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New Regimens to Prevent Tuberculosis in Adults with HIV Infection

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ABSTRACT

BACKGROUND

Treatment of latent tuberculosis in patients infected with the human immunodeficiency virus (HIV) is efficacious, but few patients around the world receive such treatment. We evaluated three new regimens for latent tuberculosis that may be more potent and durable than standard isoniazid treatment.

METHODS

We randomly assigned South African adults with HIV infection and a positive tuberculin skin test who were not taking antiretroviral therapy to receive rifapentine (900 mg) plus isoniazid (900 mg) weekly for 12 weeks, rifampin (600 mg) plus isoniazid (900 mg) twice weekly for 12 weeks, isoniazid (300 mg) daily for up to 6 years (continuous isoniazid), or isoniazid (300 mg) daily for 6 months (control group). The primary end point was tuberculosis-free survival.

RESULTS

The 1148 patients had a median age of 30 years and a median CD4 cell count of 484 per cubic millimeter. Incidence rates of active tuberculosis or death were 3.1 per 100 person-years in the rifapentine–isoniazid group, 2.9 per 100 person-years in the rifampin–isoniazid group, and 2.7 per 100 person-years in the continuous-isoniazid group, as compared with 3.6 per 100 person-years in the control group ($P>0.05$ for all comparisons). Serious adverse reactions were more common in the continuous-isoniazid group (18.4 per 100 person-years) than in the other treatment groups (8.7 to 15.4 per 100 person-years). Two of 58 isolates of *Mycobacterium tuberculosis* (3.4%) were found to have multidrug resistance.

CONCLUSIONS

On the basis of the expected rates of tuberculosis in this population of HIV-infected adults, all secondary prophylactic regimens were effective. Neither a 3-month course of intermittent rifapentine or rifampin with isoniazid nor continuous isoniazid was superior to 6 months of isoniazid. (Funded by the National Institute of Allergy and Infectious Diseases and others; ClinicalTrials.gov number, NCT00057122.)

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Tuberculosis is the most common opportunistic infection and the leading cause of death in adults infected with the human immunodeficiency virus (HIV), especially in Africa, where tuberculosis rates have increased sharply in the past two decades.[1] Previous trials have shown that preventive treatment of HIV-infected patients with isoniazid for 6 to 12 months or a combination of isoniazid and rifampin for 3 months reduces the risk of tuberculosis by 32 to 64%.[2-6] Despite this evidence and a World Health Organization policy endorsing routine use of isoniazid, the number of programs providing preventive treatment against tuberculosis is exceedingly low.[1,7,8] Concerns about low completion rates,[9] the potential for reinfection,[10,11] and selection of drug-resistant mycobacterial strains[12] contribute to the reluctance of public health programs to implement preventive treatment widely.

To address these concerns, we studied the use of 12-week courses of rifapentine given weekly or rifampin given twice weekly, both with isoniazid. The choice of these regimens was based on evidence of increased potency and improved adherence.[13-16] We also studied continuously administered isoniazid, which may be more potent than shorter courses and may prevent reinfection in areas where tuberculosis transmission is common.

Methods

Study Design

The protocol (available with the full text of this article at NEJM.org) was approved by the institutional review boards of Johns Hopkins Medicine and the University of the Witwatersrand, the Food and Drug Administration (FDA) (Investigational New Drug Application 62,611), and the Medicines Control Council of South Africa. The protocol was designed by the authors, and all data were collected by the authors and study staff in Soweto, South Africa. The authors made the decision to submit the article for publication and vouch for the completeness and accuracy of the data presented and the adherence of the study and this report to the protocol.

Patients

The study was conducted in Soweto, a community with a high prevalence of HIV infection and tuberculosis. HIV-infected adults with an induration that was 5 mm or more in diameter in response to a tuberculin skin test were screened for enrollment from September 2002 through June 2005. Eligible patients were at least 18 years of age, were not pregnant or breast-feeding, and did not have active tuberculosis, as ruled out on the basis of symptom review, chest radiography, and, if indicated, sputum culture. Patients were also excluded if they had ever received tuberculosis therapy for more than 2 months, were currently receiving antiretroviral therapy, or had a CD4 cell count of less than 200 per cubic millimeter. Written informed consent was obtained from all patients.

Treatment Groups and Administration

This was an open-label, randomized trial of rifapentine (Priftin, Sanofi Aventis; 900 mg) plus isoniazid (900 mg) once weekly for 12 weeks (rifapentine–isoniazid), rifampin (600 mg) plus isoniazid (900 mg) twice weekly for 12 weeks (rifampin–isoniazid), isoniazid (300 mg) daily for the duration of the study (≤6 years) (continuous isoniazid), or a control regimen of isoniazid (300 mg) daily for 6 months (6-month isoniazid). All patients received pyridoxine (25 mg) with each dose of antituberculosis medication. Treatment in the rifapentine–isoniazid and rifampin–isoniazid groups was directly observed in the study clinic, whereas in the 6-month–isoniazid and continuous-isoniazid groups, the study drugs were self-administered. Treatment allocation was by a computer-generated algorithm that randomly assigned patients in blocks of 2:2:2:1 to the rifapentine–isoniazid, rifampin–isoniazid, 6-month–isoniazid, and continuous-isoniazid groups, respectively.

Study Procedures

During the treatment period, scheduled visits occurred once weekly for the rifapentine–isoniazid group and twice weekly for the rifampin–isoniazid group, every 2 weeks for the first 6 months for the two isoniazid groups, and monthly thereafter for the continuous-isoniazid group. Patients who had completed the assigned study regimen or had discontinued it were seen every 6 months until the end of the trial.

At each study visit, patients were screened for tuberculosis symptoms by a study nurse. For those with symptoms, assessment of a sputum smear, mycobacterial culture, and chest radiography were performed. The National Health Laboratory Service in Johannesburg, South Africa, performed the mycobacterial culture and drug-sensitivity testing using a mycobacterial-testing system (BACTEC mycobacterial growth indicator tube [MGIT] 960,

BD). Species determination was achieved by means of nucleic acid amplification (AccuProbe, Gen-Probe), and drug-susceptibility testing was conducted with the use of critical concentrations of isoniazid and rifampin in MGIT culture.

Alanine and aspartate aminotransferase levels were measured in all patients 1, 2, and 6 months after randomization, as well as every 6 months thereafter in the continuous-isoniazid group. CD4 cell counts were measured every 6 months, and CD4 cell counts and HIV viral loads were measured every 3 months in patients whose CD4 cell count was less than 350 per cubic millimeter beginning in the second quarter of 2004. Patients eligible for antiretroviral therapy were referred to an HIV clinic for the initiation of such therapy but remained in the study. The first-line antiretroviral regimen in use in South Africa during the trial consisted of stavudine, lamivudine, and efavirenz or nevirapine. Women who became pregnant while receiving rifapentine–isoniazid or rifampin–isoniazid were switched to the 6-month–isoniazid group, and treatment was stopped after they had received isoniazid for a total of 6 months. All patients who discontinued therapy were followed until the end of the study.

STUDY END POINTS

The primary end point was tuberculosis-free survival. Cases were classified as confirmed, probable, or possible tuberculosis. Confirmed tuberculosis was defined as the presence of clinical signs and symptoms and a positive culture for *Mycobacterium tuberculosis* from any site. Probable tuberculosis was defined as the presence of signs and symptoms with acid-fast bacilli in a sputum smear or caseous necrosis in a tissue-biopsy specimen. Possible tuberculosis was defined as the presence of signs and symptoms without microbiologic or histologic evidence of *M. tuberculosis* but with a clinical response to antituberculosis therapy.

Patients who had signs and symptoms of tuberculosis without microbiologic or biopsy confirmation and without a clinical response to therapy were categorized as having "suspected tuberculosis," but these cases were not counted as events. Diagnosed cases of tuberculosis and deaths were ascertained through active follow-up of patients who missed scheduled visits. Clinical records and death certificates were obtained whenever possible. An independent end-point committee reviewed and categorized all end points.

The secondary outcomes of the study were adherence to the study regimen, adverse events, discontinuation of study medication for any reason, and mycobacterial drug resistance in patients with tuberculosis. Serious adverse events were defined as grade 3 or 4 adverse events according to the Division of AIDS toxicity table, hospitalization, or death. Pregnancy also was reported as a serious adverse event but was not analyzed as such.

STATISTICAL ANALYSIS

Patients with confirmed, probable, or possible tuberculosis and those who died were included in the intention-to-treat analyses of the primary end point. The trial was originally designed to show the superiority of the three new regimens for preventing tuberculosis over the standard therapy of isoniazid for 6 months. We assumed that the annual risk of tuberculosis would be 6% in the 6-month isoniazid group, on the basis of data from trials conducted elsewhere in Africa[8,9]; that the rifapentine–isoniazid and rifampin–isoniazid regimens would reduce the incidence of tuberculosis by 50%, to 3% per year, on the basis of studies in animals[17,18]; and that the continuous-isoniazid regimen would reduce the incidence by 82%, to 1.1% per year, by preventing reinfection.

With a minimum of 3 years of follow-up per patient, we anticipated a total of 124 tuberculosis cases among the 1148 study patients. The probability of a type I error was set at 0.05, and the power of the study was estimated at 90%. Incidence-rate ratios and corresponding exact 95% confidence intervals for tuberculosis and for tuberculosis or death were calculated, after censoring of data for patients lost to follow-up. The primary statistical analysis was performed with the use of the log-rank test. No adjustment was made for multiple comparisons. A formal interim analysis of efficacy with respect to the tuberculosis end point, with the use of the O'Brien–Fleming alpha spending function,[9] was planned at the time of 50% accrual of cases and took place when there was a total of 51 tuberculosis cases; tests were performed with a significance level of 0.006 for each of the three pairwise comparisons with the 6-month–isoniazid group.[19]

On the recommendation of the independent data and safety monitoring board, which was concerned that patients might die of tuberculosis before it was diagnosed, the follow-up period was extended, and the primary end point was changed

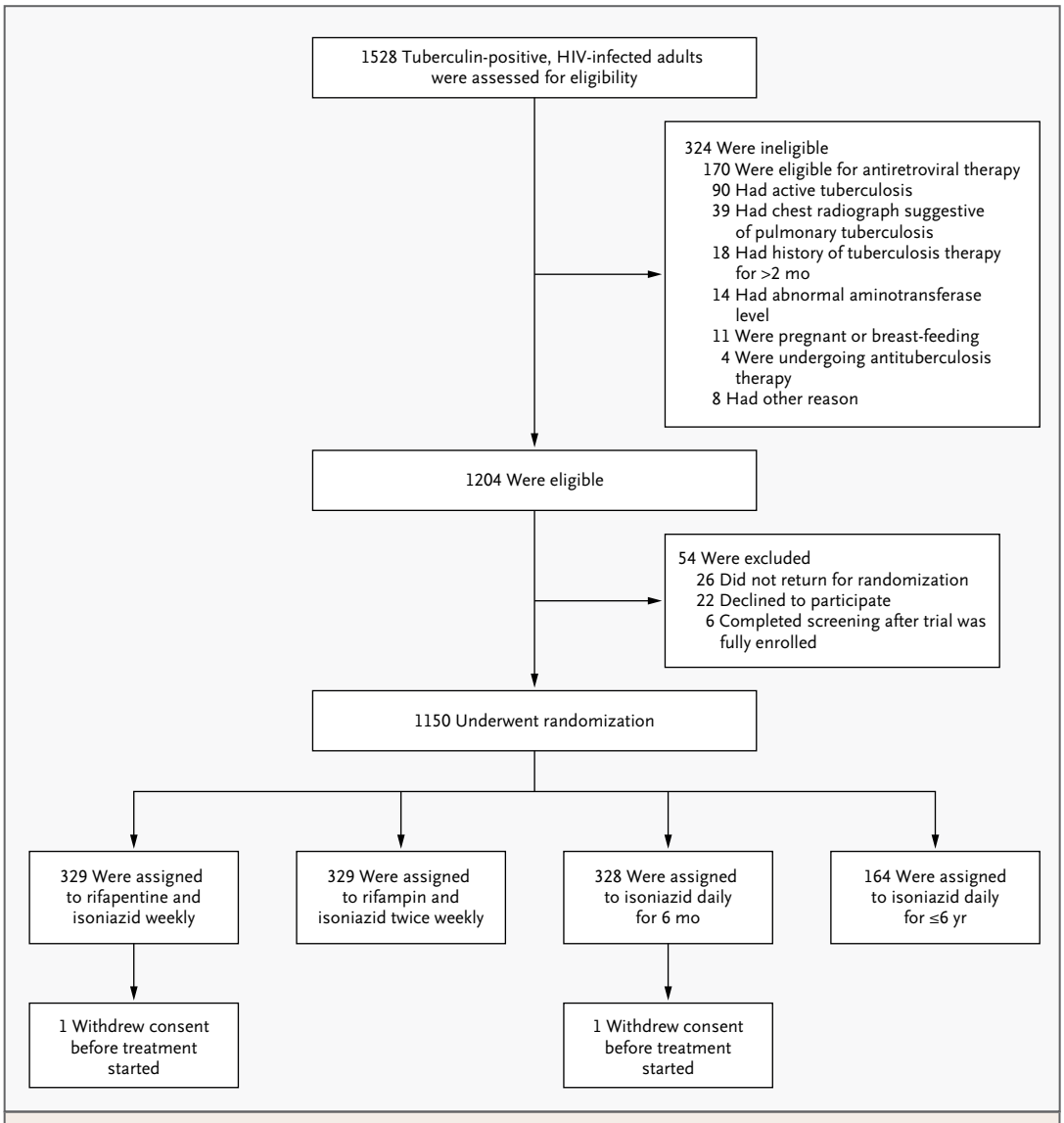


Figure 1. Recruitment and Randomization of Study Patients.
Patients could have more than one reason for ineligibility.

to tuberculosis or death. A second interim analysis was conducted when there were 115 events for this end point, with tests at a significance level of 0.02. At the end of the study, there were 128 events, with a final test at a significance level of about 0.04.

An as-treated analysis was performed with data for patients who had received more than 2 months of study therapy and who did not have tuberculosis in the first 3-month period after randomization. Data for participants who discontinued their study therapy prematurely were censored 60 days after the medication was stopped to ensure that end points that might have led to discontinuation were included.

RESULTS

STUDY PARTICIPANTS AND FOLLOW-UP

From September 2002 through June 2005, a total of 1528 tuberculin-positive, HIV-infected adults were screened; 1176 (77.0%) were eligible for the study, of whom 1150 (97.8%) were enrolled and randomly assigned to a study regimen (Fig. 1).

Table 1. Baseline Characteristics of the Study Patients, According to Treatment Group.

Characteristic	Rifapentine with Isoniazid Weekly for 12 Wk (N=328)	Rifampin with Isoniazid Twice Weekly for 12 Wk (N=329)	Isoniazid Daily for ≤6 Yr (N=164)	Isoniazid Daily for 6 Mo (N=327)	All Patients (N=1148)
Female sex — no. (%)	277 (84.5)	267 (81.2)	139 (84.8)	273 (83.5)	956 (83.3)
Age — yr					
Median	30.3	30.5	30.2	30.4	30.4
Interquartile range	26.3–35.0	27.0–34.3	25.4–34.2	26.3–34.9	26.4–34.7
Black race — no. (%)*	325 (99.1)	327 (99.4)	163 (99.4)	327 (100.0)	1142 (99.5)
≥12 Yr of schooling — no. (%)	93 (28.4)	102 (31.0)	61 (37.2)	117 (35.8)	373 (32.5)
Formal employment — no. (%)	40 (12.2)	34 (10.3)	12 (7.3)	39 (11.9)	125 (10.9)
Imprisoned before enrollment — no. (%)	48 (14.6)	52 (15.8)	21 (12.8)	40 (12.2)	161 (14.0)
Diameter of induration from tuberculin skin test — mm					
Median	14.5	15.0	15.0	15.0	15.0
Interquartile range	12–19	12–19	12–19	11–18	12–19
CD4 count — cells/mm^3					
Median	471	498	476	490	484
Interquartile range	352–666	353–696	346–644	340–670	350–672
Viral load — $\log_{10}$ copies/ml					
Median	4.3	4.0	4.2	4.2	4.2
Interquartile range	3.6–4.8	3.4–4.7	3.6–4.7	3.6–4.7	3.6–4.7
Body-mass index					
Median	25.0	24.7	25.3	24.9	24.9
Interquartile range	21.8–29.2	21.9–28.4	22.6–29.3	22.1–29.5	22.1–29.0

* Black race was self-reported.

The main reasons for nonenrollment were eligibility for antiretroviral therapy (170 patients) and diagnosis of active tuberculosis during the screening process (90 patients). The median age of patients was 30.4 years, and 83.3% were women. The median CD4 cell count was 484 per cubic millimeter, the $\log_{10}$ HIV viral load was 4.2 copies per milliliter, and the body-mass index (the weight in kilograms divided by the square of the height in meters) was 24.9. The baseline characteristics were balanced among the four treatment groups (Table 1).

The median follow-up time was 4.0 years in the rifapentine–isoniazid group, 4.1 years in the rifampin–isoniazid group, 3.9 years in the continuous-isoniazid group, and 3.9 years in the 6-month–isoniazid group. At the end of the study, 887 of the 1148 patients (77.3%) had been seen in the previous 6 months or had a known date of death. During the follow-up period, 215 patients (18.7%) were started on antiretroviral therapy; the median CD4 cell count at the initiation of antiretroviral therapy was 185 per cubic millimeter (interquartile range, 148 to 234). Cumulatively, patients received antiretroviral therapy for less than 10% of total follow-up time.

ADHERENCE

The proportions of patients who reported taking or were observed taking more than 90% of their assigned doses of study medication in the time allotted were 95.7% in the rifapentine–isoniazid group, 94.8% in the rifampin–isoniazid group, and 83.8% in the 6-month–isoniazid group. Patients in the continuous-isoniazid group took isoniazid for 89.1% of the total follow-up time; 60.4% of patients received daily isoniazid for more than 3 years, and 43.3% for more than 4 years. The median duration of receipt of continuous isoniazid was 3.3 years (interquartile range, 2.1 to 4.3). Other

Table 2. Rates of Study End Points According to Treatment Group.*

End Point	Rifapentine–Isoniazid	Rifampin–Isoniazid	Continuous Isoniazid	6-Mo Isoniazid	All
Tuberculosis					
No. of cases	24	24	8	22	78
Person-yr of follow-up	1187.5	1219.7	561.0	1143.9	4112.1
Incidence rate per 100 person-yr	2.0	2.0	1.4	1.9	1.9
Death					
No. of cases	17	16	8	25	66
Person-yr of follow-up	1223.6	1269.8	574.2	1180.0	4247.6
Incidence rate per 100 person-yr	1.4	1.3	1.4	2.1	1.6
Death or tuberculosis					
No. of cases	37	35	15	41	128
Person-yr of follow-up	1187.5	1219.7	561.0	1143.9	4112.1
Incidence rate per 100 person-yr	3.1	2.9	2.7	3.6	3.1
Tuberculosis					
Crude incidence-rate ratio (95% CI)	1.05 (0.56–1.97)	1.02 (0.55–1.91)	0.74 (0.29–1.73)	Reference 1.0	
P value	0.87	0.94	0.48		
Death					
Crude incidence-rate ratio (95% CI)	0.66 (0.33–1.26)	0.59 (0.30–1.16)	0.66 (0.26–1.50)	Reference 1.0	
P value	0.18	0.10	0.31		
Death or tuberculosis					
Crude incidence-rate ratio (95% CI)	0.87 (0.54–1.39)	0.80 (0.50–1.29)	0.75 (0.38–1.38)	Reference 1.0	
P value	0.54	0.34	0.34		

* P values are for the comparison with the 6-month regimen of isoniazid. CI denotes confidence interval.

data regarding study completion and adherence over time are shown in Figure 1 in the Supplementary Appendix (available at NEJM.org).

TUBERCULOSIS CASES AND DEATHS

Numbers and rates of cases of tuberculosis, death, or either event are shown in Table 2. Tuberculosis was diagnosed in 78 patients, of whom 62 (79%) had confirmed tuberculosis, 11 (14%) had probable tuberculosis, and 5 (6%) had possible tuberculosis. The overall incidence of all tuberculosis was 1.9 cases per 100 person-years. There were 66 deaths during the follow-up period, for an overall incidence of 1.6 deaths per 100 person-years. There were no significant differences in the incidences of tuberculosis or death between any of the three groups treated with the newer regimens and the control group (P>0.05 for all comparisons, by the log-rank test). Kaplan–Meier estimates of the risk of reaching the primary end point (tuberculosis or death) in the intention-to-treat population are shown in Figure 2.

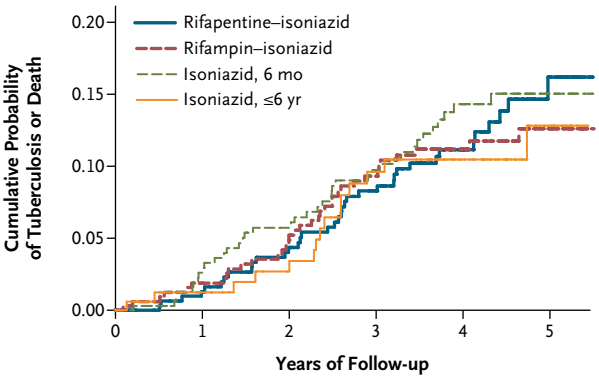
A post hoc, as-treated analysis included data from patients who had received the assigned study therapy for at least 2 months, with data censored 60 days after premature discontinuation of the regimen. Because of the high rates of treatment completion in the three groups with the shortest treatment phase, most censoring occurred in the continuous-isoniazid group. Thus, most of the follow-up data for the groups treated with the shorter regimens were obtained after the completion of therapy, whereas most of the follow-up data for the continuous-isoniazid group were collected while the patients were receiving therapy. The rate of tuberculosis or death was much lower in the continuous-isoniazid group than in the other three groups in this analysis. In a Cox proportional-hazards analysis, the continuous-isoniazid group had a risk of tuberculosis or death that was 58% lower than the risk in the control group (P=0.02). The rate of tuberculosis escalated markedly after discontinuation of continuous-isoniazid treatment.

DISCONTINUATION OF THERAPY, ADVERSE EVENTS, AND DRUG RESISTANCE

The leading reasons for stopping preventive treatment were pregnancy (accounting for 34 patients), initiation of highly active antiretroviral therapy (27 patients, all in the continuous-isoniazid group), and withdrawal from the study because of work responsibilities (14 patients).

The types and rates of adverse events are shown in Table 3. For the three shorter regimens, almost all adverse events occurred after completion of treatment, whereas 87.3% of adverse events in the continuous-isoniazid group occurred during the medication phase. Rates of serious adverse events (grade 3 or 4 toxic effects, death, and active tuberculosis) while patients were receiving the study drugs were 8.7 per 100 person-years in the rifapentine–isoniazid group, 10.6 per 100 person-years in the rifampin–isoniazid group, 18.4 per 100 person-years in the continuous-isoniazid group, and 15.4 per 100 person-years in the 6-month–isoniazid group (P>0.05 for all comparisons with the 6-month–isoniazid group). There were no deaths attributed to a study drug. A grade 3 or 4 elevation in the aspartate or alanine aminotransferase level occurred during the treatment phase in 1.5%, 2.4%, 28.0%, and 5.5% of patients in the rifapentine–isoniazid, rifampin–isoniazid, continuous-isoniazid, and 6-month–isoniazid groups, respectively (P<0.001 for the comparison of continuous isoniazid with 6-month isoniazid). The median time from randomization to the first detected grade 3 or 4 elevation in the aminotransferase level was 47 days (interquartile range, 36 to 57), 28 days (interquartile range, 8 to 68), 571 days (interquartile range, 358 to 674), and 175 days (interquartile range, 56 to 182) in the rifapentine–isoniazid, rifampin–isoniazid, continuous-isoniazid, and 6-month–isoniazid groups, respectively.

Drug-susceptibility testing was performed in 58 of 62 *M. tuberculosis* isolates (94%). Two cases of isoniazid-resistant tuberculosis and three cases of rifampin-resistant tuberculosis were detected. Multidrug-resistant tuberculosis (resistance to both isoniazid and rifampin) was detected in 2 of the isolates (3%), 1 from a patient in the rifapentine–isoniazid group and the other from a patient in the continuous-isoniazid group (Table 4).



No. at Risk

Rifapentine–isoniazid	326	299	275	249	160	52
Rifampin–isoniazid	327	301	284	252	162	56
Isoniazid, 6 mo	327	289	260	238	145	49
Isoniazid, ≤6 yr	164	144	131	109	73	26

Figure 2. Kaplan–Meier Estimates of the Risk of Tuberculosis or Death in the Intention-to-Treat Population, According to Treatment Group.

The four treatment regimens were rifapentine and isoniazid weekly for 12 weeks, rifampin and isoniazid twice a week for 12 weeks, isoniazid daily for up to 6 years (continuous regimen), and isoniazid daily for 6 months (control regimen).

DISCUSSION

We found that three new prophylactic regimens against tuberculosis in HIV-infected adults were not superior to the control regimen of isoniazid therapy for 6 months. The overall rate of tuberculosis was 1.9 cases per 100 person-years, with no significant difference between any of the three new regimens and the control regimen. Among HIV-infected people in Africa with a positive tuberculin skin test who are not receiving antituberculosis treatment, the expected annual rate of tuberculosis ranges from 5 and 10%.[2,4,6,7] The rate of tuberculosis in the control group was also substantially lower than anticipated, suggesting that all the treatments used in this study performed better than regimens used in earlier African studies.[10,11] The shorter, rifamycin-based regimens had higher adherence rates than did the 6-month isoniazid regimen and did not appear to select for drug-resistant *M. tuberculosis* in the small number of isolates cultured. These results are consistent with an earlier study showing the efficacy of daily isoniazid and rifampin in adults with HIV infection,[2] but we found that a twice-weekly regimen was also efficacious.

No clinically significant safety concerns were identified with the once-weekly regimen of rifapentine and isoniazid in our study, a finding that is similar to the results of a smaller trial involving household contacts of patients with tuberculosis

Table 3. Adverse Events, Including Those Occurring after Discontinuation of Study Medications, and Status of Study Medications after the Adverse Events.

Event	Rifapentine–Isoniazid (N=328)	Rifampin–Isoniazid (N=329)	Continuous Isoniazid (N=164)	6-Mo Isoniazid (N=327)	Total (N=1148)
Adverse event — no. (rate per 100 enrolled patients)*					
Hospitalization	95 (29.0)	89 (27.1)	38 (23.2)	104 (31.8)	326 (28.4)
Pregnancy†	81 (24.7)	74 (22.5)	31 (18.9)	49 (15.0)	235 (20.5)
Death	17 (5.2)	16 (4.9)	8 (4.9)	25 (7.6)	66 (5.7)
Grade 3 toxic effect	17 (5.2)	15 (4.6)	35 (21.3)	17 (5.2)	84 (7.3)
Grade 4 toxic effect	4 (1.2)	9 (2.7)	18 (11.0)	14 (4.3)	45 (3.9)
Other	3 (0.9)	7 (2.1)	7 (4.3)	7 (2.1)	24 (2.1)
Total	217 (66.2)	210 (63.8)	137 (83.5)	216 (66.1)	780 (67.9)
Treatment status after event — no. (% of total no. with adverse event)					
Treatment discontinued					
Temporarily	5 (2.3)	7 (3.3)	39 (28.5)	15 (6.9)	66 (8.5)
Permanently	4 (1.8)	8 (3.8)	50 (36.5)	4 (1.9)	66 (8.5)
Not receiving study regimen at time of event	207 (95.4)	195 (92.9)	17 (12.4)	183 (84.7)	602 (77.2)
Treatment uninterrupted	1 (0.5)	0	29 (21.2)	12 (5.6)	42 (5.4)
Treatment restarted	0	0	2 (1.5)	2 (0.9)	4 (0.5)

* Note that rates are not in person-years. Because some patients had more than one event, rates are reported instead of proportions.

† Pregnancy was considered an adverse event because rifapentine and rifampin have not been proven safe for use in pregnancy (FDA Category C).

in Brazil.[14] A recent, large trial of this regimen as compared with 9 months of isoniazid in a population largely uninfected with HIV showed noninferiority, which is consistent with our results.[20] The use of intermittent, short-course rifamycin regimens to prevent tuberculosis is appealing because adherence is improved, therapy can be supervised, and adverse reactions should be minimized. Use of rifamycins is problematic in patients receiving HIV protease inhibitors, which are metabolized by P-450 cytochromes, but concomitant use of rifampin and efavirenz does not appear to compromise antiviral activity.[21]

We found no additional benefit of continuous isoniazid as compared with 6 months of isoniazid as preventive treatment in our intention-to-treat analysis. Our study was not blinded, however, and patients assigned to continuous isoniazid discontinued treatment for a number of reasons. Our post hoc analyses suggest that continuous isoniazid was effective while patients were taking the drug but that its effectiveness was lost when treatment ended. Hepatotoxic adverse events were more common with continuous isoniazid than with the 6-month regimen, but none of these events were fatal. Our results support data from a trial in Botswana comparing a 3-year course of isoniazid therapy with the 6-month regimen, in which the longer regimen was superior.[22] The Botswana trial was placebo-controlled, and the rate of treatment discontinuation with prolonged isoniazid treatment was lower in that study than in ours. Taken together, these data suggest that longer courses of isoniazid are efficacious but that the benefit will be compromised by discontinuation of treatment and adverse events.

Adherence to antituberculosis therapy was good in our trial, a finding that is consistent with reports from African programs showing that 70 to 90% of HIV-infected adults given isoniazid completed treatment.[23,24] In our trial, adherence to the three shorter regimens was better than adherence to continuous isoniazid.

Intermittent rifapentine therapy for active tuberculosis in patients with advanced HIV infection has been associated with the emergence of organ-

Table 4. Cases of Tuberculosis, Culture-Confirmed Cases, and Drug-Resistant Isolates, According to Treatment Group.

Tuberculosis Cases	Rifapentine–Isoniazid	Rifampin–Isoniazid	Continuous Isoniazid	6-Mo Isoniazid	Total
			number of cases		
All cases*	24	24	8	22	78
Culture-confirmed cases	21	18	5	18	62
Drug-resistant isolate					
Total tested	21	16	5	16	58
Resistant					
To isoniazid†	1	0	1	0	2
To rifampin†	2	0	1	0	3
To both	1	0	1	0	2

* The numbers include possible, probable, and confirmed cases of tuberculosis.
† The numbers include multidrug-resistant cases.

isms that are resistant to rifampin.[25] Overall, the prevalence of multidrug-resistant tuberculosis in our study was 3.4%, which is similar to estimates in South Africa at the time of our study.[26] We did not detect increased selection of resistant organisms, probably because of the reduced bacterial load in latent tuberculosis; however, our sample was small.

The prevalence of active tuberculosis was 5.9% among the adults screened for this trial, which is similar to the prevalence among HIV-infected patients in South Africa and other areas with a high burden of tuberculosis when they begin to receive antiretroviral therapy[27,28] or prenatal care.[29] The World Health Organization has recently revised its guidelines for antituberculosis therapy[30] to recommend the use of isoniazid for all HIV-infected persons at high risk for tuberculosis, including pregnant women, children, and patients receiving antiretroviral therapy, regardless of tuberculin status. We studied only HIV-infected adults with a positive tuberculin skin test, who account for up to 50% of HIV-infected patients in southern Africa and make up a group at particularly high risk for the development of tuberculosis; thus, our results may not be generalizable to lower-risk groups.

In summary, short-course, rifamycin-based preventive treatment had similar, not superior, efficacy to 6 months of isoniazid in tuberculin-positive adults infected with HIV. Use of these regimens in clinical practice could substantially increase the number of patients who receive and complete preventive therapy. Our findings, along with those of other investigators,[22] suggest that continuous treatment with isoniazid may be effective in preventing reactivation of and reinfection with *M. tuberculosis* in Africa. More widespread use of preventive therapy, regardless of the regimen chosen, is essential to help control the epidemic of HIV-related tuberculosis.

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