MAJOR ARTICLE

How Soon after Infection with HIV Does the Risk of Tuberculosis Start to Increase? A Retrospective Cohort Study in South African Gold Miners

Pam Sonnenberg,[1] Judith R. Glynn,[1] Katherine Fielding,[1] Jill Murray,[2] Peter Godfrey-Faussett,[1] and Stuart Shearer[3]

[1]Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, United Kingdom; [2]National Institute for Occupational Health, Department of Health and Department of Community Health, University of the Witwatersrand, and [3]Gold Fields Limited, Johannesburg, South Africa

(See the editorial commentary by Srikantiah et al., on pages 147–9.)

Background. Infection with human immuodeficiency virus (HIV) increases the risk of tuberculosis (TB), but no study has assessed how this risk changes with time since HIV seroconversion.

Methods. The incidence of pulmonary TB was estimated in miners with and those without HIV infection in a retrospective cohort study. HIV test results were linked to routinely collected TB, demographic, and occupational data. The rate ratio (RR) for the association between HIV status and TB was estimated by time since HIV seroconversion, calendar period, and age.

Results. Of the 23,874 miners in the cohort, 17,766 were HIV negative on entry, 3371 were HIV positive on entry, and 2737 seroconverted during follow-up (1962 had a seroconversion interval of ≤2 years). A total of 740 cases of TB were analyzed. The incidence of TB increased with time since seroconversion, calendar period, and age. TB incidence was 2.90 cases/100 person-years at risk (pyar) in HIV-positive miners and was 0.80 cases/100 pyar in HIV-negative miners (adjusted RR, 2.9 [95% confidence interval {CI}, 2.5–3.4]). TB incidence doubled within the first year of HIV infection (adjusted RR, 2.1 [95% CI, 1.4–3.1]), with a further slight increase in HIV-positive miners for longer periods, up to 7 years.

Conclusion. The increase in the risk of TB so soon after infection with HIV was unexpected. Current predictive models of TB incidence underestimate the effect of HIV infection in areas where TB is endemic.

Infection with HIV greatly increases the risk of tuberculosis (TB), but the extent of the increase varies in different studies. Although the risk of TB depends on the degree of immunosuppression, no study has adequately assessed how soon after infection with HIV the risk of TB increases and how the risk changes with time since HIV seroconversion. Understanding this changing risk is important for modeling the coepidemics, for estimating the effect of the HIV epidemic on the risk of TB over time, and for planning interventions, including assessing the impact of antiretrovirals.

Most cohort studies have enrolled individuals with prevalent HIV infection, and, although CD4 cell counts have been measured in some studies, data on time since HIV seroconversion have not been included. Few studies have estimated the incidence of TB in HIV-positive individuals with known dates of seroconversion [1–5]. The studies in factory workers in Kinshasa (2 TB cases among 94 individuals) [3] and in blood donors in Côte d'Ivoire (3 TB cases among 104 individuals) [1] lacked power to analyze time since HIV seroconversion as a risk factor for TB. A study in Haiti followed 42 individuals with known dates of HIV seroconversion for a median of 66 months and found 9 cases of TB (incidence, 3.8 cases/100 person-years at risk [pyar]) [5]. However, there was no HIV-negative control group, and many of the participants had been receiving isoniazid

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Reprints or correspondence: Dr. Pam Sonnenberg, Communicable Disease Surveillance Centre, 61 Colindale Ave., London NW9 5EQ, United Kingdom (pam.sonnenberg@lshtm.ac.uk).

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chemoprophylaxis. In a study in Uganda, the incidence of TB was not reported separately for those with incident HIV infection and those with prevalent HIV infection [4]. There was no HIV-negative control group in a European study that grouped heterogenous populations of injection drug users (IDUs), but the incidence of TB increased with time since HIV seroconversion, and the crude incidence during the first 3 years was higher than that in HIV-negative individuals in other studies [2].

The rates of TB in South African gold miners are among the highest in the world [6, 7]. This has been attributed to a number of factors, including high rates of TB in the region, silica dust exposure, crowding, and, more recently, HIV infection. Although the miners live in all-male hostels, they have contact with the local community, and a complex network of heterosexual relationships that extends to the surrounding communities, to nearby urban areas, and to rural areas has been described [8]. It was in this context that a dramatic increase in HIV prevalence occurred at the mines—from 1.3% in 1990 [9] to an estimated 20%–30% in 1996 [10].

The South African gold mines provide an opportunity to study the effect of HIV infection on the risk of TB. The mines have a stable population, good medical records, extensive infrastructure, and high-quality health-care services. Miners who are HIV positive work and live in the same environment as those who are HIV negative. This contrasts with many other settings, where such social factors as homelessness are risk factors for both HIV infection and TB.

We have conducted a retrospective cohort study of the association between HIV infection and first-episode pulmonary TB in a large cohort of gold miners in South Africa. We have already reported the effect of HIV infection on the risk of TB in both HIV-positive and -negative miners [11]. In the present study, we show that the risk of TB increases unexpectedly soon after infection with HIV.

SUBJECTS AND METHODS

The study was conducted at 4 gold mines in Gauteng Province, South Africa, with a total population of ~28,000 men. Data came from routine sources (personnel and medical records) and were linked by use of unique industry numbers. The study was approved by the ethics committee of the London School of Hygiene and Tropical Medicine and by the Gold Fields Health Services Research Committee, South Africa.

The miners, all black men 18–65 years old, are from rural areas of South Africa, Botswana, Lesotho, Mozambique, and Swaziland and live on site in all-male hostels. Medical services are provided free of charge at a 240-bed hospital and satellite clinics.

Since 1989, the hospital laboratory has kept a confidential database of all HIV test results. HIV tests have been performed, with consent, either as part of cross-sectional seroprevalence surveys conducted during the early 1990s on random samples of the workforce (10%) or in clinics or the hospital. These results are available only to the hospital medical staff who care for the miners, and not to the mining company management. Infection with HIV was diagnosed if the results of 3 tests were positive (either 3 ELISAs or 2 ELISAs and 1 Western blot). A single negative ELISA was considered to be an HIV-negative result. Results were considered to be indeterminate if tests were borderline ($n = 120$) or contradictory ($n = 130$) or if only a single positive ELISA was available ($n = 112$). Initially, a program was in place to counsel HIV-positive miners, and this was subsequently expanded to include pre- and posttest counseling for all those tested. No antiretroviral treatment or isoniazid prophylaxis was used during the study period.

The TB control program includes annual chest-radiograph screening and contact tracing, although most patients receive diagnoses after self-presentation to medical facilities at one of the mines. Investigations are conducted irrespective of HIV status. Men who are clinically suspected of having TB have at least 3 sputum smear examinations (by fluorescence microscopy). One specimen is cultured, by use of BACTEC, and is tested for drug resistance. All patients are treated with a short-course anti-TB regimen in a program of directly observed therapy (2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by 4 months of isoniazid and rifampicin).

The outcome of the present study was a first episode of pulmonary TB. Cases either were culture confirmed or were classified as "probable TB" by use of a previously validated algorithm [12] that scores the results of chest radiographs, sputum smear examinations, tuberculin tests, histological tests, and a therapeutic clinical trial.

All miners who had an HIV test performed between 1 January 1991 and 31 December 1997 were eligible for the study. Tests and miners with indeterminate or missing data were excluded as shown in figure 1. To avoid the bias that would result if the HIV test result was known only because the miner had TB, all HIV tests that were performed in conjunction with a diagnosis of TB (confirmed, probable or possible, or new or recurrent) were excluded. A cutoff of 2 weeks before and 2 weeks after diagnosis of TB was used. Miners with a known history of pulmonary TB were excluded as far as was possible, but this history was known only for those who had received diagnoses after 1990.

Analysis. All miners were enrolled into the cohort on the date of their first HIV test. Follow-up continued until 31 December 1997, unless they died or left the mine earlier, developed TB, or were censored for other reasons (see below). The cohort included those who were HIV negative throughout, those who were HIV positive on entry into the cohort (prevalent HIV in-

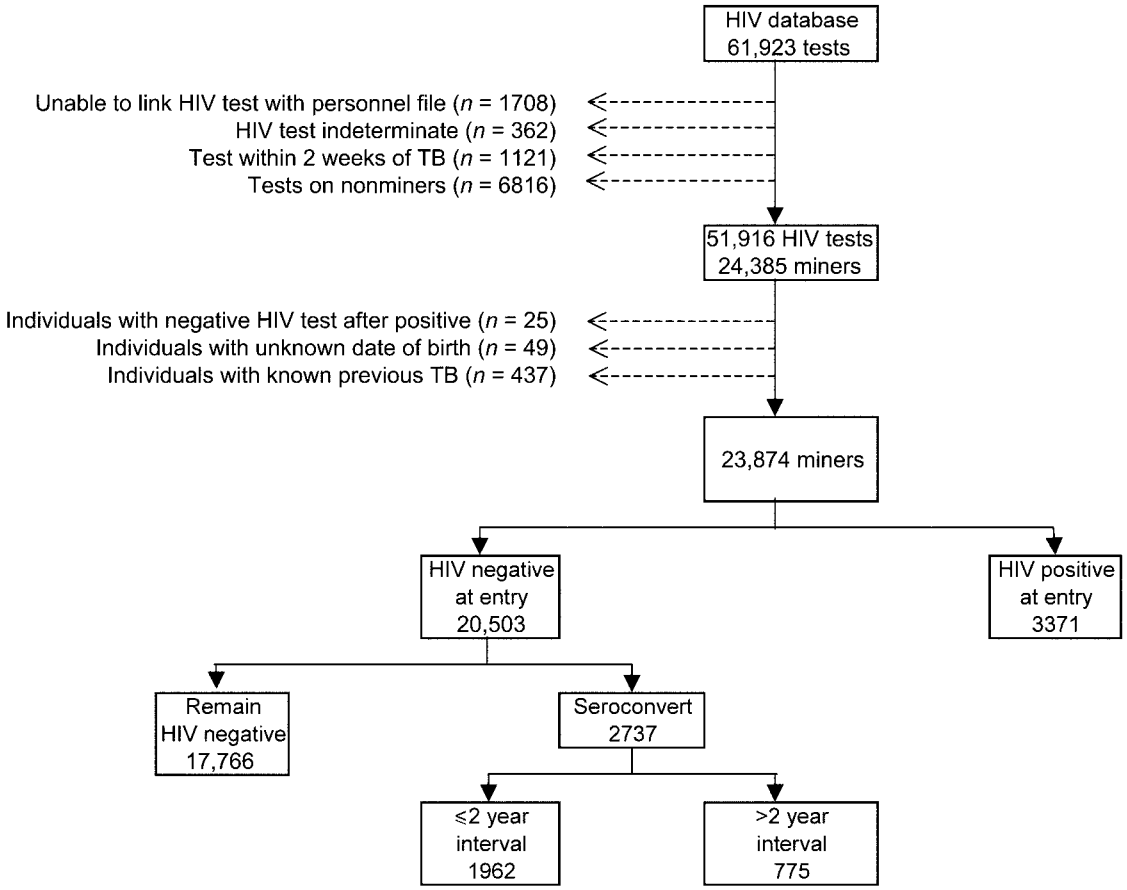

Figure 1. Study profile showing the no. of miners included in the study

fection), and those who seroconverted during the study period (incident HIV infection). Person-years at risk were calculated from the dates of censoring and of HIV tests. Age, calendar period, and HIV status were all treated as time-varying covariates.

In the HIV-negative group, miners were censored 1 year after their last negative test (or, for 14 miners, on the date of a single unconfirmed positive test), to minimize the chance of inadvertently including unknown seroconverters. For those who seroconverted, the "seroconversion interval" was defined as the period between the last negative and the first positive HIV test. When the interval was ≤2 years, the date of seroconversion was taken to be the midpoint between the 2 dates. Thus, these miners were included in the HIV-negative group until this time and were subsequently included in the incident-HIV-infection group. Those miners with a seroconversion interval of >2 years were considered to be HIV negative until 1 year after the last negative HIV test and were then excluded from the analysis until the first positive HIV test, at which time they were included in the prevalent-HIV-infection group. The value for person-years at risk for HIV-negative miners therefore includes the total follow-up period for those miners who remained HIV negative throughout follow-up and the estimated HIV-negative period for those miners who seroconverted during follow-up.

Rate ratios (RRs) were calculated by use of Poisson regression. The effects of potential confounding variables and effect modifiers (age and calendar year) on the RRs were assessed. Sensitivity analyses were performed to assess the following censoring and exclusion criteria used: (1) censoring HIV-negative miners at their last negative test rather than 1 year later (to avoid the inadvertent inclusion of unknown seroconverters in the HIV-negative group); (2) excluding all HIV tests done in the medical or TB wards or classified as "other sources" (to avoid biased ascertainment of rapid progressors); (3) excluding tests done within 1 month before or after the date of diagnosis of TB, rather than within 2 weeks (to minimize detection bias); and (4) restricting the analysis to seroconverters with a seroconversion interval of ≤1 year (to minimize the uncertainty of seroconversion dates). We also performed further analyses to determine whether there was an increased risk of TB during the seroconversion interval that was associated with acute seroconversion illness or that was due to concurrent transmission of HIV and TB.

RESULTS

The cohort consisted of 23,874 individuals who were followed for a total of 53,296 person-years. Of the miners in the cohort, 17,766 were HIV negative on entry, 3371 were HIV positive on entry, and 2737 were known to have seroconverted during follow-up, of whom 1962 (72%) had a seroconversion interval of ⩽2 years (figure 1). On entry to the cohort, 80% were <40 years old. The HIV-positive miners were younger than the miners who remained HIV negative during follow-up ($P < .0001$), and the miners who seroconverted during follow-up were younger than the miners who were HIV positive on entry ($P < .0001$). The median age at seroconversion was 31.1 years (interquartile range [IQR], 26.7–36.6 years). Seventy percent of the cohort was enrolled during 1991–1993. Most miners were tested as part of the seroprevalence surveys (26%), in sexually transmitted disease (STD) clinics (41%), or in the hospital (26%).

During follow-up, there were 747 new cases of pulmonary TB (701 culture confirmed) in the cohort. Seven of these cases and 1714 pyar occurred during the period of unknown HIV status in the miners with long seroconversion intervals; these were excluded. On 31 December 1997, 5398 miners were still in the cohort (4829 had died or left the mine earlier, 747 had developed pulmonary TB, and 12,900 HIV-negative miners were censored before the end of the study, according to the study design). The median follow-up was 1.1 years (range, 0–7 years). More than one-half of the HIV-negative miners had only a single test and were thus censored at 1 year.

The overall incidence of TB in the cohort was 1.43 cases/100 pyar (95% CI, 1.33–1.54 cases/100 pyar). The incidence of TB by HIV status, age, and calendar period is shown in table 1. HIV-positive miners were significantly more likely to develop TB than were HIV-negative miners. The incidence was significantly higher in the prevalent-HIV-infection group than in the incident-HIV-infection group (unadjusted RR, 1.27 [95% CI, 1.04–1.55]). There was a significant increase in the incidence of TB with increasing age ($P_{trend} < .0001$) and with calendar period ($P_{trend} < .0001$). Results adjusted for age and calendar period are shown in table 1. There were no significant interactions. The incidence of TB in miners who had their first HIV test as part of a seroprevalence survey was similar to that in miners who had their first HIV test at an STD clinic (RR adjusted for age and calendar period, 1.12 [95% CI, 0.91–1.38]).

In the incident-HIV-infection group, the median seroconversion interval was 266 days (8.7 months; IQR, 4.1–14.7 months). The incidence of TB during the seroconversion interval was 0.68 cases/100 pyar (95% CI, 0.38–1.23 cases/100 pyar) (based on 11 cases).

The incidence of TB by time since HIV seroconversion is shown in table 2 and figure 2. The incidence of TB doubled within the first year and increased 4-fold after 2 years. The later increase was less marked after adjustment for calendar period, but the early increase remained.

The results of the sensitivity analyses are shown in table 3. The same patterns were seen in all analyses. There were no significant differences in the adjusted RRs for TB in HIV-positive versus HIV-negative miners between the main analysis and the sensitivity analyses, and the increase in the incidence of TB with both age and calendar period remained. In all analyses, there was a significant increase in the risk of TB in the first year after HIV seroconversion, compared with that in HIV-

Table 1. Incidence of tuberculosis (TB), by HIV status, age, and calendar period.

Category	Pyar	No. of TB cases	Incidence, cases/100 pyar (95% CI)	Rate ratio (95% CI)	
				Unadjusted	Adjusted[a]
HIV status					
HIV-negative miners	36,020	289	0.80 (0.71–0.90)	1	1
HIV-positive miners	15,561	451	2.90 (2.64–3.18)	3.61 (3.12–4.19)	2.90 (2.48–3.38)
Prevalent infection	9981	313	3.14 (2.81–3.50)	3.91 (3.33–4.59)	3.05 (2.58–3.61)
Incident infection	5581	138	2.47 (2.09–2.92)	3.08 (2.51–3.77)	2.60 (2.11–3.20)
Age					
<30 years	15,483	103	0.67 (0.55–0.81)	1	1
30–39 years	24,645	387	1.57 (1.42–1.73)	2.36 (1.90–2.93)	2.04 (1.64–2.54)
40–49 years	8670	176	2.03 (1.75–2.35)	3.05 (2.39–3.89)	2.58 (2.02–3.30)
⩾50 years	2783	74	2.66 (2.12–3.34)	4.00 (2.97–5.39)	3.93 (2.91–5.30)
Calendar period					
1991–1992	8919	54	0.61 (0.46–0.79)	1	1
1993–1994	20,521	179	0.87 (0.75–1.01)	1.44 (1.06–1.95)	1.19 (0.88–1.61)
1995–1997	22,141	507	2.29 (2.10–2.50)	3.78 (2.86–5.01)	2.21 (1.65–2.95)

NOTE. Miners with prevalent HIV infection are those who were HIV positive on entry to the study; miners with incident HIV infection are those who seroconverted during follow-up. CI, confidence interval; pyar, person-years at risk.

[a] Adjusted for the other variables in the table.

Table 2. Incidence of tuberculosis (TB), by time since HIV seroconversion.

Category	Pyar	No. of TB cases	Incidence, cases/100 pyar (95% CI)	Rate Ratio (95% CI)			
				Unadjusted		Adjusted[a]	
				Value	P_{trend}	Value	P_{trend}
HIV-negative miners	36,020	289	0.80 (0.71–0.90)	1		1	
HIV-positive miners, time since HIV seroconversion[b]					.001		.09
<1 year	1849	30	1.62 (1.13 –2.32)	2.02 (1.39–2.94)		2.11 (1.45–3.09)	
1–1.9 years	1449	29	2.00 (1.39–2.88)	2.50 (1.70–3.66)		2.25 (1.53–3.31)	
2–2.9 years	1024	37	3.61 (2.62–4.99)	4.50 (3.20–6.34)		3.47 (2.44–4.93)	
3–3.9 years	692	24	3.47 (2.32–5.17)	4.32 (2.85–6.55)		2.94 (1.92–4.51)	
4–7 years	567	18	3.17 (2.00–5.04)	3.96 (2.46–6.37)		2.55 (1.57–4.16)	

NOTE. CI, confidence interval; P_{trend}, P for trend of time since HIV seroconversion, calculated within the HIV-positive group; pyar, person-years at risk.

[a] Adjusted for age and calendar period.

[b] Only the 1962 HIV-positive miners with a seroconversion interval of ≤2 years are included.

negative miners; in all analyses, this increased risk was sustained during the following years. In most analyses, there was an increase in the RR with time since HIV seroconversion.

DISCUSSION

In the present large cohort study, we have shown that the risk of TB doubles within a year of infection with HIV. This early increase in risk was sustained and increased slightly during the following years. Our study estimated the risk only during the early years after infection with HIV; the risk is likely to continue to increase during later years, as CD4 cell counts decrease further [13, 14].

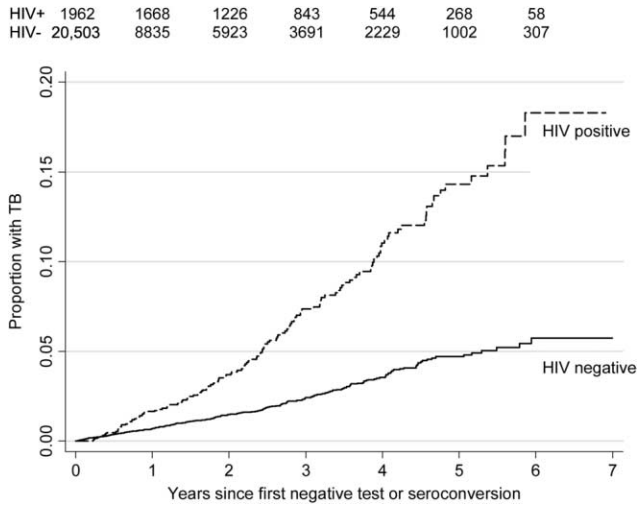

Figure 2. Nelson-Aalen cumulative hazard estimate of tuberculosis (TB) incidence, by HIV status. HIV-negative miners are included beginning with the first test. Miners with incident HIV infection are included beginning with the estimated date of HIV seroconversion. The data above the graph show the no. of miners being followed at the beginning of each year. At the end of 1 year, the no. of HIV-negative miners being followed decreases from 16,841 to 8835 because of censoring.

Models of the effect of HIV infection on the risk of TB have usually assumed that there is no increase in risk during the first few years after infection [15–19]. The early increase we found was therefore unexpected; however, no previous study would have had the power to examine it. In Kinshasa, the point estimate was similar to ours, but the CIs were very wide (RR, 2.2 [95% CI, 0.55–9.1]; for up to 2 years of follow-up) [3]. A recent study of European IDUs found an increased risk of TB during years 4–6, compared with that during years 1–3, after infection with HIV (RR, 2.8 [95% CI, 1.3–6.3]); however, the study did not have the power to examine any variation in risk within the first 3 years (9 TB cases) and had no HIV-negative control group [2].

There are other measures of HIV-associated TB that support the notion that the increased risk of TB occurs soon after infection with HIV. In Thailand, an increase in HIV-associated TB was noted very early during the epidemic, and TB was seen in young adults who were unlikely to have been infected for many years [20]. Large studies of HIV seroconverters show detectable increases in AIDS and death within 2 years of seroconversion [21], suggesting that there is an alteration in immune function soon after infection with HIV.

It has been noted that TB, and especially pulmonary TB, occurs relatively early in the HIV-related spectrum of diseases and often before other AIDS-defining conditions [22, 23]. Our findings may support the suggestion that pulmonary TB should not be considered an AIDS-defining condition [24], but the early pulmonary TB cases could have occurred in rapid progressors.

The results of the present study were not an artifact of the study design. They were not due to biased inclusion of patients with TB, since HIV tests performed because of TB were excluded. Our sensitivity analyses—changing the censoring criteria, excluding all tests from the medical and TB wards and from other sources, extending the period of exclusion around a TB diagnosis, and restricting the analysis to miners with a

Table 3. Comparison of results from the main analysis and sensitivity analyses.

Category	Main analysis	Sensitivity analyses			
		HIV-negative miners censored at their last negative test	HIV tests from medical/TB/ other sources excluded	HIV tests within 1 month of TB excluded	Only seroconverters with interval of ⩽1 year analyzed
Total miners, no.	23,874	14,344	20,273	23,863	23,874
HIV-negative miners, no.	17,766	8227	15,586	17,763	17,766
RR analysis					
HIV-negative miners with TB, no. of cases	289	195	150	279	289
HIV-positive miners (incident and prevalent combined) with TB, no. of cases	451	451	321	445	449
TB incidence in HIV-negative miners, cases/100 pyar	0.80	1.01	0.52	0.77	0.80
TB incidence in HIV-positive miners, cases/100 pyar	2.90	2.90	2.56	2.61	2.98
Unadjusted RR	3.61 (3.12–4.19)	2.88 (2.43–3.40)	4.88 (4.02–5.92)	3.69 (3.18–4.29)	3.73 (3.22–4.32)
Adjusted RR[a]	2.90 (2.48–3.38)	2.18 (1.82–2.60)	3.90 (3.18–4.79)	2.96 (2.53–3.47)	2.98 (2.55–3.49)
RR analysis in miners who HIV seroconverted					
HIV-positive miners (incident infection) with TB, no. of cases	138	138	95	136	82
Adjusted RR[a] (95% CI) in HIV-positive miners, by time since HIV seroconversion					
<1 year	2.11 (1.45–3.09)	1.61 (1.09–2.37)	2.44 (1.47–4.03)	2.05 (1.39–3.03)	2.68 (1.76–4.07)
1–2 years	2.25 (1.53–3.31)	1.69 (1.13–2.51)	2.77 (1.67–4.60)	2.34 (1.59–3.45)	2.19 (1.34–3.58)
2–3 years	3.47 (2.44–4.93)	2.58 (1.79–3.71)	5.26 (3.41–8.12)	3.63 (2.55–5.17)	2.34 (1.38–3.96)
3–4 years	2.94 (1.92–4.51)	2.17 (1.40–3.37)	5.10 (3.08–8.43)	3.08 (2.01–4.74)	2.95 (1.74–5.00)
4–7 years	2.55 (1.57–4.16)	1.88 (1.14–3.10)	4.82 (2.80–8.28)	2.68 (1.65–4.37)	2.35 (1.27–4.32)
P_{trend}	.09	.09	.01	.07	.52

NOTE. CI, confidence interval; P_{trend}, P for trend of time since HIV seroconversion, calculated within the HIV-positive group; pyar, person-years at risk; RR, risk ratio; TB, tuberculosis.

[a] Adjusted for age and calendar period.

seroconversion interval of ≤1 year—validate the results. The losses in numbers of miners followed (figure 2) were mainly due to the censoring criteria.

An early increase in the risk of TB after infection with HIV could be explained by an excess risk associated with seroconversion illness [25] or by concurrent acquisition of HIV and TB. We found no increased risk of TB during the seroconversion interval, and concurrent acquisition is unlikely, given that the prevalence of TB is much higher inside the mine than outside the mine and that HIV infection is acquired outside the mine.

In this setting, with an extremely high risk of TB even for HIV-negative miners (incidence, 0.8 cases/100 pyar), there is a high level of suspicion of TB among health-care workers. We do not believe that TB is more likely to be diagnosed in HIV-positive than in HIV-negative miners; detection bias is therefore an unlikely explanation for our results. Indeed, HIV-positive individuals may have atypical clinical presentations that result in underascertainment of TB, suggesting that our results may underestimate the increased risk.

The association between HIV infection and TB is complex. After infection with *M. tuberculosis,* TB may arise within 5 years as primary disease, or it may arise later by reactivation or reinfection [26]. The rates of development of primary and post-primary disease depend on time since HIV seroconversion and on age [27]. The rate of decrease due to reinfection will also depend on the risk of infection. HIV infection probably increases the risks of primary disease, reactivation disease, and disease after reinfection, but possibly not all to the same extent [28]. It may also increase the risk of TB infection, given exposure, but this is unknown. In some contexts, HIV-positive individuals are also at increased risk of exposure to TB. These variations make the results of different studies difficult to compare directly, since different proportions of the population will be at risk for the different mechanisms of TB. RRs for the association between HIV infection and TB in cohort studies have varied between 3.7 and 26 [3, 29–37]. This variation also reflects differences in time since HIV seroconversion, in age groups, and in types of TB included.

Molecular typing has been used to investigate the proportion of TB due to either reactivation or recent transmission. This information is not available for most cases in this study, but we do have data from a study that included all TB cases in these mines in 1995 [38]. Restriction fragment–length polymorphism (RFLP) data were available from 29 miners with incident HIV infection, 70 miners with prevalent HIV infection, and 134 HIV-negative miners from the present cohort. Of the HIV-negative miners, 70% shared RFLP patterns with at least 1 other miner (suggesting recent or ongoing transmission), and 30% had unique isolates (suggesting reactivation). Of the miners who developed TB within the first 2 years of infection with HIV, 57% (8/14) had unique isolates, compared with 20% (3/15) of miners who developed TB later ($P = .04$). Unique isolates were found in 34% of miners with prevalent HIV infection. Although the numbers are small and the time window is short, this suggests that, soon after infection with HIV, the increased risk of TB may be mainly due to reactivation of latent TB, and that, later after infection with HIV, TB due to recent transmission plays a larger role.

Our finding of an overall RR for TB (comparing HIV-positive with HIV-negative miners) of 2.9 (95% CI, 2.5–3.4) is lower than that reported in previous cohort studies and probably reflects the large number of incident HIV infections included. A study at other South African mines during the same period also found low RRs, especially during the early years of HIV infection in this population [31]. It is possible that some TB in HIV-positive miners is missed due to miners with advanced HIV infection leaving the mines, but many miners choose to remain for the access to health-care facilities. The rate of TB in HIV-positive miners (incidence, 2.9 cases/100 pyar [95% CI, 2.6–3.2 cases/100 pyar]) is similar to that reported in many previous studies [3, 29, 30, 33, 34, 36, 37] but is lower than that reported in the placebo arm of preventive-therapy trials for tuberculin-positive participants (range, 3.4–20.9 cases/100 pyar) [39].

The gold mines are unusual in that all miners are adult males who already have high rates of TB because of silica dust exposure and crowded living and working conditions. In the present study, we did not have data on duration of employment in the mining industry or radiographic evidence of silicosis. If the duration of silica dust exposure were shorter among miners infected with HIV, this would bias the RR downward. In an analysis of 296 miners with new TB in 1995 [7], HIV-positive miners had a duration of employment in the mining industry similar to that of HIV-negative miners (mean, 15.4 years vs. 16.6 years; $P = .2$). There was a strong correlation between age and duration of employment in the mining industry ($r = 0.84$), and we did control for age. In another study, which included data on employment history and silicosis and which adjusted for them, the crude and adjusted RRs for the effect of HIV infection on the risk of TB were very similar, even though silicosis is a strong risk factor for TB [31]. Silica dust increases the risk of TB via damage to the phagosomal membranes of macrophages [40]. The mechanism of increased risk of TB in individuals with silicosis is therefore likely due to altered local immunity rather than to cell-mediated immunity. Overall, although the absolute rates of TB are high in the miners, the relative rates, and the changes in the relative rates by time since HIV seroconversion, should be more generalizable.

As the time since HIV seroconversion increases and severe immunosuppression occurs, the risk of TB is likely to increase further. The ultimate height of the RR is unknown but could be very high [41]. It is possible that all individuals infected

with *M. tuberculosis* who become severely immunosuppressed will develop TB and that the high rates of TB found at autopsy of patients with AIDS in Africa [42, 43] are simply a measure of *M. tuberculosis* infection rates.

Interventions are needed now to curb this increase. Such interventions should target the causes of high TB rates (silicosis, living conditions, and high risk of HIV infection) as well as TB directly. Antiretroviral drugs have been shown to reduce TB incidence [14, 44, 45] and have been advocated for use in the control of TB [17, 46], but it is unlikely they would have prevented the early cases [14]. At the mines, innovative interventions, such as mass chemoprophylaxis with isoniazid, may be appropriate, because even HIV-negative miners are at high risk for TB.

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