ORIGINAL INVESTIGATION

Preventive Therapy for Tuberculosis in HIV-Infected Persons

Analysis of Policy Options Based on Tuberculin Status and CD4⁺ Cell Count

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Background: To facilitate decisions about the possible implementation of isoniazid preventive therapy (IPT) for human immunodeficiency virus (HIV)–infected persons on a large scale, the benefits and associated costs of various policy options of IPT should be evaluated.

Methods: Variable values based mainly on a prospective cohort study performed in Italy were used in an epidemiological model to assess the effects of the administration of IPT to the following groups of HIV-infected individuals: (1) tuberculin positive; (2) anergic, with various levels of immunosuppression; and (3) all HIV-infected individuals. The calculations of the costs associated with each policy option were based on the situation within the Italian national health care system. Outcome measures were average cohort survival times, total quality-adjusted life years lived in the cohort, total economic costs, and marginal costs per marginal quality-adjusted life year saved for each policy option.

Results: Median life expectancy gains from IPT were 104 to 149 days for tuberculin-positive individuals and 19 to 27 days for anergic patients. The largest gains were achieved for individuals with the lowest levels of immunosuppression. For tuberculin-positive individuals, savings from a reduced number of active tuberculosis cases were greater than the costs of the intervention, even for low patient compliance levels. Preventive therapy for anergic persons can result in cost reductions at levels of tuberculosis infection of 15% or higher for a compliance level of at least 95%. For infection levels of less than 10%, cost-effectiveness ratios are unfavorable.

Conclusions: Isoniazid preventive therapy administered to tuberculin-positive, HIV-infected patients increases life expectancies and reduces medical costs. Its extension to anergic patients may be justifiable on economic grounds in populations with a high prevalence of tuberculosis infection.

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TUBERCULOSIS IS an extremely important infectious disease, causing an estimated 3 million deaths worldwide each year.[1] The disease has reemerged as a relevant public health issue also in several industrialized countries during the past decade. This resurgence has been attributed in part to the spread of human immunodeficiency virus (HIV).[1] In fact, HIV-infected persons have a greatly increased risk of developing active tuberculosis as a consequence of reactivation of a latent tuberculosis infection or because of rapid progression to clinically overt disease of a newly acquired infection.[2,3] Active tuberculosis may boost HIV replication in vivo,[4] and results of recent empirical studies show significant increases in mortality from tuberculosis in HIV-infected individuals with advanced immunosuppression and in patients with acquired immunodeficiency syndrome.[5-7] These observations establish a potential role for isoniazid preventive therapy (IPT) to prolong survival after HIV infection.

It is well established that IPT significantly reduces the risk of active disease in patients with latent tuberculosis infection.[8] Evidence from observational studies and clinical trials suggests that this effect also occurs in tuberculin-positive HIV-infected individuals.[9-14] With respect to the overall survival of tuberculin-positive HIV-infected individuals, the effect of IPT was not statistically significant in some clinical trials,[10,12,14] but the results of 1 trial[13] show a significant prolongation of survival times. A small, nonsignificant reduction in the incidence of tuberculosis among anergic HIV-infected patients undergoing IPT has been observed in 2 recent clinical trials.[14,15] Results of these studies also show no life expectancy gain.

PATIENTS AND METHODS

EPIDEMIOLOGICAL MODEL

We constructed a model to analyze outcomes and costs of various policies for IPT in a hypothetical cohort of 100 000 HIV-infected adults for 10 years. The cohort was initially stratified into 3 groups with different $CD4^+$ cell counts ($>0.35 \times 10^9$/L, 0.35-0.20 $\times 10^9$/L, and $<0.20 \times 10^9$/L). Each of these groups was further classified as purified protein derivative (PPD) positive (tuberculin positive), PPD negative (tuberculin negative [nonanergic], ie, reactive on skin tests to at least 1 recall antigen other than PPD), or anergic. These 9 groups were defined on the basis of data from a prospective study[22] performed in Italy (Gruppo Italiano di Studio Tubercolosi e AIDS [GISTA] study) in which different risks of developing active tuberculosis were identified for each combination of response to skin tests and $CD4^+$ cell count. The distribution of HIV-infected patients in different groups was based on empirical data collected at enrollment in this prospective study. Uncertainty ranges were established for possible levels of tuberculosis infection in tuberculin-positive and tuberculin-negative, nonanergic cohort members to account for the diagnostic limitations of the PPD skin test. Results of the GISTA study[22] show a level of PPD positivity of 19% in the nonanergic population (ie, tuberculin positive and tuberculin negative, nonanergic). Taking into account the technical difficulties in interpreting results of anergy skin testing,[18] we used 20% prevalence of infection as the highest tuberculosis infection prevalence and 0% as a lower bound estimate. The complete initial stratification of the cohort and all uncertainty ranges are shown in **Table 1**.

A decision tree was used to analyze the effects of IPT on each of the 9 groups in the cohort (**Figure 1**). We modeled the effect of IPT as a reduction of the level of tuberculosis infection in groups receiving therapy. Noncompliance was assumed to be equivalent to not receiving IPT (ie, we assumed no efficacy of the intervention and no adverse effects). Isoniazid preventive therapy induces a certain risk of hepatitis.[23-25] The efficacy of IPT after hepatitis in compliant persons in the model was reduced to 25% of a full course of therapy, assuming that hepatitis would occur, on average, during the third month of therapy.[26] Ranges of estimates for IPT efficacy, IPT-induced hepatitis, and death from hepatitis were derived from published data[23-25] (Table 1). The output of this decision tree is a new distribution of tuberculosis-infected and tuberculosis-uninfected cohort members in the 3 groups with different $CD4^+$ cell counts and the number of deaths from IPT-induced hepatitis.

Projections of further epidemiological developments for each group in the cohort were simulated with the Markov chain model[27] shown in **Figure 2**. The model uses yearly probabilities for the indicated movements between various epidemiological states. This time step was assumed to be of sufficient length to accommodate epidemiological-processes of long duration, such as the development, detection, and treatment of active tuberculosis cases. After the yearly movements, cohort members in each group are in 1 of the following stages: dead, tuberculosis uninfected, tuberculosis infected (previous infection), tuberculosis infected (new infection), or active tuberculosis. For the next yearly simulation step, patients are assigned to the matching initial stage of the Markov model, accounting for the probability of moving to a stage with a lower $CD4^+$ cell count. Most of the transfer probabilities within the Markov model were based on empirical observations from the 3-year follow-up data of the GISTA study.[22] Point estimates and 95% confidence intervals for cumulative transition probabilities were calculated using the Kaplan-Meier method. For the remaining transfer probabilities, ranges of values were derived from published data (Table 1).

UNCERTAINTY ANALYSIS AND POLICY OPTIONS

For model uncertainty analyses, we defined each variable derived from empirical observation in the Italian prospective study[22] as a triangular probability distribution, where the point estimate was given the highest probability of being sampled. Uniform distributions were used for the remaining variables. Each analysis was based on 500 model simulations during which all variable distributions were sampled independently and simultaneously. Sampling was performed using the Latin Hypercube technique[28] to ensure that each variable was sampled across the complete range of the probability distribution.

The following analytic steps were performed to determine the potential effect of IPT in the cohort. First, we simulated the expected epidemiological development of cohorts with various initial $CD4^+$ cell counts ($>0.35 \times 10^9$/L, 0.35-0.20 $\times 10^9$/L, and $<0.20 \times 10^9$/L) and a $CD4^+$ cell count distribution as observed in the GISTA study.[22] For the latter, we determined the median of the resulting 500 values of potential life expectancies and used the associated variable combination to establish the potential effects of IPT for individuals with various levels of immunosuppression and PPD and anergy status. This analysis accounted for the uncertainty about rates of hepatitis, death from hepatitis, and IPT efficacy (Table 1). The variable combination was further used to establish the effects of the following policy options for IPT: (1) IPT for tuberculin-positive cohort members only; (2a) IPT for tuberculin-positive cohort members and anergic cohort members with $CD4^+$ cell counts lower than 0.20×10^9/L; (2b) IPT for tuberculin-positive cohort members and anergic cohort members with $CD4^+$ cell counts lower than 0.35×10^9/L; (2c) IPT for tuberculin-positive cohort members and all anergic cohort members; and (3) IPT for all HIV-infected cohort members regardless of PPD status.

The effects of the various policies were analyzed in a stepwise fashion, indicating the marginal gains from successively broader applications of IPT. We assumed a baseline value of 75% compliance among cohort members for preventive therapy scenarios and varied the rates for IPT

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Different policies for the use of IPT as a routine intervention for HIV-infected persons have been proposed. National and international public health agencies agree about giving IPT to tuberculin-positive HIV-infected individuals. In contrast, whether to give IPT to anergic HIV-infected individuals remains contentious. In 1991, the Centers for Disease Control and Prevention (CDC) recommended considering IPT for anergic persons from groups in which the prevalence of tuberculosis infection is 10% or more.[16] According to the British Thoracic Society, anergic individuals should receive IPT if they are at high risk of tuberculosis infection and have

efficacy, isoniazid-induced hepatitis, and death from hepatitis across the ranges indicated in Table 1. For comparison of the effects of alternative policies for IPT, we ran the model with a set of 500 variables, which were chosen by simultaneous and independent sampling of all variables, using the Latin Hypercube sampling method. The same set of 500 variable combinations was used for all alternative policy options, and the assessment of the incremental effect of each policy option was based on analyzing the distribution of the 500 differences in outcome values for model runs with the same variable combinations. Following standard recommendations,[29] health outcomes from these analyses were expressed as quality-adjusted life years (QALYs) using medians of recently published quality-of-life adjustment factors for the various levels of immunosuppression in HIV infection.[30] Finally, we used the variable combination resulting in median QALY gains from policy 1 to analyze the effects of varying patient compliance rates from 5% to 100% for policy 1. Because the incremental effects of policy 2c were also dependent on the levels of tuberculosis infection among anergic patients, we determined these incremental gains for all possible combinations of compliance rates from 5% to 100% and levels of tuberculosis infection from 0% to 50%.

All calculations were performed with a spreadsheet program (Lotus 1-2-3, Lotus Development Corp, Cambridge, Mass).

COST ANALYSIS

Economic costs for most screening and treatment procedures were estimated on the basis of an analysis recently performed in Italy.[31] For procedures for which an empirical cost analysis was unavailable, charges incurred within the Italian National Health System were applied,[32] in line with recent recommendations for the conduct of cost-effectiveness analyses.[29] We assumed that the decision about IPT would be made for patients with known HIV status and $CD4^+$ cell counts, and we did not account for costs to obtain this information. All future costs and effects were discounted at an annual rate of 3%.[29]

The following items were included in the cost calculations (**Table 2**):

- *General screening*. In policy 1, screening is offered to all members of the cohort and consists of PPD skin testing performed by the Mantoux procedure using 5 IU of PPD. In policies 2a, 2b, and 2c, in addition to PPD skin testing, anergy testing is performed using a 7-antigen multipuncture device. No skin testing is performed in policy 3 and in the "No-IPT" scenario.
- *Specific screening for candidates to IPT*. Irrespective of the policy option considered, all candidates for IPT undergo a clinical examination and chest radiography to exclude the presence of active tuberculosis. In addition, liver function tests (total and fractionated serum bilirubin, serum alanine aminotransferase, and aspartate aminotransferase) are performed.
- *Preventive therapy*. Preventive therapy consists of 300 mg of isoniazid administered daily for 1 year; in addition, pyridoxine hydrochloride is administered daily. Patients undergoing IPT receive liver function tests monthly during the first 3 months and every other month thereafter.
- *Treatment of adverse effects from IPT*. We assumed that 90% of all patients with hepatitis are treated on an ambulatory basis[33]; on average, 3 clinical visits are made for each patient, during which liver function tests are routinely performed. For the 10% of patients with hepatitis who would require hospitalization, hospital stay was assumed to be, on average, 7 days. Apart from checking liver function, treatment usually consists of clinical observation without specific interventions.
- *Treatment of active tuberculosis*. We assumed that all HIV-infected cohort members with active tuberculosis are hospitalized. On the basis of a retrospective clinical chart review performed on HIV-infected patients with tuberculosis admitted during 1995 in 7 clinical centers in Italy, we assumed a median value of hospital stay of 30 days (G.A., unpublished observations, 1995). After this period, patients continue treatment on an ambulatory basis. Cost of treatment was estimated by the room costs per hospital day supplemented by the charges for an average number of diagnostic and therapeutic procedures derived from the above-mentioned survey.

Patients with active tuberculosis within the cohort will infect people outside the cohort (either HIV or non–HIV infected). To account for the associated costs, we used the following assumptions: an untreated case of active tuberculosis would cause 10 new infections, and a treated case would cause 2 new infections.[34] The proportion of these new infections that would occur within the HIV-infected population is unknown. To account for this uncertainty, we used the assumption of homogeneous mixing and an HIV prevalence of 0.2% within the general population[35] as a lower boundary estimate and a level of 20% new infections within the HIV-infected population (assuming more heterogeneous mixing) as an upper limit. We assumed that 5% of non–HIV-infected persons who acquire a new tuberculosis infection would develop active disease over an evaluation period of 10 years.[36] Two studies[22,37] established annual incidences of active disease after new infections in HIV-infected persons between 4.7% and 13.9%. These values were used as boundaries for the uncertainty analysis.

Two recent studies[38,39] in Italy reported levels of multidrug-resistant (MDR) tuberculosis among HIV-infected persons between 3.0% and 5.0%. We used these data to define an uncertainty range for the proportion of MDR cases during model calculations. Cost data for MDR cases in Italy are unavailable. However, results of a recent analysis[40] from the United States show that the costs for the treatment of MDR tuberculosis exceed those for non-MDR cases by a factor of 13.7. We used a factor of 10 as a conservative estimate.

a $CD4^+$ cell count below 0.20×10^9/L.[17] Difficulties in interpreting anergy skin test results[18] and the results of clinical studies[14,15] recently prompted the CDC to revise their previous guidelines, recommending IPT only for anergic patients with an ongoing high risk for exposure to *Mycobacterium tuberculosis*.[19]

In an environment of increasing financial limitations, rational health policymaking demands that the expected benefits of an intervention are related to its costs before widespread implementation as a public health measure is recommended. A cost analysis for IPT needs to take into account that additional costs for the program

Table 1. Model Variables for Baseline Analysis*

Variable	Point Estimate	Range	Source†
Initial Cohort Stratification			
Distribution by $CD4^+$ cell count, $\times 10^9$/L, %			Antonucci et al[22]
>0.35	38.0	. . .	
0.35-0.20	23.6	. . .	
<0.20	38.4	. . .	
Distribution by delayed-type hypersensitivity status in $CD4^+$ cell count strata, %			Antonucci et al[22]
$>0.35 \times 10^9$/L			
Tuberculin positive	10.7	. . .	
Tuberculin negative, nonanergic	51.1	. . .	
Anergic	38.2	. . .	
$0.35\text{-}0.20 \times 10^9$/L			
Tuberculin positive	8.8	. . .	
Tuberculin negative, nonanergic	36.1	. . .	
Anergic	55.1	. . .	
$<0.20 \times 10^9$/L			
Tuberculin positive	3.0	. . .	
Tuberculin negative, nonanergic	9.3	. . .	
Anergic	87.7	. . .	
Prevalence of tuberculosis infection by delayed-type hypersensitivity status			Definition
Tuberculin positive	. . .	0.9-1	
Tuberculin negative, nonanergic	. . .	0.0-0.05	
Anergic	. . .	0-20	
Efficacy and Adverse Effects of IPT			
Compliance with IPT	75	. . .	Estimated
Efficacy of IPT	. . .	85-95	Pape et al[10] and Graham et al[11]
IPT-induced hepatitis, %	. . .	0.3-6.4	Salpeter,[23] Israel et al,[24] and Snider and Caras[25]
Efficacy of IPT after hepatitis	25	. . .	International Union Against Tuberculosis Committee on Prophylaxis[26]
Death from IPT-induced hepatitis, %	. . .	0.06-8.7	Salpeter,[23] Israel et al,[24] and Snider and Caras[25]
Annual Transition Probabilities by $CD4^+$ Cell Count			
$>0.35 \times 10^9$/L			
Active tuberculosis	.02	.005-.08	Calculated
Death from active tuberculosis	.25	.04-.87	Calculated
$CD4^+$ cell count $0.35\text{-}0.20 \times 10^9$/L	.22	.20-.25	Calculated
$CD4^+$ cell count $<0.20 \times 10^9$/L	.06	.05-.08	Calculated
Death from other causes	.02	.01-.03	Calculated
$0.35\text{-}0.20 \times 10^9$/L			
Active tuberculosis	.08	.03-.20	Calculated
Death from active tuberculosis	.25	.09-.59	Calculated
$CD4^+$ cell count $0.35\text{-}0.20 \times 10^9$/L	NA	NA	
$CD4^+$ cell count $<0.20 \times 10^9$/L	.28	.24-.32	Calculated
Death from other causes	.04	.02-.05	Calculated
$<0.20 \times 10^9$/L			
Active tuberculosis	.12	.05-.30	Calculated
Death from active tuberculosis	.36	.23-.53	Calculated
$CD4^+$ cell count $0.35\text{-}0.20 \times 10^9$/L	NA	NA	NA
$CD4^+$ cell count $<0.20 \times 10^9$/L	NA	NA	NA
Death from other causes	.29	.26-.32	Calculated
Other Variables			
Detection of active tuberculosis, %	. . .	80-100	Estimated
Risk of new tuberculosis infection, % per year	. . .	1.5-2.5	Estimated
Risk of tuberculosis after new infection, per 100 person-years	. . .	4.7-13.9	Antonucci et al[22] and Markowitz et al[37]
New tuberculosis infections generated by treated or untreated patients, No.	. . .	2-10	Styblo[34]
Prevalence of HIV among patients who acquire new tuberculosis infection outside the cohort, %	. . .	0.2-20	Scalia-Tomba[35]
Multidrug-resistant tuberculosis, % of the overall tuberculosis	. . .	3.0-5.0	Girardi et al[38] and Angarano et al[39]

**IPT indicates isoniazid preventive therapy; HIV, human immunodeficiency virus; ellipses, point estimate or range not used in the model; and NA, not applicable.*

†For initial cohort stratification, enrollment data from a prospective study on risk of tuberculosis in HIV-infected patients carried out in Italy were used.[22] Point estimates and 95% confidence intervals for annual transition probabilities by $CD4^+$ cell count were derived from 3 years of follow-up data from the same study.[22] For the remaining variables, point estimates or ranges of values were estimated or derived from published data.

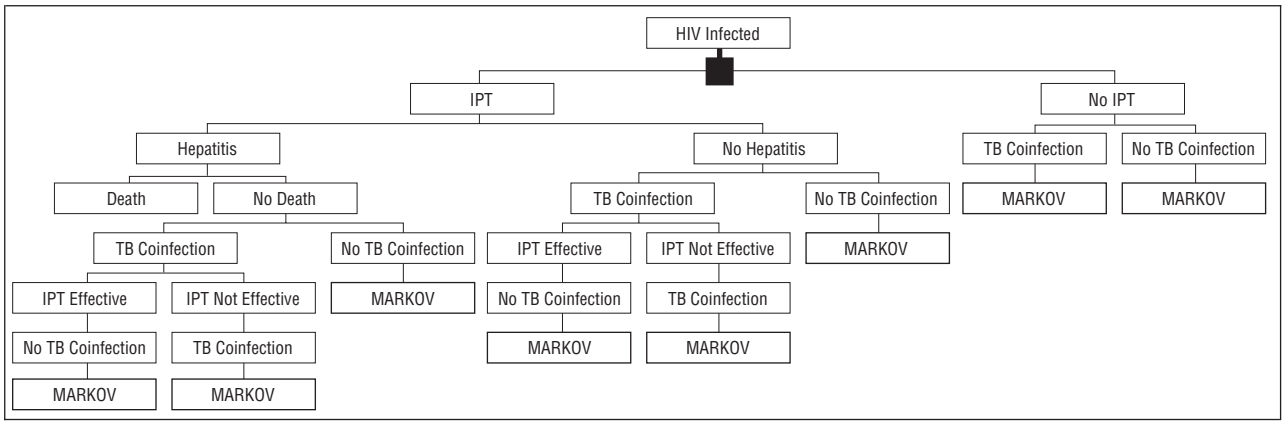

Figure 1. *Decision model used to evaluate the effects of isoniazid preventive therapy (IPT) for tuberculosis (TB) in a cohort of individuals infected with human immunodeficiency virus (HIV). The black square represents the decision point. According to different policy options, cohort members may or may not receive IPT. The effect of IPT is modeled as a reduction of the level of TB coinfection in groups of patients receiving IPT. MARKOV represents a Markov chain model detailed in Figure 2.*

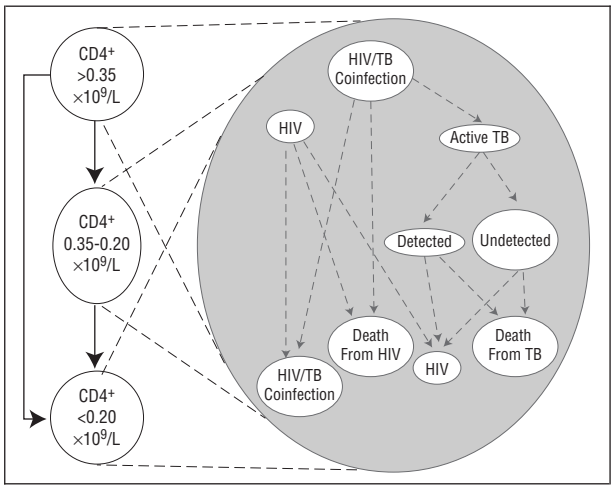

Figure 2. *Markov chain model. Cohort members move between 3 levels of immunosuppression, indicated by 3 CD4+ cell count levels (left side); within each level of immunosuppression, persons with or without tuberculosis (TB) infection (TB and human immunodeficiency virus [HIV] coinfection or HIV) have various probabilities of moving to different epidemiological states, indicated by arrows (right side). All transitions are repeated annually.*

may be balanced by reduced costs for the care of patients with active tuberculosis. Using simulation models, results of 2 studies from Africa suggest that providing IPT to HIV-infected individuals may be justifiable on economic grounds.[20,21] However, no analysis has been performed for this situation in high-income countries. In the present study, we used cost data from Italy to assess the cost-effectiveness of various IPT policies in this situation. A prospective cohort study on the incidence of tuberculosis among HIV-infected persons from Italy[22] provided variable values for model calculations to assess the potential health gains from IPT.

RESULTS

LIFE EXPECTANCY WITH DIFFERENT LEVELS OF IMMUNOSUPPRESSION

We simulated life expectancy values for patients with 3 different initial levels of CD4+ cell counts and for a cohort with an initial distribution of CD4+ cell counts as observed in the Italian prospective study.[22] Median life expectancies were 8.0 years for cohort members with initial CD4+ cell counts of greater than 0.35×10^9/L, 5.6 years for those with CD4+ cell counts between 0.35×10^9/L and 0.20×10^9/L, and 2.8 years for those with initial CD4+ cell counts of less than 0.20×10^9/L. For the total cohort, the median of all simulated life expectancy values was 5.4 years. These results are in

Table 2. Cost Estimates Used in the Analysis*

Procedure	Cost, US $
General screening for all HIV-infected individuals	
Tuberculin skin test	6.18
Skin test with other antigens	17.65
Total	**23.83**
Specific screening for all patients eligible for IPT	
Chest radiography	52.94
ALT and AST	6.56
Serum bilirubin (total and fractionated)	5.81
Total	**65.31**
Preventive therapy for tuberculosis	
1 clinical visit	52.94
Isoniazid	52.69
Pyridoxine hydrochloride	64.32
ALT and AST×7	45.92
Total	**215.87**
Treatment of active tuberculosis	
Hospital room cost for 30 d	3230.47
Average diagnostic procedures	880.03
Drugs	225.57
Total	**4336.07**
Treatment of adverse effects of IPT	
3 clinical visits and 3 ALT and AST measurements	178.49
Hospital room cost for 7 d and 3 ALT and AST measurements	773.44
Average Total†	**237.99**

**All cost data are derived from Migliori et al[31] and Ministero della Sanità.[32] Costs were calculated in 1997 Italian lira and converted to US dollars at a rate of $1 = Lit1700 for use in the analysis. HIV indicates human immunodeficiency virus; IPT, isoniazid preventive therapy; ALT, serum alanine aminotransferase; and AST, serum aspartate aminotransferase.*

†This figure is calculated assuming that 90% of patients with IPT-induced hepatitis are treated on an ambulatory basis and that the remaining 10% require hospitalization.

agreement with those of previous studies on the life expectancy of HIV-infected persons[41-45] and confirm the validity of the model calculations.

POTENTIAL LIFE EXPECTANCY GAINS FROM IPT

The potential effect of IPT for patients with various levels of immunosuppression and PPD status is summarized in **Table 3**. Results are based on the assumption of 75% patient compliance. Uncertainty ranges indicate the impact of various levels of adverse effects and IPT efficacy shown in Table 1. Life expectancy gains are generally higher for tuberculin-positive patients compared with anergic patients. In both groups, life expectancy gains are more evident for cohort members with less advanced immunosuppression. Among anergic cohort members, median life expectancy gains ranged from 6 to 9 days in scenarios with a tuberculosis infection level of 5% and from 23 to 33 days in scenarios with an infection level of 20% according to different levels of immunosuppression. The provision of preventive therapy to tuberculin-negative, nonanergic persons may lead to minimal decreases in life expectancy in some simulations.

COHORT EFFECTS OF VARIOUS IPT POLICIES

Table 4 summarizes the effects of various IPT policies on a cohort of 100 000 HIV-infected persons. Outcome measures are shown for the baseline scenario without preventive therapy, and differences resulting from IPT are directly indicated. The effects of the various policies were analyzed in a stepwise fashion, indicating the marginal gains from successively broader applications of preventive therapy. We assumed that the first level of implementation would be the provision of IPT only to patients with a positive PPD test result (policy 1); the next level would be extension of the policy to anergic patients, analyzed separately for 3 different options based on initial $CD4^+$ cell count (policies 2a-c); and finally, we analyzed the marginal effect of providing IPT to all HIV-positive patients regardless of PPD status and $CD4^+$ cell count (policy 3).

Policy 1 results in a median increase of QALYs lived by the cohort of 1153 (range, 1026-1245 QALYs). Resulting from the decreased number of expected patients with active tuberculosis, health care costs are expected to decrease by US $6.5 million to US $9 million (median, US $7.7 million). Cohort life expectancies can be further increased by extending IPT to anergic patients (policies 2a-c), and these policies generally lead to further cost reductions. When additional expenditures are required (some simulations for policy 2a), cost-effectiveness ratios range from US $1 to US $1786 per QALY gained. Policy 3 may lead to decreases of the average cohort life expectancy. For those scenarios in which cohort life expectancies could be increased by this policy, cost-effectiveness ratios are high, up to a maximum of US $2.6 million per additional QALY.

EFFECTS OF VARIOUS LEVELS OF PATIENT COMPLIANCE AND TUBERCULOSIS INFECTION

The incremental effects of various IPT policies were analyzed assuming a patient compliance rate of 75%. Because the actual compliance rates under field conditions may be substantially lower, we investigated the impact of changing compliance rates for policies 1 and 2c. The marginal effects of policy 2c also depend on the level of tuberculosis infection among anergic patients. The incremental effects of this policy were therefore explored for all possible combinations of compliance level and tuberculosis infection.

Even for minimal patient compliance levels of 5%, neither policy results in a reduction of average patient life expectancy (data not shown). Policy 2c does not result in a reduction of average patient life expectancy even for a tuberculosis infection level as low as 0%. The ef-

Table 3. Estimated Life Expectancy Gains From Isoniazid Preventive Therapy in Human Immunodeficiency Virus–Infected Patients by $CD4^+$ Cell Count and Delayed-Type Hypersensitivity Skin Test Status*

$CD4^+$ Cell Count, $\times 10^9$/L	Status		
	Tuberculin Positive	Anergic	Tuberculin Negative, Nonanergic
>0.35	149 (135 to 160)	27 (9 to 37)	7 (0 to 9)
0.35 to 0.20	146 (129 to 157)	26 (8 to 36)	6 (–3 to 9)
<0.20	104 (95 to 111)	19 (3 to 25)	5 (1 to 6)

**Values are median (range) number of days. Calculations are based on the assumption of 75% patient compliance with preventive therapy.*

Table 4. Estimated Marginal Effects of Various Isoniazid Preventive Therapy (IPT) Policies in Human Immunodeficiency Virus (HIV)–Infected Cohort Members*

Policy	Provider Cost, Million US $	Quality-Adjusted Life Years (QALYs)	Cost-effectiveness Ratios, US $ per QALY
No IPT	61.9 (57.8 to 66.1)	313 475	NA
1	–7.7 (–6.5 to 9.0)	1153 (1026 to 1245)	NA
2a	–0.8 (–2.3 to 0.5)	1057 (874 to 1163)	578 (1 to 1786)
2b	–2.2 (–1.3 to 3.3)	528 (386 to 593)	NA
2c	–1.7 (–0.7 to 2.7)	460 (245 to 539)	NA
3	2.7 (2.3 to 3.1)	192 (–166 to 305)	14 405 (8504 to 2 633 750)

**Values are medians (ranges). National Health System costs for treating HIV-related tuberculosis and QALYs were estimated for 100 000 HIV-infected cohort members for a scenario with no IPT, and the difference achieved by the policies for IPT was calculated. The policies are described in the text. Values for policy 1 show differences to the baseline scenario. Policy differences are analyzed stepwise, indicating the marginal gains from successively broader applications of IPT. NA indicates not applicable.*

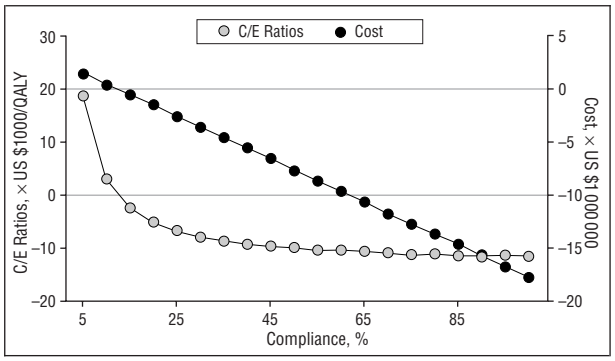

Figure 3. *Incremental costs and cost-effectiveness (C/E) ratios of a policy of providing isoniazid preventive therapy to tuberculin-positive, human immunodeficiency virus–infected cohort members (policy 1), according to different levels of patient compliance. Cost differences between this policy and a policy of providing no preventive therapy are given in millions US currency. Cost-effectiveness ratios are calculated as incremental costs divided by differences in quality-adjusted life years (QALYs) lived by the cohort.*

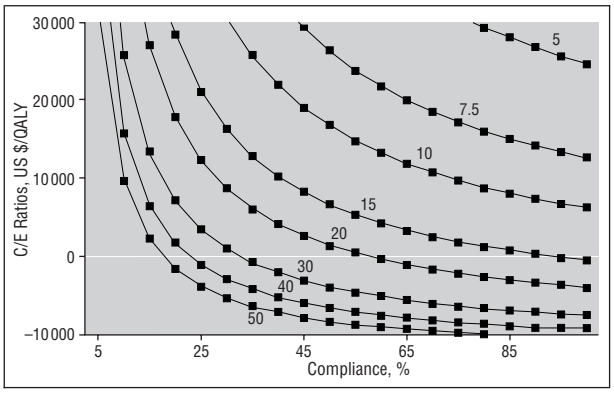

Figure 4. *Cost-effectiveness (C/E) ratios of a policy of providing isoniazid preventive therapy to tuberculin-positive and anergic human immunodeficiency virus–infected patients (policy 2c), according to different levels of patient compliance and different levels of tuberculosis infection in anergic patients. Cost-effectiveness ratios are calculated as incremental costs divided by differences in quality-adjusted life years (QALYs) lived by the cohort for policy 2c compared with a policy of providing isoniazid preventive therapy to tuberculin-positive patients only (policy 1). The different lines indicate various levels of tuberculosis infection among anergic patients; numbers above the lines, percent prevalence rates. Negative C/E ratios indicate scenarios with net cost savings.*

fects of the uncertainty analysis on cost-effectiveness ratios are shown in **Figure 3** and **Figure 4**. Policy 1 could result in a reduction in medical costs for compliance levels of 15% or higher. Additional costs per QALY are less than US $10 000 for compliance levels between 10% and 15% (Figure 3).

Policy 2c does not result in a reduction of medical costs compared with policy 1 for level of tuberculosis infection less than 15% for all levels of compliance. Reduction of medical costs can be achieved if the level of tuberculosis infection is 15% or higher for a compliance level of at least 95%, or 20% or higher for a compliance level of at least 60%. Marginal costs per additional QALY are less than US $10 000 for tuberculosis infection levels of 20%, 15%, and 10% for compliance levels of at least 30%, 45%, and 75%, respectively. However, marginal costs per additional QALY are greater than US $10 000 for all scenarios with tuberculosis infection levels of less than 10% (Figure 4).

COMMENT

The overall mortality of HIV-infected persons increases if active tuberculosis occurs during the course of HIV infection.[5,6] Therefore, the prevention of active tuberculosis through IPT has the potential to increase the life expectancy of HIV-infected individuals. Results of the present analysis, based mainly on empirical data from a prospective cohort study, show that among HIV-infected patients, IPT may result in life expectancy gains ranging from 104 to 149 days for tuberculin-positive individuals and from 19 to 27 days for anergic patients. In both groups, the largest gains are achieved for individuals with the lowest level of immunosuppression.

One previous study[46] attempted to quantify these potential life expectancy gains through a decision analysis based on data from various studies on the natural history of HIV infection and mortality risks associated with tuberculosis. In that study, potential gains from 99 days to 285 days were identified for tuberculin-positive patients. These results are similar to those found in our analysis. The gains estimated in our model for tuberculin-positive individuals are also consistent with the results of a clinical trial of IPT in HIV-infected patients in which patients who received IPT had a median time to death of 5.3 months longer than control subjects.[10] Moreover, the gains for tuberculin-positive patients estimated in our model are of the same order of magnitude as those observed for other preventive therapy regimens recommended as a standard of care for HIV-infected individuals. In a clinical trial of sulfamethoxozole-trimethoprim prevention of *Pneumocystis carinii* pneumonia, treated patients had a mean survival of approximately 10 months longer than controls,[47] and the survival gain estimated in a model simulation was approximately 7 months.[48]

The previously mentioned decision analysis also showed potential gains for tuberculin-negative persons.[46] However, the effect of testing for anergy to other recall antigens in addition to PPD testing was not evaluated in that analysis. Our results show that providing IPT to anergic HIV-infected persons may result in life expectancy gains. The benefits for anergic patients are substantially lower than those estimated for tuberculin-positive patients. Moreover, they are dependent on the level of tuberculosis infection in the population and are lower than 10 days in scenarios with a 5% prevalence of tuberculosis infection. This prevalence may reflect the epidemiological situation of most high-income countries. A clinical trial conducted in the United States to evaluate the effects of IPT among anergic patients demonstrated a decrease, although not significant, in the incidence of tuberculosis among treated patients, but it failed to show any effect on short-term survival.[15] Our results underscore the importance of performing PPD tests early in the course of HIV infection because the probability of identifying patients with positive PPD results is higher among those with less severe immunosuppression.[49] Previously published guidelines[17] recommend the provision of IPT to anergic individuals with more advanced immunosuppression. This recommendation is not sup-

ported by our analysis because the potential benefits to these patients are minimal.

A POLICY OF providing IPT also to tuberculin-negative HIV-infected individuals has been suggested for countries with a high prevalence of tuberculosis infection.[50] In these patients, the only potential benefit of IPT would be a reduced susceptibility to new tuberculosis infections during treatment. In our model, based on empirical data collected in a high-income country, providing IPT to tuberculin-negative, nonanergic persons resulted in minimal life expectancy gains or, in some simulations, in life expectancy decreases because of adverse effects of isoniazid use.

Our analysis of the effect of IPT on life expectancy underscores the importance of providing IPT to tuberculin-positive HIV-infected individuals and suggests that it should be considered also for anergic persons. Economic aspects of IPT, however, should be evaluated before its widespread implementation as a public health intervention.

Results of the present study show that IPT administered to tuberculin-positive HIV-infected persons not only increases life expectancy but can also reduce medical costs if the costs of the intervention are compared with the costs of detecting and treating patients with active tuberculosis. Therefore, it can be regarded as a dominant strategy. The issue of compliance has been discussed as an unresolved problem for IPT programs,[51] and empirical data have shown that the obtainable levels may indeed be low.[52,53] We, therefore, analyzed the effect of varying compliance levels. For a policy of providing IPT to tuberculin-positive individuals only, a reduction in medical costs can be expected for compliance levels as low as 15%. Additional costs may result from very low compliance levels. However, for a compliance level of 10%, the costs of this policy do not exceed US $10 000 per QALY and thus compare favorably with those of other preventive interventions recommended for HIV-infected persons.[48,54] The conclusion would be that although obviously every effort should be made to achieve high compliance levels, the observation of low compliance should not necessarily preclude the further implementation of the intervention.

When deciding whether to extend IPT to anergic patients, the compliance rate and the level of tuberculosis infection in a given population are important issues. In 1991, the CDC proposed to consider IPT for HIV-infected anergic individuals coming from a population with at least a 10% prevalence of tuberculosis infection.[16] In our model calculations, extending IPT to anergic patients in a population with a tuberculosis infection level of 10% results in additional costs—from US $6035 to US $9000 per QALY if compliance is higher than 70%. This additional cost can be regarded as justifiable for high-income countries. Provision of IPT to anergic patients in a population with a tuberculosis infection level less than 10% results in cost-effectiveness ratios greater than US $10 000 per QALY, even if compliance rates achieve 100%. For a compliance rate of 75%, which can probably be achieved under field conditions, a reduction in medical costs can be expected only if the tuberculosis infection rate is 17.5% or higher. These results could facilitate decisions about the implementation of an IPT program for HIV-infected anergic individuals in varying epidemiological situations and under different program performances.

Some limitations should be kept in mind when interpreting our results. First, we found that the degree of immunosuppression of HIV-infected patients affects the benefits expected from an IPT program. The distribution of immunosuppression levels in our model calculations was based on empirical data from all patients presenting consecutively at several facilities, and we are confident that it represents the actual distribution among all HIV-infected individuals in Italy. However, it may not necessarily represent that of other countries with different epidemiological situations.

Second, model variables for progression to death and incidence of tuberculosis were derived from an observational study carried out before the advent of combination antiretroviral therapy and protease inhibitors. This new therapeutic approach may prolong survival of HIV-infected persons and may also affect the incidence of opportunistic infections.[55] However, a recent study[56] provides no evidence of changes in the incidence of tuberculosis after wide use of combination antiretroviral therapy.

Third, our cost analysis was made for the situation in a high-income country (Italy), and the cost of treatment of active cases was assumed to be high because of hospitalization. Accordingly, expected savings from the prevention of tuberculosis cases were large. The situation depicted in our model seems to be similar to that observed in other high-income countries, where inpatient treatment accounts for the largest proportion of expenditures for health care for tuberculosis,[57] although the cost data used in our model may differ from the cost of preventive therapy or the cost of care for tuberculosis of other industrialized countries, such as the United States. In the United States, for example, costs for tuberculosis-associated hospitalization estimated from observational studies or derived from Medicare reimbursement may be higher than those used in our analysis.[58] Conversely, in middle- or low-income countries, costs for tuberculosis prevention and treatment are different from that used in our analysis. For example, patients with tuberculosis are generally treated on an ambulatory basis, and the associated costs can be low. This means that the potential economic benefits of case prevention estimated in our study should not be extrapolated to these countries. However, a model simulation carried out with data from Africa suggests that providing IPT to HIV-infected individuals could be more cost-effective than tuberculosis treatment in low-income countries also.[21]

Finally, the economic benefits of IPT were evaluated with respect to its use as a tuberculosis control intervention and not from a societal viewpoint.[29] Therefore, our results showing that providing IPT may compare favorably with treatment of patients with active tuberculosis do not imply overall cost reductions.

Results of a recent study[59] suggest that an IPT program for HIV-infected persons could be one of the most effective interventions for tuberculosis control in the United States. Our results add an economic argument: compared with the costs of treating patients with active tuberculosis in a high-income country, IPT may result in savings for the health care provider when targeted to tuberculin-positive individuals.

The possible extension of this intervention to anergic patients has been questioned recently on the basis of considerations about difficulties in interpreting anergy skin test results[18] and the results of clinical studies.[14,15] Our results support recent CDC recommendations[19] against routine use of anergy skin testing to identify candidates for preventive therapy among HIV-infected persons. However, the provision of IPT to anergic patients may be justified in high-income countries under an economic point of view when targeted to specific groups with a high risk of tuberculosis infection. To optimize the effectiveness of this intervention, more information on the feasibility and operational problems of IPT programs in different settings, in particular those related to patient compliance, are needed.

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