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Adverse Events with 4 Months of Rifampin Therapy or 9 Months of Isoniazid Therapy for Latent Tuberculosis Infection

A Randomized Trial

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Background: Treatment of latent tuberculosis infection with isoniazid for 9 months is complicated by poor patient adherence and the need for close follow-up of side effects, especially hepatotoxicity. Shorter and safer regimens are needed.

Objective: To compare the frequency of adverse events and treatment completion in 2 treatment regimens for latent tuberculosis infection.

Design: Multicenter, randomized, open-label trial.

Setting: Tuberculosis clinics located in university hospitals in Canada, Brazil, and Saudi Arabia.

Patients: 847 patients without a contraindication for rifampin and requiring treatment for latent tuberculosis infection.

Intervention: Four months of daily rifampin therapy or 9 months of daily isoniazid therapy.

Measurements: Grade 3 to 4 drug-related adverse events resulting in drug discontinuation (primary outcome), and on-time treatment completion, grade 1 to 2 drug-related adverse events, and changes in liver enzymes and hematologic variables (secondary outcomes).

Results: Seventeen of 422 participants who started isoniazid therapy developed grade 3 to 4 adverse events compared with 7 of 418 who started rifampin therapy (risk difference [rifampin minus isoniazid], −2.3% [95% CI, −5% to −0.1%]; $P = 0.040$). Grade 3 or 4 hepatitis occurred in 16 of 422 isoniazid recipients compared with 3 of 418 rifampin recipients (risk difference, −3.1% [CI, −5% to −1%]; $P = 0.003$). Grade 1 or 2 adverse events attributed to study drugs occurred with similar frequency. Asymptomatic reduction in platelet and leukocyte counts were more frequent in rifampin recipients. More patients completed rifampin treatment (78%) than isoniazid treatment (60%) (difference, 18% [CI, 12% to 24%]; $P < 0.001$]).

Limitation: The study did not measure efficacy, and the open-label design may increase the chance of bias in ascertainment of adverse events.

Conclusion: Treatment of latent tuberculosis with 4 months of rifampin leads to fewer serious adverse events and better adherence than 9 months of isoniazid. These findings justify a large-scale trial to compare the efficacy of rifampin with that of isoniazid.

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After detection and treatment of active tuberculosis cases, the next priority in tuberculosis control is the diagnosis and treatment of persons with latent tuberculosis infection (LTBI) who are at increased risk for active tuberculosis. Treatment of such individuals can provide individual and public health benefits (1–4). The current recommended standard therapy in most countries is 9 months of isoniazid therapy (4, 5). The drug has more than 90% efficacy if taken the entire 9 months (6), but completion rates under routine practice conditions are about 50% or less (7–9). Another important disadvantage of isoniazid therapy is the occurrence of serious adverse events, particularly drug-induced hepatitis (10). Drug-induced hepatitis was not recognized as a complication of isoniazid therapy in early trials involving more than 50 000 participants (11), but it was a frequent and potentially severe problem after isoniazid was recommended for tuberculosis prevention in 1970 (12) and was subsequently used more widely (13, 14). This complication makes close monitoring necessary, increasing costs.

These problems have stimulated considerable interest in finding shorter and safer regimens for the treatment of LTBI (15). One alternative, 2 months of daily rifampin–pyrazinamide, was recommended in 2000 (4) on the basis of evidence from several trials (16–18). However, subsequent reports of severe and fatal hepatotoxicity (19, 20) have rendered this regimen unacceptable for most patients.

The remaining recommended alternative is 4 months of daily rifampin, but published outcome information is limited and systematic reviews on this regimen have not been done. In the only published trial that compared 3 months of daily rifampin therapy with 6 months of daily isoniazid therapy in 332 patients, efficacy and safety were similar (21). In 2 uncontrolled case series, 6 months of daily rifampin was well tolerated in 49 homeless persons in Boston (22) and in 157 high school students in California

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Context

Isoniazid is hepatotoxic and must be taken for 9 months by patients with latent tuberculosis infection.

Contribution

In this trial comparing 4 months of rifampin therapy with 9 months of isoniazid therapy, patients who took rifampin had fewer adverse events and were more likely to complete treatment.

Caution

The investigators did not compare efficacy of the 2 treatments.

Implication

These safety and adherence data justify a larger trial to compare the efficacy of rifampin and isoniazid for latent tuberculosis infection.

—The Editors

(23). Two nonrandomized studies have described better treatment completion and less hepatotoxicity with 4 months of rifampin than with 9 months of isoniazid under program conditions (8, 9). However, rifampin has been reported to cause other problems—notably drug interactions (24), a flu-like syndrome (24), and rare hematologic problems (immune-mediated thrombocytopenia and anemia) (25). Also, development of drug resistance is a theoretical concern.

Given the experience with isoniazid and 2 months of rifampin–pyrazinamide, both of which were thought to be safe on the basis of early studies but caused deaths when used more widely, we designed a multicenter, randomized trial to compare the frequency of serious adverse events and treatment completion rates in patients given 4 months of daily rifampin or 9 months of daily isoniazid for LTBI.

METHODS

Setting, Study Sample, and Randomization

This open-label trial was conducted at 9 university-affiliated hospitals: 7 in Canada and 1 each in Saudi Arabia and Brazil. We considered patients to be eligible if they were age 18 years or older and had a documented tuberculin skin test that met the criteria for a positive result (5) and if their primary treating physician initially recommended isoniazid for LTBI following national or international guidelines (4, 26, 27). Patients were ineligible if they were contacts of isoniazid- or rifampin-resistant cases (28), were allergic to isoniazid or rifamycins, or were taking concomitant medications that had clinically significant potential drug interactions that could not be easily managed. To ensure a realistic assessment of adverse events, we considered all other adults eligible, regardless of age or additional risk factors for adverse events, as long as their treating physician felt that therapy for LTBI was indicated. A Web-based program verified eligibility and randomly assigned participants (by using a random-number generator), after they signed informed consent, to 4 months of daily rifampin (10 mg per kg of body weight, up to 600 mg/d) or 9 months of daily isoniazid (5 mg/kg, up to 300 mg/d) in blocks of varying size, stratified by center. A team at the University of Sherbrooke, Sherbrooke, Quebec, Canada, prepared the Web-based program and allocation sequence.

Study personnel in the different centers enrolled and registered participants, obtained consent, verified assignment, and administered treatment. All study participants signed informed consent before randomization. Institutional review boards in each participating institution approved the study.

Processes and Outcomes

Patients were followed in routine fashion by their usual treating physician, who made all management decisions, including discontinuation of therapy. By study protocol, all patients had blood tests (complete blood count, liver aminotransferase levels [aspartate aminotransferase and alanine aminotransferase], and bilirubin level) before and after 1 and 2 months of therapy and were seen every month for the first 4 months of therapy and (for those receiving 9 months of isoniazid) at physician discretion every 6 weeks thereafter. Adverse events could be detected at any time throughout the course of therapy. When the treating physician suspected an adverse event and therapy was suspended, investigations, including blood tests, were performed according to study protocol. The treating physician decided whether to discontinue, rechallenge with, or restart the study therapy, although the protocol specified that participants with grade 3 or 4 adverse events (**Appendix Table 1**, available at www.annals.org) were not to be rechallenged. When all investigations were complete, and if therapy was permanently discontinued in response to the event, the patient's clinical course and results of investigations and rechallenge (if any) were made available to a 3-member independent review panel who were blinded to study drug. If therapy was resumed (for example, after resolution of a grade 1 or 2 adverse event) and the event did not recur, the patient's information was not reviewed by the panel.

Each review panel member had substantial experience and expertise in clinical and epidemiologic aspects of tuberculosis, and each independently judged the type and severity of the adverse events and its likely relationship to the study drug. We graded adverse events as recommended by the National Cancer Institute Common Terminology Criteria for Adverse Events, version 2.0 (29) (**Appendix Table 1**). Liver aminotransferase levels that increased to 5 to 10 or 3 to 10 times the upper limit of normal in the presence of compatible symptoms met criteria for grade 3 hepatotoxicity, whereas those that exceeded 10 times the upper limit of normal met criteria for grade 4 toxicity (30). In the event of disagreement, panel members re-reviewed

the information; if disagreement remained, the majority opinion was used.

The study's primary outcome was the frequency of grade 3 or 4 adverse events that resulted in study drug discontinuation and were judged by the review panel to be probably related to the drug (**Appendix Table 1**). The study's secondary outcome was on-time treatment completion, defined as taking more than 80% of doses within a maximum of 150 days for 4 months of rifampin or 301 days (43 weeks) for 9 months of isoniazid. Doses taken were measured with the Medical Event Monitoring System, an electronic device in the pill container cap that recorded the date and time of bottle opening (APREX Corporation, Fremont, California). Other secondary outcomes included grade 1 or 2 adverse events that were judged by the independent panel to be probably study drug–related and resulted in permanent discontinuation of therapy and changes in liver aminotransferase levels and leukocyte and platelet counts before and 1 and 2 months after beginning treatment.

Statistical Analysis

We initially calculated a trial sample size by assuming that the frequency of serious adverse events would be significantly higher with rifampin. We calculated that 630 patients per group would provide 90% power (2-sided $\alpha = 0.05$) to detect a difference between frequency of adverse events of 9% and 4% in the rifampin and isoniazid groups, respectively. This estimate also accounted for an anticipated 15% dropout rate during therapy. Because we were unsure about the actual frequency of adverse events with rifampin, we also noted that 630 patients per group provided 80% power to detect a statistically significant difference between rates of adverse events in the 2 groups if the event rates were 2% and 5% in the rifampin and isoniazid groups, respectively, and the dropout rate was 15%.

To ensure safety of study participants, we planned 3 interim analyses for when 25%, 50%, and 75% of the planned total sample size had been randomly assigned. The data safety and monitoring board, blinded to the identity of the 2 groups, reviewed the overall rate of serious adverse events in each group. If the rate was significantly higher in 1 group, then the results were unblinded and the data safety and monitoring board made a decision, based on clinical judgment and statistical input, about stopping or continuing the trial. We used an α value of 0.01 to account for multiple testing (31).

We reported summary baseline liver function test results for each group as the ratio of each patient's test result to the upper limit of normal for the laboratory where the test was performed, averaged over all participants in the group. We assessed differences between nonparticipants and participants for statistical significance by using chi-square tests for categorical variables and *t* tests for continuous variables (32). We expressed differences in outcomes between the 2 treatment groups as risk differences (rifampin minus isoniazid) with 95% CIs. We tested changes in liver aminotransferase levels and hematologic variables for statistical significance by using *t* tests if normally distributed, Wilcoxon rank-sum tests if nonnormally distributed, and chi-square tests for categorized results (32). We made exploratory analyses of the relationship of these adverse events with baseline characteristics by using these same statistical testing approaches. All analyses were conducted by using SAS, version 9.1 (SAS Institute, Cary, North Carolina).

Role of the Funding Source

The Canadian Institutes of Health Research funded the study. The funding source had no role in the design, conduct, or analysis of the study or in the decision to submit the manuscript for publication.

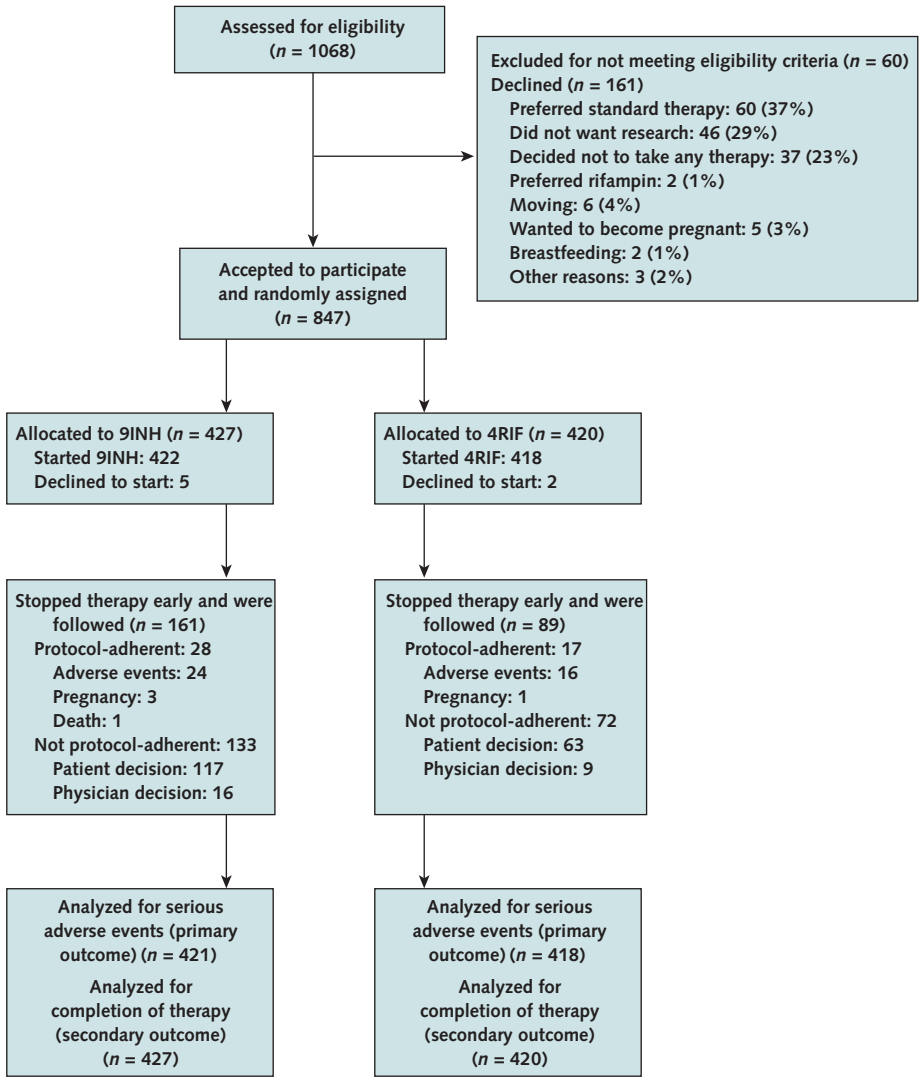
RESULTS

In January 2007, the third planned interim analysis revealed that the frequency of serious adverse events was significantly lower in 1 trial group. When the data safety and monitoring board was unblinded and learned that 4 months of rifampin had the lower rate of serious adverse events, they recommended discontinuation of enrollment.

Between 27 April 2004 and 31 January 2007, 1068 patients were advised by their treating physician to take 9 months of isoniazid for LTBI and were referred to the study for screening. Sixty screened patients were ineligible, and 161 declined to participate (**Figure 1**; **Appendix Tables 2** and **3**, available at www.annals.org). The only characteristic significantly associated with declining to participate was Aboriginal ethnic origin among Canadian-born participants. All baseline characteristics were similar in participants randomly assigned to the 2 regimens (**Table 1**). Seventy participants had abnormal baseline aminotransferase levels, although only 10 (2%) had baseline aminotransferase levels that were more than twice the upper limit of normal. One patient had aminotransferase levels more than 5 times the upper limit of normal before starting therapy. Additional risk factors for drug-induced hepatotoxicity were daily alcohol use, reported by 44 participants, and intravenous drug use, reported by 9 participants. A total of 376 participants (44%) were age 35 years or older. The distribution of these risk factors was similar in the 2 groups.

Of 420 participants randomly assigned to 4 months of rifampin, 328 (78%) completed therapy compared with 255 of 427 participants (60%) randomly assigned to 9 months of isoniazid (risk difference, 18% [95% CI, 12% to 24%]; $P < 0.001$) (**Figure 2**). Of the 418 who started rifampin, 7 developed grade 3 or 4 adverse events attributed to study therapy by the independent panel compared with 17 of the 422 participants who started isoniazid (risk difference, −2.3% [CI, −5% to −0.1%]; $P = 0.040$). As seen in **Table 2**, the difference was entirely attributable to drug-induced hepatitis, which developed in 3 participants

Figure 1. **Study flow diagram.**



4RIF = 4-month rifampin therapy; 9INH = 9-month isoniazid therapy.

(0.7%) taking rifampin compared with 16 participants (3.8%) taking isoniazid (risk difference, −3.1% [CI, −5% to −1%]; $P = 0.003$). Of these 19 participants, 11 had grade 3 hepatitis and 8 had grade 4 hepatitis. In an analysis restricted to participants who took at least 1 month of therapy, 3 of 389 taking rifampin and 16 of 392 taking isoniazid developed grade 3 or 4 hepatotoxicity (risk difference, −3.3% [CI, −5.5% to −1.1%]).

Median aspartate aminotransferase levels were 240 U/L (interquartile range [IQR], 147 to 421 U/L) among 16 participants taking 9 months of isoniazid and 153 U/L (IQR, 97 to 509 U/L) among 3 participants taking 4 months of rifampin. Corresponding alanine aminotransferase levels were 348 U/L (IQR, 265 to 653 U/L) and 326 U/L (IQR, 173 to 606 U/L), respectively. Hepatotoxicity developed in 7 participants (2 taking rifampin) in the first 2 months, 7 participants (1 taking rifampin) in the third and fourth months, and 5 participants taking isoniazid in the fifth to eighth months. In exploratory analyses, hepatotoxicity (with either drug) was significantly associated with other comorbid illnesses, history of allergy, or intravenous drug use but not with age, sex, country of birth, bacille Calmette–Guérin vaccination, reason for treatment, history of smoking or alcohol use, or pretreatment aminotransferase levels, although rates were doubled in participants older than 35 years of age (data not shown). In total, 1 patient taking rifampin and 6 patients taking isoniazid dropped out, and no information was available regarding their health status when they stopped therapy. In a worst-case scenario, if all had developed grade 3 or 4 adverse events, the magnitude of the observed difference in these events would have increased, favoring rifampin.

Grade 1 or 2 adverse events that resulted in permanent discontinuation of therapy and were judged by the study's independent panel to be related to the study drug were less common and similar in frequency in the 2 regimens (**Table 2**). The more common of these problems was rash, which occurred in more patients taking rifampin. In exploratory analyses, rash was statistically significantly associated with a history of allergy ($P = 0.030$) but not with age, sex, bacille Calmette–Guérin vaccination, and reason for treatment (data not shown). Minor symptoms or other problems that the treating physicians or independent panel did not think were related to the study drug were common and generally similar for the 2 regimens. Of patients with such problems, 85% and 67% completed rifampin and isoniazid treatment compared with 91% and 74% of those without such problems.

Between 16% and 24% of patients were missing laboratory assessments before treatment or during the first 2 months of treatment. The most common reason was a missing visit. In participants who had these parameters measured, pretreatment aminotransferase levels and hematologic variables did not significantly differ between the 2 groups. However, changes of these variables did significantly differ between the 2 groups during the first 2 months of therapy, as seen in **Table 3**. Baseline aminotransferase levels were abnormal in 25 patients randomly assigned to rifampin; of whom, 20 (80%) returned to normal and none developed grade 3 or 4 hepatitis. In contrast, 33 patients randomly assigned to isoniazid had abnormal baseline aminotransferase levels; of whom 10 (30%) returned to normal and 3 (9%) developed grade 3 to 4 hepatic reactions (**Appendix Tables 4** and **5**, available at www.annals.org). Of 325 patients taking rifampin who had platelet counts measured before and during the first 2 months of therapy, 38% had a reduction in platelet count of at least 25×10^9 cells/L and 2% had a reduction in platelet count of more than 100×10^9 cells/L, although the final platelet counts exceeded 100×10^9 cells/L in all patients. Reduction in leukocyte count of at least 1.00×10^9 cells/L was seen in 41% of 330 participants taking rifampin (with a full set of measurements), and 10% had a reduction of 2.50×10^9 cells/L or more. Two participants had grade 3 adverse events judged to be probably related to rifampin. Their baseline neutrophil counts were 1.90×10^9 cells/L and 1.76×10^9 cells/L, which decreased to nadir levels of 0.66 and 0.81×10^9 cells/L, respectively, after 4 to 5 weeks of therapy. Both participants remained asymptomatic, and neutrophil counts returned to near-baseline levels within 2 weeks after therapy was stopped.

DISCUSSION

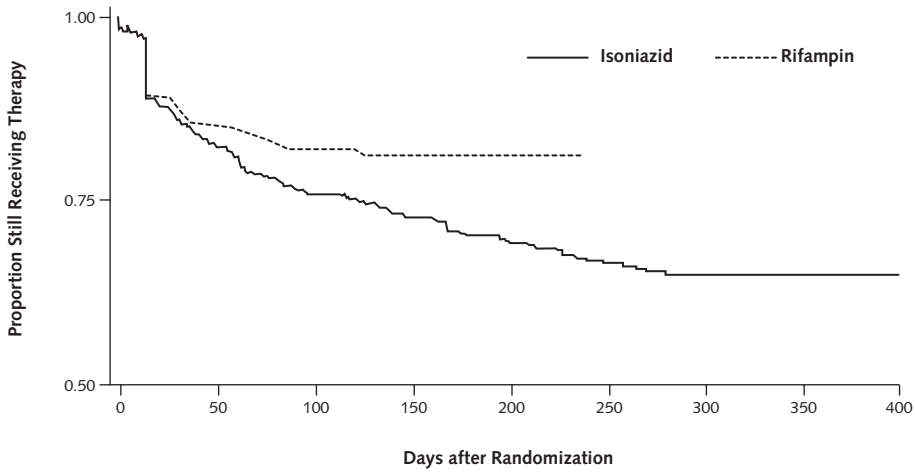
In this trial, we found that the frequency of serious adverse events, particularly grade 3 or 4 hepatitis, was significantly higher among participants taking isoniazid than among those taking rifampin. The frequency of minor ad-

Table 1. **Baseline Characteristics of Participants Randomly Assigned to the 2 Regimens**

Characteristic	4 Months of Rifampin ($n = 420$), *n (%)*	9 Months of Isoniazid ($n = 427$), *n (%)*
Age		
18–34 y	229 (55)	242 (57)
≥35 y	191 (45)	185 (43)
Sex		
Male	218 (52)	228 (53)
Female	201 (48)	199 (47)
Canadian sites		
Canadian-born		
Aboriginal	15 (4)	21 (5)
Nonaboriginal	48 (11)	55 (13)
Other (by tuberculosis incidence)		
Low	17 (4)	6 (1)
Intermediate	28 (7)	26 (6)
High	227 (54)	235 (55)
Brazil site	58 (14)	59 (14)
Saudi Arabia site	25 (6)	25 (6)
Risk factors		
HIV infection	6 (1)	7 (2)
Abnormal chest radiograph	117 (28)	105 (25)
Contact with active tuberculosis case	131 (31)	135 (32)
TST conversion	30 (7)	28 (7)
Recent immigrant	29 (7)	33 (8)
Other	107 (25)	119 (28)
TST size		
5–9 mm	23 (6)	20 (5)
10–14 mm	150 (36)	132 (31)
≥15 mm	247 (59)	275 (64)
History of BCG vaccination		
Yes	224 (54)	199 (47)
No	101 (24)	121 (28)
Unknown	95 (33)	107 (25)
Other medical problems	105 (25)	102 (24)
Use of hormonal contraception	21 (5)	19 (5)
Taking other medications	17 (4)	13 (3)
Intravenous drug use	6 (7)	3 (7)
Alcohol use		
Heavy (daily)	27 (6)	17 (4)
Slight to moderate	140 (33)	136 (32)
None	253 (60)	274 (64)
Cigarette smoking		
Currently	80 (19)	86 (20)
Ex-smoker	28 (7)	29 (7)
Never	312 (74)	312 (73)
Pretreatment aminotransferase levels		
Normal	366 (87)	363 (85)
Above normal to twice normal	25 (6)	34 (8)
Above twice normal	5 (1)	6 (1)
Not measured*	24 (6)	24 (6)
Pretreatment leukocyte count		
Normal	361 (86)	355 (83)
Below normal limit	32 (8)	36 (8)
Not measured†	27 (6)	36 (8)

BCG = bacille Calmette–Guérin; TST = tuberculin skin test.
* Pretreatment aminotransferase levels were missing in 48 participants. Of these, none developed hepatic serious adverse events, 29 (60%) did not complete therapy, and another 12 (25%) did not complete therapy on time.
† Pretreatment leukocyte counts were missing in 63 participants. Of these, none developed hematologic serious adverse events, 42 (67%) did not complete therapy, and another 10 (16%) did not complete therapy on time.

Figure 2. **Interval from randomization to dropout or treatment completion.**



All patients included.

verse events was similar, whereas treatment completion was significantly better with rifampin. The trial was not designed to have adequate power to assess efficacy.

Providers and patients are often reticent to use isoniazid to treat asymptomatic LTBI because drug-induced hepatotoxicity is difficult to detect and can be fatal. Therefore,

Table 2. **Final Outcomes of All Study Participants**

Variable	4 Months of Rifampin (n = 420), n (%)	9 Months of Isoniazid (n = 427), n (%)	Risk Difference (95% CI), %*
Completed therapy			
Subtotal	328 (78)	255 (60)	18 (12 to 24)
Had no symptoms or problems	180 (43)	119 (28)	15 (8 to 21)
Had symptoms but never stopped therapy	139 (33)	121 (28)	5 (−1 to 11)
Had symptoms, so physician stopped therapy; restarted and completed	9 (2)	15 (4)	−1 (−4 to 1)
Did not complete therapy (not protocol-adherent)			
Never started†	2 (0.4)	5 (1)	–
Started but no return visits (early patient default)	31 (7)	36 (8)	−1 (−4 to 3)
Had no symptoms or problems but did not complete (patient default)‡	18 (4)	44 (10)	−6 (−9 to −2)
Had symptoms, so physician did not stop therapy, but patient defaulted‡	17 (4)	47 (11)	−7 (−10 to −3)
Had symptoms, so physician stopped therapy; restarted, but patient defaulted later‡	0 (0)	1 (0.2)	–
Had problems, so physician stopped therapy permanently; physician default‡	9 (2)	16 (4)	−2 (−4 to 1)
Did not complete therapy (protocol-adherent)§			
Drug-related adverse events subtotal	16 (3.8)	24 (5.7)	−2 (−5 to 1)
Grade 3 or 4 adverse events			
Subtotal	7 (1.7)	17 (4.0)	−2 (−5 to −0.1)
Hepatotoxicity	3 (0.7)	16 (3.8)	−3 (−5 to −1)
Hematologic	2 (0.5)	1 (0.2)	–
Drug interaction	1 (0.2)	0 (0)	–
Rash	1 (0.2)	0 (0)	–
Grade 1 or 2 adverse events			
Subtotal	9 (2.2)	7 (1.7)	1 (−1 to 3)
Rash	8 (1.9)	5 (1.2)	1 (−1 to 3)
Gastrointestinal intolerance	1 (0.2)	2 (0.5)	–
Not related to study drug			
Death	0 (0)	1 (0.2)	–
Pregnancy	1 (0.2)	3 (0.7)	–

* No risk difference or CI calculated if fewer than 10 events in total.
† Physician stopped therapy permanently because of symptoms, but the independent review panel did not feel this was justified according to the study protocol.
‡ In total, 128 patients in these 3 groups defaulted. Information regarding their health status after they stopped therapy was available in 121 patients, but no information was available for 1 participant taking 4 months of rifampin and 6 participants taking 9 months of isoniazid.
§ In these groups, the severity, type, and relationship to study drug were judged by an independent, 3-member panel that was blinded to participant allocation. Two participants who never started rifampin therapy and 5 participants who never started isoniazid therapy were excluded from these comparisons.

Table 3. **Changes in Liver Aminotransferase Levels and Hematologic Values during the First 2 Months of Treatment***

Variable	4 Months of Rifampin	9 Months of Isoniazid	*P* Value†
Pretreatment			
AST level			
Patients, *n*	396	403	
Mean ratio to ULN (SD)	0.61 (0.24)	0.63 (0.31)	0.20
ALT level			
Patients, *n*	396	403	
Mean ratio to ULN (SD)	0.53 (0.36)	0.57 (0.47)	0.120
Leukocyte count			
Patients, *n*	393	391	
Mean count (SD), $\times 10^9$ *cells/L*	6.74 (1.78)	6.80 (1.959)	0.70
Platelet count			
Patients, *n*	393	391	
Mean count (SD), $\times 10^9$ *cells/L*	261 (65)	264 (67)	0.50
Change from pretreatment to after 1–2 months, *n (%)*			
AST level			
Missing before or during treatment	89 (16)	80 (19)	
Remained within normal limits	333 (79)	304 (71)	0.002
1 to 3 times ULN	17 (4)	38 (9)	
>3 times ULN	1 (0.2)	5 (1)	
ALT level			
Missing	67 (16)	79 (19)	
Remained within normal limits	328 (78)	301 (70)	0.020
1 to 3 times ULN	22 (5)	41 (10)	
>3 times ULN	3 (1)	6 (1)	
Leukocyte count			
Missing	80 (19)	104 (24)	
Increase of $\geq 1.00 \times 10^9$ cells/L	23 (5)	47 (11)	<0.001
No change	176 (42)	194 (45)	
Decrease of $1.00–2.50 \times 10^9$ cells/L	105 (25)	71 (17)	
Decrease of $\geq 2.50 \times 10^9$ cells/L	36 (9)	11 (3)	
Platelet count			
Missing	85 (20)	103 (24)	
Increase of $\geq 25 \times 10^9$ cells/L	17 (4)	42 (10)	<0.001
No change	192 (46)	226 (53)	
Decrease of $25–100 \times 10^9$ cells/L	118 (28)	51 (12)	
Decrease of $\geq 100 \times 10^9$ cells/L	8 (2)	5 (1)	

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.
* All patients who had blood tests performed are included.
† *P* value from *t* test for baseline values. Chi-square test was used for categorical variables. Participants with missing values were excluded from these comparisons.

our findings of significantly less hepatotoxicity with rifampin together with corroborative published evidence have very important implications for tuberculosis prevention and control. In an earlier trial among men with silicosis in Hong Kong, none of the 165 participants who received 3 months of rifampin treatment developed clinical hepatitis, even though 99% were older than 35 years (21). In nonrandomized studies, hepatotoxicity occurred in 0 of 49 homeless persons (with a high rate of alcoholism) (22) and 1 of 157 adolescents (0.6%) (23) who received 6 months of rifampin treatment. Of patients treated with 4 months of rifampin under routine practice conditions, 1 of 1374 (0.1%) in Maryland (8) and 0 of 261 in New Jersey (9) developed hepatotoxicity. In a meta-analysis of patients who were treated for active tuberculosis disease, 2.6% of those treated with isoniazid plus rifampin had hepatotoxicity compared with 1.6% treated with regimens containing isoniazid but not rifampin (33)—an important potential disadvantage of 3 to 4 months of daily isoniazid and rifampin, which is used by some centers to treat LTBI (34).

In initial randomized trials, the incidence of hepatotoxicity with isoniazid, and later with 2 months of rifampin–pyrazinamide, was substantially lower (11, 16) than that after these regimens were widely used in routine practice (13, 14, 19). Although the reasons for this difference are unknown, we were concerned that it may have resulted from inclusion of persons at lower risk for adverse events. Therefore, we excluded only patients in whom rifampin was clearly contraindicated. This meant that patients who were eligible included those older than age 35 years and those with abnormal baseline liver aminotransferase levels or other risk factors for drug-induced hepatitis, as long as the treating physician considered the benefits of isoniazid to outweigh the risks. In addition, because of the multicenter design, the study sample was very diverse, strengthening generalizability of the findings and further enhancing the accuracy of the estimates of hepatotoxicity, although further surveillance is needed.

The severe but rare hematologic complications of immune-mediated thrombocytopenia or anemia with ri-

fampin are well described (25). However, we could find only 1 previously published report of a more frequent but milder hematologic effect of rifampin (35), in which participants with active tuberculosis who were taking rifampin experienced an average decrease in platelet count of approximately 80 to 90 $\times$ 10^9 cells/L compared with baseline (35). This effect was not related to rifampin dose or frequency or to rifampin antibodies and had no apparent clinical consequences (35). In the present trial, no patient exhibited clinical manifestations of changes in hematologic variables. Therefore, the clinical implications of those changes are unclear, but careful hematologic monitoring in future studies is clearly warranted.

The frequency of all adverse events considered together was similar in the 2 groups, largely because grade 1 or 2 rash occurred equally in the 2 groups. Although rash from rifampin (or isoniazid) is important, it is easily identified at an early stage by patients and providers. We have emphasized the differences in changes in aminotransferase levels and drug-induced hepatitis, even though no hepatotoxic deaths occurred in the trial, because both isoniazid and rifampin–pyrazinamide are known to be common causes of elevated aminotransferase levels, with a spectrum of severity from asymptomatic mild increases to fulminant hepatic failure (14, 19, 20, 36). Data on fatal hepatotoxicity will probably be available only with more widespread use of 4 months of rifampin, but this trial and other published studies suggest that the risk should be very low.

An important potential limitation of this study was its open-label design. We considered this justified because a double-blind design would have required all participants to take at least 2 tablets for 9 months, including a placebo that discolored urine as rifampin does. This would have compromised comparisons of the secondary study outcomes of treatment completion and adherence. Awareness of the regimen may have influenced patients' reporting and providers' recording of symptoms, as well as physicians' decision to discontinue therapy. To minimize such possible bias, we diagnosed hepatic and hematologic changes on the basis of laboratory measurements and graded them by using a standardized, widely used classification (37). We diagnosed rash on the basis of photographs of the affected areas. Most important, a blinded independent panel reviewed all possible adverse events, thereby eliminating bias in attribution or grading of adverse events.

Patient adherence and treatment completion may have been better in the trial than they would be under routine practice conditions. This could occur because of selection of more motivated patients into the trial, or because patients' behavior was influenced by the knowledge that every opening of the pill container was recorded electronically (necessary to enhance accuracy of adherence assessment) (38, 39). However, the completion rate of 9 months of isoniazid in this trial was similar to that reported elsewhere under routine conditions (8, 9). In addition, any bias in the estimates of adherence and completion should have affected both groups equally and would not have accounted for the finding of significantly better completion with 4 months of rifampin. The enhanced completion rate found in this trial, an earlier trial (40), and 2 nonrandomized studies (8, 9) suggest that rifampin is better accepted and tolerated than isoniazid. This experience is in marked contrast to trials with 2 months of rifampin–pyrazinamide treatment, in which completion of the 2-month regimen was, surprisingly, not substantially better than 6 or 12 months of isoniazid (41)—a largely overlooked finding that might have served as a harbinger of the toxicity of the regimen.

Although evidence consistently suggests the superior safety and completion rate of rifampin, little evidence of its efficacy is available. Among patients with silicosis and LTBI, 3 months of rifampin treatment had 63% protective efficacy relative to placebo (21). In 2 nonrandomized studies involving 244 participants who took 6 months of rifampin treatment, no cases of disease occurred compared with 11 cases expected (22, 23). These limited, albeit promising, results emphasize the lack of data regarding efficacy of the 4-month rifampin-only regimen. Without this, 4 months of rifampin cannot be considered a true replacement for 9 months of isoniazid, which must remain the standard of care given the available evidence for its efficacy.

Evaluation of the efficacy of any regimen for LTBI is a major undertaking because a large-scale trial is required. Such a trial would be justified only if evidence shows that the regimen has superior treatment completion or less toxicity than 9 months of isoniazid therapy. The 4-month rifampin regimen seems to meet both criteria, with significantly lower rates of grade 3 or 4 hepatotoxicity and better completion. The findings from this trial provide strong justification for a large-scale trial to assess the efficacy of 4 months of rifampin treatment.

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Appendix Table 1. Grading System for Adverse Events Used by Independent Panel*

Grade	Meaning
Hepatotoxicity grade	
0	ALT and AST levels within normal limits
1–2	ALT and AST levels 1–3 times ULN plus symptoms suggestive of hepatotoxicity (nausea, anorexia, vomiting, fatigue, abdominal pain), or ALT and AST levels 1–5 times ULN and no symptoms
3	ALT and AST levels 3–10 times ULN plus symptoms, or ALT and AST levels 5–10 times ULN and no symptoms
4	ALT or AST levels >10 times ULN
Rash grade	
1	Itching only or limited to limbs, trunk, or face only; no abnormality of vital signs and no mucosal or conjunctival involvement
2	Rash affects limbs and trunk or more than 50% of total body surface area or rash is confluent in areas
3	Rash affects 100% of body surface area or mucus membranes, conjunctivae are affected, vital signs are abnormal (fever or low blood pressure), or there is wheezing
Hematologic grade	
0	No change in hematologic parameters at 1 or 2 months from baseline
1–2	Neutrophil counts <1.50–1.00×10^9 cells/L or platelet counts <100–50×10^9 cells/L
3	Neutrophil counts <1.00–0.50×10^9 cells/L or platelet counts <50–25×10^9 cells/L
4	Neutrophil counts $<0.50 \times 10^9$ cells/L or platelet counts $<25 \times 10^9$ cells/L
Gastrointestinal grade	
1	Some stomach upset with nausea or loss of appetite, but no vomiting and no change in bowel habits
2	Nausea with some vomiting, abdominal pain that is severe enough to disturb daily routine, or persistent diarrhea
3	Protracted nausea and vomiting or severe abdominal pain that disrupts daily life (for example, cannot sleep), severe diarrhea (≥5 bowel movements per day)
Drug interaction grade	
0	No potential drug interactions (or no other medications)
1	Potential drug interaction noted, but no change in therapy required and neither short- nor long-term effect detected
2	Potential drug interaction is noted, but after an initial change in therapy, no further problems and therapy does not have to be changed
3	Drug interaction noted and therapy has to be modified repeatedly but eventually this is successful; patient does not have any untoward clinical effect, and LTBI therapy can be continued
4	Drug interaction noted; care providers unable to adjust therapy successfully to achieve therapeutic effects; LTBI therapy must be discontinued

*Based on references 29 and 30.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; LTBI = latent tuberculosis infection; ULN = upper limit of normal.

Appendix Table 2. **Comparison of Characteristics of Ineligible and Eligible Participants***

Characteristic	Ineligible Participants (*n* = 60), *n (%)*	Eligible Participants (*n* = 1008), *n (%)*
Age		
18–34 y	28 (49)	570 (57)
≥35 y	32 (53)	437 (43)
Sex		
Male	24 (40)	526 (52)
Female	36 (60)	482 (48)
Country of birth		
Canadian sites		
Canada	8 (13)	181 (18)
Aboriginal	3 (37)	59 (35)
Nonaboriginal	5 (63)	122 (65)
Other (by tuberculosis incidence)		
Low	4 (7)	24 (2)
Intermediate	6 (10)	67 (7)
High	39 (65)	560 (56)
Brazil site	0 (0)	123 (12)
Saudi Arabia site	3 (5)	50 (5)
Foreign-born		
Arrived in past 2 years	19 (39)	228 (35)
Arrived ≥2 years ago	30 (61)	426 (65)
Reason for treatment		
HIV-positive	2 (3)	13 (1)
Abnormal chest radiograph	23 (38)	262 (26)
Contact with active tuberculosis case	8 (13)	314 (31)
TST conversion	3 (5)	68 (7)
Recent immigration	5 (8)	36 (4)
Other risk factors	19 (32)	315 (31)
TST size		
5–9 mm	1 (2)	50 (5)
10–14 mm	15 (25)	329 (33)
≥15 mm	43 (73)	629 (62)

TST = tuberculin skin test.
*No statistical testing performed.

Appendix Table 3. **Comparison of Eligible Persons Who Declined to Participate with Those Who Participated**

Characteristic	Declined to Participate (*n* = 161), *n (%)*	Participated (*n* = 847), *n (%)*	*P* Value
Age			0.12
18–34 y	100 (62)	471 (56)	
≥35 y	61 (38)	376 (44)	
Sex			0.49
Male	80 (50)	446 (53)	
Female	81 (50)	401 (47)	
Country of birth			
Canadian sites			
Canada	42 (26)	139 (16)	0.007
Aboriginal	23 (14)	36 (4)	<0.001
Nonaboriginal	19 (12)	103 (12)	
Other (by tuberculosis incidence)			
Low	1 (1)	23 (3)	
Intermediate	13 (8)	54 (6)	
High	98 (61)	462 (55)	
Brazil site	6 (4)	117 (14)	
Saudi Arabia site	0 (0)	50 (6)	
Foreign-born			0.6
Arrived in past 2 years	42 (37)	186 (34)	
Arrived ≥2 years ago	71 (63)	355 (66)	
Reason for treatment			0.3
HIV-positive	0 (0)	13 (2)	
Abnormal chest radiograph	40 (25)	222 (26)	
Contact with active tuberculosis case	48 (30)	266 (31)	
TST conversion	10 (6)	58 (7)	
Recent immigration	9 (6)	27 (3)	
Other risk factors	54 (34)	261 (31)	
TST size			0.5
5–9 mm	7 (4)	43 (5)	
10–14 mm	47 (29)	282 (33)	
≥15 mm	107 (66)	522 (62)	

TST = tuberculin skin test.

Appendix Table 4. **Association of Baseline Aminotransferase Levels with Levels during Treatment***

Aminotransferase Level during Treatment†	Normal Baseline ALT and AST Levels, *n (%)*	Above-Normal Baseline AST or ALT Levels, *n (%)*	*P* Value‡
4 months of rifampin			0.050
Normal§	295 (92)	20 (80)	
Abnormal (any level)	26 (8)	5 (20)	
9 months of isoniazid			<0.001
Normal§	268 (86)	10 (30)	
Abnormal (any level)	44 (14)	23 (70)	
4 months of rifampin			>0.20
Normal§ or grade 1 or 2	318 (99)	25 (100)	
Abnormal (grade 3 or 4 hepatitis)	3 (1)	0 (0)	
9 months of isoniazid			>0.20
Normal§ or grade 1 to 2	299 (96)	30 (91)	
Abnormal (grade 3 to 4 hepatitis)	13 (4)	3 (9)	

ALT = alanine aminotransferase; AST = aspartate aminotransferase.
* 18 participants whose therapy was stopped early because of other adverse events are excluded from this analysis.
† Aminotransferase levels during treatment were missing in 123 participants, of whom 111 (90%) did not complete therapy and 6 (4%) did not complete therapy on time.
‡ *P* value from chi-square test comparing subgroups within each treatment group.
§ Normal values taken from each participating laboratory.

Appendix Table 5. **Change in Aminotransferase and Hematologic Values from Pretreatment to during the First 2 Months of Treatment**

Variable	Pretreatment	During First 2 Months of Treatment	*P* Value
Median change in AST level ratio to ULN (IQR)	0.03 (−0.06 to 0.13)	0.08 (0 to 0.17)	<0.001
Median change in ALT level ratio to ULN (IQR)	0.01 (−0.09 to 0.18)	0.03 (−0.05 to 0.14)	0.30
Median absolute change in platelet count (IQR), × 10^9 *cells/L*	−17 (−35 to −4)	−2 (−16 to 15)	<0.001
Median absolute change in leukocyte count (IQR), × 10^9 *cells/L*	−0.78 (−1.65 to −0.18)	−0.128 (−1.00 to 0.625)	<0.001

ALT = alanine aminotransferase; AST = aspartate aminotransferase; IQR = interquartile range; ULN = upper limit of normal.