Costs and Cost-effectiveness of Four Treatment Regimens for Latent Tuberculosis Infection

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Rationale: Isoniazid given daily for 9 months is the standard treatment for latent tuberculosis infection (LTBI), but its effectiveness is limited by poor completion rates. Shorter course regimens and regimens using directly observed therapy result in improved adherence but have higher upfront costs.

Objectives: To evaluate the costs and cost-effectiveness of regimens for the treatment of LTBI.

Methods: We used a computerized Markov model to estimate total societal costs and benefits associated with four regimens for the treatment of LTBI: self-administered isoniazid daily for 9 months, directly observed isoniazid twice-weekly for 9 months, directly observed isoniazid plus rifapentine once weekly for 3 months, and self-administered rifampin daily for 4 months. In the base-case analysis, subjects were assumed to have newly positive tuberculin skin tests after recent exposure to infectious tuberculosis.

Measurements and Main Results: We determined the costs of treatment, quality-adjusted life-years gained, and cases of active tuberculosis prevented. In the base-case analysis, rifampin dominated (less costly with increased benefits) all other regimens except isoniazid plus rifapentine, which was more effective at a cost \$48,997 per quality-adjusted life year gained. Isoniazid plus rifapentine dominated all regimens at a relative risk of disease 5.2 times the baseline estimate, or with completion rates less than 34% for isoniazid or 37% for rifampin. Rifampin could be 17% less efficacious than self-administered isoniazid and still be cost-saving compared with this regimen.

Conclusions: In our model, rifampin is cost-saving compared with the standard therapy of self-administered isoniazid. Isoniazid plus rifapentine is cost-saving for extremely high-risk patients and is cost-effective for lower-risk patients.

Keywords: antitubercular agents; cost-benefit analysis; HIV infections

Contact tracing with subsequent treatment of individuals latently infected with *Mycobacterium tuberculosis* is a cornerstone of tuberculosis (TB) control in the United States and other low-burden countries (1). These patients, who have been infected with *M. tuberculosis* but in whom the organism remains dormant, are at risk of developing active disease throughout their lives (2–4), although treatment can substantially reduce their likelihood of activation (5). Per recommendations from the Centers for Disease Control and Prevention (CDC), isoniazid given daily for 9 months is the standard treatment (2), but the overall effectiveness of this regimen is limited by the

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

The Centers for Disease Control and Prevention describes several different regimens for the treatment of latent tuberculosis infection in adults, but how they compare in terms of costs and effectiveness is largely unknown.

What This Study Adds to the Field

Four months of rifampin is more effective and less expensive than standard therapy with 9 months of isoniazid. Three months of isoniazid plus rifapentine is likely to be a cost-effective alternative if this regimen proves effective.

fact that roughly half of the patients who start it fail to complete a full course (6, 7). Isoniazid can also be given twice weekly as directly observed treatment (DOT) but still must be given over 9 months, and the cost of DOT adds a significant expense with uncertain benefit. Rifampin given daily for 4 months is an accepted treatment (2) and leads to greater completion rates (8, 9), but fewer data are available demonstrating the efficacy of this regimen.

Rifapentine is a rifamycin derivative with a half-life amenable to weekly administration (10). It is approved for use in the continuation phase of treatment for active TB given once-weekly in combination with isoniazid (11, 12) and has been considered as a treatment for latent TB infection (LTBI). One small study has been completed (13), and a large multicenter trial is underway to determine the efficacy of once-weekly isoniazid plus rifapentine in preventing active TB among high-risk latently infected individuals (clinicaltrials.gov ID NCT00023452).

The cost of this potential new regimen remains an issue. Rifapentine is substantially more expensive than isoniazid and rifampin (M. Kelbaugh, personal communication, December 21, 2007), and the recommendation for DOT adds additional costs. However, increased completion rates of the shorter therapy could compensate for the higher cost if more cases of active TB were prevented (8). In an effort to inform public health policy, we have developed a decision model to examine the overall costs of using these four regimens to treat LTBI given the different resource needs, adherence rates, and effectiveness.

METHODS

We created a Markov model using TreeAge Pro (release 1.2, 2008; TreeAge Software, Inc., Williamstown, MA) to compare the costs, benefits, and cost-effectiveness of four different treatment regimens for treating a hypothetical cohort of individuals with LTBI (Figure 1): (1) Isoniazid 300 mg given as daily self-administered therapy for 9 months (9H); (2) Isoniazid 900 mg given twice weekly by DOT for 9 months (9H-DOT); (3) Isoniazid 900 mg + rifapentine 900 mg given once weekly by DOT for 12 weeks (3HP); (4) Rifampin 600 mg given as daily self-administered therapy for 4 months (4R). We also included

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Figure 1. Schematic diagram of model showing the Markov node (labeled “M”). ^aAll patients on the “no treatment” arm start in the “off treatment” branch. ^bPatients whose treatment is complete or who stop due to toxicity or nonadherence return to the “off treatment” branch; patients who will continue treatment return to the “on treatment” branch.

a “no treatment” strategy for comparison. We assumed the patient population was recently infected with TB (e.g., contacts to an infectious case) and that all patients were adults with an average age of 39 years.

We assumed that individuals assigned to a regimen were moved to “off treatment” if they completed their regimen, became non-adherent, experienced a treatment-limiting adverse event, developed active TB, or died (Figure 1). Individuals who developed active TB were at risk of death from TB during the period of TB treatment. After the treatment course, patients were considered cured and moved to the post-TB state. We assumed that no patient developed TB more than once.

Expected value calculations were used to analyze the model using cycles of 1 month duration. Payoffs were calculated for costs, number of active cases, and quality-adjusted life-years (QALYs). We followed the recommendations of the Panel on Cost Effectiveness in Health and Medicine as appropriate (14) and assumed that a strategy was a good use of our economic resources if the incremental cost-effectiveness ratio was \$50,000 per QALY or less. Costs and QALYs were discounted at 3%. All costs were converted to 2008 U.S. dollars using the Gross Domestic Product deflator (15).

The base-case analysis estimates and sources for transition probabilities are shown in Table 1, and baseline estimates for costs are shown in Tables 2 and 3. Further information on the estimates used in our analysis can be found in the online supplement.

RESULTS

The results from the base-case analysis are shown in Tables 4 and 5. Rifampin (4R) was the least expensive regimen, with an average lifetime cost per contact of \$495.21. All regimens reduced costs compared with no treatment except for directly observed isoniazid (\$2,002.40 vs. \$1,527.30 for 9H-DOT and no treatment, respectively). Compared with no treatment, 9H, 9H-DOT, 4R, and 3HP prevented 43.7, 54, 52, and 56.3 additional cases per 1,000 contacts treated, respectively. All four drug regimens provided increased life expectancy (Table 4).

In an analysis of the cost-effectiveness of the alternative strategies, all regimens were dominated (i.e., more expensive with a lower quality-adjusted life expectancy) by 4R, except 3HP, which was more effective than 4R, at a cost of \$48,997 per QALY in the base-case analysis (Table 5 and Figure 2). Compared with 9H, 3HP was more effective, at a cost of \$25,207 per QALY (Figure 2). Cost-effectiveness results were not sensitive to adjustments in the utility scores over the specified range.

Sensitivity Analyses

Risk of TB. Figure 2 shows the cost-effectiveness plots for the regimens under different assumptions of the relative risk of activation. Increasing the underlying risk of activation resulted in more cases of active TB and therefore higher costs for all regimens, with the greatest cost increases in regimens that prevented the fewest cases. At double the relative risk of activation, 4R and 3HP dominated all other regimens, and 3HP was more effective than 4R, at a cost of \$20,099 per QALY. At a relative risk of activation above 5.2 times baseline (consistent with the risk associated with old, healed TB on chest radiograph [4]), 3HP dominated all other options. 9H-DOT was cost-effective compared with 9H above a relative risk of 5.2 times baseline and was cost-saving compared with 9H at a relative risk of 10 times baseline but was never cost-effective compared with 4R or 3HP.

Adherence. In one-way sensitivity analyses of adherence, 4R dominated all regimens except 3HP as long as the completion rate for 4R was greater than 54% (base case value = 80%), compared with base-case estimates for other regimens. 3HP dominated all other regimens in situations where poor adherence to both of the self-administered regimens was present (completion rates of 34 and 37% for 9H and 4R, respectively).

Efficacy. When estimated risk reductions from treatment were varied over the range of possible values, rifampin maintained a cost advantage even with substantially reduced efficacy. 4R could be up to 17% less efficacious than 9H and still be less expensive and more effective than 9H. If the risk reduction from 3HP was less than the base-case estimate of 93% (i.e., less efficacious than 9H), the incremental cost-effectiveness ratio crossed the \$50,000 per QALY cost-effectiveness threshold.

Toxicity. Results were not sensitive to changes in the probabilities of severe toxicity, hospitalization from toxicity, or death from toxicity over the specified ranges.

Costs. Because the costs associated with DOT had an impact on the up-front expenditures of the two regimens that used this strategy, we conducted sensitivity analyses to determine threshold values of cost and adherence estimates. First, in a simple, one-way sensitivity analysis, we determined that DOT had to cost less than \$1.00 per dose (base-case value = \$22.32) before

TABLE 1. INPUT VARIABLES AND SOURCES

Variable	Base-Case Estimate	Range	Source
Lifetime risk of TB	0.06	0.06–0.4	(2–4, 16)
TB risk reduction from 9H-SAT or DOT			
0–2 months	0		(5)
3–5 months	0.21	0.14–0.21	(5)
6–8 months	0.69	0.44–0.69	(5)
9 months	0.93	0.60–0.93	(5)
TB risk reduction from 3HP			
0–1 months	0		(Assumed)
2 months	0.47	0.30–0.47	(Interpolated)
3 months	0.93	0.60–0.93	(5, 13)
TB risk reduction from 4R***			
0–1 months	0		(Assumed)
2 months	0.40	0.26–0.40	(Interpolated)
3 months	0.81	0.52–0.81	(Interpolated)
4 months	0.93	0.60–0.93	(Assumed)
Completion rates			
9H-SAT	0.53	0–1	(6, 9)
9H-DOT	0.87	0–1	(24)
3HP	0.94	0–1	(13)
4R	0.81	0–1	(6, 9)
Probability of stopping from toxicity			
Isoniazid-containing	0.014	0.001–0.2	(5, 6, 27, 28)
Rifampin-only	0.0035	0.001–0.2	(7, 29–31)
Probability of hospitalization for toxicity			
Isoniazid-containing	0.0014	0.00042–0.0057	(28)
Rifampin-only	0.00035	0–0.0057	(Assumed)
Probability of death from drug toxicity			
Isoniazid-containing	0.00014	0.000042–0.00057	(5, 28)
Rifampin	0.000035	0–0.00057	(Assumed)
Probability of extended treatment (active disease)	0.124		(11)
Probability of death from TB	0.03		(20, 32)
Number of secondary cases per active case	1.2	0–1.2	(5, 33)
Quality of life adjustments (life-years)			
LTBI treatment	0.97	0.95–0.97	(34)
Treatment-limiting toxicity	0.75	0.65–0.85	(Assumed)
Hospitalization	0.5	0.40–0.60	(Assumed)
Treatment of active TB	0.90	0.64–0.93	(32)
Prior TB	0.95	0.85–1	(Assumed)

Definition of abbreviations: DOT = directly observed therapy; LTBI = latent tuberculosis infection; TB = tuberculosis; 9H-DOT = isoniazid daily for 9 mo by directly observed therapy; 3HP = isoniazid plus rifapentine weekly for 3 mo; 9H-SAT = isoniazid daily for 9 mo by self-administered therapy; 4R = rifampin daily for 4 mo.

3HP would become less expensive than, and therefore dominate, 4R. Next, we considered the impact of not using DOT for 3HP, in which case the cost of delivering the doses would be \$0. (We did not include 9H-DOT in this analysis because without DOT it would be equivalent to 9H.) Without DOT, completion rates for 3HP would have to be at least 88% to remain cost-effective and at least 93% to be cost-saving, due mostly to the higher cost of rifapentine.

We then examined the effects of a price reduction for rifapentine on the results of our model. If costs for DOT are included, there is no threshold cost for rifapentine below which 3HP becomes cost-saving. If direct observation is not used, 3HP would become cost-saving at or below a price of \$0.46 per rifapentine pill (the same cost per pill as rifampin) at a completion rate of 80%.

The primary results were not sensitive to the costs of treatment of active disease (including hospitalization). They

TABLE 2. COSTS OF TREATMENT OF LATENT TUBERCULOSIS INFECTION PER MONTH

	Cost Estimate	Cost Range	Reference
Monthly visit costs			
Nursing visit (\$31.97/h)	\$17.41		(34)
Labs*	\$7.70		(34)
Physician visit*	\$0.36		(34)
Total visit cost	\$66.35	\$59.72–\$73.00	
DOT costs			
Outreach worker (\$16.75/h)	\$16.75		(36, 37)
Patient time (6 min @ \$14.86/h)	\$1.49		(36, 37)
Driving (10 mi at \$0.40/mi)	\$4.08		(36, 37)
Total DOT cost	\$22.32	\$0–\$33.47	
Drug costs			
Isoniazid, 300 mg	\$0.02		(M. Kelbaugh, personal communication)
Rifapentine, 150 mg	\$2.20		(M. Kelbaugh, personal communication)
Rifampin, 300 mg	\$0.46		(M. Kelbaugh, personal communication)
Pyridoxine, 50 mg	\$0.01		(M. Kelbaugh, personal communication)
Total monthly costs			
9H	\$26.37		
9H-DOT	\$204.56		
3HP (with DOT)	\$167.82		
4R	\$53.07		
Toxicity costs			
Lab monitoring	\$158.36		(35)
Hospitalization (7 d)	\$5,320.77	\$4,250–\$8,000	(23)

Definition of abbreviation: DOT = directly observed therapy.

* Average cost of routine monitoring and evaluation for mild toxicity assuming 40% of patients will require monthly monitoring of hepatic enzymes and 1.4% will have toxicity requiring physician evaluation that does not limit treatment.

were also not sensitive to the costs of toxicity included in the analysis.

Conclusion

In our analysis, 4R was the least expensive regimen for the treatment of LTBI. Over the patient's lifetime, the 4R regimen was less expensive and more effective than the current standard of care (i.e., 9H) over a wide range of estimates for adherence and efficacy. Although more expensive than 4R or 9H, 3HP was more effective, at a cost of \$48,997 per QALY compared with 4R and \$25,207 compared with 9H, and would therefore be considered cost-effective using our threshold of \$50,000 per QALY. Furthermore, this regimen became cost-saving for patients at very high risk or at extreme likelihood of treatment nonadherence. For example, patients with HIV infection have a risk of activation approximately 10 times the baseline estimate (16), so 3HP may be cost-saving in these individuals. However, the cost-effectiveness of 3HP at baseline risk was highly sensitive to its efficacy relative to 9H and to our estimates for adherence. If the ongoing large clinical trial shows that 3HP is less efficacious than 9H, its use would likely be restricted to these highest-risk individuals unless the price is reduced and self-administered therapy is considered an acceptable option.

TABLE 3. COSTS OF TREATING ACTIVE TUBERCULOSIS

	Units	Cost/Unit	Total Cost	Range	Reference
Diagnosis			\$447.54	\$0–671.31	(36)
Inpatient treatment					
Duration, days	11	\$760.11	\$8,361.21		(23)
Patient time, hours	10	\$14.86	\$1,634.60		(36)
Total inpatient treatment			\$9,995.81	\$5,000–50,000	(36)
Outpatient treatment (mo 1 and 2)					
Drug, doses	8	\$9.06	\$72.48		Table 2
DOT, visits	8	\$22.32	\$178.53		Table 2
Nursing (30 min)	0.5	\$31.97	\$15.99		(36)
Patient time per monthly visit, hours	1.5	\$14.86	\$22.29		(36)
Monitoring, visits	1	\$20.23	\$20.23		(36)
Total outpatient (mo 1 and 2)			\$309.51	\$245.00–460.00	
Outpatient treatment (mo 3+)					
Drug, doses	8	\$0.99	\$7.92		Table 2
DOT, visits	8	\$22.32	\$178.53		Table 2
Nursing (30 min)	0.5	\$31.97	\$15.99		(36)
Patient time per monthly visit, hours	1.5	\$14.86	\$22.29		(36)
Monitoring, visits	1	\$20.23	\$20.23		(36)
Total outpatient treatment (mo 3+)			\$244.95	\$195.00–370.00	
Contact tracing/testing (90% of contacts screened)	5.2	\$100.33	\$469.52	\$375.00–715.00	(22, 23)
Total per case—6 months			\$12,511.71		
Total per case—9 months			\$13,246.57		

Definition of abbreviation: DOT = directly observed therapy.

* Average cost of routine monitoring and evaluation for mild toxicity assuming 40% of patients will require monthly monitoring of hepatic enzymes and 1.4% will have toxicity requiring physician evaluation that does not limit treatment.

Isoniazid given by DOT for 9 months was very expensive in our model and did not compare favorably to the other regimens. Nonetheless, this regimen may be useful in instances where nonadherence to self-administered therapy is likely and rifamycins are contraindicated, such as in patients taking boosted HIV protease inhibitors. Additionally, two studies looking at the cost-effectiveness of observed isoniazid in drug users found it to be cost-saving compared with no therapy (17, 18). In both instances, however, the costs of DOT were very low because the procedures were performed by clinic staff already seeing the patients for other purposes, and no shorter regimens were compared.

Our model is the first to directly compare all three CDC-recommended regimens for the treatment of LTBI. Our data are consistent with recent cost data obtained by Aspler and colleagues in a randomized, controlled trial of isoniazid versus rifampin (19). Based on their cost projections, 4 months of rifampin could be 20% less efficacious than isoniazid and still be cost-saving. Conversely, Kahn and colleagues compared isoniazid, rifampin, and rifampin plus pyrazinamide in recent

immigrants and found that rifampin was more costly than isoniazid for most patients (but more effective), although their estimated drug costs for rifampin were substantially higher than our current data (\$97.70/mo vs. \$27.70/mo). A notable difference between this study and ours is their focus on drug resistance patterns. We assumed that everyone in our model was infected with organisms susceptible to all drugs. However, because isoniazid resistance is the most common resistance pattern seen in the United States (20), incorporation of susceptibility patterns into our model would have biased the results further toward rifampin monotherapy.

One significant limitation to our study is the fact that limited data exist to derive point estimates for the efficacy and adherence to 3HP. We used a wide range of parameters in sensitivity analyses, but adherence rates for this regimen without DOT have never been published. In one retrospective study comparing adherence to daily and weekly self-administered alendronate, patients taking the weekly regimen were more adherent over a 1-year period (21), but whether this pattern would be shared with 3HP in a population of patients with LTBI is

TABLE 4. COSTS, QUALITY-ADJUSTED LIFE-YEARS (QALY), AND NUMBER OF ACTIVE CASES OF TUBERCULOSIS FOR EACH OF THE FOUR REGIMENS, REFERENCED TO NO TREATMENT

Regimen	Average Lifetime Cost Per Contact	Incremental Cost Per Contact	QALY	Incremental Effectiveness (QALY)	Cases Per 1,000 Contacts, n	Cases Prevented*, n
No treatment	\$1,527.33	(Ref)	22.59614	(Ref)	64.0	(Ref)
9H	\$679.52	−\$847.81	22.64505	0.048911	20.3	43.7
9H-DOT	\$2,002.42	\$475.10	22.65644	0.060299	10.0	54.0
4R	\$495.21	−\$1,032.12	22.66509	0.068955	12.0	52.0
3HP	\$776.27	−\$751.06	22.67083	0.074692	8.7	55.3

Definition of abbreviations: 3HP = isoniazid plus rifapentine weekly for 3 mo; 9H = isoniazid daily for 9 mo by self-administered therapy; 9H-DOT = isoniazid daily for 9 mo by directly observed therapy; 4R = rifampin daily for 4 mo.

* Compared with no treatment.

TABLE 5. COSTS, QUALITY-ADJUSTED LIFE-YEARS (QALY), AND INCREMENTAL COST-EFFECTIVENESS RATIOS FOR THE FOUR REGIMENS, REFERENCED TO THE LOWEST-COST REGIMEN (4R)

Regimen	Average Lifetime Cost Per Contact	Incremental Cost Per Contact	QALY	Incremental Effectiveness (QALY)	Incremental Cost-Effectiveness Ratio
4R	\$495.21	(Ref)	22.66509	(Ref)	(Ref)
9H	\$679.52	\$184.31	22.64505	-0.02005	(Dominated)
3HP	\$776.27	\$281.06	22.67083	0.005736	\$48,997.34
No treatment	\$1,527.33	\$751.06	22.59614	-0.07469	(Dominated)
9H-DOT	\$2,002.42	\$1,226.15	22.65644	-0.01439	(Dominated)

Definition of abbreviations: 3HP = isoniazid plus rifapentine weekly for 3 mo; 9H = isoniazid daily for 9 mo by self-administered therapy; 9H-DOT = isoniazid daily for 9 mo by directly observed therapy; 4R = rifampin daily for 4 mo.

unknown. If TB programs begin to use isoniazid plus rifapentine in the future without direct observation, publication of data on adherence would be necessary to evaluate its overall utility.

In our model, the costs for each regimen were driven largely by the costs associated with active cases. We used a conservative approach, attempting to reproduce the current costs of treating active TB as much as possible. Other studies have used data from Brown and colleagues (22) in their estimates of the cost of treating an active case, but in that study an average of 77% of patients were hospitalized for an average of 20 days. More recent data from Taylor and colleagues (23) suggest that many fewer patients are hospitalized and for shorter periods, and we used these estimates in our study. There is also some controversy over the total costs associated with active TB. Most studies only include the costs of acute treatment of active disease. However, Pasipanodya and colleagues (24) demon-

strated significant respiratory impairment after the treatment of active TB (2), and the societal costs associated with this morbidity may be over \$150,000 per case (23). If these costs are included, our model predicts that 3HP would be more effective and less expensive even for very low-risk individuals (data not shown).

Isoniazid remains the standard of care for treating LTBI in adults in the developed world. However, if the efficacy of isoniazid plus rifapentine is confirmed in the ongoing clinical trial, our model suggests that this combination will be a more effective and less expensive alternative for high-risk individuals, particularly those with HIV, and will be cost-effective even for lower-risk patients. Meanwhile, our results indicate that increased use of 4 months of rifampin in place of 9 months of isoniazid to treat LTBI would be cost-saving for most programs in the United States and Canada.

Figure 2. Cost-effectiveness plots for each of the four regimens plus no treatment under different relative risk of disease activation. (A) Costs and effectiveness for the base-case lifetime risk (6%). In this scenario, rifampin daily for 4 months (4R) is less expensive and more effective than all regimens except isoniazid plus rifapentine weekly for 3 months (3HP), which is more effective at a cost of \$48,997 per quality-adjusted life-year (QALY) (shown in the figure as the inverse slope of the solid line connecting 4R and 3HP). 3HP is more effective than 9H, at a cost of \$20,207 per QALY (dotted line). (B) The same plot in patients with double the relative risk of activation. In this scenario, 4R and 3HP dominate other options, and 3HP is more effective than 4R, at a cost of \$20,099 per QALY (solid line). (C) The plot for patients with relative risk of disease 5.2 times the baseline. Here, 4R and 3HP are equivalent in cost, but 3HP is more effective. (D) The plot for patients with 10 times the relative risk of disease. 3HP dominates all strategies.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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