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Isoniazid prophylactic therapy for tuberculosis in HIV-seropositive patients — a least-cost analysis

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The expected upsurge in the number of new cases of tuberculosis resulting from the HIV/AIDS epidemic prompted an examination of the feasibility of prevention strategies to limit the increase in clinical tuberculosis. A computer spreadsheet model was developed to estimate the costs and benefits that would result from isoniazid chemoprophylaxis for tuberculosis in a hypothetical cohort of 100 000 HIV-seropositive people in South Africa over a period of 8 years. At a 50% prevalence of tuberculosis infection among those at high background risk, and 5 - 10% among those at low risk, there would have been 34 000 cases of active tuberculosis in the cohort and their contacts if no prophylactic therapy had been used. On the other hand, a chemoprophylaxis policy would have meant only 12 200 cases of tuberculosis, if a patient compliance rate of 68,5% had been assumed. Such a policy would have prevented 21 800 cases of active tuberculosis. The estimated total discounted cost of a chemoprophylaxis programme would have been R51,3 million. In the absence of preventive therapy the discounted cost of treating patients with active tuberculosis would have been R91,9 million over the 8-year period. Therefore, if the benefits of chemoprophylaxis were defined in terms of averted health care costs, such a policy would have resulted in net savings of R40,6 million. This study did not estimate losses in production associated with tuberculosis treatment or the value of preventing tuberculosis *per se*, though such indirect costs would have increased the benefit of the prevention programme. Sensitivity analysis suggests that although a 6-month chemoprophylaxis policy appears justifiable on economic considerations, this is critically dependent on the annual risk of developing tuberculosis, patient compliance and the validity of assumptions on the efficacy and duration of protection of isoniazid prophylaxis.

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Tuberculosis remains a cause of substantial morbidity and mortality in South Africa.[1] As the risk of reactivation of tuberculosis in people infected with both HIV and tuberculosis is approximately 8% per annum,[2,3] several thousand additional cases of tuberculosis related to HIV/AIDS can be expected to occur each year. This added burden will constitute a considerable challenge to the Tuberculosis Control Programme, which is already unable to provide adequate care to many South Africans with tuberculosis.

While effective treatment of patients with tuberculosis remains a key strategy to reduce the incidence thereof (by removing sources of infection), such an approach is unlikely to contain the rise in incidence resulting from HIV/AIDS.[4] Most cases of tuberculosis in people with HIV/AIDS result predominantly from reactivation of latent infection.[2,5] This prompted us to examine the feasibility of preventive strategies which could limit the increase in active tuberculosis that is expected from dual HIV/tuberculosis infection.

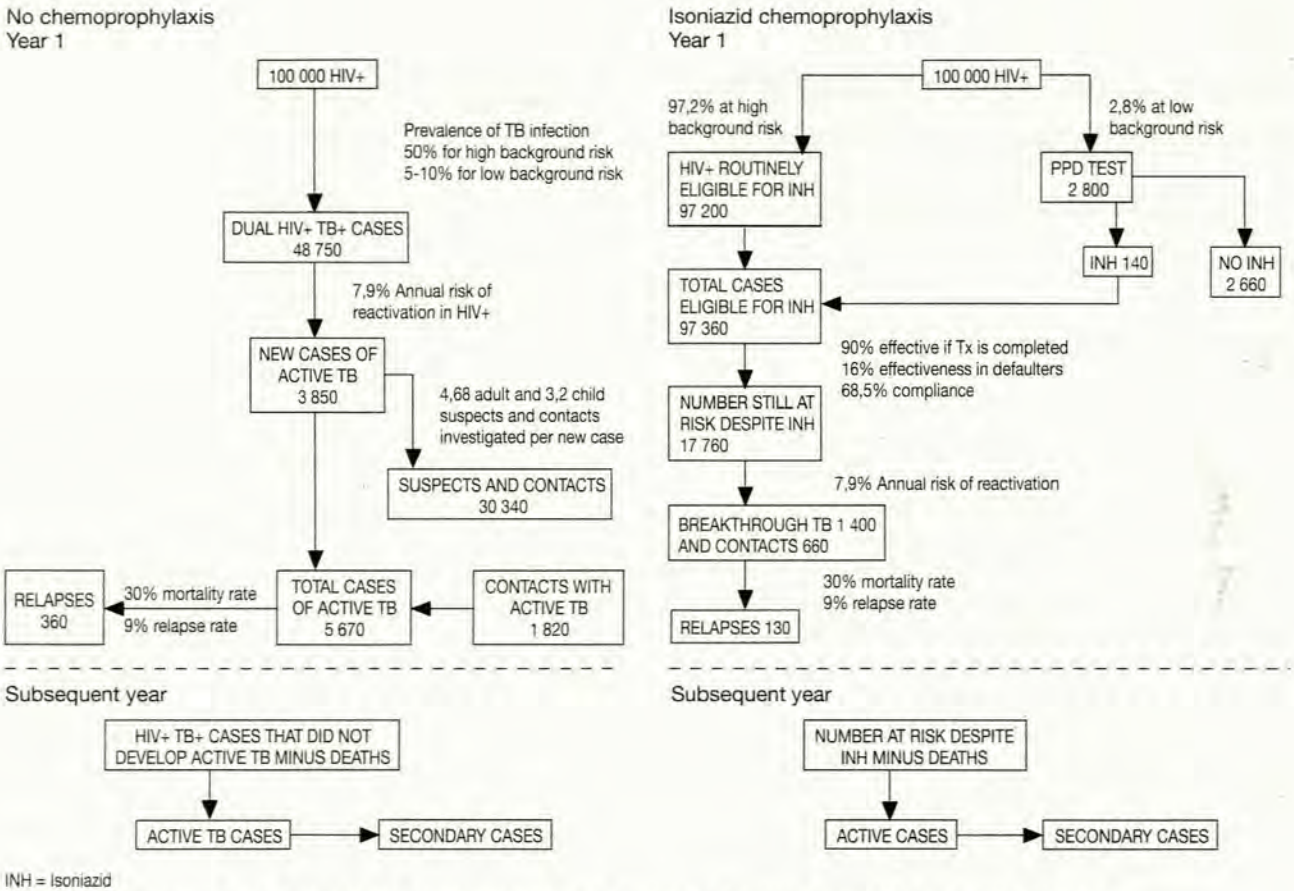
Preliminary investigations have established the efficacy of prophylactic therapy with isoniazid in significantly reducing the incidence of active tuberculosis in HIV-infected people.[6,7] The use of isoniazid chemoprophylaxis in HIV-seropositive people was also explored through a decision analysis by Jordan *et al.*[8] who, in our view, argued persuasively that this intervention is profoundly beneficial. It is important, however, that the decision to initiate such an intervention should not be based only on the clinical effectiveness of isoniazid. A number of other factors, including the feasibility of treating a substantial number of HIV-positive patients with isoniazid and patient compliance with treatment, as well as the cost of such an intervention, should be evaluated so that limited health sector resources can be utilised in an optimal manner.

This article assesses the feasibility of isoniazid prophylactic therapy from the perspective of cost minimisation. We constructed a computer spreadsheet model which takes as inputs epidemiological, health service and economic data to estimate the costs and savings of isoniazid preventive therapy for tuberculosis in a hypothetical cohort of 100 000 HIV-positive adults over 8 years. The first section of the paper sets out the assumptions underlying our least-cost analysis. In the second part we estimate the costs and benefits of isoniazid preventive therapy against no prophylaxis and treatment of all cases of tuberculosis. The third section presents the results, describes some conceptual problems in the model and discusses the policy implications of the study.

Methods

The epidemiological model

The epidemiological model, shown in Fig. 1, posed a choice between two alternatives for a cohort of 100 000 HIV-infected people — 6 months of isoniazid chemoprophylaxis, or no chemoprophylaxis and thus treatment of active tuberculosis when it occurs. The cohort was stratified into two background risks of tuberculosis and data on prevalence of tuberculosis infection[9] were used to calculate the number of dual HIV- and tuberculosis-infected people in the cohort. We assumed that the prevalence rate of



INH = Isoniazid

Fig. 1. Epidemiological model used for the isoniazid/no isoniazid decision in a cohort of 100 000 HIV-positive patients.

tuberculosis infection among those with a high background risk approaches 50%, and varied this rate between 5% and 10% for those at lower background risk. The number of new cases of active tuberculosis in HIV-positive patients was then estimated by multiplying the total number of people with dual infections by the annual risk of reactivation of tuberculosis in these people, over a period of 8 years.

Cases of active tuberculosis are also associated with a number of contacts, some of whom will convert from a negative to a positive tuberculin skin test. The number of contacts, based on Western Cape tuberculosis control programme data, was estimated at 4,68 adult[7] and 3,2 child contacts per tuberculosis patient. Six per cent of contacts develop active tuberculosis. Finally, we assumed that 30% of severely ill patients requiring inpatient treatment died,[10] while data show that the relapse rate among those with HIV-associated tuberculosis after treatment is approximately 9 - 12%.[11]

Those dually infected patients who did not develop active tuberculosis in the first year were followed up during subsequent years. Since the cohort still faces the general population risk of dying from any cause, the number of dual infections during the following year is reduced by population mortality. Population-specific mortality data were obtained from Van Rensburg *et al.*[12] In each subsequent year, the number of active tuberculosis cases is calculated on the basis of surviving number of dually infected people, annual risk of reactivation, contacts and relapses.

The proportion of patients eligible for chemoprophylaxis during the first year was estimated by assuming that all HIV-positive patients at high background risk of tuberculosis infection would be offered isoniazid routinely. This is estimated to be 97,2%.[13] PPD tests were assumed for the remaining 2,8% at low background risk. Of the latter, we further assumed that 5% would have positive PPD tests and would be eligible for chemoprophylaxis. We then calculated the number of cases of breakthrough tuberculosis in those who received chemoprophylaxis and the associated secondary cases.

The cost minimisation model

Cost minimisation analysis is used to assess costs and benefits of alternative health care programmes so that policy-makers can identify the least-cost alternative. We defined chemoprophylaxis to include the costs of PPD testing, administration of isoniazid, clinical services, transport and treatment of breakthrough tuberculosis, secondary tuberculosis cases and isoniazid-induced hepatitis. These costs were then compared with those of treating active tuberculosis and secondary cases in the absence of chemoprophylaxis. We calculated the benefits-to-costs ratio of chemoprophylaxis for the health sector only, and did not estimate any indirect costs or the value of preventing tuberculosis *per se*.

Assumptions for model

In addition to the assumptions made above with regard to prevalence of tuberculosis infection, the number of contacts and new infections per tuberculosis case, and the relapse rate, the following are also relevant.

Risk of active tuberculosis in HIV-seropositive patients

A prospective study among drug users in New York showed a 7,9% annual rate of clinical tuberculosis among those with dual HIV/tuberculosis infection.[2] The annual risk has also been calculated at 6,2% for Zaire.[14] Emerging consensus puts the risk of developing active tuberculosis in patients with both HIV and tuberculosis interaction between 5% and 8% per annum (Table I), with a lifetime cumulative risk greater than 30%.[4]

Table I. Annual risk of clinical tuberculosis in HIV/tuberculosis-infected people*

Country	Year of study	Method	% Annual risk of tuberculosis HIV+TB+	HIV−TB+
USA[2]	1989	Prospective study, intravenous drug users	7,9	0
Zaire[15]	1991	Retrospective study, women of childbearing age	6,2	0,2
Rwanda[1]	1991	Prospective study of women attending antenatal clinics	5,5	0,2
Zaire[3]	1991	Prospective study of factory workers and spouses	5,6	0,8

*Adapted from Narain *et al.*[4]

Effectiveness of isoniazid therapy

The efficacy of preventive therapy with isoniazid in HIV-free populations has been estimated at approximately 90% for patients who finish their treatment,[15,16] and up to 16% for defaulters.[17] There is now evidence to suggest that such therapy may also be effective in those with dual infection. In a single-blind, placebo-controlled clinical trial in Zambia,[6] 544 adults with Western blot-confirmed HIV infection and *no* active tuberculosis were randomised to receive either isoniazid daily for 6 months or a placebo. Over a 12-month follow-up period, the annual incidence of active tuberculosis was found to be significantly lower among those on isoniazid (1% per annum) than among the placebo group (7,6% per annum). Another study on the feasibility of isoniazid chemoprophylaxis for HIV-associated tuberculosis in Uganda[18] found that active tuberculosis occurred in only 3,3% of those on isoniazid.

Compliance with preventive therapy

We assumed that compliance with the preventive programme once people were enrolled was 68,5%, as reported by Aisu *et al.*[18] for patients who took 80% or more of their prescribed medicine over 6 months. Because controversy surrounds this matter, we varied compliance in the sensitivity analysis over a range of values.

Risk of isoniazid therapy

The major side-effect associated with isoniazid is hepatitis, and death in a small proportion of patients. We have used a hepatitis risk rate of 0,48% for those older than 35 years and have kept it at zero for those under 35 years.[19] Varying case fatality rates for isoniazid-induced hepatitis are reported,[20] and we have assumed a rate of 0,14 deaths per 1 000 hepatitis cases.

Cost estimates

All costs are based on a consensus view of procedures for managing HIV-related tuberculosis that are considered feasible in an adequately functioning tuberculosis control programme.[21] Prices are quoted in 1993 rands and costs occurring in the future have been discounted at 4% to make them comparable to year 1 costs. Sensitivity analysis also tested the effect of an 8% discount rate.

Cost of treating active tuberculosis

All costs of treating tuberculosis in our cohort are summarised in Table II, and explained below.

Table II. Discounted cost (R) of diagnosis and treatment of active tuberculosis arising in a cohort of 100 000 HIV-positive individuals and their contacts over an 8-year period

Total number of cases over 8 years	34 000
Cost of diagnosis	2 866 846
Chest radiographs	
Sputum culture (35% of patients)	
Full blood count (25% of patients)	
ESR (25% of all patients)	
Hospitalisation (for 30% of patients for 90 days) + post-hospital care	47 789 291
Cost of ambulatory drugs (for 70% of cases)	1 137 655
Isoniazid 300 mg for 6 months	
Rifampicin 450 - 600 mg for 6 months	
Pyrazinamide 1,5 g for 2 months	
Ethambutol 1 200 mg for 2 months (20% of patients)	
Pyridoxine for 6 months (10% of cases)	
Cost of clinical services to SAC	2 428 472
Physician consultation	
Clinic visits with a nurse	
Cost of transport	993 407
Cost of disease related to contacts	15 399 527
Cost of treating relapsed cases	21 075 245
Cost of managing side-effects (mainly skin lesions)	213 907
Total direct costs	91 904 352

Cost of diagnosis

Cost of diagnosis was based on three chest radiographs taken at initial consultation, during and on completion of treatment respectively. A sputum culture and an erythrocyte sedimentation rate (ESR) were assumed to have been taken in 35% and 25% of patients respectively.[21] A full blood count was assumed to have been done only when clinically indicated (approximately 25% of cases). The cost of

diagnosis was estimated at R528 799 in year 1 (discounted value of R2 866 846 during years 1 - 8).

Cost of hospitalisation and post-hospital care

On the basis of the consensus developed in the previous paper,[21] we assumed that 30% of tuberculosis patients would be hospitalised for an average period of 90 days, and that they would thereafter complete treatment as outpatients. Total hospital costs were estimated by multiplying total cases by the cost per day of hospitalisation and length of stay. The cost of post-hospital care was estimated on the basis of number of cases initially treated in hospital, reduced by an in-hospital mortality rate of 30%.[10] These patients receive a triple drug therapy for 3 months. Thus, the total costs of hospitalisation and post-hospital care were calculated at R8 843 187 in year 1 (R47 789 291 discounted cumulative value over 8 years).

Cost of ambulatory drugs

The remaining 70% of tuberculosis patients were assumed to be solely on supervised ambulatory care (SAC). Chemotherapy was estimated on the basis of 6 months of isoniazid (300 mg/day) and rifampicin (450-600 mg/day) with pyrazinamide (1,5 g/day) added for the first 2 months. The cost of ethambutol (1 200 mg/day) was calculated for 2 months for 20% of patients in areas of known high isoniazid resistance and in disseminated tuberculosis infection. The costs of ambulatory drugs were estimated at R210 525 during year 1 (discounted costs of R1 137 655 over 8 years).

Cost of clinical services for SAC

Staff costs were based on an initial consultation with a physician and monthly follow-up visits with a nurse. These were calculated at R449 392 for year 1 and R2 428 472 for the period under review.

Cost of transport for SAC

Transport expenses were assumed to cover visits to contacts of index cases and a proportion of patients who default. We assumed that patients live on average 5 km from the health service point. The costs of transport, based on the AA rate per km for capital costs, maintenance and fuel for typical health centre vehicles would be R183 832 in the first year (discounted cumulative value of R993 409 over 8 years).

Costs attributable to contacts of HIV-positive tuberculosis cases

The cost of tracing, investigating and treating all contacts was R2 849 707 in year 1 (R15 399 527 over the period under review).

Cost of treating relapsed patients

Relapsed patients are managed in the same way as the original patients, except that a culture and a drug sensitivity test have to be done. The costs of treating these patients were estimated at R3 899 888 for the first year of the cohort (R21 075 245 over 8 years).

Cost of managing side-effects

Adverse side-effects due to treatment (mainly skin lesions) occur in 35% of cases.[22] Management of such adverse reactions, based on cost of analgesics provided during follow-up visits, would cost R39 584 in year 1 (R213 907 over 8 years).

Cost of chemoprophylaxis programme, including treatment of breakthrough tuberculosis

The costs of the various chemoprophylaxis components of a programme are shown in Table III. Apart from the treatment of breakthrough cases, all other expenditure occurs in year 1.

Table III. Discounted costs (R) of an isoniazid chemoprophylaxis programme for tuberculosis, including treatment of breakthrough cases, in a cohort of 100 000 HIV-positive people

	No. of cases	Direct costs
PPD testing	2 800	13 328
Administration of drugs		136 387
Isoniazid 5 times per week for 6 months	97 360	
Pyridoxine for 10% of cases	9 736	
Clinical staff		12 980 000
Transport		131 007
Treatment of breakthrough tuberculosis, including contacts	12 200	37 747 818
Isoniazid-induced hepatitis	460	325 414
Liver function tests		
Hospitalisation (20% of cases for an average of 7 days)		
Ambulatory (80% of cases)		
Total		51 333 954

Cost of PPD testing and isoniazid

All those with a high background risk of tuberculosis are given isoniazid routinely. Those at low background risk are offered a PPD test. The cost of testing, based on the number eligible for test and the cost of a PPD test and staff, was estimated at R13 328. The direct cost of chemoprophylaxis was estimated on the basis of administration of 300 mg isoniazid 5 times a week for 6 months to all eligible patients. It was also assumed that 10% of patients would receive pyridoxine supplementation. The cost of isoniazid tablets and pyridoxine was R136 387 in this cohort.

Cost of clinical services

Estimates from one well-functioning SAC service[23] put the ratio of health worker to SAC patient at 1:90 at any one time. We thus calculated that 487 additional health workers would have to be employed to carry out the chemoprophylaxis programme, including contact tracing. The costs of clinical services, based on the median wage for a community health nurse, were estimated at R12 980 000.

Cost of transport

The main transport expenses, once people are enrolled in the chemoprophylaxis programme, will consist of visits to a

proportion of patients who default and those who develop tuberculosis despite chemoprophylaxis. The costs of transport, calculated in the same way as in the treatment arm, would be R131 007.

Cost of treating active tuberculosis that occurs despite isoniazid prophylaxis, including relapses

The protection obtained from prophylaxis is closely related to two variables: compliance and clinical effectiveness of isoniazid. As mentioned above these two parameters were estimated at 68,5% and 90% respectively. Thus, a proportion of patients will still acquire tuberculosis despite having taken isoniazid. The costs of hospital and SAC treatment of breakthrough tuberculosis in index cases and their contacts, and that of prophylaxis for child contacts were estimated at R3 912 717 in the first year (R37 747 818 cumulative discounted costs by year 8).

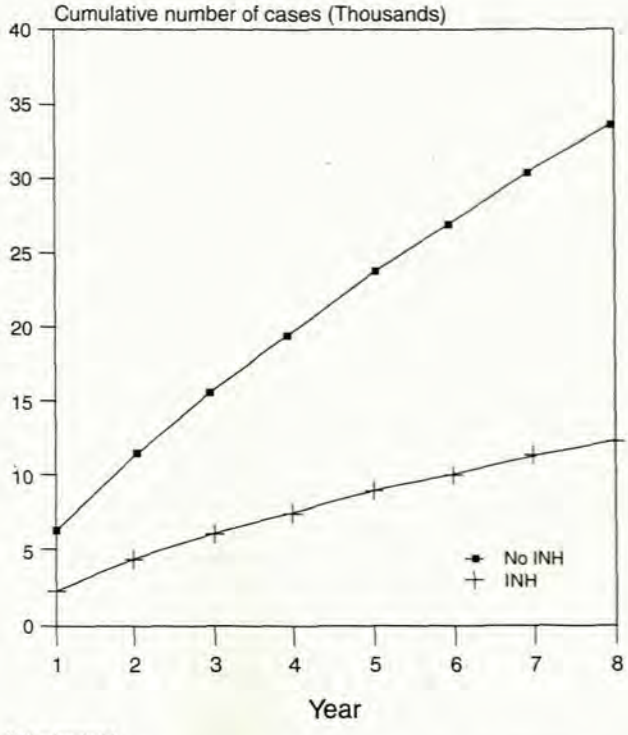
Cost of managing isoniazid-induced hepatitis

The cost of managing isoniazid-induced hepatitis was based on a 7-day average hospital stay at a cost per day of R260[24] for 20% of cases. Ambulatory costs were calculated on the basis of doctor's consultations for the remaining 80%. The costs of liver function tests were estimated on the basis of three sets of tests at R91,40 per set. Table III shows that treatment of hepatitis would have accounted for R325 414.

Benefits

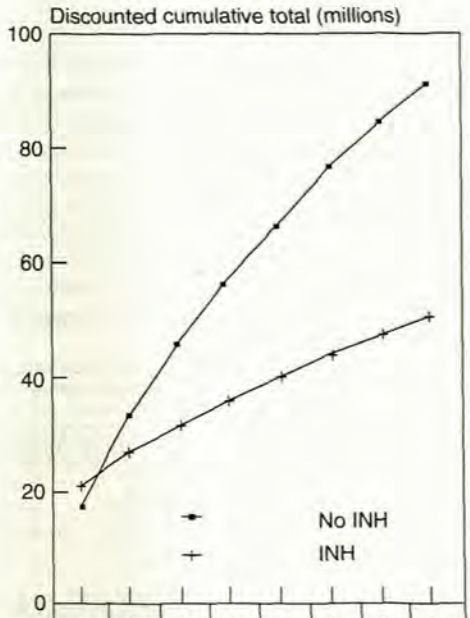
The benefits of chemoprophylaxis were defined in terms of the number of tuberculosis cases prevented, and treatment costs averted as a result of that prevention. Fig. 2 shows that if the annual risk of reactivation is 7,9%, the number of additional cases of active tuberculosis in this cohort would have been 5 600 during the first year and 34 000 by year 8. On the other hand the number of active tuberculosis cases in this cohort and its contacts would have been just over 2 000 in year 1 (12 200 cumulatively by year 8) with the chemoprophylaxis programme, assuming 68,5% compliance.[18] Implementation of a chemoprophylaxis programme would therefore have resulted in 21 800 fewer cases of active tuberculosis in this cohort over the 8-year period.

The estimated cumulative costs of a chemoprophylaxis programme versus no chemoprophylaxis are shown in Fig. 3. The discounted cost of a preventive programme, including the cost of treating the 12 200 cases that do arise, would be R51 333 954, while treatment of the 34 000 patients with active tuberculosis would cost R91 904 352 over the 8 years. Because the isoniazid programme prevents tuberculosis, these averted future costs can be regarded as the benefits of preventive therapy. The relative cost-savings of the preventive strategy would be R40 551 952 if only direct costs are considered.



INH = Isoniazid

Fig. 2. Number of cases of tuberculosis in a cohort of 100 000 dual HIV/tuberculosis-positive patients in South Africa over 8 years, with and without prophylactic isoniazid.



	1	2	3	4	5	6	7	8
Annual cost: No INH	17	14.9	13.2	11.7	10.4	9.1	8.1	7.2
Annual cost: INH	20.4	6	5.3	4.7	4.1	3.6	3.2	2.8

INH = Isoniazid

Fig. 3. Cumulative direct costs of isoniazid v. no isoniazid in a cohort of 100 000 HIV-positive persons over an 8-year period (discounted to year 1).

Discussion

We have reported the results of an economic assessment of the costs of a chemoprophylaxis policy for tuberculosis in a hypothetical cohort of 100 000 HIV-positive people in South Africa over 8 years. The net savings in direct health care costs would have been R40,6 million during this period, which suggests that chemoprophylaxis may be a beneficial strategy.

The costs of R20,4 million for prophylaxis in the first year are slightly higher than the costs of treating active cases occurring in that year. However, because isoniazid is administered only in the first year and only a small number of patients require treatment in subsequent years, these costs decline substantially after the first year. As Fig. 3 shows, the chemoprophylaxis programme begins to show savings by the second year, where the cumulative costs of treatment are R14,9 million compared with R6 million for prevention. A strategy of chemoprophylaxis could result in substantial savings in health care costs.

Many of the parameters described above are to some extent debatable. To explore the impact of alternative assumptions on the costs, we performed a sensitivity analysis (Table IV) of the key assumptions, including compliance rate and annual risk of clinical tuberculosis. We varied the compliance rate from 41% — a suggested typical level that chemoprophylaxis programme can achieve (R. O'Brien: WHO — personal communication) — to 68,5%. For example, given a steady 7,9% rate of infection, a drop in compliance to 41% increases the costs of chemoprophylaxis by 57% to R80 436 830 (because more of those in the prophylactic arm will need treatment in future). As a result the relative savings of chemoprophylaxis decline to R10,5 million from R40,6 million. However, as Chaulet[25] has pointed out, compliance with chemotherapy is nothing more or less than the outcome of a process involving a chain of responsibilities extending from decision-makers at central/provincial level to health workers responsible for treatment. It is this chain that determines the success or failure of a tuberculosis programme. It is thus conceivable that a well-functioning chemoprophylaxis programme carefully targeted at motivated HIV-positive patients presenting to the health service, can increase compliance to the level seen in the Uganda study.[18]

Table IV. Impact of changes in compliance rate and annual risk of clinical tuberculosis on the net present value (1993 rands) of isoniazid chemoprophylaxis

		Annual risk of clinical tuberculosis		
Compliance with chemoprophylaxis	41%	5,5%	6,2%	7,9%
		-2 068 226	1 538 566	10 574 299
	68,5%	22 624 241	26 952 775	40 570 398

If the annual risk of developing active tuberculosis is closer to 5%, as some studies suggest, then the costs of treating future cases decrease far more than the costs of prevention, since almost the same number of people require prophylaxis regardless of the annual reactivation rate. The net benefit is consequently halved at the higher compliance rate and turns into a net loss at the lower compliance rate.

We also explored the impact of various social time preferences on our results. With an 8% rate of discount the total cost of chemoprophylaxis was R47 533 566, while that of the treatment strategy was R82 761 300. A change to the discount rate therefore does not alter the scale of savings and the preferred strategy.

A number of arguments has been raised against the use of chemoprophylaxis in dual HIV/tuberculosis-infected people. One relates to the duration of protective effect of isoniazid. The evidence concerning duration of protection is as yet scanty. Our analysis assumes that isoniazid has a long-term protective effect (O'Brien: WHO — personal communication). Wadhawan *et al.*[5] have nevertheless presented preliminary data which suggest that the incidence of active tuberculosis increases with the post-prophylaxis period, particularly in patients in the advanced stages of AIDS. This is obviously an important issue that could influence the benefit of a chemoprophylaxis programme.

A further concern relates to fears about isoniazid's potential hepatotoxic effects. Using American data Comstock[26] has, however, argued that the risks of hepatitis and subsequent mortality are quite small and can be reduced even further by informing patients about the symptoms of hepatitis, monitoring them for these symptoms at least monthly, and stopping therapy before liver damage is too advanced.

The benefits of chemoprophylaxis calculated here are open to debate for another reason. We do not include in our estimates the highly variable cost of identifying HIV-seropositive individuals. If an individual's HIV serostatus were detected as part of ongoing and routine operations, it could be argued that these costs do not have to be added to the cost of chemoprophylaxis. If, however, serostatus tests have to be carried out to identify potential chemoprophylaxis candidates, the cost of these tests should be added to the prophylaxis programme. This would markedly increase the cost of chemoprophylaxis. However, the calculations reported here are not contingent on national programmes or universal coverage. For any individual who tests HIV-positive, chemoprophylaxis will save R405 on average compared with a strategy of no chemoprophylaxis.

Our estimates apply only to adults; no attempt was made to estimate the costs of tuberculosis in children aged 15 years and younger. Infants born to HIV-positive mothers are at risk of tuberculosis and are likely to incur substantial treatment costs. Finally, no attempt was made to quantify costs associated with work time lost due to tuberculosis morbidity and premature mortality, and the benefits of reduced pain and grief to dual HIV/tuberculosis-infected people and their families as morbidity and mortality decline. The relative benefits of preventive therapy would be even greater if these effects were accounted for.

Conclusion

The interaction between HIV/AIDS and tuberculosis will severely challenge the already overextended South African Tuberculosis Control Programme. The potential rise in the number of new cases makes it imperative that the limited health care resources be used in a cost-effective manner.

This economic appraisal aimed to provide a basis for the consideration of isoniazid chemoprophylaxis in dual HIV/tuberculosis-infected people. Despite the limitations described above, the analysis provides an adequate indication of the potential impact of HIV/AIDS on

tuberculosis and the costs of two alternative strategies for managing the tuberculosis epidemic. We feel the costs reported here are not excessive to prevent tuberculosis in HIV-positive individuals, and to prevent its spread in the community. In the evaluation of chemoprophylaxis policies, however, other considerations must influence the decision. These include the annual risk of developing tuberculosis, patient compliance with the chemoprophylaxis programme, the optimal period for administration of chemoprophylaxis, levels of resistance to isoniazid and the duration of its protective effect. By characterising the magnitude of the resource costs of prevention compared with treatment of active tuberculosis, we hope to open debate on these equally important considerations.

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