

Rifapentine and isoniazid once a week versus rifampicin and isoniazid twice a week for treatment of drug-susceptible pulmonary tuberculosis in HIV-negative patients: a randomised clinical trial

The Tuberculosis Trials Consortium*

Summary

Background Rifapentine has a long half-life in serum, which suggests a possible treatment once a week for tuberculosis. We aimed to compare rifapentine and isoniazid once a week with rifampicin and isoniazid twice a week.

Methods We did a randomised, multicentre, open-label trial in the USA and Canada of HIV-negative people with drug-susceptible pulmonary tuberculosis who had completed 2 months of a 6-month treatment regimen. We randomly allocated patients directly observed treatment with either 600 mg rifapentine plus 900 mg isoniazid once a week or 600 mg rifampicin plus 900 mg isoniazid twice a week. Primary outcome was failure/relapse. Analysis was by intention to treat.

Findings 1004 patients were enrolled (502 per treatment group). 928 successfully completed treatment, and 803 completed the 2-year 4-month study. Crude rates of failure/relapse were 46/502 (9.2%) in those on rifapentine once a week, and 28/502 (5.6%) in those given rifampicin twice a week (relative risk 1.64, 95% CI 1.04–2.58, $p=0.04$). By proportional hazards regression, five characteristics were independently associated with increased risk of failure/relapse: sputum culture positive at 2 months (hazard ratio 2.8, 95% CI 1.7–4.6); cavitation on chest radiography (3.0, 1.6–5.9); being underweight (3.0, 1.8–4.9); bilateral pulmonary involvement (1.8, 1.0–3.1); and being a non-Hispanic white person (1.8, 1.1–3.0). Adjustment for imbalances in 2-month culture and cavitation diminished the association of treatment group with outcome (1.34; 0.83–2.18; $p=0.23$). Of participants without cavitation, rates of failure/relapse were 6/210 (2.9%) in the once a week group and 6/241 (2.5%) in the twice a week group (relative risk 1.15; 95% CI 0.38–3.50; $p=0.81$). Rates of adverse events and death were similar in the two treatment groups.

Interpretation Rifapentine once a week is safe and effective for treatment of pulmonary tuberculosis in HIV-negative people without cavitation on chest radiography. Clinical, radiographic, and microbiological data help to identify patients with tuberculosis who are at increased risk of failure or relapse when treated with either regimen.

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Introduction

Short-course treatment with a regimen containing rifampicin is highly effective for cure of tuberculosis.^{1,2} Directly-observed treatment with rifampicin prevents acquired drug resistance, increases cure rates, and reduces incidence of secondary cases of tuberculosis.³ Treatment with a rifampicin-containing regimen can be given twice a week after an initial daily phase, which greatly simplifies treatment and facilitates directly-observed therapy.⁴ Although less frequent dosing (eg, once a week) would further facilitate therapy, treatment once a week with isoniazid and rifampicin is not sufficiently effective, and a substantial proportion of patients receiving this regimen have various adverse reactions, including thrombocytopenia and flu-like syndrome.⁵

Rifapentine is a rifamycin derivative with excellent activity against *Mycobacterium tuberculosis* in vitro and in animals.^{6,7} Rifapentine has a longer half-life in serum than rifampicin (10–15 h⁸ vs 2–3 h⁹), and therefore could be effective for treatment of tuberculosis once a week. Compared with the standard regimen twice a week, treatment once a week during the continuation phase would reduce by 30% the number of contacts needed between patient and provider of directly-observed treatment. We did a randomised, open-label, multicentre trial to compare the once a week rifapentine-based treatment with the standard twice a week rifampicin-based treatment in the last 4 months (continuation phase) of a 6-month regimen for patients with pulmonary tuberculosis.

Methods

Patients

Patients 18 years of age or older, who were HIV-negative with pulmonary tuberculosis confirmed by culture from a respiratory specimen, were assessed for inclusion in the study. Patients were excluded if their isolate was resistant to 1.0 mg/L isoniazid or 1.0 mg/L rifampicin on solid media. Other exclusion criteria were intolerance to study drugs, tuberculosis of the central nervous system or bones or joints, silicosis, pregnancy or breastfeeding, or the following abnormal laboratory values: haemoglobin less than 70 g/L, platelets less than $50 \times 10^9/L$, serum aspartate aminotransferase three or more times the upper limit of normal, serum bilirubin 2.5 or more times the upper limit of normal, or creatinine two or more times the upper limit of normal.

The study was approved and overseen by institutional review boards at the US Centers for Disease Control and Prevention (CDC) and at every clinical site. All participants gave informed consent.

Procedures

All patients received isoniazid, rifampicin, pyrazinamide, and either ethambutol or streptomycin during the intensive phase (first 2 months).¹⁰ For the first 2 weeks,

treatment was daily; thereafter, four-drug therapy could be given daily, three times a week, or twice a week, at the discretion of the doctor at the local site. Four-drug therapy had to include a minimum of 40 observed daily doses (or equivalent intermittent doses), and had to be completed within 70 days. All intermittent and more than 70% of daily doses were given as directly-observed therapy.

To enrol a patient who had completed the intensive phase, the coordinator or investigator from a study site telephoned CDC. CDC staff ran a computer program that confirmed eligibility and randomly assigned patients to one of the two treatment groups. The randomisation program included blocking by study site ($n=29$; a list of sites is given at the end of the report) and by HIV status. Patients were allocated either 16 doses once a week of rifapentine 600 mg and isoniazid 15 mg/kg (maximum 900 mg), or 32 doses two times a week of rifampicin 10 mg/kg (maximum 600 mg) and isoniazid 15 mg/kg (maximum 900 mg), all given under direct observation. Results in HIV-1-seropositive patients have been reported.¹¹

A study nurse or doctor assessed every patient every 4 weeks during treatment, and 3, 6, 9, 12, 18, and 24 months after completion of therapy. Patients provided one sputum sample at all scheduled visits, and whenever the patient had symptoms consistent with recurrent tuberculosis. The primary outcome, termed failure/relapse, included culture-positive failure, clinical failure, culture-positive relapse, clinical relapse, and failure after non-adherence (see Definitions).

Culture in liquid media (supplemented by solid media at some sites) was done in certified clinical laboratories at participating sites. Staff in these laboratories sent isolates obtained at diagnosis and at time of suspected treatment failure or relapse to the CDC laboratory for confirmatory susceptibility testing with solid media and the proportional method.¹² We compared isolates taken at randomisation and at failure or relapse by IS6110 restriction fragment length polymorphism testing,¹³ with further analysis with the secondary probe pTBN12 for isolates having fewer than six hybridising bands on IS6110 testing (DNA fingerprint).¹⁴

Definitions

Culture-positive failure was defined as having any of the following, arising after 8 weeks of treatment (ie, 4 months after starting treatment for tuberculosis): one sputum culture positive for *M tuberculosis* with ten or more colonies on solid media; two or more sputum cultures with any amount of growth on solid or in liquid media; or one positive culture from an extrapulmonary site. Clinical failure was defined as evidence of progressive tuberculosis by clinical methods, radiography, or both, which was not confirmed by positive culture, after 8 weeks of study therapy, in a patient who did not have another probable cause and who subsequently responded to altered or lengthened anti-tuberculosis treatment. Patients who defaulted before completion of therapy, and who later returned with culture-positive tuberculosis, were termed failures after nonadherence. Culture-positive relapse was defined as a positive culture—with the criteria above—after completion of treatment. Definition of clinical relapse was analogous to that of clinical failure, but included events occurring after completion of treatment.

All positive cultures after 2 months of treatment were assessed for possible cross-contamination. Patients in whom only one culture was positive, whose DNA fingerprint was changed when compared with the initial isolate, and for whom there was little clinical or

radiographic evidence of recurrent tuberculosis were classified as false-positive cultures.¹⁵ All outcomes were reviewed and classified by a committee that did not know the treatment regimen used.

Patients treated more than 14 days beyond the scheduled end of study treatment, or with more than 14 days of treatment with other anti-tuberculosis drugs, were designated by the protocol as having received a non-study regimen, but were included in the intention to treat analysis. Patients were classified as having cavitation or bilateral disease if these signs were present on the chest radiograph obtained at diagnosis or at the end of the intensive phase (as documented by the site radiologist or principal investigator). Patients were defined as underweight if they were more than 10% below ideal bodyweight at diagnosis.¹⁶

Statistical analysis

We assumed an event rate of 3.5% with standard treatment. Sample size was specified to detect a 5% difference in the event rate (ie, $\geq 8.5\%$) after 2 years, with 95% confidence and 80% power. The sample size needed was about 700 HIV-negative participants, which was increased to 1000 on the assumption that 30% of patients

	Rifapentine once a week (n=502)	Rifampicin twice a week (n=502)
Demographic features		
Age (years, mean [SD])	45 (15)	45 (15)
Men	372 (74%)	380 (76%)
Ethnic origin		
Non-Hispanic white	88 (18%)	89 (18%)
Non-Hispanic black	206 (41%)	193 (38%)
Hispanic	123 (25%)	129 (26%)
Asian/Pacific Islander	67 (13%)	72 (14%)
Native American	18 (4%)	19 (4%)
Birthplace		
USA or Canada	326 (65%)	320 (64%)
Mexico	69 (14%)	68 (14%)
Other	107 (21%)	114 (23%)
Sociological features		
Less than high-school graduate	286/501 (57%)	271 (54%)
Homeless >6 months in past 5 years	92 (18%)	95 (19%)
Drug use in past 5 years	109 (22%)	100 (20%)
Daily alcohol use in past 5 years	223 (44%)	223/501 (45%)
>1 month in prison in past 5 years	58 (12%)	53 (11%)
Clinical features		
Reported diabetes	75 (15%)	80 (16%)
Underweight at diagnosis of tuberculosis	151 (30%)	138/501 (28%)
Bodyweight (kg, mean [SD])	64 (13)	64 (13)
Haemological features		
Haemoglobin (g/dL, mean [SD])	13 (2)	13 (2)
White blood cell count ($\times 10^9/L$, mean [SD])	7 (3)	7 (2)
Platelet count ($\times 10^9/L$, mean [SD])	299 (105)	291 (107)
Treatment		
Days of intensive therapy (mean [SD])	63 (5)	63 (5)
Total intensive phase dose (mean [SD])	54 (9)	54 (8)
Treatment two times a week during the intensive phase	253 (50%)	248 (49%)
Use of streptomycin during intensive phase	37 (7%)	39 (7%)
Physical signs		
Cavitation on chest radiograph	278/488 (57%)	246/487 (51%)
Bilateral disease on chest radiograph	290/498 (52%)	269/498 (48%)
Sputum positive by smear	73/480 (15%)	53/486 (11%)
Sputum positive by culture	102/443 (23%)	78/443 (18%)

Data are number (%) unless otherwise stated.

Table 1: Characteristics of patients after randomisation

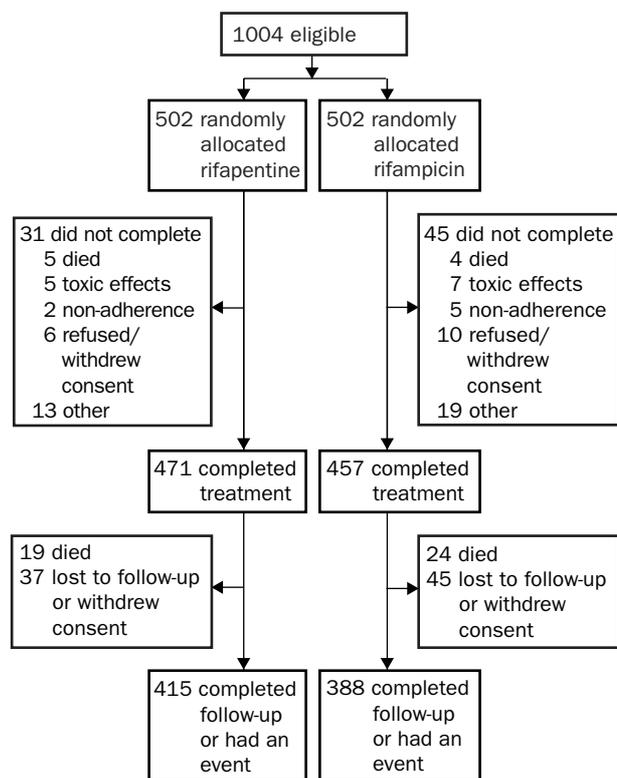


Figure 1: Trial profile

enrolled would be not assessable for primary endpoint (because of death, loss to follow-up, etc).

We analysed data with SAS version 6.12 (SAS Institute, Cary, NC, USA) and EpiInfo version 6.04d (CDC, Atlanta, GA, USA) software packages. Analysis was by intention to treat. We compared categorical variables (such as sex or ethnic origin) with two-tailed Fisher's exact test or χ^2 , and continuous variables (such as age) with t test or Wilcoxon two-sample test if non-parametric methods were appropriate. We analysed life-table survival with the log-rank test. We used multivariate Cox proportional-hazards regression analysis to assess risk factors for failure or relapse, with stepwise selection of factors significantly associated ($p < 0.05$) with failure or relapse on univariate Cox analysis.

A data and safety monitoring board reviewed outcome data five times, with the Lan-Demets spending function approach and an O'Brien-Fleming stopping rule.¹⁷ Critical p values for the five interim analyses were 0.0002, 0.0011, 0.0033, 0.0071, and 0.0472.

Role of the funding source

This study was supported by the US Centers for Disease Control and Prevention. Hoechst Marion Roussel, the manufacturer of rifapentine, provided rifapentine and contributed to the cost of three investigator meetings, but did not participate in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

1004 HIV-seronegative patients were enrolled between April, 1995, and November, 1998; follow-up ended in March, 2001. Table 1 shows characteristics of patients at randomisation. Regimens used during the intensive phase were similar for both treatment groups. Patients randomised to rifapentine were more likely to have cavitory disease on chest radiography and to be positive by

sputum smear or sputum culture at the end of the intensive phase of therapy.

31 (6%) of 502 patients who received rifapentine once a week and 45 (9%) of 502 on twice a week rifampicin did not complete treatment. Reasons for non-completion included death ($n=8$), drug toxic effects (12), non-adherence (7), refusal or withdrawal of consent (16), physician judgment (3), treatment failure (11), pregnancy (5), receipt of nonstudy regimen (8), or other (6). None of these reasons differed significantly between treatment groups. The numbers of patients completing each phase of the study are shown in figure 1. Mean duration of follow-up after completion of treatment was 20.4 months (SD 6.4) in the rifapentine group and 20.3 months (6.3) in the rifampicin group. Of 928 patients who successfully completed treatment, 455 (97%) of 471 in the rifapentine group and 440 (96%) of 457 in the rifampicin group completed at least 12 months of follow-up.

Failure/relapse occurred in 46 (9.2%) of 502 patients in the once a week rifapentine group and in 28 (5.6%) of 502 in the twice a week rifampicin group ($p=0.04$; table 2). The difference in crude event rates between treatment groups was 3.6% (95% CI 0.004–0.068). Life-table rates of failure/relapse were 10.3% (SD 1.5) in the rifapentine group and 5.9% (1.1) in the rifampicin group ($p=0.035$).

On multivariate Cox proportional-hazards analysis, five factors were identified as being independently associated with failure/relapse (table 3): non-Hispanic white race, being underweight, bilateral pulmonary involvement, cavitation on chest radiograph, and positive sputum culture at 2 months. In a Cox regression model, which included only treatment group and outcome, the hazard ratio for failure/relapse between treatment groups was 1.6 (95% CI 1.0–2.6; $p=0.04$). If positive sputum culture at 2 months and cavitation were added to this model, the hazard ratio fell to 1.34 (0.83–2.18; $p=0.23$).

In the Cox analysis, the strength of association with these five risk factors was not significantly affected if relapse alone was used as the primary endpoint, if only culture-positive events were used (ie, clinical events excluded), or if relapse due to reinfection with a different strain of *M tuberculosis* was excluded. Furthermore, restriction of the analysis to patients who completed treatment as planned, or to patients in the rifampicin group only, identified the same five factors with similar hazard ratios, except that the associations with bilateral pulmonary involvement and white race were no longer significant (data not shown). The sputum smear result at 2 months did not retain predictive value for failure/relapse in multivariate analysis even when the 2-month sputum culture was removed from the analysis (data not shown).

Table 4 shows results of a post-hoc analysis of rate of failure/relapse in patients with or without the five risk factors. Sputum smear result was not associated with

	Rifapentine (n=502)	Rifampicin (n=502)	Relative risk (95% CI)
Event			
Culture-positive failure	5 (1%)	3 (<1%)	1.67 (0.40–6.94)
Clinical failure	0	0	..
Failure after non-adherence*	0	3 (<1%)	..
Culture-positive relapse	39 (8%)	22 (4%)	1.77 (1.07–2.95)
Clinical relapse	2 (<1%)	0	..
All failures	5 (1%)	6 (1%)	0.83 (0.26–2.71)
All relapses	41 (8%)	22 (4%)	1.86 (1.13–3.08)
All failures and relapses	46 (9%)	28 (6%)	1.64 (1.04–2.58)

*Culture-positive failures.

Table 2: Primary outcome

	Univariate		Multivariate	
	p	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)*
Demographic				
Non-Hispanic white race	0.0005	2.4 (1.5–3.9)	0.02	1.8 (1.1–3.0)
Social				
Less than 8 years' education	0.008	0.4 (0.2–0.8)	0.08	..
Use of illicit drugs	0.007	2.0 (1.2–3.2)	0.09	..
Clinical				
Underweight at randomisation	0.0001	3.8 (2.4–6.1)	<0.0001	2.8 (1.7–4.7)
Radiographic features				
Cavitation	0.0001	4.7 (2.5–8.7)	0.001	3.0 (1.5–5.8)
Bilateral abnormalities	0.0007	2.5 (1.5–4.3)	0.05	1.8 (1.0–3.2)
Laboratory tests at randomisation (2 months)				
Platelet count >300×10 ⁹ /L	0.0002	2.4 (1.5–3.9)	0.20	..
White blood cell count >9×10 ⁹ /L	0.0007	2.5 (1.5–4.2)	0.17	..
Positive sputum acid-fast smear	0.0001	2.7 (1.6–4.5)	0.56	..
Positive sputum culture	0.0001	5.0 (3.1–8.0)	<0.0001	2.8 (1.7–4.7)
Treatment				
Total number of directly observed doses	0.02	1.03 (1.01–1.06)	0.06	..
Treatment with once a week rifapentine plus isoniazid	0.037	1.6 (1.03–2.64)	0.21	..

*Variables with $p > 0.05$ were not retained in the final regression model.

Table 3: Risk factors for treatment failure or relapse

increased risk of treatment failure/relapse on multivariate analysis (table 3), but was included in this analysis because the result is available soon after the specimen is obtained, and could be available in areas of the world in which mycobacterial culture is not routinely done. Of patients without pulmonary cavitation, the crude rates of failure/relapse were closely similar between rifapentine and rifampicin groups (relative risk 1.15, 95% CI 0.38–3.50, $p=0.81$). Event rates in patients with risk factors for failure/relapse were high in both treatment groups. Life-table rates of failure/relapse in patients with cavitation were 15.8% and 9.5% in patients on rifapentine and rifampicin, respectively (figure 2). Event rates were especially high in patients with multiple risk factors (for example, for patients with both cavitation and positive sputum culture at 2 months, 26.8% in the rifapentine group and 21.8% in the rifampicin group).

Daily treatment (usually given only 5 days per week) or treatment three times a week during the first 2 months was associated with a lower rate of failure/relapse compared with treatment two times a week during this phase (31/503 [6.2%] *vs* 43/501 [8.6%], $p=0.18$).

	Rifampicin*	Rifapentine*
Ethnic origin		
Non-Hispanic white	11.2% (10/89)	15.9% (14/88)
Other	4.4% (18/413)	7.7% (32/414)
Weight at 2 months		
Underweight	11.6% (16/138)	18.5% (28/151)
Not underweight	3.3% (12/363)	5.1% (18/351)
Chest radiographical features		
Cavitation	8.9% (22/246)	14.4% (40/278)
No cavitation	2.5% (6/241)	2.9% (6/210)
Bilateral infiltrates	8.2% (22/269)	11.7% (34/290)
Unilateral or no infiltrates	2.6% (6/229)	5.8% (12/208)
2-month sputum results		
Culture-positive	16.7% (13/78)	23.5% (24/102)
Culture-negative	3.8% (14/365)	5.6% (19/341)
Smear-positive	13.2% (7/53)	17.8% (13/73)
Smear-negative	4.8% (21/433)	7.9% (32/407)

Data are percentage (number with failure or relapse/number assessed). *Not all patients enrolled ($n=1004$) are included in each analysis because of missing data.

Table 4: Rate of treatment failure or relapse by presence of specified risk factor

Mycobacterial isolate pairs were available in 70 of 72 culture-positive endpoints; 68 (97%) had matching DNA fingerprints, and two (both in the rifapentine group) did not match. One of these two events with non-matching fingerprint was a clinically typical relapse, taking place in the first year of follow-up. The other was a patient with few symptoms, who was on high-dose prednisone for severe lupus and who had an unexpectedly positive culture late in follow-up.

In nine patients, results of confirmatory testing at CDC showed low-level isoniazid resistance (resistant at 0.2 mg/L, but susceptible at 1.0 mg/L). One of these patients failed; the isolate had identical drug susceptibility. Only one patient acquired drug resistance: this patient, who received isoniazid and rifampicin twice a week, had a drug-susceptible isolate at enrolment, but relapsed after treatment with a rifampicin-monoresistant isolate that had an identical DNA fingerprint.

Of the 1004 people enrolled, 56 (6%) died (table 5). No deaths were attributable to complications of treatment. The only death from tuberculosis was associated with massive haemoptysis, arising between enrolment and first dose of study treatment. There were no differences between treatment groups in frequency of grade 4 adverse events, grade 4 events attributable to study treatment, grade 3 or 4 hepatotoxicity, or severe thrombocytopenia (table 5). A closely similar proportion of patients in each treatment group permanently discontinued treatment because of an adverse event. There were no cases of rifamycin 'flu-like syndrome.

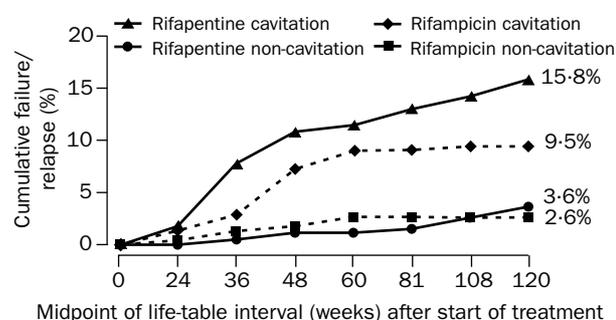


Figure 2: Cumulative percentage failure or relapse by treatment group stratified by presence or absence of cavitation

	Rifapentine (n=502)	Rifampicin (n=502)
Adverse event		
Death (total)	26 (5%)	30 (6%)
Death during study treatment	5 (1%)	4 (1%)
Death during follow-up	21 (4%)	26 (5%)
Any grade 4 adverse event (events/patients)	44/29	72/51
Grade 3 or 4 event attributed to study treatment (events/patients)	24/16	25/23
Serum ALT >5 times upper limit of normal (events/patients)	15/13	24/18
Platelet count (<25×10 ⁹ /L)	1 (<1%)*	1 (<1%)†
Study drug permanently discontinued because of an adverse event	14 (3%)	14 (3%)

ALT=alanine aminotransferase. *Patient's platelet count fell to 25 000 during induction with rifampicin, rose to 50 000 at enrolment, and fell to 6000 after one dose of rifapentine; all rifamycins held and patient completed a non-rifampicin regimen. †Patient with chronic lymphocytic leukaemia on chemotherapy.

Table 5: Number of adverse events by treatment group

Discussion

We have shown that 600 mg rifapentine plus 900 mg isoniazid once a week is safe and effective for continuation phase treatment of pulmonary tuberculosis. In the unadjusted analysis, treatment once a week with rifapentine and isoniazid was less effective at prevention of failure/relapse than treatment twice a week with rifampicin and isoniazid (9.2% *vs* 5.6%). Two risk factors—cavitation and positive sputum culture—were unequally distributed between treatment groups (table 1), and this occurrence could have led to an excess of failure/relapse. These factors have previously been associated with an increased risk of relapse.^{18–20} When the effect of these factors was controlled by proportional-hazards regression analysis, the hazard ratio for treatment with rifapentine fell from 1.65 to 1.34, and the difference between the two treatment groups was no longer statistically significant.

Both regimens were well tolerated. Continuation with rifapentine was not associated with excess adverse events, especially 'flu-like syndrome, by contrast with the 10–22% rates of hypersensitivity reactions reported with once a week rifampicin-containing regimens.⁵

The patients we studied were demographically and clinically similar to the overall population of HIV-negative patients with tuberculosis in the USA; therefore, our results should be generalisable to similar practice settings in which effective directly-observed therapy is used.²¹

In two clinical trials,^{22,23} treatment once a week with 600 mg rifapentine plus isoniazid was less active than standard rifampicin-based therapy. Researchers from Hong Kong^{22,24} used rifapentine that was manufactured in mainland China and that was reported to have suboptimal bioavailability. However, because that trial gave all study doses with a high-fat meal, the concentrations in serum achieved were similar to those among patients in our study.²⁵ In the Hong Kong trial, a standard three times a week rifampicin-based intensive phase treatment was given for 2 months, with random allocation after this time to either rifapentine and isoniazid once a week, rifapentine and isoniazid once a week for 2 of every 3 weeks, or standard three times a week rifampicin and isoniazid. Crude rates of failure/relapse after 2 years of follow-up were 9.0%, 9.9%, and 3.7%, respectively.²²

A trial done in South Africa and North America²³ included one group of patients who received rifapentine for the entire 6 months of treatment. After a 2-month

intensive phase that included rifapentine twice a week, patients were continued for 4 months on rifapentine and isoniazid once a week. Failure/relapse occurred in 13.4% of patients in the rifapentine and isoniazid group versus 9.4% of those given standard rifampicin and isoniazid twice a week.²³ The results of that trial²³ are more difficult to interpret than those of the Hong Kong trial²² because of poor adherence during the intensive phase in the rifapentine group and high losses to follow-up. By contrast to these two studies,^{22,23} we used a rifapentine preparation with excellent bioavailability, enrolled more patients, had a low rate of loss to follow-up, and used directly-observed therapy throughout. After review of data from the South African trial²³ and of interim results from our study, rifapentine was approved for use in treatment of tuberculosis in the USA in June, 1998. However, the results of these studies suggest that 600 mg rifapentine once a week is less potent than rifampicin twice a week. This finding could be attributable to the dose of rifapentine used.²⁶ The decision to study the 600 mg rifapentine dose was based on promising results in animals⁷ and pharmacokinetic data (peak/minimum inhibitory concentration ratio of 375 *vs* 67 for rifampicin),^{27,28} which suggested that rifapentine at this dose would be as effective as the standard dose of rifampicin. However, researchers subsequently noted that the higher protein binding of rifapentine than of rifampicin (97% *vs* 85%) could result in a suboptimal concentration of free active drug.^{29,30} In a study by the Tuberculosis Trials Consortium,³¹ 900 mg and 1200 mg rifapentine was well tolerated, suggesting that higher doses can be safely used. However, use of less isoniazid in the once-a-week regimen (900 mg *vs* 1800 mg per week) could be partly responsible for the decrease in efficacy.^{5,25} The emergence of rifampicin resistance among HIV-seropositive patients we have reported suggests a deficiency of isoniazid in the once-a-week regimen.

We did not record any acquired drug resistance in HIV-negative patients treated with rifapentine once a week, and no resistance was noted in the other two rifapentine trials of HIV-negative people.^{22,23} This finding contrasts strikingly with our results in HIV-positive patients with tuberculosis, which included four rifampicin-resistant relapses in 30 patients.¹¹ The absence of such relapses among HIV-negative patients suggests that advanced HIV disease, and its attendant polypharmacy, produce conditions favourable to the emergence of resistant strains.^{11,25} Until this issue can be resolved, rifapentine should be reserved for tuberculosis treatment in HIV-negative people.

Because of the slightly reduced overall efficacy of the rifapentine regimen, we sought to define the optimum conditions for clinical use of rifapentine in tuberculosis treatment. As shown in table 4, both rifapentine once a week and rifampicin twice a week led to good results in patients who did not have cavitation (such patients represent about 40% of patients with tuberculosis in the USA). This observation provides a practical strategy for use of rifapentine. In settings such as the USA and Canada, HIV-negative patients who do not have cavitation on chest radiograph can be treated with rifapentine and isoniazid once a week in continuation phase with good efficacy, and with substantial reduction in cost of directly-observed therapy.³²

With readily available clinical information, we identified subgroups of patients treated with directly observed short-course therapy for pulmonary tuberculosis who have high rates of treatment failure or relapse. Independent risk factors associated with unfavourable outcome were:

non-Hispanic white ethnic origin; underweight at enrolment; cavitation or bilateral infiltrates on chest radiograph; and positive sputum culture at the end of intensive phase of treatment. The association between these variables and adverse treatment outcomes is strengthened by the consistency of finding these same five factors with relapse alone as the outcome variable or when analysis was restricted to controls or to patients treated as specified in the protocol.

Workers on two studies have assessed risk factors for relapse after directly-observed therapy,^{18,19} one of which used the results of multiple clinical trials in Hong Kong and east Africa.¹⁸ Neither of these studies assessed regimens of 6 months of rifampicin and 2 months of pyrazinamide, which are the standard components of short-course therapy,¹⁰ although most regimens used rifampicin throughout the course of treatment. Despite these differences, the similarity of the risk factors for relapse identified in these studies and ours is striking. Three of the risk factors identified in our study, including the two with the highest hazard ratios (cavitation and positive culture), have consistently been identified in other studies of relapse after directly-observed treatment.^{18,19}

These consistent associations suggest that two factors have a major effect on risk of relapse: extent and severity of pulmonary involvement (bilateral disease, cavitation); and response to the four-drug intensive phase of treatment (positive culture at 2 months). The association between cavitation and relapse could be attributable to poor drug penetration into the devascularised cavity or surrounding fibrotic tissue; alternatively, cavitation could be a marker for high bacillary burden from extensive disease. A positive culture at 2 months could indicate high initial bacillary burden, poor response to intensive-phase treatment, or both. Results of analyses have shown that culture at 2 months is more closely associated with relapse than is initial bacillary burden alone.¹⁸

In view of the identification of risk factors for treatment failure or relapse, how adequate are current recommendations for rifampicin-based regimens for selected subgroups of patients with tuberculosis? In patients with multiple risk factors (eg, cavitation and positive culture at 2 months), risk of treatment failure or relapse was similar to that of patients with silicotuberculosis, a recognised indication for lengthened therapy.³³

In conclusion, rifapentine is an important addition to the few effective anti-tuberculosis agents. As shown by our results, use of rifapentine and isoniazid once a week for treatment in the continuation phase of pulmonary tuberculosis is effective in selected patients, and offers the potential for substantial reduction in cost of this treatment. We also identified risk factors for treatment failure and relapse with standard treatment. Further studies should investigate how best to treat these high-risk patients.

TBTC Study 22 Writing Group

This report was prepared by the TBTC Study 22 Writing Group, whose membership included Debra Benator MD, Mondira Bhattacharya MD, Lorna Bozeman MS, William Burman MD, Antonino Catanzaro MD, Richard Chaisson MD, Fred Gordin MD, C Robert Horsburgh MD, James Horton MD, Awal Khan PhD, Christopher Lahart MD, Beverly Metchock DPH, Constance Pachucki MD, Llewellyn Stanton RN, Andrew Vernon MD (chair), M Elsa Villarino MD, Yong Cheng Wang PhD, Marc Weiner MD, and Stephen Weis DO. The draft report was prepared by Andrew Vernon, C Robert Horsburgh, and William Burman. Data analyses were done by Yong Cheng Wang, Awal Khan, and Andrew Vernon. All writing group members participated in the preparation, review, and approval of the final report.

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Conflict of interest statement

None declared.

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