# EFFICACY OF SECONDARY ISONIAZID PREVENTIVE THERAPY AMONG HIV-INFECTED SOUTHERN AFRICANS: TIME TO CHANGE POLICY?

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*Objective*. To determine the efficacy of secondary preventive therapy against tuberculosis (TB) among goldminers working in South Africa.

*Design*. An observational study.

*Methods*. The incidence of recurrent TB was compared between two cohorts of HIV-infected miners: one cohort had received secondary preventive therapy with isoniazid and the other had not.

*Setting*. Health service providing comprehensive care for goldminers.

*Participants*. 338 men received secondary preventive therapy and 221 did not.

*Main outcome measure*. Incidence of recurrent TB.

*Results*. The overall incidence of recurrent TB was reduced by 55% among men who received isoniazid preventive therapy (IPT) compared to those who did not (incidence rates 8.6 and 19.1 per 100 person-years respectively, incidence rate ratio 0.45; 95% CI 0.26 – 0.78). The efficacy of isoniazid preventive therapy was unchanged after controlling for CD4 count and age. The number of person-years of isoniazid preventive therapy required to prevent one case of recurrent TB among individuals with a CD4 count < 200/µl and ≥ 200/µl was 5 and 19, respectively.

*Conclusion*. Secondary preventive therapy reduces TB recurrence: the absolute impact appears to be greatest among individuals with low CD4 counts. International TB preventive therapy guidelines for HIV-infected individuals need to be expanded to include recommendations for secondary preventive therapy in settings where TB prevalence is high.

The World Health Organisation (WHO) recommendations for tuberculosis (TB) control focus on curing patients presenting with their first episode of TB, with the aim of interrupting TB transmission. In countries with a high TB incidence, recurrent TB accounts for a significant proportion of all cases,[1,2] and HIV infection is a strong risk factor for recurrent TB[3-6] along with post-TB scarring, cavities, drug regimen used to treat the initial episode of TB and a low CD4 count.[4-8] In settings of lower TB incidence, recurrent TB occurs more commonly among HIV-infected patients, though the absolute difference in rates is small.[9] Recurrent TB may result from either recrudescence of disease with the original infecting organism, or reinfection with a new *Mycobacterium tuberculosis* strain.[6,10] Reinfection, with rapid progression to disease, has been shown to be an important cause of recurrence among HIV-infected individuals in settings with high rates of TB transmission.[6]

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Current international guidelines recommend TB preventive therapy (PT) for HIV-infected individuals who have never had TB previously (primary TB PT).[11] However, there is increasing evidence of the efficacy of secondary PT for HIV-infected individuals.[12,13]

The objective of our study was to determine the efficacy of secondary isoniazid PT (IPT) by comparing the TB incidence rates between two cohorts of HIV-infected goldminers in South Africa with a history of previous TB who had or had not received isoniazid PT.

## METHODS

### STUDY POPULATION AND SITE

The study was conducted at a single goldmining company in the Free State province of South Africa. The mine hospital is the sole source of tertiary care for mine employees and manages the TB control programme. Clinics situated at most of the surrounding mine shafts provide primary health care to miners and dispense TB treatment and IPT.

### TB CONTROL PROGRAMME

The TB control programme includes directly observed rifampicin-based short-course chemotherapy regimens, use of combination tablets and active case detection using a miniature radiograph screening programme. Treatment regimens are in line with those recommended by the national TB control programme: four drugs are used for first episodes of TB, and regimens for drug-resistant cases are modified to ensure treatment with two or more drugs to which the isolate is sensitive.

Miners with suspected TB are investigated according to a standard protocol. Three sputum specimens are collected over 2 days. Smears are made from concentrated sputum and stained with auramine for fluorescence microscopy. Positive smears are confirmed with Ziehl-Neelsen staining. Following decontamination with 4% sodium hydroxide, sputum is inoculated onto Lowenstein-Jensen (LJ) slopes and incubated for up to 8 weeks. An initial identification step for *M. tuberculosis* is carried out on LJ slopes with more than five colonies, using a colorimetric ribosomal RNA hybridisation test (Accuprobe, *M. tuberculosis* complex probe kit, Gen-Probe, San Diego, CA). Positive cultures are sent to the National Health Laboratory for drug susceptibility testing of *M. tuberculosis* strains.

### COHORT SELECTION

In this study we included miners with HIV infection and a history of previous TB with documented successful completion of TB treatment. Men who failed therapy for the previous TB episode or had an unknown treatment outcome were excluded from the study, as were men treated for non-tuberculous mycobacterial disease.

Participants receiving IPT (300 mg/d) were derived from a cohort of HIV-infected men receiving isoniazid and co-trimoxazole indefinitely as part of a clinical trial. The control cohort comprised men attending a routine HIV clinic who did not receive IPT because of a history of previous TB, an exclusion criterion in accordance with current international and local guidelines. Men in the control cohort received co-trimoxazole prophylaxis if their CD4+ T cell-lymphocyte (CD4) count was below 250/µl if symptomatic or 200/µl regardless of symptoms. The incidence of TB recurrence in the two cohorts was compared using a database listing all episodes of TB among company employees since 1979.

### TIME AT RISK

At the time of recruitment to their respective cohorts, men had blood taken for a CD4 count and were screened for TB using symptoms, chest radiography and sputum smears and cultures. In order to minimise the risk of including a case of TB diagnosed at the time of screening as a study case, the date of entry into this study was defined as three months after the date of TB screening. Men receiving TB treatment at the time of recruitment, or who were diagnosed with TB at the time of screening, entered time at risk after completing TB treatment. Time at risk was censored at the time of first TB episode during the study, death, loss to follow up or end of study (31 December 2000 for the IPT cohort and 31 July 2001 for the control cohort).

### CASE DEFINITIONS

Recurrent TB was defined as *definite* if there were compatible clinical features and sputum or tissue culture was positive for *M. tuberculosis*; *probable* if there were compatible clinical features and two sputum smears were positive for acid-fast bacilli, or sputum or tissue culture was positive for mycobacteria that were not further speciated, or histological examination was positive (acid-fast bacilli present or granulomatous disease); and *possible* if there were compatible clinical features and a response to treatment with anti-tuberculosis drugs.

### GRADING OF SILICOSIS AND POST-TREATMENT SCARRING

The standard-sized chest radiographs of study participants, taken at the time of recruitment to their respective cohorts, were assessed for the presence and grade of silicosis using a modified International Labour Organisation (ILO) scoring system. For the purposes of this study silicosis was categorised as none (0/0 or 0/1) or definite (ILO category 1/0 and above). The radiological extent of post-treatment scarring was determined by dividing the lung on each side into three equal zones and allocating a score according to the total number of zones involved. The presence or absence of cavities was also noted.

### DATA ANALYSIS

Data were analysed with STATA 6.0 software (STATA Corporation, Texas, USA). Differences between categorical variables were investigated using the chi-square test or Fisher's exact test where appropriate. The differences in length of follow-up between the two groups were assessed

using the Wilcoxon rank-sum test. Poisson regression was used to calculate univariate and adjusted TB incidence and mortality rate ratios for different variables. Overall significance, tests for trends for ordinal variables with more than two categories and tests for effect modification were determined using the likelihood ratio test.

### ETHICAL APPROVAL

Ethical approval for the clinical trial from which the IPT cohort was drawn was obtained from the Anglogold Health Services and UNAIDS ethical review boards; all participants gave informed consent. The evaluation of the routine health service clinic from which the control cohort was drawn was given ethical approval by the ethics committees of Anglogold Health Service and London School of Hygiene and Tropical Medicine.

## RESULTS

All study participants were HIV-infected black male miners; 338 men who received IPT (IPT cohort) were compared with 221 who did not (control cohort). The characteristics of the two cohorts are presented in Table I. The two cohorts were similar with respect to age, CD4 count, number of previous TB episodes, silicosis grade, presence of cavitation and extent of post-treatment scarring. The control cohort had their preceding episode of TB significantly longer before study entry than did the IPT cohort, and had a shorter duration of follow-up within the study (median 0.41 v. 0.91 years). Recruitment to the IPT cohort began and ended a year earlier than recruitment to the control cohort.

**TABLE I. SUMMARY OF DEMOGRAPHIC VARIABLES, BY COHORT**

| | IPT | | Control | | |
|---|---|---|---|---|---|
| | *N* | % | *N* | % | *p*-value |
| Total | 338 | | 221 | | |
| Time at risk (yrs) | | | | | |
| Median (IQR) | 0.91 (0.60, 1.33) | | 0.41 (0.19, 0.84) | | < 0.001 |
| Age group (yrs) | | | | | |
| < 30 | 17 | 5 | 11 | 5 | 0.5 |
| 30 - 39 | 154 | 46 | 86 | 39 | |
| 40 - 49 | 139 | 41 | 104 | 47 | |
| 50+ | 28 | 8 | 20 | 9 | |
| CD4 group (/µl)* | | | | | |
| < 200 | 114 | 34 | 65 | 33 | 0.2 |
| 200 - 499 | 181 | 54 | 95 | 49 | |
| 500+ | 42 | 12 | 35 | 18 | |
| Time since end of previous TB episode (mo.) | | | | | |
| 6 - 12 | 256 | 76 | 131 | 59 | < 0.001 |
| 12 - 24 | 49 | 14 | 38 | 17 | |
| 24+ | 33 | 10 | 52 | 24 | |
| Calendar year of entry | | | | | |
| 1998 | 59 | 17 | 0 | 0 | < 0.001 |
| 1999 - 2000 | 279 | 83 | 140 | 63 | |
| 2001 | 0 | 0 | 81 | 37 | |
| Number of previous TB episodes | | | | | |
| 1 | 273 | 81 | 173 | 78 | 0.5 |
| > 1 | 65 | 19 | 48 | 22 | |
| Silicosis | | | | | |
| Absent | 307 | 91 | 206 | 93 | 0.3 |
| Present | 31 | 9 | 15 | 7 | |
| Cavitation | | | | | |
| Absent | 265 | 78 | 165 | 75 | 0.3 |
| Present | 73 | 22 | 56 | 25 | |
| Number of zones | | | | | |
| 0 | 57 | 17 | 42 | 19 | 0.7 |
| 1 - 2 | 177 | 52 | 117 | 53 | |
| 3+ | 104 | 31 | 62 | 28 | |

*1 and 26 results missing for IPT and control cohorts, respectively.
IPT = isoniazid preventive; therapy; IQR = inter-quartile range.

**TABLE II. SUMMARY OF TB EVENTS, BY COHORT**

| Factor | IPT | | Control | | *p*-value |
|---|---|---|---|---|---|
| | N | % | N | % | |
| Total | 28 | | 23 | | |
| Case definition | | | | | |
| Definite | 17 | 61 | 18 | 78 | 0.2 |
| Probable | 11 | 39 | 5 | 22 | |
| Classification | | | | | |
| PTB | 22 | 79 | 18 | 78 | 0.7 |
| ETB | 4 | 14 | 2 | 8 | |
| PTB + ETB | 2 | 7 | 3 | 13 | |
| CD4 group (/µl)* | | | | | |
| < 200 | 12 | 43 | 10 | 50 | 0.5 |
| ≥ 200 | 16 | 57 | 10 | 50 | |

*CD4 group at baseline. CD4 count missing for 3 individuals from the control cohort.

A log of all treatment dispensed to the primary health care clinic and collected by the study participants on a monthly basis was kept. Of men in the IPT cohort 76% (256/338) collected at least 80% of the isoniazid dispensed; 19/28 (68%) of the TB cases from the IPT cohort collected at least 80% of their prescribed isoniazid. IPT was interrupted, and then restarted, in 4 patients due to skin rash (2), abdominal pain (1) and nausea (1). IPT was stopped and not restarted in a further 3 patients, all due to skin rash. There were no episodes of hepatitis or peripheral neuropathy.

Fifty-one cases of TB were diagnosed during the study period, 28 (8.3%) among the IPT cohort and 23 (10.4%) among the control cohort. The recurrent TB cases in the two groups were similar with respect to the proportion classified as definite, site of disease and CD4 count at baseline (Table II). There was no significant difference in the prevalence of isoniazid resistance between the IPT and control cohorts (20% [2/10] and 23% [3/13], respectively, $p = 1.0$).

Results of incidence rates (IR) of recurrent TB, unadjusted incidence rate ratios (IRR) and 95% confidence intervals (CI) are presented in Tables III and IV. There was a significantly lower incidence of TB among the IPT cohort compared with the control cohort (IRR 0.45; 95% CI 0.26 - 0.78). There was no difference in efficacy of IPT when adjusted for age, silicosis, extent of post-treatment scarring or presence of cavitation, CD4 count and time since

**TABLE III. UNADJUSTED INCIDENCE RATES OF RECURRENT TB AND INCIDENCE RATE RATIOS BY NUMBER OF PREVIOUS TB EPISODES, CD4 GROUP, TIME SINCE PREVIOUS TB EPISODE AND TB CASE DEFINITION**

| | | *N* | Events*/pyrs | IR | IRR (95% CI) |
|---|---|---|---|---|---|
| **All** | | | | | |
| Overall | IPT | 338 | 28/324.3 | 8.6 | 0.45 (0.26, 0.78) |
| | Control | 221 | 23/120.3 | 19.1 | 1 |
| Previous episodes of TB | | | | | $P_i$ =0.03† |
| 1 episode | IPT | 273 | 19/268.3 | 7.1 | 0.33 (0.18, 0.61) |
| | Control | 173 | 21/97.2 | 21.6 | 1 |
| > 1 episode | IPT | 65 | 9/56.0 | 16.1 | 1.85 (0.40, 8.58) |
| | Control | 48 | 2/23.1 | 8.7 | 1 |
| CD4 category (/µl) | | | | | $P_i$ = 0.55† |
| < 200 | IPT | 114 | 12/87.8 | 13.7 | 0.40 (0.17, 0.92) |
| | Control | 65 | 10/29.1 | 34.3 | 1 |
| ≥ 200 | IPT | 223 | 16/234.8 | 6.8 | 0.57 (0.26, 1.25) |
| | Control | 135 | 10/83.0 | 12.0 | 1 |
| Time since previous TB episode | | | | | $P_i$ =0.86† |
| < 12 mo. | IPT | 202 | 13/183.5 | 7.1 | 0.52 (0.22, 1.27) |
| | Control | 111 | 8/59.3 | 13.5 | 1 |
| 12 - 24 mo. | IPT | 83 | 10/87.1 | 11.5 | 0.37 (0.15, 0.94) |
| | Control | 50 | 8/26.0 | 30.8 | 1 |
| >24 mo. | IPT | 53 | 5/53.7 | 9.3 | 0.47 (0.15, 1.47) |
| | Control | 60 | 7/35.1 | 19.9 | 1 |
| **Probable/definite‡** | | | | | |
| Overall | IPT | 338 | 17/324.3 | 5.2 | 0.35 (0.18, 0.68) |
| | Control | 221 | 18/120.3 | 15.0 | 1 |
| Previous episodes of TB | | | | | $P_i$ = 0.02† |
| 1 episode | IPT | 273 | 11/268.3 | 4.1 | 0.23 (0.11, 0.50) |
| | Control | 173 | 17/97.2 | 17.5 | 1 |
| >1 episode | IPT | 65 | 6/56.0 | 10.7 | 2.47 (0.30, 20.5) |
| | Control | 48 | 1/23.1 | 4.3 | |

IR = incidence rate per 100 person-years (pyrs); IRR = incidence rate ratio; CI = confidence interval; IPT = isoniazid preventive therapy. *Number of TB recurrences. †*P*-value for the interaction between variable of interest and cohort group. ‡See text for case definitions.

completion of treatment for previous TB episode (adjusted IRR = 0.45, 95% CI 0.26 - 0.79). The effect of IPT on TB incidence remained significant when the analysis was restricted to TB cases defined as probable or definite (Table III). Likewise, the effect of IPT remained highly significant if the analysis was restricted to those in whom the previous TB episode had been culture positive for *M. tuberculosis* (IRR 0.19; 95% CI 0.09 - 0.42) (Table IV).

Among men with only one previous episode of TB, the incidence of recurrent TB in the IPT cohort was significantly lower than in the control cohort (Table III). Among men with more than one previous episode of TB, recurrences occurred more often in those on IPT, though the difference was not statistically significant (Table III). The interaction between the number of previous TB episodes and the efficacy of IPT was significant overall ($P_{interaction}$ = 0.03), when the analysis was restricted to those cases classified as probable or definite ($P_{interaction}$ = 0.02) (Table III) and when the preceding TB episode was culture positive for *M. tuberculosis* ($P_{interaction}$ = 0.001) (Table IV). The effect of IPT was strongest in men with only one previous episode of TB that was culture positive for *M. tuberculosis*, among whom there was an 89% reduction in incidence of recurrent TB (IRR 0.11; 95% CI 0.04 – 0.27).

The effect of IPT was not significantly modified by time since completion of previous TB treatment ($P_{interaction}$ = 0.86) or by CD4 category ($P_{interaction}$ = 0.55) (Table III). However, the incidence of recurrent TB increased with

**TABLE IV. UNADJUSTED INCIDENCE RATES OF RECURRENT TB AND INCIDENCE RATE RATIOS RESTRICTED TO INDIVIDUALS WHOSE PREVIOUS TB EPISODE WAS CULTURE POSITIVE FOR M. TUBERCULOSIS**

| | | *N* | Events*/pyrs | IR | IRR (95% CI) |
|---|---|---|---|---|---|
| **All** | | | | | |
| Overall | IPT | 186 | 10/176.4 | 5.7 | 0.19 (0.09, 0.42) |
| | Control | 119 | 17/58.1 | 29.3 | 1 |
| Previous episodes of TB | | | | | $P_i$ = 0.01† |
| 1 episode | IPT | 155 | 6/151.1 | 4.0 | 0.11 (0.4, 0.27) |
| | Control | 94 | 17/46.4 | 36.6 | 1 |
| > 1 episode | IPT | 31 | 14/25.3 | 15.8 | - |
| | Control | 25 | 0/11.7 | 0 | |

IR = incidence rate per 100 person years (pyrs); IRR = incidence rate ratio; CI = confidence interval; IPT = isoniazid preventive therapy. †Number of TB recurrences. **p*-value for interaction of the number of previous TB episodes.

## TABLE V. MORTALITY RATES AND RATE RATIOS BY COHORT

| | | Events*/pyrs | MR | MRR (95% CI) | *p*-value |
|---|---|---|---|---|---|
| All individuals | IPT | 33/339.8 | 10.0 | 0.70 (0.39, 1.24) | 0.22 |
| | Control | 18/129.3 | 13.9 | 1 | |
| CD4 < 200/µl, on co-trimoxazole† | IPT | 30/93.1 | 33.3 | 0.73 (0.39, 1.38) | 0.33 |
| | Control | 14/31.8 | 44.1 | 1 | |

MR = mortality rate per 100 person years (pyrs); MRR = mortality rate ratio; CI = confidence interval; IPT = isoniazid preventive therapy.
*Number of deaths. †114 and 60 individuals from the IPT and control cohorts, respectively.

decreasing CD4 count (CD4 count ≥ 500/µl: 6.9/100 person-years (pyrs); CD4 count 200 – 499/µl: 8.6/100 pyrs; < 200/µl: 18.8/100 pyrs; $P_{trend}$ = 0.008) and hence the number needed to treat to prevent a case of recurrent TB was substantially lower for individuals with lower CD4 counts. (The number of pyrs on IPT required to prevent one case of recurrent TB was 10 pyrs overall, 5 pyrs for CD4 count < 200/µl and 19 pyrs for CD4 count ≥ 200/µl.)

Overall mortality was not significantly lower among the IPT cohort compared with the control cohort (mortality rate ratio 0.7; 95% CI 0.39 - 1.24) (Table V). In order to control for any possible effect of co-trimoxazole on mortality, the analysis was restricted to those men with a CD4 count of 200/µl or below who were taking co-trimoxazole, but this did not affect the result (mortality rate ratio 0.73; 95% CI 0.39 - 1.38).

## DISCUSSION

The concept of TB PT was developed in the pre-HIV era, based on the idea that treatment of asymptomatic latent or recently acquired TB infection would reduce the risk of developing active TB disease.[14] In industrialised countries, the contribution of exogenous reinfection to active disease was declining in the mid-20th century,[15] and PT was thought to have no effect among those who had been previously treated for TB[16] and secondary PT was therefore not recommended. The clinical trials that demonstrated the efficacy of TB PT among HIV-infected individuals were based on this same principle, and hence only included individuals who had no history of previous TB. However, with the development of molecular 'fingerprinting' techniques, it has become clear that recurrent TB may occur either as a result of recrudescence of disease from the original infecting organism (relapse) or due to reinfection with a new strain of TB, particularly in settings with a high rate of TB transmission.[6,10]

In this study, in a setting where the prevalence (and hence also the risk of transmission) of TB is high, secondary IPT was associated with a 55% reduction in the incidence of recurrent TB among HIV-infected individuals. The results are consistent with small prospective randomised trials of secondary IPT from Haiti[12] and Abidjan,[13] and a study from the Democratic Republic of Congo that demonstrated a reduction in TB recurrence among HIV-infected individuals in whom treatment was extended by 6 months with twice-weekly isoniazid and rifampicin.[17]

The effectiveness of secondary PT is likely to be limited to communities with high rates of TB transmission, such as the South African goldmining industry, where there are high rates of TB recurrence following documented cure, particularly among HIV-infected individuals.[4,6] DNA fingerprinting data suggest similar rates of relapse between HIV-infected and uninfected individuals, but higher rates of reinfection with rapid progression to TB disease among HIV-infected individuals.[6] In this setting, secondary PT may prevent acquisition of new infection or treat recently acquired infection that may have occurred following completion of treatment of the previous TB episode.

Our study suggests that the effectiveness of secondary IPT may be limited to HIV-infected individuals with only one previous episode of TB. This may be because individuals who have had more than one recurrence of TB are more likely to have drug-resistant TB than those individuals presenting with their first recurrence;[18] the number of individuals in this study with isoniazid-resistant TB was too small to provide data supporting this hypothesis. Limiting secondary PT to individuals who have only had one previous episode of TB seems rational but requires additional studies to confirm a lack of benefit in those individuals with more than one previous TB episode.

Current WHO recommendations regarding TB preventive therapy for HIV-infected individuals in resource-poor settings have not been widely implemented.[19] In sub-Saharan Africa the majority of HIV-infected individuals are unaware of their HIV status[19] and many discover their status only when an opportunistic infection, often TB, is diagnosed, at which point it is too late for primary PT. Furthermore, owing to limited eligibility criteria and logistical difficulties of excluding active disease prior to commencing PT there is a high attrition of patients during the screening process.[20] Consequently, the number of patients who start primary PT compared with the number

screened is small. Secondary TB PT may be easier to implement than primary PT. HIV testing should have been offered at the time of TB diagnosis, a tuberculin skin test (TST) and chest radiograph are not required and exclusion of active TB at the end of treatment, by sputum smear examination, is done routinely according to WHO TB control programme guidelines. For these reasons it seems logical to offer secondary PT to HIV-infected individuals in settings of high TB prevalence where primary TB PT is being offered.

In this study, the risk of recurrent TB increased significantly with declining CD4 count, but the relative effect of IPT was not significantly modified by CD4 count. Hence fewer patients with advanced HIV disease would need to be treated to prevent a case of TB compared to patients with less advanced HIV disease. It may be more cost-effective to target IPT to those with advanced HIV disease, based on CD4 count or clinical staging. Of note, absolute numbers needed to treat depend on TB incidence and hence where TB incidence is lower, the numbers needed to treat will be higher.

In other studies[12,17] the effectiveness of secondary PT was evaluated in the immediate post-TB treatment period.[13] Our study demonstrated effectiveness of secondary IPT regardless of the interval between the previous TB episode and commencing IPT. We therefore propose no restriction by time since previous episode for offering secondary PT to HIV-infected individuals.

Although secondary IPT significantly reduced the incidence of TB recurrence in this study, the rate of recurrence in the IPT cohort remained unacceptably high (8.6 per 100 person-years) and mortality was not significantly reduced. In resource-poor settings secondary IPT may be a safe and, at less than $10 per person per year, affordable way to reduce morbidity among HIV-infected individuals with a history of previous TB. Antiretroviral therapy (ART) is likely to have a greater effect in reducing morbidity and mortality from TB and AIDS-defining conditions in this group of patients.[21,22] However, TB incidence remains high among individuals on ART with low CD4 counts living in communities with endemic TB,[22] and thus TB preventive therapy will remain an important intervention for individuals receiving ART in these settings.

In this study, we were able to include a relatively large number of individuals with a large number of events. Since this was not a randomised controlled trial, there could have been differences between the two cohorts that we were not able to control for. However, we had access to detailed data on potential confounding factors, and the two cohorts had similar baseline characteristics. Although the two cohorts differed in terms of time since last TB episode, there was no difference in efficacy of IPT when adjusted for time since last TB episode. The risk of recurrent TB in the IPT cohort may have been greater because of the longer duration of follow-up and hence increased chance of disease progression. If so, we may have underestimated the efficacy of IPT.

Secondary IPT was administered indefinitely in this study, which contrasts with current international guidelines of 6 - 9 months of isoniazid for primary PT[11,23] and other studies of secondary PT.[12,13] Further work is needed to determine the optimum duration of both primary and secondary TB PT in settings with high rates of TB transmission, and to establish how best to target PT.

There is a growing body of evidence of the efficacy of secondary TB PT for HIV-infected individuals in communities with a high incidence of TB. HIV-infected individuals may benefit from secondary PT, and international recommendations need revision to take this into account.

REFERENCES


1. Churchyard GJ, Kleinschmidt I, Corbett EL, Mulder D, De Cock KM. Mycobacterial disease in South African gold miners in the era of HIV infection. *Int J Tuberc Lung Dis* 1999; **3:** 791-798.
2. Weyer K, Kleeberg HH. Primary and acquired drug resistance in adult black patients with tuberculosis in South Africa: results of a continuous national drug resistance surveillance programme involvement. *Tuberc Lung Dis* 1992; **73:** 106-112.
3. Pablos-Mendez A, Raviglione MC, Laszlo A, *et al.* Global surveillance for antituberculosis-drug resistance, 1994-1997. World Health Organization-International Union against Tuberculosis and Lung Disease Working Group on Anti-Tuberculosis Drug Resistance Surveillance. *N Engl J Med* 1998; **338:** 1641-1649.
4. Mallory KF, Churchyard GJ, Kleinschmidt I, De Cock KM, Corbett EL. The impact of HIV infection on recurrence of tuberculosis in South African gold miners. *Int J Tuberc Lung Dis* 2000; **4:** 455-462.
5. Banda H, Kang'ombe C, Harries AD, *et al.* Mortality rates and recurrent rates of tuberculosis in patients with smear-negative pulmonary tuberculosis and tuberculous pleural effusion who have completed treatment. *Int J Tuberc Lung Dis* 2000; **4:** 968-974.
6. Sonnenberg P, Murray J, Glynn JR, Shearer S, Kambashi B, Godfrey-Faussett P. HIV-1 and recurrence, relapse, and reinfection of tuberculosis after cure: a cohort study in South African mineworkers. *Lancet* 2001; **358:** 1687-1693.
7. Pulido F, Pena JM, Rubio R, *et al.* Relapse of tuberculosis after treatment in human immunodeficiency virus-infected patients. *Arch Intern Med* 1997; **157:** 227-232.
8. Johnson JL, Okwera A, Vjecha MJ, *et al.* Risk factors for relapse in human immunodeficiency virus type 1 infected adults with pulmonary tuberculosis. *Int J Tuberc Lung Dis* 1997; **1:** 446-453.
9. Sterling TR, Alwood K, Gachuhi R, *et al.* Relapse rates after short-course (6-month) treatment of tuberculosis in HIV-infected and uninfected persons. *AIDS* 1999; **13:** 1899-1904.
10. Van Rie A, Warren R, Richardson M, *et al.* Exogenous reinfection as a cause of recurrent tuberculosis after curative treatment. *N Engl J Med* 1999; **341:** 1174-1179.
11. Preventive therapy against tuberculosis in people living with HIV. *Wkly Epidemiol Rec* 1999; **74:** 385-398.
12. Fitzgerald DW, Desvarieux M, Severe P, Joseph P, Johnson WD jun, Pape JW. Effect of post-treatment isoniazid on prevention of recurrent tuberculosis in HIV-1-infected individuals: a randomised trial. *Lancet* 2000; **356:** 1470-1474.
13. Haller L, Sossouhounto R, Coulibaly IM, *et al.* Isoniazid plus sulphadoxine-pyrimethamine can reduce morbidity of HIV-positive patients treated for tuberculosis in Africa: a controlled clinical trial. *Chemotherapy* 1999; **45:** 452-465.
14. Rieder HL. Interventions for tuberculosis control and elimination. International Union Against Tuberculosis and Lung Disease (Monograph), 2002.
15. Canetti G, Sutherland I, Svandova E. Endogenous reactivation and exogenous reinfection. Their relative importance in the outbreak of nonprimary tuberculosis. *Bull Int Union Tuberc* 1972; **47:** 116-134.
16. Ferebee SH. Controlled chemoprophylaxis trials in tuberculosis. A general review. *Adv Tuberc Res.* 1970; **17:** 28-106.
17. Perriens JH, St Louis ME, Mukadi YB, *et al.* Pulmonary tuberculosis in HIV-infected patients in Zaire. A controlled trial of treatment for either 6 or 12 months. *N Engl J Med* 1995; **332:** 779-784.
18. Kritski AL, Rodrigues de Jesus LS, Andrade MK, *et al.* Retreatment tuberculosis cases. Factors associated with drug resistance and adverse outcomes. *Chest* 1997; **111:** 1162-1167.
19 Colebunders R, Lambert ML. Management of co-infection with HIV and TB. *BMJ* 2002; **324:** 802-803.
20. Aisu T, Raviglione MC, van Praag E, *et al.* Preventive chemotherapy for HIV-associated tuberculosis in Uganda: an operational assessment at a voluntary

counselling and testing centre. *AIDS* 1995; **9:** 267-273.
21. Harries AD, Hargreaves NJ, Kwanjana JH, Salaniponi FM. Recurrent tuberculosis: definitions and treatment regimens. *Int J Tuberc Lung Dis* 1999; **3:** 851-854.
22. Badri M, Wilson D, Wood R. Effect of highly active antiretroviral therapy on incidence of tuberculosis in South Africa: a cohort study. *Lancet* 2002; **359:** 2059-2064.
23. American Thoracic Society / Centres for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. *Am J Respir Crit Care Med* 2000; **161:** S221-S247.

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## Commentary by G J Churchyard and A D Grant

South Africa is classified by the World Health Organisation as one of the 22 high TB burden countries world-wide.1 Approximately 2 million South Africans are co-infected with TB and HIV, and the estimated incidence of all forms of TB was 509 per 100 000 population for 2002, with 60% of adult cases being HIV-infected.[1]

As in other countries with endemic TB, recurrent disease accounts for a significant proportion of all TB in South Africa. HIV infection increases the risk of recurrence following successful treatment of TB.[2] Risk factors for recurrence of HIV-associated TB are initial treatment regimens with less than 6 months of rifampicin,[2] post-TB scarring, cavities, and a low CD4 count.

The importance of new infection as a cause of recurrent TB has been clearly shown in a prospective strain-typing study among TB patients in a South African goldmine.[3] HIV-infected miners had recurrent TB disease due to a new strain of TB (reinfection) at 18.7 times the rate in HIV-uninfected miners, but there was no increase in their risk of recurrent disease due to the original strain (relapse). In settings of lower TB incidence, recurrent TB still occurs more frequently among HIV-infected patients, although the absolute difference is smaller. These observations suggest that that there is little to gain from intensifying the treatment regimens currently used in South Africa, but that consideration should be given to secondary TB preventive therapy in settings of high TB transmission. The article by Churchyard *et al.*[4] reproduced in this journal contributes to the body of evidence supporting the use of secondary TB preventive therapy among HIV-infected individuals. Although the South African HIV Clinicians Society guidelines recommend TB preventive therapy for HIV-infected individuals who have had an episode of TB more than 2 years previously, the Department of Health's TB preventive therapy guidelines do not advocate the use of secondary TB preventive therapy. Further research is needed to establish how to use secondary TB preventive therapy most effectively among HIV-infected people, and to determine whether secondary TB preventive therapy has a role to reduce TB recurrence among individuals receiving antiretroviral therapy.

REFERENCES

1. Corbett EL, Watt CJ, Walker N, *et al.* The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. *Arch Intern Med* 2003; **163**(9): 1009-1021.
2. Korenromp EL, Scano F, Williams BG, Dye C, Nunn P. Effects of human immunodeficiency virus infection on recurrence of tuberculosis after rifampin-based treatment: an analytical review. *Clin Infect Dis* 2003; **37:** 101-112.
3. Sonnenberg P, Murray J, Glynn JR, Shearer S, Kambashi B, Godfrey-Faussett P. HIV-1 and recurrence, relapse, and reinfection of tuberculosis after cure: a cohort study in South African mineworkers. *Lancet* 2001; **358:** 1687-1693.
4. Churchyard GJ, Fielding K, Charalambous S, *et al.* Efficacy of secondary isoniazid preventive therapy among HIV-infected southern Africans: time to change policy? *AIDS* 2003; **14:** 2063-2070.