Human Immunodeficiency Virus and the Prevalence of Undiagnosed Tuberculosis in African Gold Miners

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We hypothesized that rapid presentation may be a general feature of tuberculosis (TB) associated with human immunodeficiency virus (HIV) that limits the impact of HIV on the point prevalence of TB. To investigate this, we performed a cross-sectional HIV and TB disease survey with retrospective and prospective follow-up. HIV prevalence among 1,773 systematically recruited miners was 27%. TB incidence was much more strongly HIV associated (incidence rate ratio, 5.5; 95% confidence interval [CI], 3.5–8.6) than the point prevalence of undiagnosed TB disease (odds ratio, 1.7; 95% CI, 0.9–3.3). For smear-positive TB, 7 of 9 (78%) prevalent cases were HIV negative, and point prevalence was nonsignificantly lower in miners who were HIV positive (odds ratio, 0.8; 95% CI, 0.1–4.2). The calculated mean duration of smear positivity before diagnosis (point prevalence/incidence) was substantially shorter for HIV-positive than HIV-negative TB patients (0.17 and 1.15 years, respectively; ratio, 0.15; 95% CI, 0.00–0.73). HIV has considerably less impact on the point prevalence of TB disease than on TB incidence, probably because rapid disease progression increases presentation and case-finding rates. The difference in mean duration of smear positivity was particularly marked and, if generalizable, will have major implications for TB control prospects in high HIV prevalence areas.

Keywords: Africa; epidemiology; human immunodeficiency virus; prevalence; tuberculosis

The mean duration of infectiousness is one of the key determinants of the dynamics of infectious disease epidemics: shortening this period will tend to reduce the number of secondary infections generated per infectious case, hence reducing the basic reproductive number, R_o, for that disease in that population (1). One of the characteristic features of tuberculosis (TB) is a long period of infectiousness (2) so that even today the mean duration of smear positivity is estimated in years, rather than months, in many resource-poor settings (2). The consequences include a high point prevalence of undiagnosed TB disease relative to incidence rates and ongoing high rates of TB transmission (2–6).

The rapid pace with which TB disease progresses in the immunosuppressed is well described (7–10). In our study site of South African gold miners, TB incidence increased greatly during the 1990s because of the human immunodeficiency virus (HIV) epidemic (11), but with relatively little change in the point prevalence of radiologically active TB detected at routine annual fitness examination (Figure 1). A mining hospital and several primary clinics provided free diagnostic investigations and healthcare for the study workforce (12). TB is an occupational disease of gold miners and is compensatable in South Africa. Because of this, awareness of TB among mining healthcare workers was likely to have been high even before the HIV epidemic. The changing relationship between incident and prevalent TB disease was apparent from the start of the HIV epidemic in the early 1990s and could not be readily attributed to changes in TB control policy or diagnostic practices or to more intensive follow-up of known miners who were HIV-positive (11). From this observation, we formed the hypothesis that a previously overlooked, but important, aspect of the natural history of HIV-associated TB may be that the mean durations of disease activity and infectiousness before diagnosis are greatly reduced compared with TB in persons who are HIV-negative.

The mean duration of infectiousness can be estimated for any given population by dividing the point prevalence of infectious TB disease by the annual incidence rate (2). To estimate HIV-specific duration of TB infectiousness in persons with no previous TB diagnosis, we combined a cross-sectional survey for HIV and TB disease with a longitudinal cohort study of the same participants, all of whom were mine workers recruited from their routine annual fitness-to-work examination. Some of the results of these studies have been previously reported in the form of abstracts (12, 13).

METHODS

Alternate miners attending annual fitness examinations between July 2000 and January 2001 were screened for prevalent TB with a symptoms questionnaire and two sputum specimens for microscopy and culture, in addition to their routine annual chest radiograph (14). Urine specimens were taken for confidential HIV testing. Laboratory methods were as previously described (14, 15). Participants with symptoms or abnormal screening results were recalled for clinical examination, repeat radiography, and sputum specimens. Smear-negative TB suspects with no response to broad-spectrum antibiotics were started on TB treatment and followed after 2 months.

Participants were followed retrospectively for 12 months before their date of enrollment and prospectively to December 2001 using a database to identify incident TB cases (11). Participants treated for TB before the start of retrospective follow-up were excluded from further analysis (Figure 2). Loss to employment was identified from payroll records. A single hospital provided free treatment. A diagnostic algorithm for TB based on microscopy, culture, radiography, and response to antibiotics was in routine use and did not depend on known HIV status (11). Miners leaving employment were screened for TB, and death from undiagnosed TB was known to be rare (16).

Case Definitions for TB Disease

The primary analysis was based on confirmed TB disease meeting definite or probable case definitions outlined later here. Because of possible

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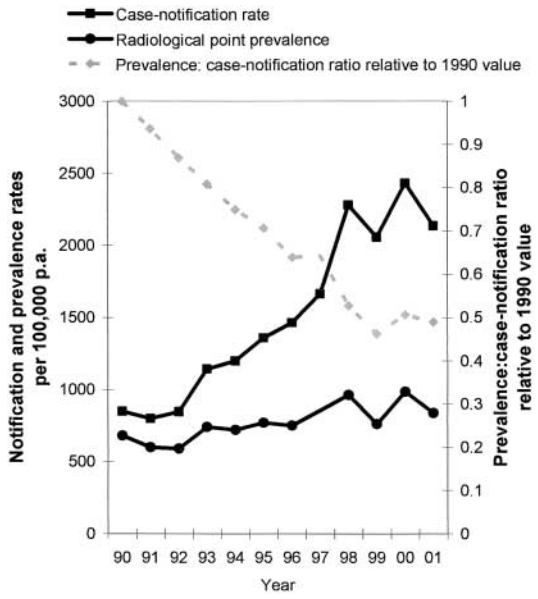

Figure 1. Time trends in observed new tuberculosis (TB) case-notification rates and the point prevalence of new radiologic TB at annual screening, also showing the progressive reduction in the ratio of these two indicators since 1990. Serial case notification and radiologic point prevalence rates for new TB disease are shown for the study workforce (Churchyard and colleagues [11] and Dr. G. Churchyard, unpublished data). Recurrent episodes of TB are not included. The *gray dotted line* refers to the values shown on the right *y* axis and illustrates the progressive decline in the ratio of these two indicators of TB control that has occurred during the 1990s. Minor modifications were made to the TB control program in 1995 to comply fully with the South Africa National TB Control Program, but the program had complied with most aspects of the directly observed therapy, short course (DOTS) strategy since the late 1980s (11). p.a. = per annum.

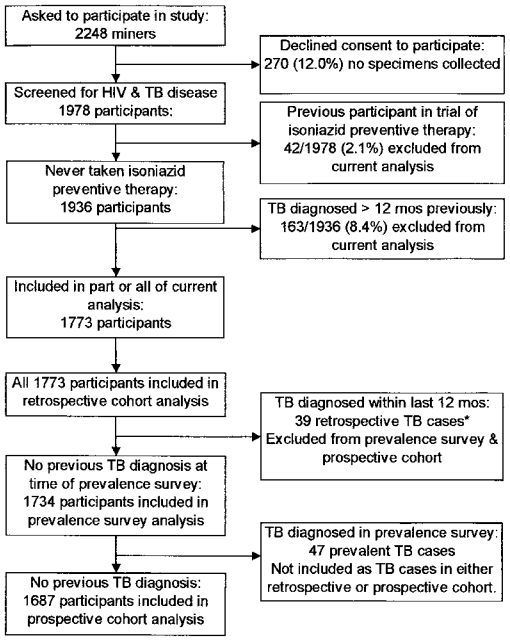

Figure 2. Study recruitment and exclusion criteria for each stage of the analysis. *Of the retrospective cases, 7 (58%) of 12 HIV-negative patients and 9 (33%) of 27 HIV-positive patients were diagnosed at the previous annual fitness screen, with the remainder self-presenting.

false-positive results, definitions of prevalent TB did not rely on screening tests alone.

Prevalent TB disease—(*1*) definite: culture positive (five or more colonies of *Mycobacterium tuberculosis*) from both screening and follow-up specimens or smear and culture positive at follow-up; (*2*) probable: radiologic features of TB with no response to broad-spectrum antibiotics plus response to TB treatment; and (*3*) possible: treated for TB but did not meet the previously mentioned definitions.

Incident TB disease—(*1*) definite: five or more colonies of *M. tuberculosis* from one or more specimens or two or more positive sputum smears or one positive smear from a normally sterile site; (*2*) probable: single smear positive without culture confirmation or radiologic features of TB with no response to broad-spectrum antibiotics plus response to TB treatment; and (*3*) possible: treated for TB but did not meet the previously mentioned definitions.

Ethical Approval

Approval was given by the ethics committees of the London School of Hygiene and Tropical Medicine, Ernest Oppenheimer Hospital, Anglogold Health Services Medical Research Ethics Committee, and the University of Witwatersrand, South Africa.

Data Analysis

STATA 7.0 software (STATA Corporation, College Station, TX) was used. Follow-up was terminated at the earliest of December 2001, first TB diagnosis, death, loss to employment (Figure 2). Poisson and logistic regression were used for univariate and multivariate analysis of cohort and cross-sectional data, respectively. Tests for trend were calculated using likelihood ratio tests. Mean disease duration before diagnosis was estimated from point prevalence of undiagnosed TB divided by annual incidence rates. Effects of covariates on duration of disease before diagnosis for categoric variables were estimated as ratios of disease duration (disease duration ratios). Bootstrap estimates of 95% confidence limits were made for disease duration and disease duration ratios.

RESULTS

The baseline characteristics of 1,773 study participants are summarized in Table 1, with participation rates and exclusions at each stage of the study as summarized in Figure 2.

Point Prevalence of Previously Undiagnosed TB Disease

The point prevalence of previously undiagnosed TB disease (Table 2) among 453 participants who were HIV-positive was 3.8% (95% confidence interval [CI], 2.2–5.9%) for all diagnosed cases, all of whom met case definitions for definite or probable TB disease. One patient had symptomatic TB lymphadenitis, with the remaining 16 patients having pulmonary or combined pulmonary and extrapulmonary TB. Two participants who were HIV-positive had positive screening smears, giving a point prevalence of smear-positive TB disease of 0.44% (95% CI, 0.02–1.1%).

Among participants who were HIV-negative, the point prevalence rates of all diagnosed and all confirmed TB disease were 2.3% (95% CI, 1.6–3.3%) and 2.2% (95% CI, 1.4–3.3%) respectively. There were seven participants who were HIV-negative with positive screening smears, giving a point prevalence of smear-positive TB disease of 0.55% (95% CI, 0.14–0.95%). These prevalence rates were not significantly different from those found in miners who were HIV-positive, as shown in Table 2, which also gives odds ratios and a breakdown of the point prevalence of confirmed TB by age and silicosis for both miners who were HIV-positive and those who were HIV-negative.

Overall, the univariate odds ratios for HIV were 1.7 (95% CI, 0.89–3.3) for confirmed TB cases and 0.81 (95% CI, 0.082–4.2) for smear-positive disease, although the latter estimate was based

TABLE 1. BASELINE CHARACTERISTICS OF STUDY PARTICIPANTS, ACCORDING TO HUMAN-IMMUNODEFICIENCY-VIRUS STATUS

	HIV+ve	HIV−ve	p Value
Total number	480	1,293	
Age group, No. (%)			0.001
18–29 yr	50 (10%)	91 (7%)	
30–39 yr	215 (45%)	488 (38%)	
40–49 yr	167 (35%)	567 (44%)	
⩾ 50 yr	48 (10%)	147 (11%)	
Employment as a miner, No. (%)			0.001
< 10 yr	118 (25%)	214 (17%)	
10–19 yr	181 (38%)	474 (37%)	
20–24 yr	82 (17%)	302 (23%)	
⩾ 25 yr	99 (21%)	303 (23%)	
Silicosis grade, No. (%)*			0.34
None (ILO 0/0)	356 (76%)	953 (75%)	
Possible (ILO 0/1)	64 (14%)	184 (15%)	
Probable (ILO 1/0)	24 (5%)	43 (3%)	
Early (ILO 1/1)	17 (4%)	64 (5%)	
Advanced (ILO 2/2 and higher)	10 (2%)	23 (2%)	
No radiograph available	9 (2%)	26 (2%)	
TB in preceding year, No. (%)†			< 0.001
Yes	27 (5.6%)	12 (0.9%)	

Definition of abbreviations: HIV+ve = HIV-positive; HIV−ve = HIV-negative; TB = tuberculosis.

* Scored from the previous annual chest radiograph. Grades correspond to ILO grades as detailed in the METHODS section. Films were missing for 9 (1.9%) HIV+ve and 26 (2.0%) HIV−ve participants respectively, none of whom had TB during this study.

† These participants were not included in the cross-sectional prevalence analysis.

on only two and seven HIV-positive and HIV-negative cases, respectively. There was an increase in the point prevalence of confirmed TB with age in both miners who were HIV-positive and those who were HIV-negative, with a statistically significant trend in participants who were HIV-positive (test for trend p = 0.006). Silicosis (ILO 1/0 or higher), however, was not a significant risk factor for prevalent TB in participants who were either HIV-positive (odds ratio, 1.2; 95% CI, 0.13–5.5) or HIV-negative (odds ratio, 0.68; 95% CI, 0.08–2.8).

There was potential for negative confounding between age and HIV status because increasing age was significantly associated with both a higher point prevalence of TB and a lower HIV prevalence (*see* Tables 1 and 2). Adjusting for differences between patients who were HIV-positive and HIV-negative in age and silicosis gave multivariate-adjusted odds ratios for HIV in confirmed and smear-positive TB disease, respectively, of 1.8 (1.00–3.5) and 0.9 (95% CI, 0.18–4.2).

TB Disease Incidence

There were 41 and 23 confirmed incident TB cases among the same cohort of HIV-positive and HIV-negative participants, respectively (Table 3), with the site being pulmonary in 37 (90%) and 19 (83%) of the patients who were HIV-positive and HIV-negative and at various extrapulmonary sites in the remainder. There was also one additional smear-positive HIV-negative participant who grew *Mycobacterium kansasii* on culture. He was considered to have mining-associated pulmonary *M. kansasii* disease, not TB, and thus is not included as a case in this analysis. TB incidence rates and univariate incidence rate ratios are shown according to HIV status in Table 3. Incidence rates were similar during both retrospective and prospective periods of follow-up (incidence rate ratios 1.1 for prospective compared with retrospective periods), and thus, data were combined and analyzed together.

For confirmed TB disease, HIV infection (univariate incidence rate ratios, 5.1; 95% CI, 3.0–9.0), silicosis, and age were each strongly and significantly associated with incident TB disease, as previously found in this workforce (14). TB incidence rates increased markedly and significantly with increasing age and with silicosis in both participants who were HIV-positive and those

TABLE 2. POINT PREVALENCE OF PREVIOUSLY UNDIAGNOSED TUBERCULOSIS DISEASE AMONG MINERS WHO WERE HUMAN IMMUNODEFICIENCY VIRUS–NEGATIVE AND THOSE WHO WERE HUMAN IMMUNODEFICIENCY VIRUS–POSITIVE

	HIV+		HIV−			
	No.	Point Prevalence (%)	No.	Point Prevalence (%)	Odds Ratio (HIV)	95% CI
Smear +ve TB*†	2/453	0.44%	7/1,281	0.55%	0.8	0.082–4.2
Culture +ve TB†	15/453	3.3%	21/1,281	1.6%	2.1	0.98–4.2
Confirmed TB†	17/453	3.8%	28/1,281	2.2%	1.7	0.89–3.3
All diagnosed TB†	17/453	3.8%	30/1,281	2.3%	1.6	0.83–3.1
Confirmed TB						
Age group‡		p_T = 0.006		p_T = 0.18		
< 30 yr	0/48	0%	0/91	0%		
30–39 yr	5/208	2.4%	11/486	2.3%		
40–49 yr	8/156	5.1%	12/562	2.1%		
⩾ 50 yr	4/41	9.8%	5/142	3.5%		
Silicosis§		p = 0.68		p = 1.00		
No	15/400	3.8%	26/1,129	2.3%		
Yes	2/44	4.6%	2/126	1.6%		

Definition of abbreviations: CI = confidence interval; HIV = human immunodeficiency virus; P_T = p value for test for trend; TB = tuberculosis; +ve = positive.

* All smear-positive cases were also culture positive for *M. tuberculosis*.

† All diagnosed TB includes all cases where TB treatment was started; confirmed TB includes all cases meeting definite or probable TB case definitions (*see* METHODS). Smear-positive TB and culture-positive TB refer only to results from the specimens taken at the time of prevalence screening and do not include positive follow-up specimens (*see* RESULTS).

‡ Age was a significant risk factor for prevalent TB in participants who were HIV-positive (test for trend p = 0.006), but the trend toward higher prevalence with older age was not significant for participants who were HIV-negative (test for trend, p = 0.18).

§ Silicosis (ILO 1/0 or higher) was not a significant risk factor for prevalent TB in either participants who were HIV-positive (p = 0.68) or participants who were HIV-negative (p = 1.00).

TABLE 3. INCIDENCE RATES OF TB DISEASE AMONG MINERS WHO WERE HUMAN IMMUNODEFICIENCY VIRUS–POSITIVE AND MINERS WHO WERE HUMAN IMMUNODEFICIENCY VIRUS–NEGATIVE

	HIV+		HIV−			
	No./PYFU	Incidence per 100 PYFU	No./PYFU	Incidence per 100 PYFU	Rate Ratio (HIV)	95% CI
Smear +ve TB*†	23/872	2.6	12/2,516	0.48	5.5	2.6–12.2
Culture +ve TB	23/872	2.6	15/2,516	0.60	4.4	2.2–9.1
Confirmed TB†	41/872	4.7	23/2,516	0.91	5.1	3.0–9.0
All diagnosed TB cases†	52/872	6.0	29/2,516	1.15	5.2	3.2–8.5
Confirmed TB						
Age group‡		$p_T = 0.003$		$p_T = 0.008$		
< 30 yr	2/95	2.1	1/183	0.55		
30–39 yr	13/401	3.2	3/955	0.31		
40–49 yr	17/298	5.7	14/1,111	1.26		
⩾ 50 yr	9/78	11.6	5/267	1.87		
Silicosis§		$p < 0.001$		$p = 0.017$		
No	28/764	3.7	16/2,218	0.72		
Yes	13/90	14.4	7/250	2.8		

Definition of abbreviations: CI = confidence interval; HIV = human immunodeficiency virus; p_T = p value for test for trend; PYFU = person-years follow-up; TB = tuberculosis; +ve = positive.

* Excludes one participant who was smear-positive and HIV-negative with probable *M. kansasii* disease. Seventeen of the HIV-positive and 8 of the HIV-negative smear-positive patients were culture positive for *M. tuberculosis*. In the remaining cases, cultures were either contaminated or negative or had not been requested.

† All diagnosed TB includes all cases in which TB treatment was started; confirmed TB includes all cases meeting definite or probable TB case definitions (*see* METHODS).

‡ Age was a significant risk factor for incident TB in both patients who were HIV-positive (test for trend p = 0.003) and those who were HIV-negative (test for trend, p = 0.008).

§ Silicosis was a significant risk factor for incident TB in both patients who were HIV-positive (p < 0.001) and those who were HIV-negative (p = 0.017).

who were HIV-negative (Table 3). Excluding participants with silicosis had only minor and nonsignificant effects on the association with HIV (incidence rate ratios for HIV, 5.1; 95% CI, 2.7–10.1). Adjusting for differences in age and silicosis prevalence between participants who were HIV-positive and HIV-negative gave multivariate-adjusted incidence rate ratios for HIV in confirmed and smear-positive TB disease of 5.5 (95% CI, 3.5–8.6) and 5.9 (95% CI, 2.9–11.9), respectively.

Duration of Active TB Disease before Diagnosis

The duration of confirmed TB disease, as estimated by dividing point prevalence by incidence, was significantly shorter for participants who were HIV-positive (0.80 years; 95% CI, 0.42–1.35) than for participants who were HIV-negative (2.39 years; 95% CI, 1.37–4.21). The difference for smear-positive disease was even more pronounced with the mean duration of smear positivity being 0.17 years (95% CI, 0.00–0.48) for miners who were HIV-positive and 1.15 years (95% CI, 0.33–2.94), respectively, as shown in Figure 3.

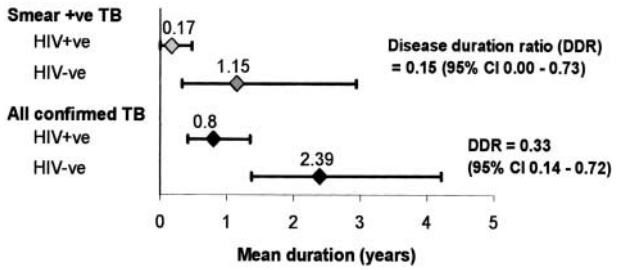

Figure 3. Mean TB disease duration before diagnosis by human immunodeficiency virus (HIV) and smear status. The *diamonds* indicate the duration before diagnosis, in years, of smear positivity (*gray*) and overall TB disease activity (*black*) in miners who were HIV-positive and HIV-negative; 95% confidence intervals are represented by the *horizontal lines*. The difference between patients who are HIV-positive and HIV-negative in estimated disease duration was significant for both smear-positive and all confirmed TB disease, as indicated by disease duration ratios (DDRs) that are significantly less than one for both comparisons.

The ratio of duration of TB disease before diagnosis (hereafter referred to as the disease duration ratio) by HIV status was 0.33 (95% CI, 0.14–0.72) for all confirmed TB disease and 0.15 (95% CI, 0.00–0.73) for smear-positive TB disease (Figure 3).

For silicosis, the disease duration ratio was 0.22 (95% CI, 0.04–0.62) for all confirmed TB disease, indicating that TB disease also progresses significantly more rapidly in silicotics compared with nonsilicotics. In contrast, older age was a significant risk factor for both incident and prevalent TB disease and had less effect on disease duration, with disease duration ratios relative to 18- to 39-year-olds being 0.76 (95% CI, 0.31–1.86) for ages 40 to 49 years and 0.74 (95% CI, 0.22–2.22) for age 50 years or older.

Potential Effects of HIV Clinic Follow-up

Neither HIV-positive nor silicotic miners had any special clinical monitoring or follow-up at this site until an HIV care clinic was started in 2000. This clinic provided cotrimoxazole prophylaxis and primary isoniazid preventive therapy after screening for active TB disease. Antiretroviral therapy did not become available until after the completion of this study. Only 4 (1%) of our 453 participants who were HIV-positive were being followed by the HIV care clinic at the time of their prevalence screen. A further 39 (9%) of our participants who were HIV-positive first attended the clinic while under prospective follow-up by this study. In total, 3 of the 41 (7%) confirmed incident TB cases in participants who were HIV-positive were diagnosed while under follow-up at the HIV care clinic. Thus, the potential impact of the clinic on this study was minor and insufficient to explain the

major differences found between miners who were HIV-positive and HIV-negative.

DISCUSSION

This study shows that HIV-associated TB has much briefer mean durations of activity and infectiousness before diagnosis than TB in gold miners who are HIV-negative. In consequence, the point prevalence of undiagnosed TB disease differs relatively little between gold miners who are HIV-positive and HIV-negative, despite major differences in the risk of incident TB disease. Our results cannot be fully or mainly explained by more intensive follow-up of miners who are HIV-positive. Instead, we think that they are most likely to reflect a basic difference in the natural rate of TB disease progression between immunocompetent and immunosuppressed individuals (7–10), resulting in more rapid presentation and case detection for HIV-associated TB disease. This interpretation is consistent with the otherwise unexplained observation that the point prevalence of new radiologic TB disease has remained relatively constant during a time period when new TB incidence rates have increased by threefold and that the ratio of incident to prevalent cases has fallen progressively as HIV prevalence has increased in this workforce from the early 1990s (Figure 1).

Gold miners are an unusual population because of occupational exposure to silica dust (14), but the principle of more rapid case detection limiting the impact of HIV on prevalent TB disease may well be a generalizable one because rapid progression is a widely reported feature of HIV-associated TB disease (7–10). Our finding that silicosis is also associated with a significantly reduced interval to diagnosis suggests that it may be relatively common for risk factors that act by compromising host defenses to also result in accelerated disease presentation. Undiagnosed active TB can end in self-cure or death as well as in diagnosis and treatment (17). HIV-associated immunosuppression may affect the absolute and relative rates at which these alternative outcomes compete with self-presentation and diagnosis. More rapid presentation and diagnosis are likely to be the predominant underlying causes of the observed difference between miners who are HIV-positive and HIV-negative in our setting because there is both unusually intensive case finding and a low rate of death from undiagnosed TB at this site (11, 16). In settings where diagnosis is less readily available, however, rapid progression to death may also contribute to a relatively short duration of infectiousness among HIV-positive persons with TB because mortality rates are high for HIV infected TB patients who are not promptly diagnosed, and undiagnosed TB disease is an extremely common cause of death among HIV-positive Africans (7–10, 17–21).

If a generalizable feature of HIV-associated TB, then a brief duration of infectiousness would be of considerable relevance to global TB control. The current global strategy, directly observed therapy, short course (DOTS), is based predominantly on improved case finding and treatment (22) and thus acts primarily through control of prevalent infectious TB disease, with any falls in TB transmission and incidence rates being achieved secondarily (22). Evaluation and monitoring, however, are almost exclusively focused on case-notification rates and treatment outcomes (3). Alarming upward trends in TB case-notification rates have been reported from other high HIV prevalence populations, and the HIV epidemic is driving a global increase in incident TB cases (3, 23). Our current results suggest that the underlying trends in TB disease prevalence rates may be quite different and also raise the possibility that controlling the point prevalence of infectious TB disease may be a realistic aim of DOTS-based TB control programs even in high HIV prevalence areas. This would give a major boost to the prospects for global TB control if confirmed in more typical populations because the point prevalence of infectious TB disease is closely correlated with the annual risk of TB infection in any given population (24). In this context, it is notable that stable or even declining rates of TB transmission and TB incidence among persons who are HIV-negative have been reported during time periods when overall TB incidence rates have increased as a result of HIV-associated disease from Tanzania, Cote d'Ivoire, Northern Thailand, Malawi, and this study workforce of South African gold miners (25–29). There have also been two conflicting reports suggesting that TB transmission has increased during the course of the HIV epidemics in Kenya and in a different workforce of South African gold miners (30, 31). Determining the underlying reasons for these differences is an important challenge for all of those concerned with TB control in high HIV prevalence populations.

This is the first study in which a representative sample from a well-defined high HIV prevalence population with a high incidence of TB has been recruited to investigate systematically TB disease incidence and prevalence by HIV status. Previous studies based in voluntary counseling and testing centers have found a higher prevalence of active TB in clients who were HIV-positive than clients who are HIV-negative (32–35), but are difficult to interpret because ill-health, including symptomatic TB, is one of the factors that motivates individuals to seek HIV testing (35). Consequently, the prevalence of TB disease in voluntary counseling and testing attendees will not be representative in either HIV status group. The same self-selection effect will apply to other healthcare settings so that trends in nososcomial TB transmission rates during an HIV epidemic may be very different to those in the general community.

There are a number of limitations and potential sources of bias in this study, but none that are likely to fully account for our main findings. A major concern in many African settings would be underdiagnosis of incident TB; however, the study work force has a low rate of undiagnosed TB as found at routine postmortem (16), and all employees are screened for TB on leaving employment. TB incidence in the retrospective element of the cohort analysis will have been underestimated to a minor degree by the failure to capture fatal TB episodes: case fatality rates are, however, relatively low at this site even among patients who are HIV-positive (36). TB incidence during the prospective follow-up will have been reduced by the cross-sectional screen, as prevalent patients with TB were not included as incident cases. This will have led to overestimation of the absolute duration of undiagnosed disease for both HIV-positive and HIV-negative subgroups, but it avoids the otherwise implicit assumption that in the absence of our intensive prevalence screen then all of our prevalent patients with TB would still have been diagnosed by the end of the prospective cohort period. We also cannot exclude an element of ascertainment bias in the prospective incidence data, which could be introduced if healthcare workers more readily investigate miners who are HIV-positive for TB disease. Our HIV-specific TB incidence rates are in the expected range for this workforce (14), however, and our overall estimate of point prevalence (3.8%) is similar to the prevalence of active TB found at autopsy of miners dying from trauma (3.9% in 1991) (37). Finally, because of limited study power, we have not considered the role of previous TB treatment, although this is known to be a risk factor for prevalent TB disease elsewhere (24).

We have shown that HIV has a marked effect on the duration of TB disease before diagnosis in miners. The impact of HIV on the point prevalence of infectious TB and, by inference, on TB transmission, is considerably less marked than the impact on TB incidence rates. In endemic TB settings, unlike in the United States, most TB transmission events occur between ca-

sual contacts in the community at large (38, 39). As such, our finding that 78% of participating miners with prevalent smear-positive TB were HIV-negative suggests that patients who are HIV-negative and have TB may still be responsible for the majority of TB transmission events in this community, even though HIV prevalence in our incident patients with TB was 64%. If correct and generalizable, then untargeted interventions to improve TB control in the whole community may be the most effective way of controlling TB transmission in high HIV prevalence populations and would complement strategies targeted to known persons who are HIV-positive, such as promotion of HIV-testing linked to antituberculous preventive therapy and antiretroviral drugs. More generally, this study illustrates the importance of assessing changes in the duration of infectiousness before the likely public health consequences of risk factors for incident infectious diseases can be fully assessed.

Conflict of Interest Statement: E.L.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this article; S.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this article; V.M.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this article; K.F. does not have a financial relationship with a commercial entity that has an interest in the subject of this article; A.D.G. does not have a financial relationship with a commercial entity that has an interest in the subject of this article; C.D. does not have a financial relationship with a commercial entity that has an interest in the subject of this article; K.M.D. does not have a financial relationship with a commercial entity that has an interest in the subject of this article; R.J.H. does not have a financial relationship with a commercial entity that has an interest in the subject of this article; B.G.W. does not have a financial relationship with a commercial entity that has an interest in the subject of this article; G.J.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this article.

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