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Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection

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ABSTRACT

BACKGROUND

Treatment of latent *Mycobacterium tuberculosis* infection is an essential component of tuberculosis control and elimination. The current standard regimen of isoniazid for 9 months is efficacious but is limited by toxicity and low rates of treatment completion.

METHODS

We conducted an open-label, randomized noninferiority trial comparing 3 months of directly observed once-weekly therapy with rifapentine (900 mg) plus isoniazid (900 mg) (combination-therapy group) with 9 months of self-administered daily isoniazid (300 mg) (isoniazid-only group) in subjects at high risk for tuberculosis. Subjects were enrolled from the United States, Canada, Brazil, and Spain and followed for 33 months. The primary end point was confirmed tuberculosis, and the noninferiority margin was 0.75%.

RESULTS

In the modified intention-to-treat analysis, tuberculosis developed in 7 of 3986 subjects in the combination-therapy group (cumulative rate, 0.19%) and in 15 of 3745 subjects in the isoniazid-only group (cumulative rate, 0.43%), for a difference of 0.24 percentage points. Rates of treatment completion were 82.1% in the combination-therapy group and 69.0% in the isoniazid-only group ($P<0.001$). Rates of permanent drug discontinuation owing to an adverse event were 4.9% in the combination-therapy group and 3.7% in the isoniazid-only group ($P=0.009$). Rates of investigator-assessed drug-related hepatotoxicity were 0.4% and 2.7%, respectively ($P<0.001$).

CONCLUSIONS

The use of rifapentine plus isoniazid for 3 months was as effective as 9 months of isoniazid alone in preventing tuberculosis and had a higher treatment-completion rate. Long-term safety monitoring will be important. (Funded by the Centers for Disease Control and Prevention; PREVENT TB ClinicalTrials.gov number, NCT00023452.)

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Tuberculosis results in nearly 2 million deaths annually worldwide.[1] More than 2 billion persons are infected with *Mycobacterium tuberculosis*,[2] and from this reservoir active tuberculosis will develop in millions of persons in coming decades. Treatment of latent *M. tuberculosis* infection among the persons at highest risk for progression to active disease is an important strategy for tuberculosis control and elimination.[3-6]

The current standard regimen for the treatment of latent *M. tuberculosis* infection is 9 months of daily isoniazid.[3] The efficacy for isoniazid was found to be 69 to 93% in a study that was published in 1982 (before the era of widespread infection with the human immunodeficiency virus [HIV]).[7] However, the effectiveness of isoniazid is limited by treatment completion rates of 30 to 64%, owing in part to the long duration of the regimen.[3,8-11] Toxic effects of the drug, especially hepatic, are also a concern.[3] A 2-month regimen of rifampin and pyrazinamide was shown to be as effective as isoniazid[12-14] but has not been recommended owing to increased rates of severe hepatotoxicity.[15]

Rifapentine, a rifamycin derivative with a long half-life and greater potency against *M. tuberculosis* than rifampin, has shown promise for treating latent tuberculosis in animal models.[16-18] Since weekly rifapentine and isoniazid are effective in the continuation phase of tuberculosis treatment in patients with a low bacillary burden,[19] we reasoned that a 3-month course of these agents would be effective for treating latent *M. tuberculosis*. A shortened course of intermittent treatment would also be more convenient for both patients and public-health programs responsible for ensuring treatment completion.

Methods

Study Treatment

We conducted a prospective, open-label, randomized trial of 3 months of once-weekly rifapentine (at a dose of 900 mg, with incremental adjustment for subjects weighing ≤50 kg) plus isoniazid (at a dose of 15 to 25 mg per kilogram of body weight, rounded up to the nearest 50 mg, with a maximum dose of 900 mg) given under direct observation (combination-therapy group), as compared with 9 months of daily self-administered isoniazid (at a dose of 5 to 15 mg per kilogram, rounded up to the nearest 50 mg, with a maximum dose of 300 mg) (isoniazid-only group). Details are provided in the Supplementary Appendix and the trial protocol, both of which are available with the full text of this article at NEJM.org.

Subjects

From June 2001 through February 2008, we recruited persons at high risk for progression from latent *M. tuberculosis* infection to active disease (Fig. 1 in the Supplementary Appendix). Formal assessment for eligibility, including reasons for declining to participate, started in March 2005. All subjects were required to be at least 12 years of age and to be a close contact of a patient with culture-confirmed tuberculosis (within 2 years before enrollment) and have had a positive result on a tuberculin skin test, have conversion to positive results on a tuberculin skin test, have HIV infection with a positive tuberculin skin test or have had close contact with a patient with tuberculosis regardless of test results, or have a positive result on a tuberculin skin test with fibrotic changes on chest radiography consistent with previously untreated tuberculosis. A positive tuberculin skin test and conversion to a positive test were defined according to criteria of the American Thoracic Society and the Centers for Disease Control and Prevention (CDC).[3]

In 2005, the inclusion criteria were expanded to include children between the ages of 2 and 11 years after rifapentine pharmacokinetic data became available for this group.[20] At that time, children 2 to 4 years of age with a positive tuberculin skin test or a negative initial skin-test result but in close contact with a patient with culture-confirmed tuberculosis also became eligible.

Exclusion criteria included confirmed or suspected tuberculosis, resistance to isoniazid or rifampin in the source case, treatment with rifamycin or isoniazid during the previous 2 years, previous completion of treatment for tuberculosis or *M. tuberculosis* infection in HIV-seronegative persons, sensitivity or intolerance to isoniazid or rifamycin, a serum aspartate aminotransferase level that was five times the upper limit of the normal range, pregnancy or lactation, HIV therapy within 90 days after enrollment, or a weight of less than 10.0 kg (for details, see the Supplementary Appendix).

Randomization and Follow-up

Subjects were assigned to study groups according to simple unrestricted randomization. In group set-

tings (e.g., households), subjects could be placed on the same regimen as the first person in the group (cluster). Therefore, only the first person in the cluster underwent randomization but all received treatment.

Subjects were followed for 33 months after enrollment and were evaluated monthly during treatment. Adverse events were reported up to 60 days after the administration of the last dose of a study drug. After treatment completion, study visits occurred every 3 months until the 21st month, then at months 27 and 33. Subjects who were lost to follow-up before 33 months were cross-matched with local and state tuberculosis databases. Subjects who discontinued a study drug early could be treated with an alternative therapy at the discretion of the local investigator, and follow-up continued.

The study was approved by the institutional review boards at the CDC and all study sites. Written informed consent was obtained from all study subjects.

END POINTS

The primary study end point was culture-confirmed tuberculosis in subjects 18 years of age or older and culture-confirmed or clinical tuberculosis in children under the age of 18 years. Secondary end points included culture-confirmed or clinical tuberculosis regardless of age among all subjects and among subjects who completed study therapy. All suspected tuberculosis cases were reviewed by the three members of an external expert committee who were unaware of the study-group assignment, with final diagnoses made by consensus.

Additional secondary end points were completion of study therapy, permanent discontinuation of therapy, permanent discontinuation because of an adverse drug reaction, any grade 3 or 4 drug-related toxic effects, death from any cause, and resistance to a study drug in *M. tuberculosis* in subjects in whom tuberculosis developed. Adverse events were graded by local investigators using common toxicity criteria[21]; investigators also determined attribution of adverse events to a study drug. (The definition of possible drug hypersensitivity is provided in the Supplementary Appendix.)

STUDY OVERSIGHT

The protocol team designed the study. Investigators from the CDC gathered data from all study sites and analyzed the data. Sanofi-Aventis, the manufacturer of rifapentine, provided the study drug at no charge but had no other role in the design or conduct of the study. Isoniazid was either purchased or provided by the local health department. All authors vouch for the completeness of the data and analyses presented and for the fidelity of this report to the study protocol.

STATISTICAL ANALYSIS

We assumed that most study subjects would have positive results on a tuberculin skin test, and have close contact with a patient with tuberculosis or have a recent conversion to a positive tuberculin skin test. Without treatment, the risk of tuberculosis in the first 2 years after *M. tuberculosis* infection is estimated to be 5% in these groups.[22-24] A 12-month regimen of isoniazid is 55 to 83% effective; 68% is the estimated effectiveness for a regimen of 9 to 12 months.[25] On the basis of an assumed effectiveness of 70% for isoniazid, we calculated that the rate of tuberculosis in the isoniazid-only group at 2 years would be 1.5%. The study was designed to assess for equivalence of the two regimens, with an equivalence margin of ±50% of the expected case rate in the isoniazid-only group (50% × 1.5% = 0.75%). This corresponded to a rate of tuberculosis in the combination-therapy group of 0.75 to 2.25 cases per 100 person-years. Thus, assuming a 15% loss to follow-up, we determined that a sample size of 4000 subjects per study group would provide a power of 80% to determine equivalence on the basis of an alpha level of 0.05 and a two-sided test.

During year 4 of study enrollment, the data and safety monitoring board noted a lower-than-expected rate of pooled events among all study subjects. In addition, consensus among experts in clinical-trial design had changed since the time of the original study design so that noninferiority trials were preferred to determine clinical equivalence. A significant result in a noninferiority trial means that the experimental regimen is at least as effective (as defined by the noninferiority margin) as the active control group.[26] The primary objective of assessing clinical equivalence was therefore restated as an evaluation of noninferiority for combination therapy with rifapentine plus isoniazid, with an absolute noninferiority margin (delta) of 0.75%. (For a detailed explanation of the noninferiority margin, see the Supplementary Appendix.) This protocol amendment was approved by the CDC and the institutional review board at each study site. Thus, a sample size of 3200 subjects per

study group would provide a power of more than 80% to show the noninferiority of combination therapy. To allow for 20% loss to follow-up and to account for clustering, 4000 subjects were targeted for enrollment in each study group.

The analysis groups were defined as follows: the modified intention-to-treat analysis included all enrolled subjects who were eligible, whereas the intention-to-treat population included all enrolled subjects, regardless of study eligibility. The per-protocol population included all eligible enrolled subjects who completed the assigned study regimen (defined as ≥11 of 12 doses of combination therapy within 16 weeks or ≥240 of 270 doses of isoniazid within 52 weeks) or subjects in whom tuberculosis developed or who died but who completed at least 75% of the expected number of doses before the event. Tuberculosis rates were assessed at 33 months after enrollment and at 24 months after the completion of therapy. In both the modified intention-to-treat analysis and the per-protocol analysis, all follow-up time was included; subjects were not required to reach 33 months of follow-up. The modified intention-to-treat analysis among subjects who were followed for up to 33 months after enrollment was considered to be the primary effectiveness analysis. The per-protocol analysis was considered to be the primary efficacy analysis. (For details, see the Supplementary Appendix.)

RESULTS

SUBJECTS

Of the 8053 subjects who were enrolled in the study, 322 were ineligible, mostly because the source case had drug-resistant tuberculosis (50% of ineligible subjects) or negative cultures for *M. tuberculosis* (32%) (Fig. 1 and Table 1 in the Supplementary Appendix). The clinical and demographic characteristics of the 7731 subjects in the modified intention-to-treat population are shown in Table 1. The subjects, who were primarily from the United States and Canada, were high-risk persons with positive results on the tuberculin skin test, including 71% who had close contact with a patient with tuberculosis and 25% who had a recent conversion to skin-test positivity. There were 10,327 patient-years of follow-up in the combination-therapy group and 9619 patient-years in the isoniazid-only group in the modified intention-to-treat population. The mean number of months in the study was 30.7 in the combination-therapy group and 30.3 in the isoniazid-only group. The proportions of subjects completing 33 months of follow-up were 88% and 86%, respectively (Fig. 2 in the Supplementary Appendix).

END POINTS

The cumulative proportion of subjects in whom tuberculosis developed was 0.19% in the combination-therapy group and 0.43% in the isoniazid-only group in the modified intention-to-treat analysis, for a difference of 0.24 percentage points (upper limit of the 95% confidence interval [CI] of the difference, 0.01%) (Table 2 and Fig. 1, which also provide results of the per-protocol analysis). The combination-therapy regimen was consistently noninferior to the isoniazid-only regimen (upper limit of the 95% CI of the difference, <0.75%). There was a trend toward superior effectiveness of combination therapy by 33 months of follow-up. Results were similar when only the first person in each cluster was included and when four adult cases of culture-negative tuberculosis were included. Results were also similar in the analysis conducted at 24 months after last treatment dose (Table 2 and Fig. 3 in the Supplementary Appendix). Tuberculosis cases were not disproportionate according to study region (United States and Canada, Brazil, and Spain) or site. Among subjects who completed 100% of their doses (regardless of the time required), tuberculosis developed in 5 of 3376 subjects (0.1%) in the combination-therapy group and in 6 of 2792 (0.2%) in the isoniazid-only group. The cumulative tuberculosis event rate increased steadily throughout 33 months of follow-up in the isoniazid-only group but tended to plateau by 20 months in the combination-therapy group (Fig. 4 in the Supplementary Appendix).

A total of 384 subjects received two doses or less of combination therapy or less than 30 days of isoniazid only but remained in the study. There were 4 tuberculosis cases among these 384 subjects, for a cumulative rate of 1.64%.

ADVERSE EVENTS

Subjects receiving combination therapy were more likely to complete treatment than those receiving isoniazid only (82.1% vs. 69.0%, P<0.001) (Table 3). However, subjects in the combination-therapy group were more likely to have permanent drug discontinuation owing to an adverse event (4.9% vs.

Table 1. Clinical and Demographic Characteristics of the Subjects in the Modified Intention-to-Treat Analysis.*

Characteristic	Isoniazid Only (N=3745)	Combination Therapy (N=3986)
Indication for treatment — no. (%)†		
Close contact with a patient with tuberculosis	2609 (69.7)	2857 (71.7)
Recent conversion to a positive tuberculin skin test	972 (26.0)	953 (23.9)
HIV infection	74 (2.0)	87 (2.2)
Fibrosis on chest radiograph	90 (2.4)	89 (2.2)
Age — yr		
Median	35	36
Interquartile range	25–46	25–47
Male sex — no. (%)	2004 (53.5)	2210 (55.4)
Race or ethnic group — no. (%)‡		
White	2160 (57.7)	2296 (57.6)
Black	947 (25.3)	978 (24.5)
Asian or Pacific Islander	490 (13.1)	494 (12.4)
North American Indian	33 (0.9)	84 (2.1)§
Multiracial (in Brazil)	115 (3.1)	134 (3.4)
Ethnic group (in U.S. and Canada) — no./total no. (%)‡		
Hispanic	1442/3341 (43.2)	1576/3542 (44.5)
Non-Hispanic	1899/3341 (56.8)	1966/3542 (55.5)
HIV infection — no. (%)	100 (2.7)	105 (2.6)
Body-mass index¶		
Median	26	27
Interquartile range	23–30	23–31
Region of enrollment		
U.S. or Canada	3341 (89.2)	3542 (88.9)
Brazil or Spain	404 (10.8)	444 (11.1)
Subjects enrolled in a cluster — no. (%)‖	1050 (28.0)	1345 (33.7)§
Completed high school — no. (%)	2126 (56.8)	2269 (56.9)
Risk factors — no. (%)		
History of incarceration	175 (4.7)	221 (5.5)
Lack of employment	390 (10.4)	424 (10.6)
History of alcohol use**	1888 (50.4)	1929 (48.4)
History of injection-drug use**	136 (3.6)	149 (3.7)
Homelessness	220 (5.9)	293 (7.4)§
Current smoker	1034 (27.6)	1112 (27.9)
Liver disease**		
Hepatitis C virus	97 (2.6)	99 (2.5)
Hepatitis B virus	60 (1.6)	42 (1.1)

* HIV denotes human immunodeficiency virus.
† Subjects were counted only once in the order presented. The total number of HIV-infected persons who were enrolled in the study is listed separately in this table.
‡ Race or ethnic group was self-reported.
§ P<0.05 by the chi-square test.
¶ The body-mass index is the weight in kilograms divided by the square of the height in meters.
‖ In group settings such as households, subjects could have been placed on the same regimen as the first person in the group (cluster).
** Data in this category were self-reported.

Table 2. Number of Subjects with Tuberculosis and Event Rates.*

Population and Study Group	No. of Subjects	Subjects with Tuberculosis			Difference in Cumulative Rate†	Upper Limit of 95% CI for Difference in Cumulative Rate
		no.	*no. per patient-yr*	*cumulative rate*	*percentage points*	
Modified intention-to-treat analysis						
Isoniazid only	3745	15	0.16	0.43	−0.24	0.01
Combination therapy	3986	7	0.07	0.19		
Per-protocol analysis						
Isoniazid only	2585	8	0.11	0.32	−0.19	0.06
Combination therapy	3273	4	0.05	0.13		

* Combination therapy consisted of 3 months of directly observed once-weekly therapy with rifapentine (900 mg) plus isoniazid (900 mg). Isoniazid-only therapy consisted of 9 months of self-administered daily isoniazid (300 mg). Data are shown for a period up to 33 months after study enrollment.
† The difference is the rate in the combination-therapy group minus the rate in the isoniazid-only group.

3.7%, P=0.009). The proportions of subjects with any adverse event, any grade 1 or 2 adverse event, or any serious adverse event were lower in the combination-therapy group than in the isoniazid-only group. There was no significant between-group difference in the proportion of subjects with grade 3 or 4 adverse events or in the risk of death; none of the deaths were attributed to a study drug.

The proportion of subjects with hepatotoxicity that was attributed to a study drug was higher in the isoniazid-only group (2.7% vs. 0.4%, P<0.001) (Table 3). The proportion of subjects who permanently discontinued a study drug because of hepatotoxicity was 0.3% in the combination-therapy group and 2.0% in the isoniazid-only group (P<0.001), with a similar difference seen among those with grade 3 or 4 hepatotoxicity (0.3% vs. 2.0%). Among other adverse events attributed to a study drug, the proportion of subjects with possible hypersensitivity or other causes was higher in the combination-therapy group (Table 3). The proportion of subjects who permanently discontinued a study drug because of possible hypersensitivity was 2.9% in the combination-therapy group and 0.4% in the isoniazid-only group (P<0.001).

RISK FACTORS

Factors that were independently associated with an increased risk of tuberculosis were tobacco smoking at the time of enrollment, HIV infection, and low body-mass index (Table 4). After adjustment for these variables, subjects receiving combination therapy were at lower risk for tuberculosis than were subjects receiving isoniazid only (adjusted hazard ratio, 0.38; 95% CI, 0.15 to 0.99; P=0.05). There were no interactions between treatment regimen and the risk factors considered.

Of the 22 subjects in whom tuberculosis was diagnosed, 20 cases were confirmed on culture. There were 2 isoniazid-resistant cases (both in the isoniazid-only group) and 1 rifampin-resistant case (in the combination-therapy group). The latter case occurred in a subject with HIV infection (CD4+ count, 271 per cubic millimeter at enrollment) and isoniazid-susceptible *M. bovis* infection (also considered to be culture-confirmed tuberculosis) who had treatment interruptions and completed therapy late.

DISCUSSION

Our study showed that directly observed, once-weekly therapy with rifapentine plus isoniazid for 3 months was as effective as self-administered daily isoniazid for 9 months, with the rate of tuberculosis in the combination-therapy group approximately half that in the isoniazid-only group. The combination-therapy group had higher treatment-completion rates and a toxicity profile similar to that of the isoniazid-only group, with lower rates of adverse events, severe adverse events, and hepatotoxicity attributable to the study drug. This simple, effective new regimen has a potential public-health benefit.

In the combination-therapy group, fewer sub-

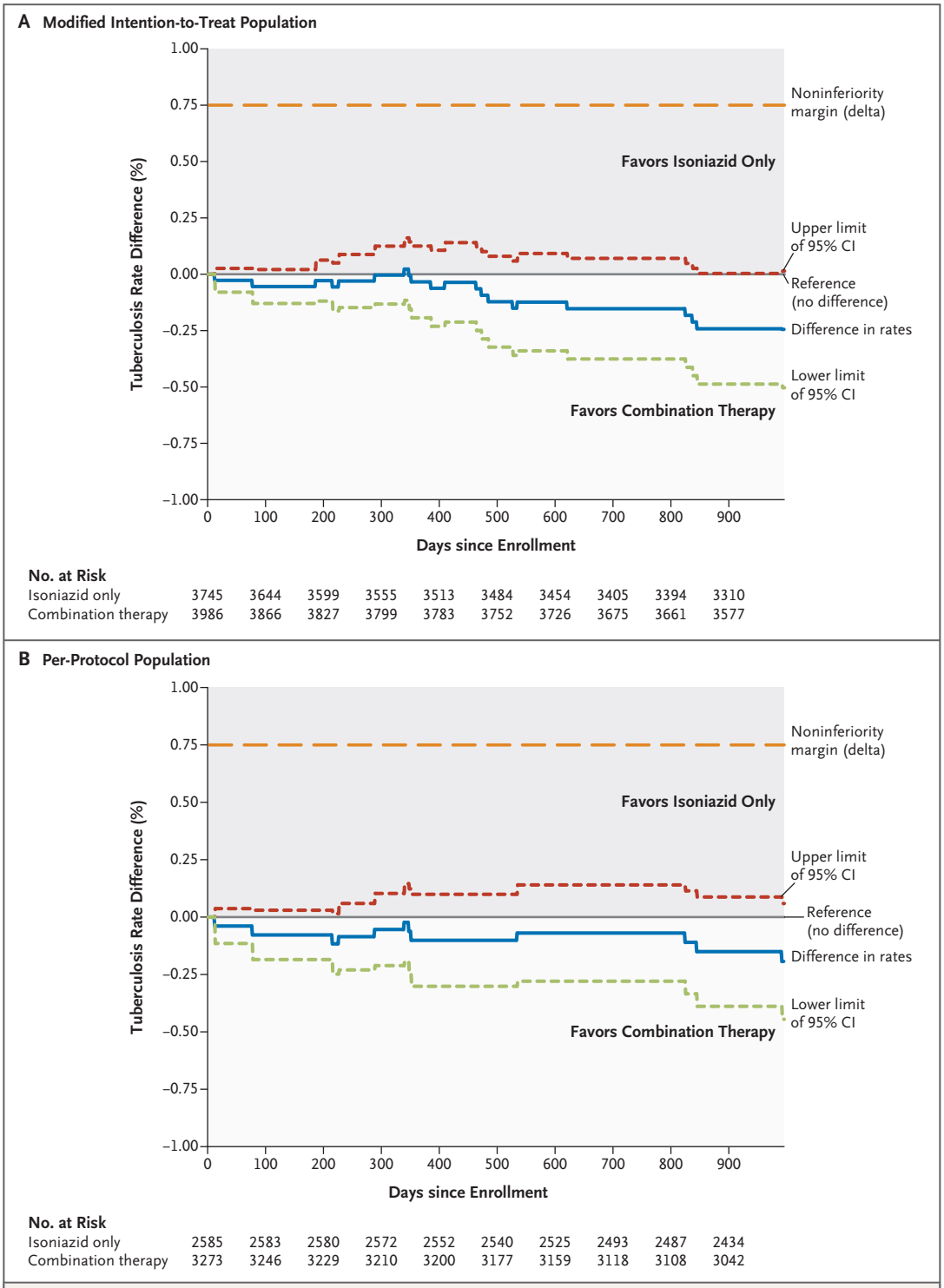

Figure 1. Difference in Rates of Tuberculosis.

Shown are the subjects in the modified intention-to-treat population (Panel A) and the per-protocol population (Panel B) up to 33 months (990 days) after enrollment who had the primary end point of culture-confirmed tuberculosis in adults and culture-confirmed or culture-negative tuberculosis in children under the age of 18 years. The difference in event rates is the rate in the combination-therapy group minus the rate in the isoniazid-only group. The noninferiority margin is 0.75%.

Table 3. Adverse Events.*

Outcome	Isoniazid Only (N=3759)	Combination Therapy (N=4040)	P Value†
Permanent drug discontinuation — no./total no. (%)			
For any reason	1160/3745 (31.0)	713/3986 (17.9)	<0.001
Because of an adverse event	139/3745 (3.7)	196/3986 (4.9)	0.009
Death — no./total no. (%)	39/3745 (1.0)	31/3986 (0.8)	0.22
Any serious adverse event — no. (%)‡	109 (2.9)	64 (1.6)	<0.001
≥1 Adverse event — no. (%)§			
Any	661 (17.6)	595 (14.7)	<0.001
Pregnancy	71 (1.9)	45 (1.1)	0.005
Medication error	37 (1.0)	27 (0.7)	0.12
All other adverse events	584 (15.5)	531 (13.1)	0.003
Attribution — no. (%)¶			
Related to drug	206 (5.5)	332 (8.2)	<0.001
Hepatotoxicity‖	103 (2.7)	18 (0.4)	<0.001
Rash	21 (0.6)	31 (0.8)	0.26
Possible hypersensitivity**	17 (0.5)	152 (3.8)	<0.001
Other drug reaction	65 (1.7)	131 (3.2)	<0.001
Not related to drug	410 (10.9)	226 (5.6)	<0.001
Severity of adverse event — no. (%)††			
Grade 1 or 2	341 (9.1)	310 (7.7)	0.03
Grade 3	202 (5.4)	193 (4.8)	0.24
Grade 4	42 (1.1)	36 (0.9)	0.32
Nongraded events	31 (0.8)	19 (0.5)	0.05

* The numbers of subjects who permanently discontinued a study drug or died were counted in the modified intention-to-treat study population. The numbers of subjects with adverse events were counted in all subjects who received at least one dose of a study drug. Of the 7799 subjects who received at least one dose of a study drug, 6543 (83.9%) had no adverse event, 1062 (13.6%) had one adverse event, and 194 (2.5%) had more than one adverse event.

† All P values were calculated with the use of the chi-square test.

‡ Serious adverse events include deaths while receiving a study drug or within 60 days after the last dose, life-threatening events, hospitalization, disability or permanent damage, and congenital anomalies or birth defects. Of subjects with serious adverse events, 157 had one event and 16 had more than one event.

§ Subjects could have more than one type of serious adverse event (i.e., pregnancy, medication error, or other adverse event).

¶ Attribution was determined by the local study investigator. Adverse events that were attributed to a study drug are further characterized into one of four event categories. One event per subject per category is included, but subjects could have events in more than one category.

‖ Excluded from this category are events that study investigators attributed to new infections with hepatitis A, B, or C virus.

** Among subjects with possible hypersensitivity reactions, six had a systolic blood pressure of less than 90 mm Hg (three with grade 1, one with grade 2, and two with grade 3).[21]

†† Included in this category are all adverse events that are described under Attribution. The highest severity grade per event category per subject was included. Nongraded events were those for which reporting investigators noted that grading was not applicable or there was insufficient information available to assign a grade.

jects permanently discontinued therapy, although they were more likely to stop therapy because of an adverse event (4.9% in combination-therapy group vs. 3.7% in the isoniazid-only group). The proportion of subjects with any adverse event attributed to a study drug was also higher (8.2% in the combination-therapy group vs. 5.5% in the isoniazid-only group); this relationship was also seen with possible hypersensitivity. These findings may be due to factors related to the drugs but could also be related to more frequent interaction between subjects and study staff in the combina-

Table 4. Univariate and Multivariate Analyses of Risk Factors for Tuberculosis.*

Risk	Univariate Analysis		Multivariate Analysis	
	Hazard Ratio (95% CI)	P Value	Adjusted Hazard Ratio (95% CI)	P Value
Combination therapy vs. isoniazid only	0.43 (0.18–1.07)	0.07	0.38 (0.15–0.99)	0.05
Age per 10-yr increase	0.87 (0.65–1.17)	0.37		
Male sex	1.50 (0.63–3.58)	0.36		
Other race or ethnic group vs. white race				
Black	1.56 (0.64–3.81)	0.33		
North American Indian	3.17 (0.41–24.35)	0.27		
Asian	0	NA		
Other	1.47 (0.19–11.32)	0.71		
Ethnic group				
Hispanic vs. non-Hispanic in U.S. or Canada	1.16 (0.47–2.86)	0.75		
Subjects outside U.S. or Canada vs. non-Hispanic in U.S. or Canada	1.34 (0.37–4.85)	0.66		
HIV infection				
HIV infection vs. no HIV infection	7.00 (2.19–22.30)	0.001	4.07 (1.26–3.16)	0.02
Unknown HIV status vs. no HIV infection	0.70 (0.28–1.77)	0.45	0.68 (0.26–1.82)	
Body-mass index per 1-unit increase	0.85 (0.78–0.93)	<0.001	0.81 (0.73–0.90)	<0.001
Region of enrollment				
Brazil vs. U.S. or Canada	1.17 (0.27–5.04)	0.83		
Spain vs. U.S. or Canada	1.42 (0.19–10.63)	0.73		
Indication for treatment				
Conversion to positive tuberculin skin text vs. close contact with a patient with tuberculosis	0.31 (0.07–1.35)	0.12		
HIV infection vs. close contact with a patient with tuberculosis	3.81 (0.89–16.43)	0.07		
Fibrosis vs. close contact with a patient with tuberculosis	0	NA		
Alcohol†				
Use vs. no use	1.36 (0.52–3.51)	0.53		
Abuse vs. no abuse	4.84 (1.58–14.78)	0.006		
Injection-drug use vs. no use	1.29 (0.17–9.59)	0.80		
Hepatitis B or C virus infection				
Combined infection vs. no infection	1.30 (0.17–9.68)	0.80		
Hepatitis status unknown vs. no infection	4.06 (0.55–30.24)	0.17		
Current smoking vs. no smoking	4.73 (1.98–11.27)	<0.001	4.89 (1.90–12.58)	0.001
No completion of high school vs. completion	1.21 (0.51–2.85)	0.66		
History of incarceration vs. no history of incarceration	3.12 (0.92–10.54)	0.07		
Lack of employment vs. employment	2.55 (0.94–6.92)	0.07		
Homelessness vs. no homelessness	2.37 (0.70–8.01)	0.16		

* The multivariate model was the most parsimonious model that contained significant (P<0.05) variables. All other variables were tested against the multivariate model and were not significant. There was no interaction between treatment regimen and any of the risk factors evaluated. HIV denotes human immunodeficiency virus, and NA not applicable.
† Alcohol use was determined by self-report by an answer of "yes" to no more than one question on the CAGE questionnaire, and alcohol abuse by an answer of "yes" to at least two questions.

tion-therapy group (weekly directly observed therapy plus monthly visits during treatment) and the open-label use of a new combination-therapy regimen. Of note, the rates of grade 3, 4, and 5 toxic effects did not differ according to study group. The definition of possible hypersensitivity was intentionally broad; a more detailed and specific evaluation of these and all other adverse events is under way. Hypersensitivity has not been reported in previous studies of combination therapy with rifapentine plus isoniazid.[27,28] The rates of adverse events that were not related to a study drug were higher in the isoniazid-only group, probably as a result of the longer treatment duration and ascertainment of adverse events in this group.

This study assessed primarily HIV-uninfected subjects and did not identify fatal adverse events. Initial studies of the 2-month rifampin–pyrazinamide regimen were conducted primarily among HIV-infected subjects and did not identify episodes of fatal hepatotoxicity that were later seen when the regimen was administered in a broader patient population.[14,15,29-31] Isoniazid-associated hepatotoxicity was not reported in early prevention trials but was reported after broader use outside clinical trials.[32] Monitoring for rare but severe events, including hypersensitivity, will be important when combination therapy with rifapentine plus isoniazid is used in clinical care.

Small studies of combination therapy with rifapentine plus isoniazid suggested that the regimen was effective for latent tuberculosis in 206 HIV-uninfected household contacts of patients with tuberculosis in Brazil[27] and in 328 HIV-infected adults in South Africa.[28] Neither study had sufficient statistical power because of the small numbers of subjects. Our study extended those findings with a sample size that was adequate to evaluate both effectiveness and side-effect profiles. In addition, our study was conducted in countries with low and medium rates of tuberculosis incidence, predominantly among close contacts of patients with tuberculosis and those with conversion to positive results on tuberculin skin tests. Our results indicate that the combination-therapy regimen can be used effectively in such settings. In areas with higher tuberculosis incidence, the risk of reinfection with *M. tuberculosis* is higher, particularly among HIV-infected persons, and these factors might reduce the effectiveness of tuberculosis-prevention therapies. We did not observe an increase in tuberculosis risk late in the follow-up phase, when reinfection might occur.

Acquired rifamycin resistance was reported in HIV-infected persons who were treated with once-weekly rifapentine plus isoniazid in the continuation phase of tuberculosis treatment.[33] In our study, there was one case of rifampin-resistant tuberculosis (in the combination-therapy group), but it is unclear whether this finding was related to the study regimen, given the small number of subjects. In a study of new therapies to prevent tuberculosis infection in HIV-infected adults, 2 of 24 tuberculosis cases were rifampin-resistant.[28] It will be important to monitor for rifampin resistance in breakthrough tuberculosis when the combination regimen is used in clinical practice.

We observed fewer tuberculosis cases than expected. One possible explanation is that the risk of tuberculosis after recent *M. tuberculosis* infection is lower than the estimates used for the sample-size calculation. However, we limited enrollment to subjects with latent *M. tuberculosis* infection who were at the highest risk for tuberculosis. In addition, among the 384 subjects who received little or no treatment, the cumulative rate of tuberculosis (1.64%) was within the range of recent estimates.[8] It must also be remembered that there was no placebo group. The isoniazid-only regimen is estimated to be 90% efficacious,[34] and our results suggest that the combination regimen was similarly efficacious.

The combination-therapy group was directly observed, which improves compliance in the treatment of latent tuberculosis.[35] Both directly observed therapy and a shorter duration of treatment probably explain the higher treatment-completion rate in the combination-therapy group. The regimen could be self-administered, but both adherence and effectiveness might be lower. Conversely, completion rates in the isoniazid-only group were higher than those in clinical practice,[8-11] probably because the subjects were participating in a clinical trial in which they agreed to be followed for 33 months and for which they received compensation for study participation. The difference in regimen effectiveness observed in this study (favoring combination therapy) would probably be greater in clinical practice, particularly if combination therapy were administered with direct observation.

Although the costs associated with combina-

tion therapy (both for the drugs and for direct observation) exceed those of isoniazid-only therapy, combination therapy was shown to be cost-effective in a previous analysis.[36] A formal cost-effectiveness analysis on the basis of data from our study is under way.

Like all rifamycins, rifapentine induces activity of cytochrome P-450 oxidative enzymes and the P-glycoprotein transport system, resulting in drug interactions with warfarin, hormonal contraceptives, HIV-1 protease inhibitors, methadone, and other agents.[37,38] Care should be taken in managing these drug interactions.

Our study has some limitations. First, the noninferiority margin (0.75%) was high in comparison with the event rate in the two study groups. This margin was based on evidenced-based estimates that were available at the time of the study design. However, even if the relative margin (50% of the rate in the isoniazid-only group) were applied to the observed rate (0.43%) in the isoniazid-only group rather than the expected rate (1.5%), noninferiority would still be shown (Fig. 5 in the Supplementary Appendix). Second, only 3% of our study population was infected with HIV. Although there is evidence that combination therapy is effective in HIV-infected adults,[28] enrollment in our study has been extended among HIV-infected subjects to obtain additional data on side-effect profiles. The enrollment of children under the age of 12 years has also been extended to assess side effects in this important subgroup.

In conclusion, 3 months of directly observed, once-weekly therapy with rifapentine plus isoniazid was as effective as self-administered daily isoniazid for 9 months. A 3-month course of once-weekly rifapentine plus isoniazid represents an advance in our ability to treat persons with latent *M. tuberculosis* infection.

The findings and conclusions in this article are those of the authors and do not necessarily represent the views of the CDC or the Agency for Toxic Substances and Disease Registry.

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