MAJOR ARTICLE

Short-Course Rifampin and Pyrazinamide Compared with Isoniazid for Latent Tuberculosis Infection: A Cost-Effectiveness Analysis Based on a Multicenter Clinical Trial

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Two months of treatment with rifampin-pyrazinamide (RZ) and 9 months of treatment with isoniazid are both recommended for treatment of latent tuberculosis infection in adults without human immunodeficiency virus infection, but the relative cost-effectiveness of these 2 treatments is unknown. We used a Markov model to conduct a cost-effectiveness analysis to assess the impact on life expectancy and costs based on the results of a recent clinical trial that compared the rates of adverse events and completion of the 2 treatment regimens. Compared with no treatment, both regimens increased life expectancy by 1.2 years, but RZ cost $273 more per patient. Sensitivity analyses showed that, assuming equal efficacy between the 2 regimens, there was no threshold completion rate for RZ at which the 2 treatments would be of equal net cost. Under most circumstances, treatment of latent tuberculosis infection with isoniazid is cost-saving than treatment with RZ.

Guidelines from the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC) published in 2000 [1] offer 3 main regimens for the treatment of latent tuberculosis (TB) infection in adults without HIV infection: isoniazid for 6–9 months, rifampin for 4 months, or rifampin-pyrazinamide (RZ) for 2 months. However, the relative cost-effectiveness of these treatments has not been rigorously evaluated. Isoniazid provided for ⩾6 months has been the standard treatment for latent TB infection for decades, but its use has been limited by toxicity, especially hepatitis [2–4], and by poor adherence to treatment [5]. A shorter course of treatment for latent TB infection with rifampin and pyrazinamide for 2 months has been shown to be effective and well tolerated in patients with HIV infection [6–8]. However, case reports of severe hepatotoxicity, including 5 related deaths, have raised concerns about the safety of RZ [9, 10] and led to revised ATS/CDC guidelines that recommend monitoring for liver injury in all patients at baseline and after 2, 4, and 6 weeks of treatment [10].

We previously conducted a multicenter, prospective, open-label trial comparing rifampin and pyrazinamide provided daily for 2 months with isoniazid provided daily for 6 months among adults without HIV infection

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who had latent TB infection (the Short-Course Rifampin and Pyrazinamide for Tuberculosis Infection [SCRIPT] study) [11]. We found that a regimen of 2 months of RZ was associated with a statistically significant higher risk of hepatotoxicity than was 6 months of isoniazid and that the RZ regimen was also more likely to be discontinued than the isoniazid regimen as a result of hepatotoxicity.

In addition, despite a shorter duration of treatment, the percentage of those who completed treatment of the 2-month regimen of RZ was comparable to the percentage completion among those who received the 6-month regimen of isoniazid. In this study, we determined the cost-effectiveness of RZ for 2 months compared with isoniazid for 6 months on the basis of results from the SCRIPT study. We also determined whether RZ would be cost-saving relative to isoniazid in populations with differing rates of completion of treatment and isoniazid-resistant TB infection.

PATIENTS AND METHODS

Study Population

All adults >17 years old with a positive tuberculin skin test result (defined by ATS/CDC criteria [1]) in whom active TB was excluded and in whom treatment of latent TB infection would ordinarily be recommended (e.g., close contact with an infectious case or medical risk factor, such as diabetes) were eligible for the study. Measurement of levels of liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase, and alkaline phosphatase), bilirubin, and creatinine were obtained. HIV testing and counseling were recommended for patients whose HIV infection status was not known, and a urine pregnancy test was performed for all women of child-bearing age. During their baseline visit, patients underwent a review of symptoms, including history of nausea, vomiting, jaundice, abdominal pain, weight loss, arthralgia, headache, and neuropathy. Institutional review boards at each site (San Francisco, Boston, and Atlanta) approved the study, and written informed consent was obtained from all patients. Guidelines for human experimentation were followed that were consistent with the US Department of Health and Human Services and the authors' institutions. Exclusion criteria included pregnancy, HIV infection, serum creatinine level of more than twice the upper limit of normal, serum aspartate aminotransferase or ALT level of >1.5 times the upper limit of normal, and a history of gout.

Study Design

Persons who met study criteria and agreed to participate were allocated in alternate weeks to receive a regimen of either rifampin (600 mg q.d.) and pyrazinamide (20 mg/kg q.d.) for 2 months or isoniazid (300 mg q.d.) for 6 months once active TB was excluded.

All patients in both groups underwent testing of serum liver enzymes and bilirubin after 1 month of treatment. Those in the isoniazid group were also tested at 3 months. Persons in the rifampin and pyrazinamide group also underwent a complete blood count, and uric acid and creatinine concentrations were measured after 1 month of treatment.

All treatment was self-administered, and specific incentives, financial or otherwise, were not provided. All patients received monthly supplies of medication and were instructed to take their medication daily and return in 1 month (or sooner if any of the above symptoms occurred). At each visit, patients were evaluated for signs and symptoms of adverse events by TB-control nurses and evaluated for adherence to treatment.

The definition of hepatotoxicity was based on the World Health Organization classification and defined as grade 1 for any serum ALT level of 51–125 U/L, grade 2 for any serum ALT level of 126–250 U/L, grade 3 for any serum ALT level of 251–499 U/L, and grade 4 for any serum ALT level of $\geqslant$500 U/L or $\geqslant$250 U/L if accompanied by compatible symptoms [12].

Outcomes

The primary outcomes included the development of any adverse events and completion of the prescribed amount of treatment. Adverse events were determined on the basis of interviews and by laboratory examination when indicated. Completion of the regimen was defined as taking $\geqslant$80% of prescribed medication.

Evaluation of Cost-Effectiveness

To evaluate cost-effectiveness of the 2 treatments, we developed a Markov model to track hypothetical cohorts of 1000 patients with latent TB infection from the age of 35 years (the mean age of the cohort in the SCRIPT study) to 99 years who received either RZ daily for 2 months, isoniazid daily for 6 months, or no treatment. Expected completion rates of treatment, adverse events, and costs were determined on the basis of data from the 350 patients in the SCRIPT study enrolled in San Francisco. All patients were at risk for developing active TB and for dying of TB or of other causes (figure 1). We assumed that no patients had infection with *Mycobacterium tuberculosis* strains that were resistant to isoniazid, although we varied the rate of isoniazid-resistant infection in our sensitivity analysis.

Baseline Model Parameters

Outcome of treatment of latent TB infection. Because the difference in completion was not statistically significant, the baseline model incorporated the completion rates for isoniazid for both groups.

Risk of TB, death due to TB, and death due to other causes. We used previous data to estimate the annual risk of developing active TB among patients with a positive tuberculin test result [14]. Previous studies were used to obtain TB-

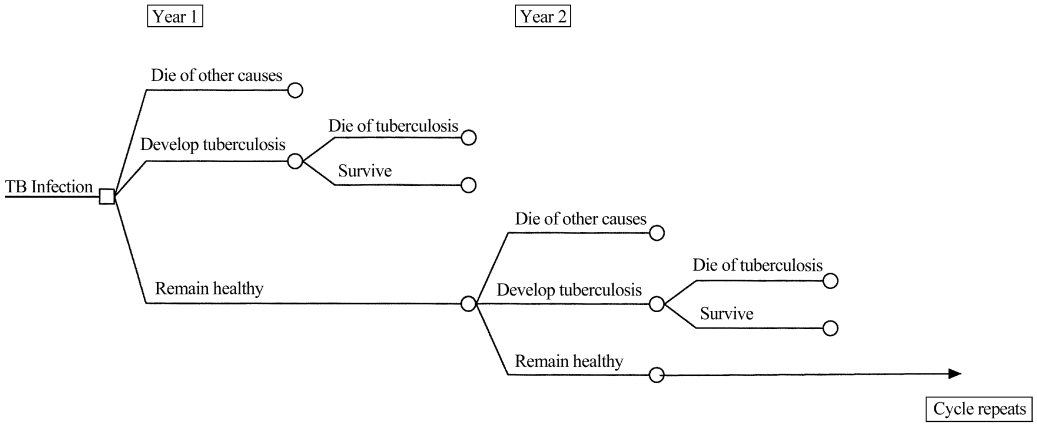

Figure 1. Illustration of the Markov process used to determine the expected number of tuberculosis (TB) cases and TB-related deaths in the study population. A 4-state Markov process [13] was developed to determine the expected number of cases of TB and TB-related deaths in the *Mycobacterium tuberculosis*–infected population aged 35–99 years. In each 1-year repeating cycle of the Markov process, MTB-infected persons may either remain well, develop TB and survive, develop TB and die, or die of other causes. Patients who develop TB are not at risk for developing TB again during the remainder of their lifetime.

specific mortality data for patients developing TB and age-specific, annual, all-cause risk of death [15–17] (table 1).

Efficacy of treatment of latent TB infection. A frequently cited previous study [18] showed that administration of isoniazid for 6 months reduced the risk of TB by 69%. Given the lack of efficacy data for adults without HIV infection, identical efficacy was inferred for patients who received RZ in the baseline case, although the efficacy of rifampin and pyrazinamide varied in the sensitivity analysis.

Outcomes and cost.We determined expected TB cases, TB-related deaths, and the difference in life expectancy between each cohort. We calculated the net incremental cost (savings) per 1000 patients treated for each treatment strategy relative to the other. Because our study focuses on how TB-control programs can identify the most cost-effective treatment strategy to prevent TB, costs were analyzed from the perspective of the health care system. All costs are in 2001 US dollars. Costs were adjusted to their 2001 values by using the medical care component of the Consumer Price Index [19]. We discounted TB cases and costs prevented by 3% annually.

Cost of treatment. Costs were determined from the San Francisco Department of Public Health. We included only variable costs (table 2). Laboratory testing for RZ recipients included determination of liver enzyme levels every 2 weeks beginning at the initiation of treatment through week 6 per ATS/CDC recommendations [10]. In contrast, routine testing of liver enzyme levels is not recommended for patients who receive isoniazid unless risk factors are present. The cost-effectiveness of baseline testing of liver enzyme levels in patients taking isoniazid was assessed in the sensitivity analysis. The weighted average cost per patient treated (table 2) was obtained by determining the cost for each outcome that we observed and then calculating the average cost on the basis of the frequency of these outcomes. Thus, cost of managing adverse events, including expenses incurred from treatment of drug-induced toxicities, was incorporated into the analysis by the weighted average cost per patient. For example, 6.5% of patients in San Francisco assigned to receive rifampin and pyrazinamide developed grade 3 or 4 hepatotoxicity, which required additional laboratory testing (e.g., viral hepatitis serologic tests and follow-up liver enzyme tests) and nursing and physician follow-up assessments that increased the average cost of this regimen.

Averted cost. Previous studies were used to estimate the average cost of treating an active TB case and cost of contact tracing and treatment [20].

Sensitivity analyses. We varied the rates of completion of treatment and the percentage of isoniazid-resistant infections, and we incorporated the cost of using 9 months of isoniazid therapy to determine the effect on the results of our analysis. Because the true efficacy of RZ for the treatment of latent TB infection in adults without HIV infection is not known, we assumed that it was equivalent to isoniazid in the baseline case but varied it in our sensitivity analysis to determine conditions in which it would be cost-saving relative to isoniazid.

RESULTS

Adverse Events and Rates of Completion of Treatment

Of the 350 patients enrolled in San Francisco, 184 received RZ and 166 received isoniazid. A high proportion of the patients were foreign-born, constituting the indication for treatment in just under 60%. The 2 groups were similar in sex, weight, and indication for treatment of latent TB infection. However, sig-

Table 1. Model parameters and data sources.

Model parameter	Value	Reference
Efficacy		
6 months of isoniazid therapy/2 months of RZ therapy	69	[1, 18]
3–5 months of isoniazid therapy/1 month of RZ therapy	20	[1, 18]
<3 months of isoniazid therapy/<1 month of RZ therapy	0	[1, 18]
Annual risk of TB for no treatment of latent infection	0.27	[14]
Age at study entry, mean years	35	[11]
Risk of death due to TB, age group		
35–44 years	3.9	[15]
45–64 years	7.4	[15]
⩾65 years	16.8	[15]
Discount rate[a]	3	

NOTE. Data are percentages unless otherwise indicated. RZ, rifampin-pyrazinamide; TB, tuberculosis.

[a] Explained in Baseline Model Parameters.

nificantly more patients who received RZ than isoniazid experienced grade 3 or 4 hepatotoxicity and, as a result, were more likely to have their treatment discontinued (table 3). Other, nonhepatotoxic adverse events occurred at a similar rate in both groups, except skin rash, which was seen more frequently in patients who received RZ. The percentage of patients who completed treatment was similar among both groups (66% of the RZ group and 68% of the isoniazid group; $P = .67$).

Costs and Cost-Effectiveness

Effectiveness of treatment of latent TB infection. Without treatment of latent TB infection in 1000 persons, 110 cases of TB and 10.8 TB-related deaths would occur. Compared with no treatment, treatment with either RZ or isoniazid prevented 57.7 future cases of TB per 1000 treated patients (29.7 discounted), prevented 5.1 deaths due to TB per 1000 treated, and prolonged survival by 1.2 years.

Initial treatment. The isoniazid strategy would cost $292 per patient, whereas the RZ strategy would cost $565 per patient (table 2). As shown table 2, the differences in the cost of treatment are mainly due to a higher cost of medications and laboratory testing among patients who received RZ.

Expected cost of TB treatment and contact tracing and treatment. On average, patients receiving no treatment of latent TB infection (most of whom will not develop active TB) will incur an expected cost of $1073 per patient for treatment of future active disease, contact tracing, and treatment. For the cohorts receiving either the isoniazid or RZ strategy, this cost is reduced to $582 per patient.

Incremental cost-effectiveness. Relative to no treatment of latent infection, only isoniazid is more effective and less costly. The isoniazid strategy would produce net incremental savings of $199 per patient treated, compared with no treatment, whereas the RZ strategy would cost $74 per patient treated. Therefore, the net incremental savings of isoniazid is $273 [($199 − (−$74)] per patient treated relative to RZ. Compared with no treatment, the RZ strategy would have a net incremental cost per additional TB case prevented of $2492. Because of the lower cost of initial treatment relative to the RZ strategy, isoniazid is cost-saving, producing net incremental savings of $273 per patient treated.

Sensitivity analyses. We varied the rate of completion of treatment to determine how this would affect the results of our cost-effectiveness analysis. If the isoniazid regimen completion rate remains 68%, we could find no threshold in the RZ regimen completion rate in which the 2 treatment strategies would be of equal net savings. However, as the isoniazid completion rate decreases, the RZ strategy becomes relatively more cost-effective. At an isoniazid regimen completion rate of ⩽36%, RZ would become cost-saving relative to isoniazid (assuming the completion rate for RZ remained at 68%).

Completion rates for RZ and isoniazid therapy differed by site. In Atlanta, 1 of the 3 sites for the SCRIPT study, completion rates for patients who took RZ were significantly higher than for those assigned to take isoniazid ($P = .03$). Despite the higher rates of completion with RZ in Boston and Atlanta, RZ was not cost-saving relative to isoniazid, and it cost $67,282 (Boston) and $11,830 (Atlanta) per additional TB case prevented.

An increase in the efficacy of RZ (to 90%), in combination with a completion rate of ⩾80%, would make this regimen cost-saving relative to isoniazid (figure 2). We also determined the cost-effectiveness of 9 months of daily isoniazid therapy, rather than 6 months, compared with 2 months of daily RZ. Increasing the duration of isoniazid therapy to 9 months did not change the overall results, although the net incremental cost savings of isoniazid was decreased to $171 per patient. A

Table 2. Initial costs for treatment of latent tuberculosis: baseline and average cost per San Francisco patient in the Short-Course Rifampin and Pyrazinamide for Tuberculosis Infection (SCRIPT) study.

Cost itemization	2 months of rifampin-pyrazinamide, US$	6 months of isoniazid, US$
Medication	184	14
Laboratory testing	164	0
Physician/nursing costs	292	333
Total (baseline case)	640	347
Average cost per patient[a]	565	292

[a] The average cost of treatment of latent infection was calculated by use of actual treatment outcomes for all patients who initiated the treatment regimen and was based on the frequency of these outcomes (table 3). See Baseline Model Parameters for details.

Table 3. Outcomes of patients in San Francisco with latent tuberculosis treated with rifampin-pyrazinamide or isoniazid in the Short-Course Rifampin and Pyrazinamide for Tuberculosis Infection (SCRIPT) study.

Variable	2 months of rifampin-pyrazinamide	6 months of isoniazid	*P*
No. of patients	184	166	
Completed treatment, no. (%)	121 (66)	113 (68)	.67
Duration of treatment among patients who did not complete therapy, months			
<1	40	NA	
1–2	23	NA	
<3	NA	40	
3–6	NA	13	
Hepatotoxicity[a]			
Grade 1	23	29	
Grade 2	5	3	
Grade 3	4	0	.004[b]
Grade 4	8	1	
Discontinued therapy as a result of hepatotoxicity	9	1	.02[c]
Other adverse events	35	29	.70
Nausea/vomiting	9	9	
Rash	13	4	.02
Epigastric pain	8	4	
Fatigue/malaise	3	9	
Other (diarrhea, dizziness)	2	3	

NOTE. Data are no. of patients, unless otherwise indicated. NA, not applicable.

[a] Grade 1 hepatotoxicity was defined as serum an alanine aminotransferase (ALT) level of 51–125 U/L; grade 2, ALT level of 126–250 U/L; grade 3, ALT level of 251–499 U/L; and grade 4, ALT level of ⩾500 U/L or ⩾250 U/L with compatible symptoms [12].

[b] OR, 11.5 (95% CI, 1.7–495) for grade 3 or 4 hepatotoxicity between groups.

[c] OR, 8.5 (95% CI, 1.2–74.1).

5% rate of isoniazid-resistant TB infection would decrease the cost savings of the isoniazid (6-month) group to $195 per patient treated, relative to RZ; a rate of 10% resistance to isoniazid would decrease the savings to $170 per patient treated. The 2 treatments have equal net cost at an isoniazid resistance rate of 42%. Finally, the addition of liver enzyme testing in 40% of patients in the isoniazid (6-month) group at baseline would raise the cost of the isoniazid strategy, but it would still save $259 per patient treated, relative to RZ.

DISCUSSION

This study shows that, for patients with latent TB infection, treatment with either isoniazid for 6 months or RZ for 2 months improves survival, compared with no treatment. Because of the lower cost of initial treatment with isoniazid, and because we assumed equal treatment completion and efficacy, isoniazid is the more cost-effective treatment of the 2 options and saves $273 per patient treated. However, compared with no treatment, the RZ strategy is almost cost-saving and has a net cost of <$2500 per additional TB case prevented.

The cost advantage of isoniazid is maintained unless completion rates are quite low (<36%) and even when the duration of treatment with isoniazid is extended to 9 months, the current ATS/CDC recommendation for treatment of latent TB infection. The cost advantage of isoniazid is maintained unless RZ is assumed to have an efficacy of 90% combined with a completion of ⩾80%. Finally, isoniazid is cost-saving, with rates of isoniazid-resistant TB up to 42%, assuming no change in efficacy of RZ.

The data used for the cost-effectiveness analysis were the observed rates of adverse events and completion among the 350 patients enrolled in San Francisco in the SCRIPT study. The SCRIPT study showed that a 2-month regimen of RZ was associated with a significantly higher risk of grade 3 or 4 hepatotoxicity than was a 6-month regimen of isoniazid and that completion rates were similar between the 2 regimens [11]. Results from the 350 patients enrolled in San Francisco were

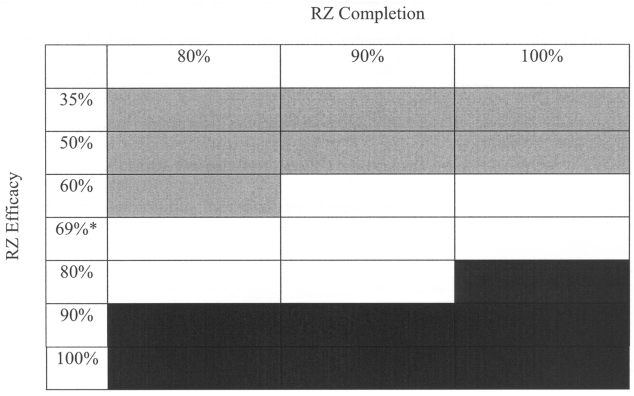

Figure 2. Net incremental effectiveness and cost of rifampin-pyrazinamide (RZ) versus isoniazid for 6 months per additional case prevented, varying the efficacy and completion rate of RZ. *Baseline efficacy (and equal to isoniazid). The chart also assumes that completion of isoniazid remains at 68%. *Gray,* less effective, more costly; *white,* more effective, more costly; *black,* more effective, less costly.

then incorporated into a Markov model to assess impact on cost-effectiveness of treatment.

The increased cost of the RZ regimen, compared with the isoniazid regimen, is largely driven by the high cost of medications and regular monitoring for liver injury that is recommended by ATS/CDC. After case reports of severe liver injury and 5 deaths were reported to the CDC, guidelines were revised. We assumed in our model that no deaths occurred in association with RZ treatment (and none occurred in the SCRIPT study at any site). However, incorporating any estimate of death due to RZ toxicity would only further increase the advantage of isoniazid. The CDC recommends establishing baseline values and determining liver enzyme levels every 2 weeks for patients treated with this regimen. In addition, it is recommended that the regimen not be used for patients with a history of liver disease, alcoholism, or isoniazid-associated liver injury. It is further recommended that therapy should be permanently discontinued when transaminase levels are >5 times the upper limit of normal in an asymptomatic patient, when they are greater than normal and accompanied by symptoms of hepatitis, or when the serum bilirubin level is greater than normal. In contrast, isoniazid can usually be provided without routine monitoring of liver enzymes in the absence of symptoms of hepatitis and costs very little (just over $2 per month for medications only). Even with the addition of liver enzyme testing in 40% of patients receiving isoniazid, it would remain cost-saving, relative to RZ. Therefore, the high cost of RZ and of routine laboratory monitoring would have to be offset by a substantial increase in completion rate and efficacy relative to isoniazid to make it more cost-effective.

As this study shows, given the relatively high completion rate with isoniazid, there was no threshold completion rate for RZ that would make it more cost-effective than isoniazid, assuming equal efficacy of the 2 regimens. However, if the rate of completion of RZ was ⩾80% and the efficacy was 90%, RZ would become cost-saving. This has important implications for TB-control programs in the United States. There may be certain settings, such as jails or homeless shelters, in which long-term adherence to treatment cannot be assured, and the completion rate for isoniazid therapy may be significantly less than that for RZ therapy. In such high-risk settings, where patients are unlikely to complete a longer course of treatment with isoniazid, RZ may be preferred in spite of its relatively high initial treatment cost, because it may permit higher treatment completion rates and therefore result in superior prevention effectiveness.

To our knowledge, previous studies have not assessed the cost-effectiveness of the use of RZ for latent TB infection among adults without HIV infection. Among HIV-infected persons, Rose [21] assessed the cost-effectiveness of isoniazid therapy and several shorter regimens, including RZ therapy. He found that isoniazid and RZ regimens increased survival and saved medical care dollars quite similarly. Because studies of RZ therapy for HIV-infected persons have not found an increased rate of hepatotoxicity, extra monitoring for liver injury in this population has not been recommended, and therefore, he did not incorporate the added costs of laboratory monitoring into his cost-effectiveness model.

There are several limitations to the present study. Because there are no efficacy studies of RZ therapy in adults without HIV infection, we assumed in the baseline case that its efficacy was equal to that of isoniazid. We did vary the efficacy of RZ in our sensitivity analysis to determine the effect on cost-effectiveness. In addition, all patients were assumed to have infection with *M. tuberculosis* strains that are susceptible to isoniazid, rifampin, and pyrazinamide. This is likely not accurate, given that most patients in our study population were from parts of the world where resistance to isoniazid is relatively common. For example, in San Francisco, for the past 5 years, 8.0% of all patients with incident TB were infected with strains resistant to isoniazid, and only 1.2% were infected with strains that were resistant to isoniazid and rifampin. Thus, isoniazid may not be an efficacious treatment in up to 10% of patients who were in our study. This cannot be known for certain, because our study was underpowered to detect a difference in TB case rates between the 2 treatment groups. Second, our results are applicable to settings in which adequate monitoring and follow-up of treatment can be undertaken. Another limitation is that, because our analysis was conducted from the perspective of the health care system, we did not include all costs relevant to an analysis from the societal perspective. Therefore, we likely underestimated the true cost-effectiveness of isoniazid therapy and RZ therapy relative to no treatment. However, because patients receive isoniazid treatment for sev-

eral months longer than RZ treatment, excluding costs incurred by the patient, including opportunity cost and other indirect costs, likely overestimates the cost-effectiveness of isoniazid therapy relative to RZ therapy.

In summary, treatment of patients who have latent TB infection with either isoniazid for 6 months or RZ for 2 months improves survival rates, compared with no treatment. Isoniazid is the more cost-effective treatment of the 2 options under most circumstances and saves $273 per patient treated, compared with RZ. The cost advantage of isoniazid is maintained unless completion rates are quite low (<36%) and even when the duration of treatment is extended to 9 months, the current ATS/CDC recommendation for treatment of latent TB infection.

THE SCRIPT STUDY INVESTIGATORS

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