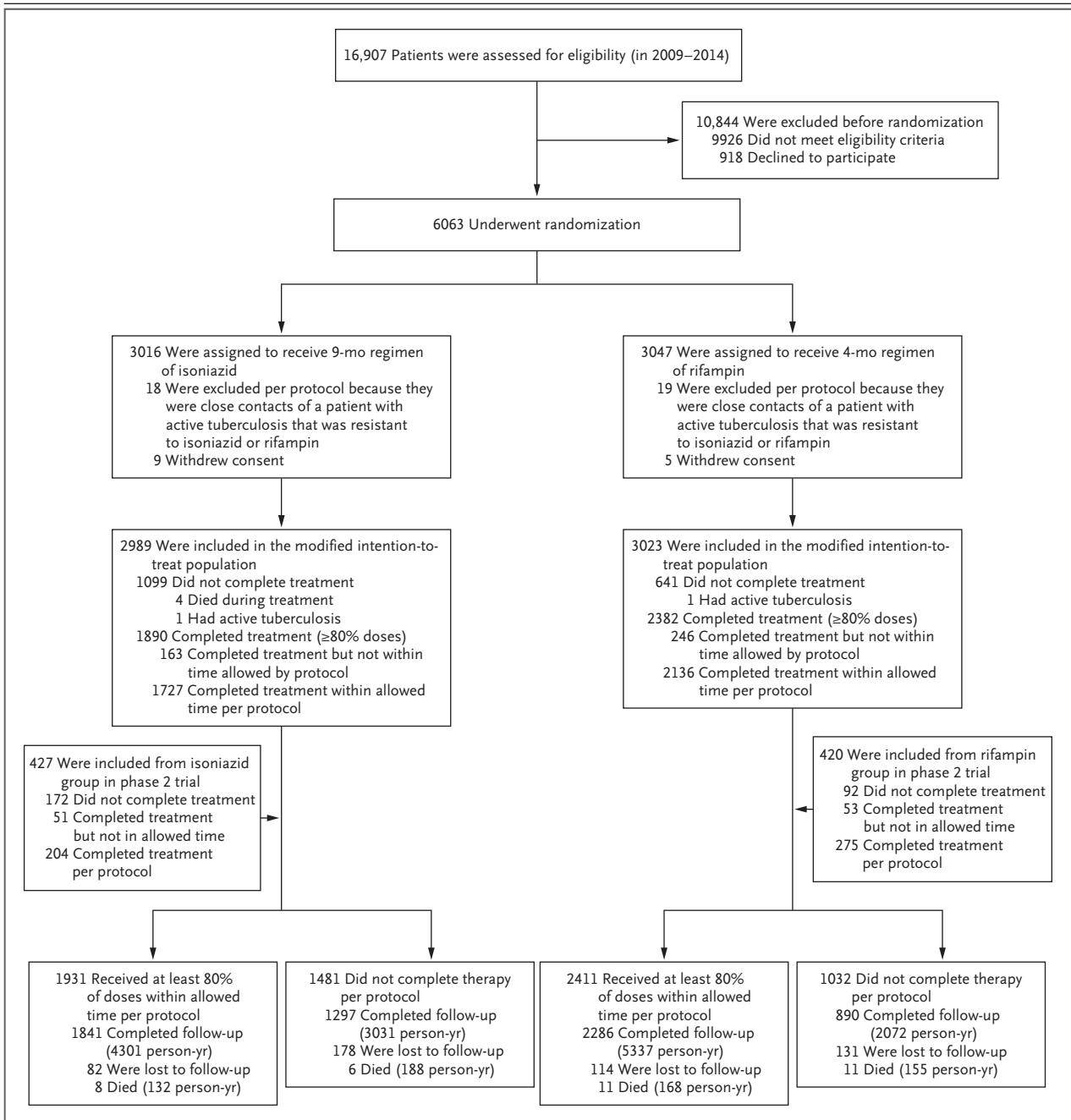


Figure 1. Adult Participants in Phase 2 and 3 Trials for Primary Outcome of Active Tuberculosis.

The number of patients from the phase 2 trial who completed the rifampin regimen per protocol was smaller than in the previous report¹⁷ because of the shorter allowed time in the current analysis. Among the patients in the isoniazid group who did not complete therapy per protocol, four died during treatment and are not included in this subgroup in the figure. In the two trial groups, the subgroups of patients who completed follow-up exclude patients in whom active tuberculosis developed. The deaths that are listed in the bottom row of boxes were deemed not to be related to tuberculosis.

The demographic and clinical characteristics of the participants in the two groups of the phase 3 trial are shown in Table 1. More than 70% of the participants were close contacts of someone with tuberculosis, and 854 of the total 6012 participants (14.2%) lived with at least one other trial participant. Table S1 in the Supplementary Appendix presents the characteristics of the participants, according to trial group, in the phase 2 and 3 trials combined.

The rate of treatment completion in the phase 3 trial was significantly higher with the 4-month rifampin regimen than with the 9-month isoniazid regimen (difference, 15.1 percentage points; 95% confidence interval [CI], 12.7 to 17.4) (Table 2). Table S2 in the Supplementary Appendix shows the results regarding treatment completion for the phase 2 and 3 trials combined.

The most common reason for noncompletion of the treatment regimen was the participant's decision to stop taking the trial drug. There were significant differences in demographic and clinical characteristics between participants who completed therapy and those who did not, and there were also significant differences between participants who completed the full 28 months of follow-up and those who were lost to follow-up. Among the participants who did not complete therapy or follow-up, there were no significant differences in characteristics between the two trial groups. Details are provided in Tables S5 through S8 in the Supplementary Appendix.

EFFICACY

There were eight cases of confirmed active tuberculosis and nine cases of clinically diagnosed active tuberculosis during active follow-up in the phase 2 and 3 trials combined (Table 3). Seven of the eight patients with confirmed tuberculosis and five of the nine patients with clinically diagnosed tuberculosis had also been reported to the local tuberculosis authorities as having received a diagnosis of active tuberculosis, but no additional cases were detected by passive case-finding procedures.

The differences in rates between the rifampin group and the isoniazid group were as follows: for confirmed tuberculosis in the modified

intention-to-treat population, the difference was less than 0.01 cases per 100 person-years (95% CI, -0.14 to 0.16), which is equivalent to a difference in the cumulative incidence over the 28-month period of less than 0.02 (95% CI, -0.33 to 0.37). The difference for confirmed or clinically diagnosed tuberculosis in the modified intention-to-treat population was less than 0.01 cases per 100 person-years (95% CI, -0.23 to 0.22, which is equivalent to -0.54 to 0.51 over the 28-month period); and for confirmed or clinically diagnosed tuberculosis in the per-protocol analysis, the difference was -0.02 cases per 100 person-years (95% CI, -0.30 to 0.26, which is equivalent to -0.70 to 0.61 over the 28-month period). Among the phase 3 trial participants who completed therapy per the protocol, the rate difference between the rifampin group and the isoniazid group for confirmed plus clinically diagnosed tuberculosis was -0.02 cases per 100 person-years (95% CI, -0.33 to 0.29, which is equivalent to -0.77 to 0.68 over the 28-month period) (Table 4).

In all these analyses, the upper boundary of the 95% confidence interval for the difference in the rates of confirmed active tuberculosis or of confirmed or clinically diagnosed tuberculosis was less than the prespecified margin for non-inferiority. However, the rifampin regimen was not superior to the isoniazid regimen.

DRUG RESISTANCE

Among the eight participants with confirmed active tuberculosis, drug-susceptibility test results were not available for four (three cases were diagnosed on the basis of histologic evidence of necrotizing granulomas, and cultures were contaminated in the fourth), two had susceptibility to all drugs tested, and isolates obtained from two participants showed drug resistance. One participant received a diagnosis of isoniazid-resistant active tuberculosis 8 weeks after starting isoniazid, and the other received a diagnosis of active tuberculosis less than 2 months after the completion of the 4-month rifampin regimen. The isolate that was obtained from this patient showed resistance to rifampin, according to Xpert MTB/RIF testing, although the isolate was

Table 1. Characteristics of the Participants in the Phase 3 Trial (Modified Intention-to-Treat Population).*

Characteristic	Isoniazid (N=2989)	Rifampin (N=3023)	Total (N=6012)
Country of trial center — no. (%)			
Australia	91 (3.0)	100 (3.3)	191 (3.2)
Benin	574 (19.2)	576 (19.1)	1150 (19.1)
Brazil	447 (15.0)	441 (14.6)	888 (14.8)
Canada	524 (17.5)	518 (17.1)	1042 (17.3)
Ghana	181 (6.1)	187 (6.2)	368 (6.1)
Guinea	428 (14.3)	444 (14.7)	872 (14.5)
Indonesia	432 (14.5)	423 (14.0)	855 (14.2)
Saudi Arabia	27 (0.9)	34 (1.1)	61 (1.0)
South Korea	285 (9.5)	300 (9.9)	585 (9.7)
Age — yr	38.5±13.8	38.3±14.0	38.4±13.9
Age group — no. (%)			
18–35 yr	1399 (46.8)	1421 (47.0)	2820 (46.9)
36–50 yr	974 (32.6)	977 (32.3)	1951 (32.5)
51–90 yr	616 (20.6)	625 (20.7)	1241 (20.6)
Male sex — no. (%)	1252 (41.9)	1208 (40.0)	2460 (40.9)
Median height (interquartile range) — m	1.6 (1.6–1.7)	1.6 (1.6–1.7)	1.6 (1.6–1.7)
Median weight (interquartile range) — kg	63.0 (55.0–73.0)	63.0 (55.0–74.0)	63.0 (55.0–73.0)
Median body-mass index (interquartile range)†	23.8 (21.0–27.0)	24.0 (21.0–27.0)	23.9 (21.0–27.0)
Reaction size on tuberculin skin test — no. (%)‡			
5–9 mm	312 (10.4)	302 (10.0)	614 (10.2)
10–14 mm	1102 (36.9)	1086 (35.9)	2188 (36.4)
≥15 mm	1525 (51.0)	1590 (52.6)	3115 (51.8)
No tuberculin skin test and IGRA-positive	50 (1.7)	45 (1.5)	95 (1.6)
Risk factor as indication for treatment — no. (%)			
HIV infection	123 (4.1)	119 (3.9)	242 (4.0)
Confirmed active tuberculosis in close contact§	2146 (71.8)	2102 (69.5)	4248 (70.7)
Confirmed active tuberculosis in casual contact	348 (11.6)	398 (13.2)	746 (12.4)
Other immunosuppressive condition or therapy¶	95 (3.2)	100 (3.3)	195 (3.2)
Upper-lobe fibronodular disease with area ≥2 cm ²	2 (0.1)	6 (0.2)	8 (0.1)
Combined risk factors — no. (%)			
Tuberculin skin test result of 10–14 mm and two of four risk factors	45 (1.5)	57 (1.9)	102 (1.7)
Tuberculin skin test result of ≥15 mm or IGRA-positive and one of four risk factors	230 (7.7)	241 (8.0)	471 (7.8)
Result on chest radiography — no. (%)			
Normal	2350 (78.6)	2365 (78.2)	4715 (78.4)
Apical or upper-lobe fibronodular abnormality			
≥2 cm ²	79 (2.6)	79 (2.6)	158 (2.6)
<2 cm ²	68 (2.3)	75 (2.5)	143 (2.4)
Granuloma	95 (3.2)	85 (2.8)	180 (3.0)
Costophrenic angle blunting	15 (0.5)	18 (0.6)	33 (0.5)

Table 1. (Continued.)

Characteristic	Isoniazid (N = 2989)	Rifampin (N = 3023)	Total (N = 6012)
Hilar lymph-node enlargement	47 (1.6)	55 (1.8)	102 (1.7)
Other possible tuberculosis-related abnormality	56 (1.9)	68 (2.2)	124 (2.1)
Abnormal result but not tuberculosis-related	279 (9.3)	278 (9.2)	557 (9.3)

* Plus–minus values are means \pm SD. There were no significant differences between the two trial groups at the 0.05 significance level. Percentages may not total 100 because of rounding. The characteristics of the participants in the phase 2 trial have been reported by Menzies et al.¹⁶ Table S1 in the Supplementary Appendix shows the characteristics of the participants in the phase 2 and 3 trials combined. HIV denotes human immunodeficiency virus.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ A total of 95 participants did not undergo a tuberculin skin test but had a positive interferon- γ -release assay (IGRA).

§ Close contacts were defined as having at least 4 hours per week of contact with a patient with confirmed active pulmonary tuberculosis. Of the close contacts, 854 (14.2% of all the participants) lived in the same household as at least 1 other trial participant, of whom 436 had been randomly assigned to the 9-month isoniazid regimen and 418 had been randomly assigned to the 4-month rifampin regimen.

¶ Other immune-suppressive condition or therapy was defined as diabetes, tumor necrosis factor α -inhibitor therapy, or renal failure.

|| The four factors were the following: born or living in a country with an incidence of tuberculosis or more than 100 cases per 100,000 population; Aboriginal Canadian living on reserve; body-mass index of less than 19; and an abnormal result on radiography of the chest that was consistent with past tuberculosis infection (upper-lobe fibronodular disease with area of <2 cm² or granulomas, calcified hilar lymph nodes, costophrenic angle blunting, or apical cap).

pansusceptible on traditional phenotypic testing. These two participants were both household contacts of participants with new cases of active tuberculosis who had been enrolled at sites where the diagnosis of index cases was based on smear microscopy alone, so drug-susceptibility results were not available for either index case. All the participants with active tuberculosis, including the two with drug-resistant isolates, were treated successfully and remained free from disease according to clinical and imaging assessments for at least 1 year after the end of treatment.

SAFETY

To account for the potential problem of differential ascertainment, owing to the fact that the duration of the isoniazid regimen was longer than the duration of the rifampin regimen, we estimated rate differences for adverse events that occurred during the first 146 days after randomization. The rifampin group had significantly lower rates of adverse events of grades 3 to 5 than the isoniazid group in analyses that included all such adverse events (rate difference, -1.1 percentage points; 95% CI, -1.9 to -0.4) and in analyses that included only adverse events that were considered by the independent panel to be related to the trial drug (-1.0 percentage point; 95% CI, -1.6 to -0.4) (Table 5).

Drug-induced hepatitis was the most common adverse event of grade 3 or 4 overall and was significantly less frequent in the rifampin group than in the isoniazid group in analyses that included all such events, that included only events that were adjudicated as being possibly or probably related to the trial drug, and that included only events occurring in the first 146 days. Table S3 in the Supplementary Appendix shows the results regarding total adverse events in the phase 2 and 3 trials combined, and Table S4 in the Supplementary Appendix shows the results for other types of adverse events.

DISCUSSION

In this trial involving more than 6800 adults in nine countries, a 4-month regimen of rifampin was not inferior to a 9-month regimen of isoniazid in preventing active tuberculosis; however, the rifampin regimen was also not superior to the isoniazid regimen. The rate of treatment completion was higher in the rifampin group than in the isoniazid group. In the rifampin group, there was a significantly lower incidence of adverse events of grades 3 to 5, particularly hepatotoxic adverse events, than in the isoniazid group in analyses that included all such adverse events, that included only events that were adjudicated as being drug-related, and that included

Table 2. Completion of Treatment in the Phase 3 Trial (Modified Intention-to-Treat Population).*

Variable	Isoniazid (N = 2989)	Rifampin (N = 3023)	Difference (95% CI)	P Value
			<i>percentage points</i>	
Treatment completed — no. (%) [†]	1890 (63.2)	2382 (78.8)	15.1 (12.7–17.4)	<0.001
Within allowed time	1727 (57.8)	2136 (70.7)	12.1 (9.6–14.6)	<0.001
Not within time allowed by protocol	163 (5.5)	246 (8.1)	2.8	
Treatment not completed for any reason — no. (%) [‡]	1099 (36.8)	641 (21.2)	-15.1	
Death during treatment period deemed to be not related to therapy	3 (0.1)	0	-0.1	
Diagnosis of active tuberculosis during treatment period	1 (<0.1)	1 (<0.1)	<0.1	
Never started therapy, by participant's decision	180 (6.0)	136 (4.5)	-2.6	
Therapy stopped permanently for event, and participant had not already completed treatment				
Grade 1–4 event	143 (4.8)	68 (2.2)	-2.6	
Grade 3 or 4 event	90 (3.0)	37 (1.2)	-1.8	
Therapy started, but participant decided to stop treatment [§]	772 (25.8)	436 (14.4)	-11.4	
Received 50–79% of doses	188 (6.3)	142 (4.7)	-1.7	
Received 1–49% of doses	585 (19.6)	295 (9.8)	-9.6	
Median no. of doses taken by participants who did not complete treatment but received ≥1 dose (interquartile range)	84 (33–122)	30 (22–60)	—	

* The modified intention-to-treat population included eligible patients who underwent randomization. The completion of treatment among the participants in the phase 2 trial is described by Menzies et al.¹⁶ Table S2 in the Supplementary Appendix shows the results regarding completion of treatment according to trial group among participants in the phase 2 and 3 trials combined. The differences in the treatment-completion rates and the risk differences for adverse events, with 95% confidence intervals, were calculated with a binomial distribution with an identity link, with the use of generalized estimating equations to account for potential clustering within families; hence, the differences may not sum as expected. This approach accounts for the correlation of participants coming from the same household. Significance testing was performed only for the two outcomes that were judged a priori to be the most important.

[†] Completion of treatment was defined as receipt of at least 80% of doses. The time allowed per protocol was 120% of 4 months (for the rifampin group) or 9 months (for the isoniazid group). A total of 11 patients had adverse events of grade 3 or 4 but had already received more than 80% of the medication doses. An additional 5 participants stopped owing to adverse events of grade 3 or 4 but then restarted and completed therapy. Data from all 16 of these participants are shown in this table as completed.

[‡] A total of 91 patients who did not complete the trial therapy started alternative therapy for latent tuberculosis infection; of these patients, 63 had stopped the trial therapy because of an adverse event and 7 never started the trial therapy (Table S2B in the Supplementary Appendix).

[§] Data include three patients who stopped owing to adverse events and then restarted but then later decided to stop trial therapy.

only events that occurred in the first 146 days after randomization.

This trial had a number of strengths. Selection bias should have been minimized by randomization and by the absence of differences in the demographic and clinical characteristics between the two trial groups among the participants who did not complete therapy and among those who did not complete follow-up. Of the 6859 participants who were included in the modified intention-to-treat analysis from the phase 2 and 3 trials, only 7.9% did not complete 28 months of follow-up, although the rate of loss to follow-up was higher

in the phase 2 trial than in the phase 3 trial. This result should have enhanced our likelihood of detecting active tuberculosis, which was further enhanced by the passive case-finding strategy to detect active tuberculosis among participants who had been lost to follow-up. The large sample size provided adequate power to detect clinically meaningful differences between the two regimens. The trial sites were in settings that had widely varying levels of resources, which may enhance the generalizability of the results. Active tuberculosis and adverse events were assessed according to detailed protocols for inves-

Table 3. Primary End Point of Occurrence of Active Tuberculosis among All Participants.*

Variable	Isoniazid	Rifampin	Rate Difference (95% CI)	P Value
Modified intention-to-treat analysis				
No. of participants	3416	3443	—	—
Completed 28 mo of follow-up — no. (%)	3138 (91.9)	3178 (92.3)	0.4 (−0.9 to 1.7)	0.57
Total person-yr of follow-up	7652	7732	—	—
No. of confirmed or clinically diagnosed cases of active tuberculosis†	9	8	—	—
Microbiologically confirmed active tuberculosis	4	4	—	—
Clinically diagnosed tuberculosis‡	5	4	—	—
No. of cases of active tuberculosis per 100 person-yr (95% CI)				
Confirmed cases	0.05 (0.02 to 0.14)	0.05 (0.02 to 0.14)	<0.01 (−0.14 to 0.16)	0.76
Confirmed or clinically diagnosed cases	0.11 (0.05 to 0.21)	0.10 (0.05 to 0.21)	<0.01 (−0.23 to 0.22)	0.98
Per-protocol analysis				
No. of participants	1931	2411	—	—
Total no. of person-yr of follow-up	4423	5503	—	—
No. of confirmed or clinically diagnosed cases of active tuberculosis	5	5	—	—
Microbiologically confirmed active tuberculosis	1	3	—	—
Clinically diagnosed tuberculosis‡	4	2	—	—
No. of confirmed or clinically diagnosed cases of active tuberculosis per 100 person-yr (95% CI)	0.11 (0.05 to 0.27)	0.09 (0.04 to 0.22)	−0.02 (−0.30 to 0.26)	0.77

* This analysis was the planned primary analysis combining the incidence of active tuberculosis among participants in the phase 3 (effectiveness) trial and the phase 2 (safety) trial. A total of 847 participants from the phase 2 trial contributed 1686 person-years of follow-up to the modified intention-to-treat analysis, and 479 contributed 1032 person-years to the per-protocol analysis. The per-protocol analysis included only participants who received at least 80% of the doses in allowed time. The rate difference and P value were estimated by a Poisson model with the use of generalized estimating equations with a log link, and the inclusion of the log of person-time as an offset. An exchangeable correlation structure with robust standard errors was used to account for the correlation of participants coming from the same household (Proc Genmod, then the NLEstimate macro in SAS software). Differences between rates of follow-up are shown in percentage points, and differences between rates of active tuberculosis are shown in numbers of cases per 100 person-years. Person-years were based on the total amount of follow-up from randomization until 28 months, date of last contact, or death or occurrence of active tuberculosis.

† All the cases of active tuberculosis were ascertained by means of active follow-up. Passive case-finding procedures did not detect any additional tuberculosis cases but did re-detect seven of the eight confirmed cases and five of the nine clinically diagnosed cases.

‡ The cases of clinically diagnosed tuberculosis were judged to be probable cases of active tuberculosis by the review panel.

tigation and management and were adjudicated in a blinded fashion by independent panels. The trial drugs were administered by the participants themselves daily, so treatment completion and the detection of adverse events are presumed to be less affected by the mode of administration than would be the case in trials that compared participant-administered isoniazid with administration of isoniazid–rifampin that was directly observed by health personnel.^{30–33}

This trial has a number of important limitations. The open-label design may have introduced bias in the ascertainment of treatment completion or adverse events; however, this approach

has been used previously in trials of rifamycin-based regimens^{30–34} to take advantage of their shorter duration. To safeguard against bias, all the final diagnoses of adverse events and active tuberculosis were made by independent review panels whose members were unaware of the trial-group assignments. Treatment completion was based on the assessments of the patients and providers in addition to pill counts, which are not highly reliable methods.^{35,36} In total, only 255 participants with HIV infection were enrolled in either phase 2 or phase 3 of the trial, which reduces the applicability of our findings to this population.

Table 4. Occurrence of Active Tuberculosis in the Phase 3 Trial.*

Variable	Isoniazid	Rifampin	Rate Difference (95% CI)	P Value
Modified intention-to-treat analysis				
No. of participants	2989	3023		
Completed 28 mo of follow-up — no. (%)	2839 (95.0)	2863 (94.7)	-0.4 (-1.5 to 0.8)	0.53
Total no. of person-yr of follow-up†	6816	6882	—	—
No. of confirmed or clinically diagnosed cases of active tuberculosis‡	9	8	—	—
Microbiologically confirmed active tuberculosis	4	4	—	—
Clinically diagnosed tuberculosis	5	4	—	—
No. of confirmed cases of active tuberculosis per 100 person-yr (95% CI)	0.06 (0.02 to 0.16)	0.06 (0.02 to 0.16)	<0.01 (-0.18 to 0.18)	0.97
No. of confirmed or clinically diagnosed cases of active tuberculosis per 100 person-yr (95% CI)	0.13 (0.07 to 0.25)	0.12 (0.06 to 0.23)	-0.02 (-0.28 to 0.24)	0.82
Per-protocol analysis§				
No. of participants	1727	2136	—	—
Total no. of person-yr of follow-up†	3991	4909	—	—
No. of confirmed or clinically diagnosed cases of active tuberculosis	5	5	—	—
Microbiologically confirmed active tuberculosis	1	3	—	—
Clinically diagnosed tuberculosis	4	2	—	—
No. of confirmed or clinically diagnosed cases of active tuberculosis per 100 person-yr (95% CI)	0.13 (0.05 to 0.30)	0.10 (0.04 to 0.24)	-0.02 (-0.33 to 0.29)	0.78

* Percentages were calculated on the basis of the modified intention-to-treat population. Differences between rates of follow-up are shown in percentage points, and differences between rates of active tuberculosis are shown in numbers of cases per 100 person-years.

† Person-years were based on the total amount of follow-up from randomization until 28 months, the date of last contact, or death or occurrence of active tuberculosis.

‡ All the cases of active tuberculosis were ascertained with the use of active follow-up. Passive case-finding procedures did not detect any additional tuberculosis cases but did re-detect seven of the eight confirmed cases and five of the nine clinically diagnosed cases. Cases of clinically diagnosed tuberculosis were judged to be probable cases of active tuberculosis by the review panel.

§ The per-protocol population included participants who received at least 80% of the doses.

A further limitation was the low event rate of active tuberculosis in each group in the modified intention-to-treat analysis, as has been seen in other trials.^{30,31} This makes the conclusions less robust. However, given the observed rate of confirmed or clinically diagnosed tuberculosis of 0.11 cases per 100 person-years among participants who completed the 9-month isoniazid regimen, and assuming 90% efficacy of this regimen,⁹ we would expect a rate of 1.2 cases per 100 person-years in the untreated population, which, if extrapolated over the 28-month duration of the trial, would be equivalent to a cumulative incidence of 2.8% — close to the anticipated cumulative incidence of 3%. Rates of disease were lower than expected among participants who did not complete treatment, in part because

the completion rate was higher than expected in the two trial groups and also because the participants who did not complete treatment received the therapy for a median of 3 months in the isoniazid group and this duration of isoniazid therapy is known to have modest efficacy.¹⁹ Another factor may have been the very small number of HIV-infected persons — a population that in other trials involving participants with latent tuberculosis infection had much higher rates of active disease.^{32,34,37,38}

This trial adds to the mounting evidence of benefits of rifamycin-containing regimens of 3 or 4 months' duration. Numerous other observational and experimental studies have shown significantly higher rates of treatment completion with the shorter rifamycin-based regimens than

Table 5. Adverse Events in the Phase 3 Trial (Safety Population).*

Variable	Isoniazid (N = 2809)	Rifampin (N = 2887)	Risk Difference (95% CI) <i>percentage points</i>	P Value
Total no. of events reviewed by data and safety monitoring board (%)	162 (5.8)	80 (2.8)	-3.0 (-4.1 to -2.0)	<0.001
Adverse event, with trial drug restarted without symptom recurrence — no. of patients (%)				
Grade 1 or 2 adverse event	4 (0.1)	5 (0.2)	<0.1 (-0.2 to 0.2)	0.77
Grade 3 or 4 adverse event†	4 (0.1)	1 (<0.1)	-0.1 (-0.3 to -0.0)	0.10
Adverse event, with trial drug stopped permanently — no. of patients (%)‡	153 (5.4)	74 (2.6)	-2.9 (-3.9 to -1.9)	<0.001
Grade 1 or 2 adverse event	53 (1.9)	31 (1.1)	-0.8 (-1.4 to -0.2)	0.01
Grade 3 event of pregnancy only§	38 (1.4)	21 (0.7)	-0.7 (-1.2 to -0.1)	0.02
All other, nonpregnancy-related grade 3–5 events¶	62 (2.2)	22 (0.8)	-1.4 (-2.1 to -0.8)	<0.001
Grade 3 or 4 hepatotoxic event	50 (1.8)	8 (0.3)	-1.5 (-2.0 to -1.0)	<0.001
Death**	4 (0.1)	0	-0.1 (-0.3 to 0.0)	0.045
Trial drug stopped permanently for grade 3–5 event judged by panel as possibly or probably related to trial drug — no. of patients (%)				
Grade 3–5 adverse event of any type	59 (2.1)	24 (0.8)	-1.3 (-1.9 to -0.6)	<0.001
Grade 3 or 4 hepatotoxic event	49 (1.7)	8 (0.3)	-1.5 (-2.0 to -0.9)	<0.001
Death††	1 (<0.1)	0	<0.1 (-0.1 to 0.0)	0.31
Trial drug stopped permanently for grade 3–5 event that occurred during first 146 days after randomization — no. of patients (%)‡‡				
Any event, regardless of whether it was judged to be related to trial drug	73 (2.6)	43 (1.5)	-1.1 (-1.9 to -0.4)	0.003
Any event judged as being possibly or probably related to the trial drug	51 (1.8)	24 (0.8)	-1.0 (-1.6 to -0.4)	0.001
Grade 3 or 4 hepatotoxic event	41 (1.5)	8 (0.3)	-1.2 (-1.7 to -0.7)	<0.001

* All the adverse events were reviewed by a three-member independent review panel whose members were unaware of the trial-group assignments. Detailed protocols regarding the management and grading of adverse events are provided in the Supplementary Appendix. Severity was graded according to published criteria from the American Thoracic Society for hepatotoxic events²¹ and from the National Cancer Society for all other events.²² Percentages were calculated on the basis of the total number of participants who took at least one dose of a trial drug (safety population). The risk difference and P value were estimated by a binomial distribution model with an identity link and generalized estimating equations. An exchangeable correlation structure and robust standard errors were used to account for correlation of patients coming from the same family. P values were not estimated for events that were judged as not being an adverse event or as not being related to the trial drugs. The occurrence of adverse events among participants in the phase 2 trial was reported by Menzies et al.¹⁶ The occurrence of adverse events among participants in the phase 2 and 3 trials combined are shown in Table S3 in the Supplementary Appendix.

† Data include three patients who were pregnant.

‡ A total of 64 patients started alternative therapy for latent tuberculosis infection, after stopping the trial drug permanently because of an adverse event.

§ Pregnancy was considered to be possibly or probably related to the trial by the independent panel if the participant was taking hormonal contraception and if conception occurred after the start of the trial drug and up to 1 month after the end of the trial-drug regimen. Data include six participants who had already received at least 80% of doses by the time the pregnancy was recognized. These patients were considered to have completed therapy and also to have had an adverse event of grade 3. Of the data shown, the panel judged that only four of these pregnancies were probably related to the trial drug.

¶ Five participants had a nonpregnancy-related adverse event of grade 3 or 4 that was considered to be related to the trial drug, but they had already completed the treatment regimen (received ≥80% of doses).

|| Details regarding other types of adverse events are provided in Table S4 in the Supplementary Appendix.

** If there were no events, the 95% confidence intervals were estimated with the use of the method of Newcombe.²⁷

†† If there were no events, the 95% confidence intervals were estimated with the use of the method of Newcombe,²⁷ and the P value (as determined from chi-square testing) was 0.31. In an analysis in which only one participant per household was counted (a crude method and an extreme assumption to account for clustering), the confidence interval was the same, and the P value was 0.31.

‡‡ This analysis was performed to account for differential ascertainment, owing to the longer duration of the isoniazid regimen, by limiting the adverse events to those that occurred only in the maximum allowed time for the rifampin regimen (120% of 4 months). The grade 3 or 4 hepatotoxic events reported here were all were judged by the panel as being possibly or probably related to the trial drug.

with 9 months of isoniazid therapy^{12-14,16,17,31} and efficacy that is at least equivalent.^{8,31,32,39,40} The findings of this trial also corroborate evidence from other trials^{17,31} and observational studies^{12,13} that rifamycin-based regimens are associated with substantially lower rates of hepatotoxic effects — a major limitation of isoniazid²¹ — and with lower overall rates of adverse events of grade 3 or 4.^{12,13,17} However, all these earlier studies may have overestimated the relative safety of 4 months of rifampin owing to ascertainment bias.

In conclusion, a 4-month regimen of rifampin was not inferior to a 9-month regimen of isoniazid for the prevention of active tuberculosis. The rifampin group had a significantly higher rate of treatment completion and fewer drug-related adverse events of grades 3 to 5.

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APPENDIX

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REFERENCES

- Global tuberculosis report 2015. Geneva: World Health Organization, 2015. (Publication no. WHO/HTM/TB/2015.22) (http://www.who.int/tb/publications/global_report/gtbr15_main_text.pdf).
- Houben RM, Dodd PJ. The global burden of latent tuberculosis infection: a re-estimation using mathematical modelling. *PLoS Med* 2016;13(10):e1002152.
- Reid A, Grant AD, White RG, et al. Accelerating progress towards tuberculosis elimination: the need for combination treatment and prevention. *Int J Tuberc Lung Dis* 2015;19:5-9.
- Uplekar M, Weil D, Lonnroth K, et al. WHO's new end TB strategy. *Lancet* 2015; 385:1799-801.
- Lönnroth K, Migliori GB, Abubakar I, et al. Towards tuberculosis elimination: an action framework for low-incidence countries. *Eur Respir J* 2015;45:928-52.
- American Thoracic Society. Targeted tuberculin testing and treatment of latent tuberculosis infection: this official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999: this is a joint statement of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC): this statement was endorsed by the Council of the Infectious Diseases Society of America. (IDSA), September 1999, and the sections of this statement. *Am J Respir Crit Care Med* 2000;161:S221-S247.
- Menzies D, Alvarez GG, Khan K. Treatment of latent tuberculosis infection. In: Menzies D, ed. Canadian tuberculosis standards. 7th ed. Ottawa: Public Health Agency of Canada, Canadian Thoracic Society, 2014:133-69.
- World Health Organization. Guidelines on the management of latent tuberculosis infection. 2015 (<http://www.who.int/tb/publications/latent-tuberculosis-infection/en/>).
- Comstock GW. How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? *Int J Tuberc Lung Dis* 1999;3:847-50.
- Hirsch-Moverman Y, Daftry A, Franks J, Colson PW. Adherence to treatment for latent tuberculosis infection: systematic review of studies in the US and Canada. *Int J Tuberc Lung Dis* 2008;12:1235-54.
- Kopanoff DE, Snider DE Jr, Caras GJ. Isoniazid-related hepatitis: a U.S. Public Health Service cooperative surveillance study. *Am Rev Respir Dis* 1978;117:991-1001.
- Page KR, Sifakis F, Montes de Oca R, et al. Improved adherence and less toxicity with rifampin vs isoniazid for treatment

- of latent tuberculosis: a retrospective study. *Arch Intern Med* 2006;166:1863-70.
13. Lardizabal A, Passannante M, Kojakali F, Hayden C, Reichman LB. Enhancement of treatment completion for latent tuberculosis infection with 4 months of rifampin. *Chest* 2006;130:1712-7.
 14. Haley CA, Stephan S, Vossell LF, Sherfy EA, Laserson KF, Kainer MA. Successful use of rifampicin for Hispanic foreign-born patients with latent tuberculosis infection. *Int J Tuberc Lung Dis* 2008;12:160-7.
 15. Hong Kong Chest Service Tuberculosis Research Centre, Madras/British Medical Research Council. A double-blind placebo-controlled clinical trial of three antituberculosis chemoprophylaxis regimens in patients with silicosis in Hong Kong. *Am Rev Respir Dis* 1992;145:36-41.
 16. Menzies D, Dion MJ, Rabinovitch B, Mannix S, Brassard P, Schwartzman K. Treatment completion and costs of a randomized trial of rifampin for 4 months versus isoniazid for 9 months. *Am J Respir Crit Care Med* 2004;170:445-9.
 17. Menzies D, Long R, Trajman A, et al. Adverse events with 4 months of rifampin therapy or 9 months of isoniazid therapy for latent tuberculosis infection: a randomized trial. *Ann Intern Med* 2008;149:689-97.
 18. Aspler A, Long R, Trajman A, et al. Impact of treatment completion, intolerance and adverse events on health system costs in a randomised trial of 4 months rifampin or 9 months isoniazid for latent TB. *Thorax* 2010;65:582-7.
 19. International Union Against Tuberculosis Committee on Prophylaxis. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. *Bull World Health Organ* 1982;60:555-64.
 20. Comstock GW, Ferebee SH. How much isoniazid is needed for prophylaxis? *Am Rev Respir Dis* 1970;101:780-2.
 21. Saukkonen JJ, Cohn DL, Jasmer RM, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med* 2006;174:935-52.
 22. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE), v4.0. 2009 (https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf).
 23. Fox GJ, Barry SE, Britton WJ, Marks GB. Contact investigation for tuberculosis: a systematic review and meta-analysis. *Eur Respir J* 2013;41:140-56.
 24. Ferebee SH. Controlled chemoprophylaxis trials in tuberculosis: a general review. *Bibl Tuberc* 1970;26:28-106.
 25. Morrison J, Pai M, Hopewell PC. Tuberculosis and latent tuberculosis infection in close contacts of people with pulmonary tuberculosis in low-income and middle-income countries: a systematic review and meta-analysis. *Lancet Infect Dis* 2008;8:359-68.
 26. SAS Institute. Estimating nonlinear combinations of model parameters (<http://support.sas.com/kb/58/775.html>).
 27. Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. *Stat Med* 1998;17:873-90.
 28. Rothmann M, Li N, Chen G, Chi GY, Temple R, Tsou HH. Design and analysis of non-inferiority mortality trials in oncology. *Stat Med* 2003;22:239-64.
 29. Kaul S, Diamond GA. Good enough: a primer on the analysis and interpretation of noninferiority trials. *Ann Intern Med* 2006;145:62-9.
 30. Villarino ME, Scott NA, Weis SE, et al. Treatment for preventing tuberculosis in children and adolescents: a randomized clinical trial of a 3-month, 12-dose regimen of a combination of rifapentine and isoniazid. *JAMA Pediatr* 2015;169:247-55.
 31. Sterling TR, Villarino ME, Borisov AS, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. *N Engl J Med* 2011;365:2155-66.
 32. Martinson NA, Barnes GL, Moulton LH, et al. New regimens to prevent tuberculosis in adults with HIV infection. *N Engl J Med* 2011;365:11-20.
 33. Schechter M, Zajdenverg R, Falco G, et al. Weekly rifapentine/isoniazid or daily rifampin/pyrazinamide for latent tuberculosis in household contacts. *Am J Respir Crit Care Med* 2006;173:922-6.
 34. Sterling TR, Scott NA, Miro JM, et al. Three months of weekly rifapentine and isoniazid for treatment of *Mycobacterium tuberculosis* infection in HIV-coinfected persons. *AIDS* 2016;30:1607-15.
 35. Cuneo WD, Snider DE Jr. Enhancing patient compliance with tuberculosis therapy. *Clin Chest Med* 1989;10:375-80.
 36. Sumartojo E. When tuberculosis treatment fails: a social behavioral account of patient adherence. *Am Rev Respir Dis* 1993;147:1311-20.
 37. Churchyard GJ, Fielding K, Charalambous S, et al. Efficacy of secondary isoniazid preventive therapy among HIV-infected Southern Africans: time to change policy? *AIDS* 2003;17:2063-70.
 38. Chaisson RE, Clermont HC, Holt EA, et al. Six-month supervised intermittent tuberculosis therapy in Haitian patients with and without HIV infection. *Am J Respir Crit Care Med* 1996;154:1034-8.
 39. Ena J, Valls V. Short-course therapy with rifampin plus isoniazid, compared with standard therapy with isoniazid, for latent tuberculosis infection: a meta-analysis. *Clin Infect Dis* 2005;40:670-6.
 40. Zenner D, Beer N, Harris RJ, Lipman MC, Stagg HR, van der Werf MJ. Treatment of latent tuberculosis infection: an updated network meta-analysis. *Ann Intern Med* 2017;167:248-55.

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