Effect of Routine Isoniazid Preventive Therapy on Tuberculosis Incidence Among HIV-Infected Men in South Africa

A Novel Randomized Incremental Recruitment Study

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Context Tuberculosis preventive therapy reduces tuberculosis incidence among human immunodeficiency virus (HIV)–infected individuals in clinical trials, but implementation has been limited and there are no data on effectiveness under routine conditions.

Objective To determine the effect on tuberculosis incidence of a clinic providing isoniazid preventive therapy to HIV-infected adults under routine conditions.

Design, Setting, and Participants Randomized intervention study with a novel incremental recruitment design. Between 1999 and 2001 (before antiretroviral therapy was available), 1655 HIV-infected male employees of a South African gold-mining company (median age, 37 years) were enrolled in the study. Median follow-up was 22.1 months.

Intervention Employees were invited in random sequence to attend a workplace HIV clinic. Isoniazid, 300 mg/d, was self-administered for 6 months among attendees with no evidence of active tuberculosis.

Main Outcome Measure Incidence of tuberculosis (including both first and recurrent episodes) during the periods before and after clinic enrollment.

Results A total of 1016 of 1655 men included in the analysis attended the clinic at least once. Six hundred seventy-nine (97%) of 702 men eligible to start primary isoniazid preventive therapy did so. The tuberculosis incidence rate before vs after clinic enrollment was 11.9 vs 9.0 per 100 person-years, respectively (incidence rate ratio [IRR] after adjustment for calendar period, 0.68; 95% confidence interval [CI], 0.48-0.96). In a multivariable analysis adjusting for calendar period, age, and silicosis grade, the tuberculosis IRR for clinic enrollment was 0.62 (95% CI, 0.43-0.89). In a further analysis excluding individuals with a history of tuberculosis (and, hence, ineligible for isoniazid preventive therapy), the adjusted IRR for clinic enrollment was 0.54 (95% CI, 0.35-0.83).

Conclusions Enrollment in a clinic offering primary isoniazid preventive therapy to HIV-infected adults reduced tuberculosis incidence by 38% overall and by 46% among individuals with no history of tuberculosis prior to the study. Tuberculosis incidence remained high despite isoniazid preventive therapy, and further work is needed to determine how to use additional interventions most effectively to reduce morbidity and mortality due to tuberculosis in HIV-infected persons.

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A MAJOR CONSEQUENCE OF THE human immunodeficiency virus (HIV) epidemic in developing countries is the increasing incidence of tuberculosis (TB).[1-3] The cornerstone of TB control programs is the World Health Organization (WHO) strategy known as DOTS (directly observed therapy, short course), which may be effective in controlling drug resistance but appears insufficient to stem rising TB incidence in regions with high HIV prevalence.[4,5]

The impact of HIV on TB is illustrated by data from gold mines in South Africa, where overall TB incidence now exceeds 4000 per 100 000 population per year (ie, 4%).[6] Tuberculosis incidence was already high in this setting before the spread of HIV infection, largely because of a high prevalence of silica dust exposure.[7] Rising HIV prevalence has resulted in increasing TB incidence,[8] despite well-implemented TB control programs using directly observed rifampicin-based short-course chemotherapy and active case detection using an annual miniature chest radiograph screening program. Additional interventions are required to reverse the rise of TB in such settings.[5]

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Clinical trials have shown that primary TB preventive therapy (ie, treatment to prevent a first episode of TB among those with no history of the disease) reduces TB incidence among HIV-infected individuals. Results of a meta-analysis suggest that isoniazid preventive therapy (IPT) reduces TB incidence by 42% overall, or by 60% among individuals who have positive tuberculin skin tests.[9] Isoniazid preventive therapy is recommended by WHO and the Joint United Nations Programme on HIV/AIDS (UNAIDS),[10] but this recommendation has not been widely implemented, partly because of operational obstacles. These include attrition during assessment for IPT, particularly nonreturn for tuberculin skin test results and noncompletion of a screen for active TB if it requires travel to another site to undergo chest radiography.[11,12]

In collaboration with the mining health service, we established a clinic for HIV-infected employees in a gold mining company in South Africa in 1999.[13] The aim of the clinic was to provide specialist care for HIV-infected employees, including preventive therapy (isoniazid and cotrimoxazole) against opportunistic infections. Using a randomized incremental recruitment study design, we took the opportunity of implementation of this service to evaluate the effect of these interventions when used as part of routine clinical care. In this article we describe the effectiveness of IPT.

METHODS

Study Design and Population

This was an intervention study with randomized incremental recruitment, designed to examine the effect of clinic enrollment on episodes of severe HIV-related disease. This study design has the advantage of not requiring an untreated control group because all participants have the opportunity to receive the intervention; it also allows the effect of disease progression over calendar time among individual participants to be taken into account in the analysis, as described below. It has been used in community randomized trials[14] but, to our knowledge, has not previously been used to randomize the order of individuals to be offered an intervention.

The study population consisted of employees of the gold-mining company who had previously tested positive for HIV within the company health service. In July 1999, we used computer-generated random numbers to arrange these employees in a random sequence and invited them to enroll at the clinic in this sequence. Each employee was interviewed individually and confidentially by a member of the research staff, who explained the aims of the clinic and invited him to attend. Those who agreed were given a clinic appointment, and written (or for participants who could not read, witnessed oral) informed consent was obtained. Those who declined were given contact details so that they could make an appointment later if they wished. Employees who missed their first clinic appointment were offered 2 further appointments. Health care staff could refer HIV-infected individuals to clinic at any time if clinically indicated.

Ethical Approval

The study was approved by the research ethics committees of Anglogold Health Service, Orkney, South Africa, and the London School of Hygiene and Tropical Medicine, London, England.

Clinic Procedures

Clinic procedures are described elsewhere.[13] At the first visit, trained nurses or research assistants took a medical history based on information from the patients as well as information in their company medical records, which document all contacts with the mining health services since the start of employment. The history focused on HIV-related symptoms, particularly those suggesting TB, and any history of HIV-related disease. A physician reviewed the history and performed a physical examination. All patients were routinely screened for active TB at clinic entry using reported symptoms, a chest radiograph, and 2 sputum specimens examined by smear and culture for mycobacteria.

Isoniazid, 300 mg/d, self-administered for 6 months or for 12 months if there was coincident silicosis, was offered routinely at clinic enrollment to attendees with no evidence of active TB; in accordance with current WHO/UNAIDS guidelines, IPT was not offered to individuals with a history of previous treatment for TB. Tuberculin skin tests were not routinely performed because the majority of employees were assumed to have latent TB infection.[15] Cotrimoxazole, 960 mg/d, was offered to individuals with a CD4 cell count below 200×10^6/L or below 250×10^6/L if they had symptomatic HIV disease. Individuals receiving isoniazid or cotrimoxazole collected their medication from their primary health center each month, at which time they were asked about symptoms suggestive of adverse events or of active TB. If these symptoms were present, they were referred to the clinic for further evaluation. Neither antiretroviral therapy (ART) nor viral load quantification was routinely available during the period of this study but are now freely available to employees of this company who fulfill appropriate medical criteria.

Ascertainment of Clinical Events

Clinic attendees were seen routinely every 6 months, or sooner if they were unwell. At each visit, information about episodes of illness in the previous 6 months was recorded. In addition, all hospital admissions of study participants were identified by research staff using the health service information systems. Research staff visited patients on the wards and, after discharge, a diagnosis was assigned using predetermined case definitions. All episodes of TB were recorded in a dedicated health service database, which was reviewed to ensure that all episodes of TB among participants were identified. As a further check, we reviewed the medical records of all participants at the time of study end or loss to follow-up to ensure that all TB episodes

were identified. Employment records were used to identify dates of loss to follow-up because of termination of employment or death.

Health service policy at the time of this study entailed suspected TB to be investigated with a chest radiograph and 3 sputum samples sent for microscopy and mycobacterial culture. Medical records were used to determine the clinical disease stage of each individual at the start of the study (July 1999) using the WHO staging system.[16]

Case Definitions

Individuals were classified as having pulmonary TB if they had compatible clinical or radiological features and (1) were sputum culture–positive for *Mycobacterium tuberculosis* with more than 5 colonies (categorized as definite); (2) were sputum smear–positive for acid-fast bacilli or had new radiological changes suggestive of TB but no response to 5 days of antibiotic treatment and improved after 2 months of TB treatment (categorized as probable); or (3) had no other cause of disease found and improved after 2 months of TB treatment or were lost to follow-up before 2 months (categorized as possible). Individuals were classified as having extrapulmonary TB if they had compatible clinical features and either (1) had *M tuberculosis* isolated from a relevant site (categorized as definite); (2) improved after 2 months of TB treatment and had other diagnostic evidence (eg, acid-fast bacilli, caseation, granuloma, characteristic cerebrospinal fluid or radiological features) (categorized as probable); or (3) had no other cause of disease found and improved after 2 months of TB treatment or were lost to follow-up before 2 months (categorized as possible).

Recurrent episodes of TB were included in the analysis only if the outcome of the previous TB episode was cure or treatment completion.

Silicosis Scoring

All mine employees have an annual fitness examination that includes screening for TB using a miniature chest radiograph. We located the latest available miniature chest radiograph for all participants taken prior to July 1, 1999, and a single reader assessed the presence and grade of silicosis using a modified International Labour Organisation grading system.[17] Grades 0/1, 1/0, and 1/1 were regarded as possible, probable, and early silicosis, respectively, and all higher grades were regarded as advanced silicosis.

Laboratory Methods

Concentrated sputum specimens were stained with auramine and examined using fluorochrome microscopy. Sputum was cultured for mycobacteria on Lowenstein-Jensen medium; cultures with more than 5 colonies underwent colorimetric ribosomal RNA hybridization testing for *M tuberculosis* (Accuprobe *M tuberculosis* complex probe kit, Gen-Probe Inc, San Diego, Calif) to distinguish them from nontuberculous mycobacteria.

Statistical Methods

Data were analyzed using STATA software, version 7 (Stata Corp, College Station, Tex). Individuals contributed follow-up time to the "preclinic" phase from July 1, 1999, until the actual date of their first clinic visit, and to the "postclinic" phase thereafter. Follow-up ended when an individual left employment or at the end of the study period (September 30, 2001), whichever was sooner. A Poisson random-effects model was used to compare the incidence of TB in the phases before and after recruitment to the clinic. We allowed for multiple TB events rather than censoring after the first event because otherwise individuals with more advanced HIV disease, who would be more likely to acquire TB early in the study, would have been excluded from the postclinic phase, resulting in a "healthy survivor" bias.

We used a random-effects model to allow for the lack of statistical independence resulting from observation of multiple events in some individuals and correlation between events in the same individual in different time periods.[18] Results were adjusted for the potential confounding effect of calendar period to take account of HIV disease progression, leading to increasing TB incidence among all individuals over time. Results were also adjusted for baseline age, WHO HIV disease stage, and silicosis grade. We excluded from the analysis all person-time during TB treatment. Since all patients were screened for TB at clinic entry, we excluded all TB episodes diagnosed within 90 days of clinic entry on the assumption that these were diagnosed as a result of this screening process. To avoid bias, for all individuals, the 90 days following clinic entry were also excluded from the total person-time at risk.

RESULTS

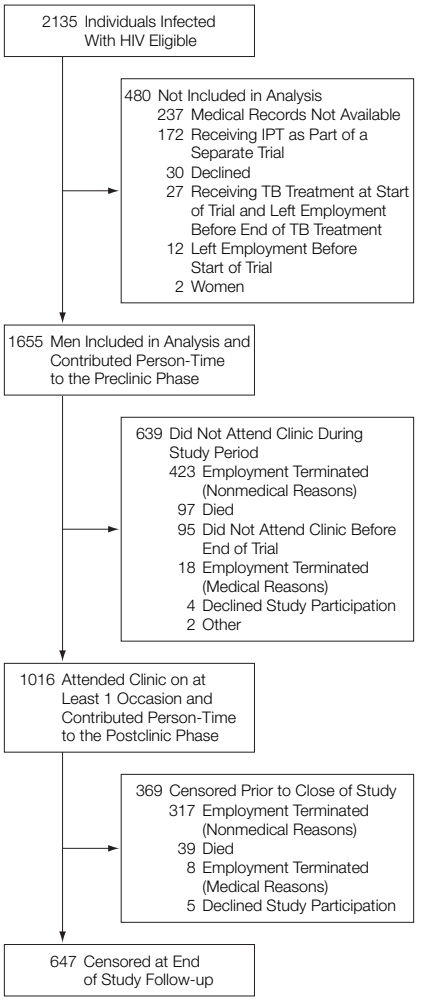
Study Population

In July 1999, 2135 individuals were identified who had had a positive HIV test result within the mining health service and were still in employment, and they were allocated a random sequence for recruitment. The first individuals were seen in clinic later the same month. The last individuals to be recruited were enrolled in clinic in September 2001, and follow-up ended on September 30, 2001.

Of these 2135 individuals, 237 were excluded because we could not obtain their full medical records, 172 were excluded because they received isoniazid prior to study entry as part of a separate clinical trial, 30 declined to participate, 27 were receiving TB treatment at the start of the study and were lost to follow-up before completing treatment, and 12 had left employment before the study start date (FIGURE). Because the number of women available for inclusion in the analysis was so small (n = 2), we also excluded them, leaving 1655 men in this analysis.

Among the 1655 men in this analysis, the median age was 37 years (interquartile range [IQR], 33-43 years), and among the 1650 with WHO HIV disease stage[16] recorded at the start of the study, 1176 (71%) were in stage 1, 109 (7%) were in stage 2, 267 (16%) were in stage 3, and 98 (6%) were in stage 4.

Figure. Participant Flow Through the Study



HIV indicates human immunodeficiency virus; IPT, isoniazid preventive therapy; TB, tuberculosis.

Recruitment to Clinic

One thousand sixteen individuals (61%) attended clinic at least once during the study period. Of these, 950 (94%) were referred to clinic by the study team on the basis of the randomized sequence and 66 (6%) were referred by health service staff earlier than the date assigned by the randomization.

Among 639 individuals who did not attend clinic during the study period, the reasons were termination of employment for nonmedical reasons prior to clinic enrollment (n=423 [66%]); death (n=97 [15%]); study termination before first clinic attendance (n=95 [15%]); termination of employment for medical reasons (n=18 [3%]); and other (n=6 [1%]) (Figure).

Six hundred seventy-nine individuals (67%) who first attended clinic during the study period started isoniazid. The main reasons for not starting isoniazid were contraindication (270/337 [80%]), most commonly history of TB (240/270 [89%]), or suspected active TB (26/337 [8%]). The median CD4 cell count among individuals who started isoniazid was 371×10^6/L (IQR, 252-530 $\times$ 10^6/L; data from 619/679 participants) compared with 277.5×10^6/L (IQR, 171-444 $\times$ 10^6/L; data from 210/240 participants) among individuals who did not start isoniazid because they had a history of previous TB ($P<.001$ by Mann-Whitney U test).

The median duration of follow-up was 22.1 months (IQR, 13.7-27.0 months) overall; the median duration of follow-up before clinic enrollment was 11.2 months (IQR, 6.6-18.5 months) and after clinic enrollment (among individuals who ever attended clinic) was 11.0 months (IQR, 5.7-17.9 months).

Outcomes

In total, there were 254 TB episodes meeting study case definitions; 225 individuals had 1 episode, 13 had 2 episodes, and 1 had 3 episodes of TB. Of these episodes, 189 (74%) were classified as definite, 52 (20%) as probable, and 12 (5%) as possible cases; 1 was unknown. One hundred seventy-three episodes (68%) were of pulmonary TB only, 46 (18%) were extrapulmonary TB only, and 35 (14%) were both pulmonary and extrapulmonary. The most common sites for extrapulmonary TB were pleural space (30 cases) and lymph nodes (19 cases). Thirty-nine TB events that occurred within 90 days of clinic entry were assumed to have been diagnosed as a result of active screening at clinic entry and were excluded from the analysis, along with 219.1 person-years of follow-up during these 90 days.

The overall incidence of TB was 11 per 100 person-years; prior to clinic enrollment, TB incidence was 11.9 per 100 person-years compared with 9.0 per 100 person-years following clinic enrollment (incidence rate ratio [IRR], 0.78; 95% CI, 0.58-1.05; $P=.10$). After adjustment for the confounding effect of calendar period, the IRR for the effect of clinic enrollment on TB incidence was 0.68 (95% CI, 0.48-0.96; $P=.03$).

TABLE 1 shows a univariable analysis of risk factors for incidence of TB and analysis of the same risk factors after adjustment for the potential confounding effect of calendar period, categorized into 6-month time bands. The risk of TB was significantly associated with increasing age, history of TB, baseline WHO HIV disease stage 3 or 4 (compared with stage 1 or 2), and a silicosis grade of "probable" or higher. Adjustment for calendar period did not substantially alter these results.

In a multivariable analysis (**TABLE 2**) examining the effect of clinic enrollment on the incidence of TB, adjustment for age, previous TB, and baseline WHO HIV disease stage did not substantially affect the result, but adjustment for baseline silicosis grade (based on 1367 individuals with an available silicosis grade) strengthened the effect, giving an adjusted IRR of 0.62 (95% CI, 0.43-0.89; $P=.009$). Restricting the analysis to cases of TB classified as definite did not change these results, nor did analyses increasing the period of time after clinic entry (up to 180 days) during which TB cases were excluded, assuming they had been detected by screening at clinic entry (data not shown). Analyses controlling for calendar period using narrower time bands did not affect the results.

In a further analysis excluding individuals who had a history of TB at the time of randomization and were therefore ineligible for IPT from the beginning of the study (Table 2), the IRR, adjusted for calendar period among the remaining 1310 individuals, was 0.62 (95% CI, 0.41-0.93; $P=.02$). Further adjustment for age and silicosis grade (based on 1041 individuals with an available baseline silicosis grade) gave an adjusted IRR of 0.54 (95% CI, 0.35-0.83; $P=.004$).

Table 1. Risk Factors for Incidence of TB: Univariable Analysis and Analysis After Adjustment for Calendar Period

	No.	Events/P-Y	Rate per 100 P-Y	Unadjusted IRR*	Adjusted IRR (95% CI)*†	*P* Value
Overall	1655	254/2304.1	11.0			
Clinic phase	1655					
Preclinic		190/1595.1	11.9	1.00	1.00	.03
Postclinic		64/709.0	9.0	0.78	0.68 (0.48-0.96)	
Age group, y	1655					
<30		24/234.5	10.2	1.00	1.00	.009‡
30-39		112/1199.9	9.3	0.91	0.91 (0.56-1.46)	
40-49		97/749.8	12.9	1.28	1.28 (0.79-2.09)	
≥50		21/120.0	17.5	1.75	1.75 (0.91-3.36)	
Previous TB	1650					
None		193/1956.8	9.7	1.00	1.00	.004
PTB >1 year ago		30/155.1	19.3	2.08	2.08 (1.33-3.25)	
PTB in past year		15/96.3	15.6	1.70	1.71 (0.94-3.10)	
EPTB		14/89.6	15.6	1.69	1.70 (0.92-3.14)	
WHO stage	1650					
1 or 2		183/1860.9	9.8	1.00	1.00	.001
3 or 4		69/437.0	15.8	1.70	1.71 (1.25-2.35)	
Silicosis grade	1367					
None or possible		197/1738.2	11.3	1.00	1.00	.001
Probable, early, or advanced		29/124.8	23.2	2.19	2.19 (1.39-3.46)	
Analysis by clinic phase restricted to individuals with no history of TB at the start of the study	1310					
Preclinic		144/1320.5	10.9	1.00	1.00	.02
Postclinic		50/593.5	8.4	0.80	0.62 (0.41-0.93)	

Abbreviations: CI, confidence interval; EPTB, extrapulmonary tuberculosis (with or without coincident pulmonary tuberculosis); IRR, incidence rate ratio; P-Y, person-years at risk; PTB, pulmonary tuberculosis; TB, tuberculosis; WHO stage, World Health Organization stage of human immunodeficiency virus disease.[16]
*Incidence rate ratios are based on a random-effects Poisson regression model.
†Adjusted for calendar period categorized into 6-month time bands.
‡Test for linear trend.

Adverse Events

Nine patients discontinued isoniazid because of a possible adverse event. Eight of these were because of skin hypersensitivity; 1 also had mild hepatitis. Two of these 8 individuals subsequently restarted isoniazid. The ninth discontinued because of mild peripheral neuropathy. An additional 13 individuals were reported to have peripheral neuropathy and 9 to have skin hypersensitivity, but all completed the course of isoniazid.

Table 2. Effect of Clinic Entry on Incidence of TB: Multivariable Analysis

	Overall (N = 1655)		Individuals With No History of TB at Study Start (n = 1310)	
	IRR (95% CI) for Effect of Clinic	*P* Value	IRR (95% CI) for Effect of Clinic	*P* Value
Univariable analysis	0.78 (0.58-1.05)	.10	0.80 (0.57-1.12)	.19
Adjusted for				
Calendar period*	0.68 (0.48-0.96)	.03	0.62 (0.41-0.93)	.02
Calendar period and age	0.67 (0.47-0.96)	.03	0.61 (0.41-0.92)	.02
Calendar period, age, and WHO stage	0.65 (0.45-0.92)†	.02	0.61 (0.41-0.91)	.02
Calendar period, age, and silicosis	0.62 (0.43-0.89)‡	.009	0.54 (0.35-0.83)§	.004

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; TB, tuberculosis; WHO stage, World Health Organization stage of human immunodeficiency virus disease.
*Calendar period was categorized into 6-month time bands.
†Based on n = 1650 with data on baseline WHO stage; univariable IRR, 0.76 (95% CI, 0.56-1.02).
‡Based on n = 1367 with data on baseline silicosis grade; univariable IRR, 0.71 (95% CI, 0.52-0.97).
§Based on n = 1041 with data on baseline silicosis grade; univariable IRR, 0.71 (95% CI, 0.50-1.02).

COMMENT

We used a novel study design to investigate the effect on TB incidence of a clinic providing IPT to HIV-infected adults under routine conditions. A reduction in TB incidence of 38% overall may appear modest in comparison with clinical trials, and some important differences in study design must be considered. First, adherence to treatment may have been less than that in clinical trial conditions, which may have resulted in a reduced effect. Second, IPT was not restricted to individuals who had a positive tuberculin skin test result, among whom the protective effect is consistently stronger.[9,19] Since it is assumed that the majority of men in this population have latent TB infection, this is unlikely to have affected the results

substantially. Third and most important, the overall analysis tests the effect of the intervention (the provision of clinic services) among the entire study population, irrespective of whether they actually received isoniazid. Overall, about one third of clinic attendees did not receive isoniazid, most often because they had previously had TB, making them ineligible according to current guidelines. When restricting the analysis to individuals who had no history of TB at the start of the study, clinic enrollment resulted in a 46% reduction in TB incidence. However, this analysis still includes individuals who had TB during the preclinic phase, who would subsequently have been at higher risk of TB but did not receive IPT because they were ineligible by the time they were enrolled in clinic. Hence, this is probably an underestimate of the protective effect of IPT among individuals with no history of TB.

Two further points are relevant to the interpretation of the results: the study was carried out over a relatively short period because, for ethical reasons, we needed to recruit eligible individuals to clinic as quickly as logistically possible. Thus, our follow-up period after clinic entry was relatively short, and follow-up time after completion of the 6-month course of isoniazid was even shorter. Evidence suggests that the protective efficacy of TB preventive therapy, particularly non–rifampicin-containing regimens, wanes over time.[20,21] Thus, our estimate of protective efficacy may have been higher than would be observed over longer follow-up. Finally, screening for TB at clinic entry and exclusion of any cases of TB detected at this point will have reduced the incidence of TB in the postclinic phase. Including these cases detected at clinic entry in the calculation of postclinic TB incidence would have created bias, since there was no equivalent active case finding at the start of the preclinic phase and, hence, we excluded these cases.

The effect of screening for TB on TB incidence in the postclinic phase will have been short-lived: in another study in this setting, TB incidence was reduced after active screening for TB, but 180 days after screening, TB incidence had returned to prescreening rates.[22] In addition, an episode of active TB detected at clinic entry must have had its onset in the preclinic phase and so arguably belongs more correctly in the preclinic phase. Subsequent clinic visits and, perhaps, more thorough investigation of TB symptoms among individuals attending clinic may have increased the probability of detecting a TB episode in the postclinic phase. Since routine clinic visits were at 6-month intervals and other work by this group has found that the duration of TB disease before diagnosis is reduced in HIV-infected compared with uninfected individuals,[23] this effect is unlikely to have been large. If TB cases were more likely to be detected in the postclinic phase, this would result in underestimation of the effectiveness of the clinic to reduce TB incidence.

Despite our intervention, the TB incidence rate in the postclinic phase remained unacceptably high at 9 per 100 person-years. This may be partly due to the prevalence of silicosis, but additional strategies are clearly required to further reduce TB incidence in this population. In this study, a history of TB was a risk factor for a subsequent episode. Individuals with a history of TB had lower median CD4 cell counts at clinic entry than those with no history of TB, putting them at higher risk of TB.[24-26] Although current guidelines do not recommend secondary TB preventive therapy (ie, for individuals with a previous history of TB), there is an increasing body of evidence to support its effectiveness.[26] In settings of high TB prevalence, it seems illogical to withhold TB preventive therapy from individuals with a history of TB, especially those with low CD4 cell counts, whose risk of TB is highest. Further work is needed to determine the optimum duration of TB preventive therapy.

ART is now being rolled out among the mining workforce. ART has been shown to reduce TB incidence at the individual level,[25,27] although in a setting with high TB prevalence, TB incidence remained high even among individuals receiving ART.[25] However, there are concerns that ART could paradoxically increase TB incidence at the community level if the net effect is to increase survival among HIV-infected individuals without completely restoring immunocompetence.[28,29] Further work is required to determine if these concerns are borne out in practice and to establish how best to use ART and TB preventive therapy to minimize morbidity and mortality due to TB among HIV-infected individuals.

In settings where TB prevalence and, hence, risk of transmission are very high, more radical approaches to TB control may be necessary, such as communitywide screening and preventive therapy for all found not to have active disease.[30] Such approaches may have only short-term benefit if the underlying risk factors are not altered, and will require careful evaluation.

Concerns are often raised about the risk of promoting isoniazid resistance when isoniazid is used as a single agent in preventive therapy. Studies from the pre-HIV era did not support this concern,[31] but close monitoring of resistance patterns to TB drugs is very important. We have too few data from this study on drug resistance among individuals who previously received IPT to report meaningful trends, but surveillance continues. Another concern is the risk of isoniazid-induced hepatitis; our study is reassuring in that only 1 individual was noted to have mild hepatitis during the study.

In conclusion, we found that enrollment in a clinic for HIV-infected individuals routinely providing IPT reduced the incidence of TB by 38% overall and by 46% among individuals with no history of TB, after adjustment for confounding factors. Additional interventions such as secondary preventive therapy and ART will be required to reduce the very high residual morbidity attributable to TB in this community. Further work is

needed to determine how best to use available interventions to minimize TB morbidity in areas where both HIV and TB are highly prevalent.

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Author Contributions: Dr Grant had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Grant, Corbett, Chaisson, De Cock, Hayes, Churchyard.
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Analysis and interpretation of data: Grant, Fielding, De Cock, Hayes, Churchyard.
Drafting of the manuscript: Grant, Churchyard.
Critical revision of the manuscript for important intellectual content: Grant, Charalambous, Fielding, Day, Corbett, Chaisson, De Cock, Hayes, Churchyard.
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