

Tuberculosis preventive therapy for HIV-infected people in sub-Saharan Africa is cost-effective

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Objective: Since antiretroviral therapy is largely unavailable to HIV-infected patients in developing countries and recent clinical trials have shown that tuberculosis (TB) preventive therapy can reduce TB and HIV-associated morbidity and mortality, we studied the effectiveness and cost-effectiveness of TB preventive therapy for HIV-infected persons in sub-Saharan Africa.

Methods: A Markov model that used results of clinical trials of TB preventive therapy in sub-Saharan Africa and literature-derived medical care costs was used to evaluate three preventive therapy regimens in HIV-infected, tuberculin-positive patients in Uganda: (1) daily isoniazid (INH) for 6 months, (2) daily INH and rifampin (RIF) for 3 months, and (3) twice-weekly RIF and pyrazinamide (PZA) for 2 months.

Results: All three regimens extend life expectancy and reduce the number of TB cases. When only medical care costs are considered, all three preventive therapy regimens cost more than not providing preventive therapy to extend life and prevent active tuberculosis. When medical care and social costs are considered together, 6-months of daily INH treatment will save money relative to no preventive therapy and when the costs associated with treating secondary infections are included, all three preventive therapy regimens are less expensive than no preventive therapy. With the inclusion of secondary infection costs, 6 months of daily INH results in savings of \$24.16 per person.

Conclusions: TB preventive therapy taken by HIV-infected tuberculin reactors in sub-Saharan Africa results in extended life-expectancy, reduction of the incidence of TB and monetary savings in medical care and social costs. TB control policy in sub-Saharan Africa should include preventive therapy. © 1999 Lippincott Williams & Wilkins

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[For editorial comment, see pp. 1581–1582]

Introduction

Tuberculosis (TB) is the leading cause of morbidity and mortality of HIV-infected people in developing countries. One study reported that 30–40% of deaths of HIV-infected people are caused or contributed to by TB [1]. HIV-infected individuals are more susceptible than HIV-uninfected persons to acquiring TB after exposure to *Mycobacterium tuberculosis* [2–4] and to

activation of latent infection [5–9]. Some recent studies have also indicated that active TB can cause progression of HIV disease; HIV-infected patients with TB have a shorter survival and a higher tendency to acquire new opportunistic infections than HIV-infected patients who have not had TB, even when matched by HIV disease stage [10–12]. Nevertheless, case-finding and treatment without preventive therapy is the predominant form of TB control in developing countries [13,14].

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Highly active antiretroviral therapy is very effective in reducing opportunistic infections and mortality [15] but it is not affordable for most patients in poorer nations [16,17]. In countries where antiretroviral therapy is unavailable, TB preventive therapy may effectively reduce HIV-related morbidity and mortality among dually infected persons. Pape *et al.* demonstrated this in a clinical trial in Haiti, in which 12 months of isoniazid (INH) prophylaxis decreased the incidence of TB and also delayed the progression to AIDS and death [18]. The options for preventive therapy increased recently when the results of clinical trials testing short-course regimens of INH with and without other antituberculosis drugs were reported. Several of the regimens were shown to be safe and effective for HIV-infected tuberculin reactors [19,20] and a systematic review found a significant reduction in mortality in tuberculin-positive subjects [21]. Because some regimens contain combinations of antituberculosis drugs that are more expensive than INH, their cost-effectiveness remains a concern, especially in developing countries. We therefore performed this study to evaluate whether different strategies of TB preventive therapy are cost-effective for HIV-infected people in sub-Saharan Africa.

Methods

We performed a cost-effectiveness analysis for a hypothetical cohort of HIV-infected people with positive tuberculin skin tests. The study was set in Uganda because of the availability of data on HIV and TB. We compared three preventive therapy regimens shown to be effective in developing countries with no preventive therapy: (1) INH 300 mg daily for 6 months; (2) INH 300 mg and rifampin (RIF) 600 mg daily for 3 months; and (3) directly observed preventive therapy with RIF 450–600 mg and pyrazinamide (PZA) 1.5–2.5 g twice-weekly for 2 months, with dosage depending on weight. The outcome measures studied were life expectancy, number of TB cases per 100,000 cohort, cost, and cost per quality-adjusted life-year (QALY) saved.

In accordance with the Panel on Cost-Effectiveness in Health and Medicine, the cost-effectiveness analysis used the societal perspective, quality-of-life adjustments, a 3% annual discount rate, and costs reported in 1997 USA dollars [22]. Costs were evaluated using three scenarios: (1) TB medical care costs alone; (2) TB medical care costs plus the social costs (indirect costs) of illness; and (3) TB medical care costs plus the social costs for both the cohort members and secondary cases caused by the spread of TB.

We used a Markov model, described in detail elsewhere [23], to calculate the outcomes for the hypothet-

ical patients. Patients who choose preventive therapy risk a fatal adverse event with some regimens. (Nonfatal adverse events are included in the analysis and affect quality of life but not survival.) Each year patients also risk developing TB. This risk is lessened by preventive therapy. Whether or not TB has occurred, each year patients risk death from any cause.

Table 1 shows the base case assumptions and the range of values for each variable and Table 2 shows the TB medical care costs. Transition probabilities were calculated with the exponential transformation [24]. A base case analysis was performed followed by a sensitivity analysis. We tested each assumption individually over the full range shown in Table 1 to determine if any variation in our assumptions caused a decrease in the calculated life expectancy. We also performed the analysis using a combination of the least favorable assumptions for preventive therapy. We then varied each cost listed in Table 2 from one-half to twice the base case cost to determine the effect on the cost-effectiveness ratios. Finally, we varied the number of secondary cases resulting from each active case to determine the threshold at which TB medical care costs, including social costs and secondary cases costs, are higher with preventive therapy than without preventive therapy.

Tuberculosis

The risk of HIV-infected tuberculin reactors developing TB is taken from the results of the placebo arms of four clinical trials conducted in developing countries. These studies reported annual TB infection rates of 3.4% to 10.0% [18,19,25,26]. The median rate, 6.7%, was used as the annual risk of active TB in patients not taking preventive therapy.

Effectiveness of preventive therapy regimens

The effectiveness of preventive therapy was taken from the results of clinical trials performed in East Africa and Haiti. Whalen *et al.* conducted a large study in Uganda of several short-course regimens. Among subjects randomized to 6 months of daily INH, the annual TB infection rate was 1.08%, a risk reduction of 67% relative to placebo [19]. This finding is consistent with the results of studies in Kenya and Zambia [25,26]. Whalen *et al.* also studied a regimen of 3 months of daily INH and RIF, and found an annual TB infection rate of 1.32%, a risk reduction of 60% relative to placebo [19].

Halsey *et al.* studied the effectiveness of a 2-month regimen of twice-weekly RIF and PZA in a clinical trial in Haiti. The comparison group took 6 months of twice-weekly INH. The annual TB infection rate in the RIF and PZA group was 1.8%, not significantly different from the rate of 1.7% in the INH group [20]. Because this trial did not include a placebo group, the base case rate with no preventive therapy, 6.7%, was

Table 1. Summary of Assumptions^a.

Variable	Base-case estimate	Range	Source
TB rate (HIV-infected, tuberculin-positive)	6.7% per year	3.4–10.0%	Pape, Hawken, Whalen, Wadhawan
Effectiveness of preventive therapy regimens			
INH for 6 months	67%	23–86%	Whalen, 1997
INH + RIF for 3 months	60%	14–82%	Whalen, 1997
RIF + PZA for 2 months	73%	30–90%	Halsey, Assumption
Duration of effectiveness	3 years, then to 0 after 5 years	1.5 years–lifetime	Assumption
All cause mortality of HIV-infected persons (per year)			
without history of TB	10%	3–16%	Whalen, 1995
after TB	35%	21–49%	Whalen, 1995
Adverse event rates (mild, moderate-to-severe, fatal)			
INH for 6 months	5.4%, 0.7%, 0.001%	1–30%, 0–10%, 0–0.2%	Whalen, 1997
INH + RIF for 3 months	3.6%, 1.1%, 0.001%	1–30%, 0–10%, 0–0.2%	Whalen, 1997
RIF + PZA for 2 months	3.0%, 0%, 0%	1–30%, 0–10%, 0–0.2%	Halsey, Assumption
Quality-of-life adjustments			
HIV-infected without opportunistic infection	0.65	0.4–1.0	Holtgrave
HIV-infected, after TB	0.62	0.4–1.0	Holtgrave
Preventive therapy adverse events: mild	0.5 for 1 week	0.25 for 1 month–0.99 for 1 day	Assumptions
Preventive therapy adverse events: moderate-to-severe	0.25 for 3 weeks	0.25 for 1 month–0.99 for 1 day	Assumptions
Secondary cases			
Number of contacts infected per case	4.7	2–10	Masobe
Percent of secondary infections HIV-infected	10%		Mulder
Demographics of secondary infections	47% children, 3% elderly		Tanzania Ministry of Health
Rate of activation of HIV-uninfected contacts	4% first 2 years, 0.1%/year thereafter		Comstock

^aTB, tuberculosis; HIV, human immunodeficiency virus; INH, isoniazid; RIF, rifampin; PZA, pyrazinamide.

used to calculate the effectiveness of the RIF and PZA regimen relative to taking no preventive therapy.

Because the duration of effectiveness has not been studied, the base case analysis used the assumption that preventive therapy maintains full effectiveness for 3 years from the start of therapy, with declining effectiveness to zero after 5 years.

Adverse events

Adverse events were classified by the clinical trials as mild, moderate and severe and included symptoms of rash, pruritus, gastrointestinal distress, arthralgias and evidence of clinical hepatitis. Neither the Ugandan study nor the Haitian study reported cases of severe or fatal hepatitis. The rates of adverse events for the 6-month INH regimen and the 3-month INH and RIF regimen were taken from the Ugandan study by using

the incremental increase in rates relative to the rate found in the placebo group [19]. Although no cases of severe or fatal INH-associated hepatotoxicity were reported, we used a rate of 0.001% per year [27,28]. The rate of adverse events for the 2-month RIF and PZA regimen was taken from the Haitian study, which found a 1% to 3% incidence of abnormal laboratory values during the first 8 weeks of RIF and PZA therapy, but no serious adverse events or discontinuation of treatment occurred [20].

Survival

The clinical trials of preventive therapy were not designed to demonstrate survival differences between groups, although the trial by Pape *et al.* did find a survival benefit from 12 months of INH preventive therapy [18] and the trial by Whalen *et al.* [19] found a non-significant trend toward improved survival. Three

Table 2. Costs of Tuberculosis Preventive Therapy, Adverse Reactions, and Therapy^a.

Variable	Cost	Source
Cost of TB (medical care)	\$113.51	Saunderson
Cost of TB (medical care and social)	\$388.17	Saunderson
Cost of preventive therapy		
INH for 6 months	\$22.95	Aisu
INH + RIF for 3 months	\$36.67	Saunderson, Aisu, Foster
RIF + PZA for 2 months	\$44.00	Saunderson, Aisu, Foster, Halsey, Assumption
Cost of mild adverse events	\$6.30	Masobe, Saunderson, Assumption
Cost of moderate-to-severe adverse events	\$50.22	Masobe, Saunderson, Assumption

^aTB, tuberculosis; INH, isoniazid; RIF, rifampin; PZA, pyrazinamide.

epidemiologic studies compared survival of HIV-infected persons with and without an episode of active TB [10–12]. Braun *et al.* retrospectively studied women of childbearing age in Kinshasa [10]. The mortality rate among 19 women with pulmonary TB, 26%, was significantly higher than the rate for the 224 women who did not have TB, 10%. Whalen *et al.* retrospectively studied patients in four USA medical centers, matching cases and controls by CD4 count. The two groups were similar in age, sex, race, history of previous opportunistic infection, and use of anti-retroviral therapy. The 1-year mortality rate in patients with a prior diagnosis of active TB, 35%, was significantly greater than the rate in patients without a history of TB, 10% [11]. Leroy *et al.* performed a large, community-based prospective study (the Aquitaine Cohort) in France, which also matched cases and controls by HIV disease stage. Annual mortality rates were significantly higher in the TB patients than in the controls, 40.7% versus 26.4% [12]. The effect of TB on long-term mortality of HIV-infected people remains a subject of controversy in the literature. With an understanding of the limitations of these studies and specifically the applicability of the USA-based study to sub-Saharan Africa, we have used the annual mortality rates found in the Whalen *et al.* study [11] as the base case assumption. The sensitivity analysis uses the mortality rates found in the other studies.

Costs

Saunderson [29] used financial reports from Kagando Hospital, Uganda and the Uganda National Tuberculosis/Leprosy Programme to determine the current costs of TB treatment. The total per patient cost of \$113.51 (adjusted to 1997 US\$ values) includes the costs of hospital overheads, medical and support staff training, diagnosis of tuberculosis, inpatient and outpatient treatment, antituberculosis drugs, and health education and counseling. The costs assume that sputum-positive patients would be admitted to the tuberculosis ward for 8 weeks of intensive therapy, after which they would be referred to a nearby clinic for the 10-month continuation phase of treatment. The cost of treating other opportunistic infections is assumed to be similar among treatment groups and is not included in this analysis. Social, or indirect costs, include the costs of transport, lodging, and food for the patient and an accompanying relative during the diagnosis and treatment of the disease. Also included in social costs are the costs associated with time away from normal activities [29]. Social costs alone were estimated to be \$274.66. Total direct and indirect costs were \$388.17.

The costs of the three preventive therapy regimens were estimated using the cost data included in studies by Saunderson in Uganda [29], and Aisu *et al.* in Uganda [30] and Foster *et al.* in Zambia [31]. In an operational assessment of an existing preventive therapy

program, Aisu *et al.* reported the cost of 6 months of daily INH preventive therapy to be \$22.95 (adjusted to 1997 US\$ values) per person successfully completing the regimen. Included in this total are the costs of the initial tuberculin skin test, screening (chest X-ray and sputum smears) for active tuberculosis, a 6-month supply of INH, and personnel and administration of the program [30]. The costs of HIV screening and counseling are not included in this total. Using the program and screening costs reported by Aisu *et al.* and the unit costs of antituberculosis medications reported by Saunderson, the cost per person was calculated to be \$36.67 for 3-months daily INH and RIF and \$44.00 for twice-weekly RIF and PZA. Costs of home visits for patients who miss follow-up appointments were included and total per patient costs were calculated using the compliance rates reported in the respective clinical trials. The total cost of the 2-month RIF and PZA regimen also includes directly observed therapy and monthly nutritional supplements for patients [20].

The costs of treating adverse events from preventive therapy were derived from a study by Masobe *et al.* [32] in South Africa, which reported the cost of managing INH-induced hepatitis as \$247. This cost was reduced by a factor of 4.9 to \$50.22 to reflect the different costs and availability of medical resources in Uganda. The multiplier, 4.9, was determined by relative TB treatment costs in South Africa and Uganda [29,32]. Using cost data from Masobe *et al.*, we estimated the cost of mild adverse events, primarily skin lesions, to be \$6.30 per person affected [32].

Quality of life

Our study applies quality of life values to each transition state in the model. Estimates are derived from a study by Holtgrave *et al.* which calculated median self-reported quality of life values from six USA studies [33]. Quality of life values assigned were: 0.65 for patients without a prior episode of TB, 0.62 during and after an episode of TB, 0.5 for 1 week during a mild adverse drug reaction and 0.25 for 3 weeks until recovery or death during a severe adverse drug reaction.

Secondary cases

The final cost scenario in this study calculates the TB medical care and social costs for cohort members and their contacts outside the original cohort who become infected and develop TB (secondary cases). Several epidemiological studies have addressed the number of secondary infections for each active case, reporting a range of 4 to 12 infections [32,34,35]. We assumed that each active case infects 4.7 others, a conservative estimate based on the study by Masobe *et al.* [32] which used epidemiological data from South Africa. We assumed that among the secondary cases, 10% are HIV-infected, 47% are children, and 3% are elderly [36,37] and that

Table 3. Prognosis of HIV-infected persons with positive tuberculin skin tests.^a

	Life expectancy (years)	QALYs	TB cases (per 100,000)
No preventive therapy	7.79	3.09	38,126
INH for 6 months	8.37	3.20	30,020
INH + RIF for 3 months	8.31	3.19	30,913
RIF + PZA for 2 months	8.43	3.21	29,246

^aTB, tuberculosis; INH, isoniazid; RIF, rifampin; PZA, pyrazinamide; QALY, quality-adjusted life years.

Table 4. Medical care and social costs of tuberculosis^a.

	TB medical care and costs ^b (per person)	TB medical care and social costs ^b (per person)
No preventive therapy	\$25.30	\$86.53
INH for 6 months	\$38.31	\$73.81
INH + RIF for 3 months	\$53.29	\$91.61
RIF + PZA for 2 months	\$57.85	\$90.90

^aTB, tuberculosis; INH, isoniazid; RIF, rifampin; PZA, pyrazinamide.

^bIncludes cost of preventive therapy and treating adverse events of preventive therapy.

HIV-infected secondary cases have the same TB activation rates and survival as in the base case analysis. For HIV-uninfected people who are newly infected with *M. tuberculosis*, we assumed that the rate of active TB is 4% in the first 2 years and 0.1% each year thereafter [38]. Using data from a Ugandan cohort survival study, we estimated life expectancies to be 53 years for children, 25 years for adults, and 5 years for elderly adults [39]. We calculated the annual mortality rate for the exposed persons based on these life expectancies [40].

Results

Our model calculates that HIV-infected tuberculin reactors who do not take preventive therapy will have an average life expectancy of 7.79 years and a quality-adjusted life expectancy of 3.09 QALYs (with future health events discounted at 3% per year). A cohort of 100,000 people will experience 38,126 TB cases over their cumulative lifetimes (Table 3). If the cohort takes the 6-month INH preventive therapy regimen, average life expectancy increases to 8.37 years, quality-adjusted life expectancy increases to 3.20 QALYs, and the number of TB cases decreases to 30,020 per 100,000.

The outcomes calculated with the other preventive therapy regimens, shown in Table 3, are not substantially different than with the 6-month INH regimen.

Cohort members who do not take preventive therapy incur an average cost of \$25.30 in TB medical care costs (with future dollars discounted at 3% per year) as a result of the active TB cases of some members (Table 4). Those who take the 6-month INH regimen incur costs of \$38.31, which includes the cost of the preventive therapy regimen and the cost to treat adverse reactions of preventive therapy. The cost to increase quality-adjusted life expectancy by 1 QALY is therefore calculated to be \$114. The total cost of TB medical care with the other regimens is higher, primarily because of the higher cost of those drugs. As a result, the 3-month INH and RIF regimen costs \$275 per QALY saved and the 2-month RIF and PZA regimen costs \$260 per QALY saved.

Inclusion of social costs in the analysis makes the 6-month INH regimen less costly than having no preventive therapy (Table 4). The other two regimens result in greater costs than the option of no preventive therapy.

The numbers of secondary cases that result from the cohort's active TB cases are shown in Table 5. A cohort of 100,000 HIV-infected tuberculin reactors can expect 38,126 primary cases and 19,667 secondary cases of TB as a result of transmission from cohort members, and TB medical care and social costs for the primary and secondary cases average \$111.88 per cohort member, when no preventive therapy regimen is used. All three preventive therapy regimens yield fewer primary and secondary cases and incur smaller costs. The regimen that results in the lowest total costs is the 6-month INH regimen.

The difference in costs of the preventive therapy regimens relative to no preventive therapy are shown in Table 6. Considering the costs of preventive therapy, the costs of treating adverse reactions to preventive therapy, and the medical care costs of treating tuberculosis, the preventive therapy regimens cost \$13.01 to \$32.55 per person. When social costs are included, the 6-month INH regimen results in savings of \$12.72 per person whereas the other two regimens result in costs of \$4.37 to \$5.08 per person relative to no preventive

Table 5. Primary and secondary cases and cost for tuberculosis medical care and social costs^a.

	Primary cases (per 100,000)	Secondary cases (per 100,000)	Medical care and social costs ^b (per person)
No preventive therapy	38,126	19,667	\$111.88
INH for 6 months	30,020	15,463	\$87.71
INH + RIF for 3 months	30,913	15,926	\$106.76
RIF + PZA for 2 months	29,246	15,061	\$103.72

^aTB, tuberculosis; INH, isoniazid; RIF, rifampin; PZA, pyrazinamide. ^bIncludes cost of preventive therapy and treating adverse events of preventive therapy.

Table 6. Costs relative to not taking preventive therapy.

	TB medical care costs (per person)	TB medical care and social costs/person ^a (savings)	TB medical care and social costs (savings)/person ^a for primary and secondary cases
INH for 6 months	\$13.01	(\$12.72)	(\$24.16)
INH + RIF for 3 months	\$27.98	\$5.08	(\$5.11)
RIF + PZA for 2 months	\$32.55	\$4.37	(\$8.16)

^aIncludes cost of preventive therapy and treating adverse events of preventive therapy. Figures in parentheses represent savings. TB, tuberculosis; INH, isoniazid; RIF, rifampin; PZA, pyrazinamide.

therapy. When the cost of secondary cases is included, the three regimens result in savings of \$5.11 to \$24.16 per person, with the greatest saving being for the 6-month INH regimen.

Sensitivity analysis

Variations of each assumption through the full range shown in Table 1, including making the assumption that preventive therapy is effective for only 1.5 years, did not result in any preventive therapy regimen reducing life expectancy relative to not taking preventive therapy. The combination of the most pessimistic assumptions regarding preventive therapy (the extreme of the ranges shown in Table 1) also did not result in any preventive therapy regimen reducing life expectancy. If the cost of preventive therapy is one-half the costs listed in Table 2, preventive therapy becomes very cost-effective: it costs \$13 to \$95 to extend life by 1 QALY and, if social costs or secondary cases are included, preventive therapy saves money. If preventive therapy costs twice the costs listed in Table 2, it costs \$315 to \$636 to extend life by 1 QALY and, if social costs and secondary cases are included, the only regimen that saves money is the 6-month INH regimen. Varying the cost of treating TB from one-half to twice the costs listed in Table 2 has a similar effect on the cost-effectiveness ratios: preventive therapy costs from \$21 to \$322 to extend life by 1 QALY through the full range. If the cost of treating TB is twice the cost listed in Table 2, all three regimens result in substantial savings. If the cost of treating TB is one-half the cost listed in Table 2, the only regimen that results in medical care cost savings is the 6-month INH regimen. Even if both the cost of preventive therapy is one-half the base case cost and the cost of treating TB is twice the base case cost, the 6-month INH regimen results in medical care cost savings (without considering social costs and secondary cases).

If the number of secondary cases per active case is 2 instead of 4.7, preventive therapy is less cost-effective: the 6-month INH regimen and the 2-month RIF and PZA regimen save less money but the 3-month INH and RIF regimen actually costs money to save QALYs. The 3-month INH and RIF regimen saves money if

the number of secondary cases per active case is 2.4 or more. If the number of secondary cases per active case is 10, preventive therapy results in substantial medical care cost savings: \$17 to \$37 per person.

If future costs and health events are discounted at 10% instead of 3%, preventive therapy is less cost-effective: it costs \$393 to \$889 to extend life by 1 QALY and, if social costs or secondary cases are included, the only regimen that saves money is the 6-month INH regimen.

Discussion

Using a Markov model, the results of recent clinical trials, and cost data from sub-Saharan Africa, we calculated the cost-effectiveness of tuberculosis preventive therapy for HIV-infected persons in Uganda. Life expectancy and quality-adjusted life expectancy are increased and the incidence of TB is reduced as a result of preventive therapy. The cost for these benefits ranges from \$114 to \$275 per QALY saved. If social costs are included with the cost of TB medical care, the 6-month INH regimen saves money. The regimen costs \$22.95 per person and, by reducing the likelihood of developing TB relative to not taking preventive therapy, recovers the investment and saves an additional \$12.72 per person. If social costs and secondary case costs are included, all three regimens result in savings in medical care costs, ranging from \$5.11 to \$24.16 per person. Wide variations in the assumptions made have little impact on these findings. However, the 6-month INH preventive therapy regimen would have to be less than half its current cost and treatment of active TB would have to be more than twice its current cost for preventive therapy to save costs in TB medical care, if social costs and secondary case costs are ignored.

Few other studies have evaluated the cost-effectiveness of tuberculosis preventive therapy in the setting of a developing country. A cost-effectiveness analysis of 6 months daily INH preventive therapy for HIV-infected patients in Zambia also found that when only the cost of TB treatment was included, monetary benefits did not exceed costs. But when the cost of patients' lost

wages was included, benefits exceeded costs by a ratio of 1.86 [31]. This model calculated that if the secondary cases prevented increased to five from their base case assumption of two, INH preventive therapy would be cost-effective even when only direct costs are included. An economic assessment of INH chemoprophylaxis for dually infected people in South Africa reported savings in health-care costs when secondary infections were included together with just direct costs [32].

Our study has several important limitations. First, we considered only TB medical care costs and did not include other medical care costs, such as HIV-related illness costs. Several observational studies have shown that HIV-infected people have a higher incidence of opportunistic infections after an episode of active TB [11,12]. If this analysis had included the cost of treating HIV-related illness in addition to treating active TB, preventive therapy would have been even more cost-effective. Secondly, this study does not include the costs of the initial HIV screening program. We assumed that patients would be referred for preventive therapy from a voluntary testing and counseling center, however, in areas where HIV testing is not available, additional costs of HIV testing and counseling would be required to facilitate this proposed program. In addition, this analysis assumes an independent preventive therapy program and does not address how integration of preventive therapy into existing national TB control programs would affect costs, follow-up, and compliance. Thirdly, this analysis used the lowest cost of TB treatment cited [29] which biased the analysis against choosing preventive therapy. The literature cites a wide range of TB treatment costs in Africa for TB treatment regimens that range from primarily inpatient to almost exclusively outpatient; all of these reported costs are higher than that used in this model [29,31,34]. Fourthly, our analysis of secondary case costs depends on a rate of spread that is uncertain, with a wide range cited in published studies [32,34,35]. We found that even the most expensive regimen, 2 months of RIF and PZA, will result in reduced TB medical care and social costs if the rate of spread is 2.4 or more secondary infections for each active case. A fifth limitation is that the duration of preventive therapy effectiveness is unknown. However, our model shows that even if preventive therapy has no effect at 2 years after treatment, it remains an effective means to extend life expectancy and reduce the incidence of TB.

It is important to note that this study is strongly grounded in the assumption that TB preventive therapy will ultimately prolong life. We acknowledge that the data on this subject remain controversial and that no single study has shown a survival benefit. However, the meta-analysis found a significant increase in survival for tuberculin-positive subjects. Therefore we have

restricted this model to a population of HIV-infected patients with positive tuberculin skin tests.

Conclusions

The addition of TB preventive therapy to the case-finding and treatment strategy currently in use in sub-Saharan Africa will result in saving money. As with any disease prevention strategy, a significant initial investment is required, but this investment is recovered and savings are seen when social and secondary case costs are considered. In countries such as Uganda where medical care costs are significantly shouldered by the patient and the patient's family, it is important to give appropriate weight to social costs in any health-care cost-effectiveness analysis. Prevention of secondary cases and financial savings are seen with an estimate of secondary cases lower than that commonly reported in the literature.

Feasibility studies of tuberculosis preventive therapy caution that screening, follow-up for test results, and adherence to therapy remain significant problems. However, this study uses the compliance data reported in similar settings and still found preventive therapy to be cost-effective. Drug resistance from poor preventive therapy adherence was not a problem in the clinical trials but remains an important concern [20].

Our study provides further rationale for the institution of tuberculosis preventive therapy in sub-Saharan Africa and other developing countries. There is now substantial evidence that TB preventive therapy is effective and may prolong life; this study reinforces that TB preventive therapy will also save money. We therefore strongly recommend that TB preventive therapy be provided for HIV-infected tuberculin reactors in developing countries.

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