HIV-1 and recurrence, relapse, and reinfection of tuberculosis after cure: a cohort study in South African mineworkers

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Summary

Background The proportion of recurrent tuberculosis cases attributable to relapse or reinfection and the risk factors associated with these different mechanisms are poorly understood. We followed up a cohort of 326 South African mineworkers, who had successfully completed treatment for pulmonary tuberculosis in 1995, to determine the rate and mechanisms of recurrence.

Methods Patients were examined 3 and 6 months after cure, and then were monitored by the routine tuberculosis surveillance system until December, 1998. IS*6110* DNA fingerprints from initial and subsequent episodes of tuberculosis were compared to determine whether recurrence was due to relapse or reinfection All patients gave consent for HIV-1 testing.

Findings During follow-up (median 25·1 months, IQR 13·2–33·4), 65 patients (20%) had a recurrent episode of tuberculosis, a recurrence rate of 10·3 episodes per 100 person-years at risk (PYAR)—16·0 per 100 PYAR in HIV-1-positive patients and 6·4 per 100 PYAR in HIV-1-negative patients. Paired DNA fingerprints were available in 39 of 65 recurrences: 25 pairs were identical (relapse) and 14 were different (reinfection). 93% (13/14) of recurrences within the first 6 months were attributable to relapse compared with 48% (12/25) of later recurrences. HIV-1 infection was a risk factor for recurrence (hazard ratio 2·4, 95% CI 1·5–4·0), due to its strong association with disease caused by reinfection (18·7 2·4–143), but not relapse (0·58; 0·24–1·4). Residual cavitation and increasing years of employment at the mine were risk factors for relapse.

Interpretation In a setting with a high risk of tuberculous infection, HIV-1 increases the risk of recurrent tuberculosis because of an increased risk of reinfection. Interventions to prevent recurrent disease, such as lifelong chemoprophylaxis in HIV-1-positive tuberculosis patients, should be further assessed.

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Introduction

Recurrent tuberculosis might be due to either relapse or exogenous reinfection. The contribution of reinfection to the epidemiology and pathogenesis of tuberculosis has important implications for tuberculosis control, vaccine design, chemoprophylaxis, and assessment of treatment regimens.[1] Findings of several anecdotal case reports show relapse or reinfection mechanisms for recurrence. Only a few studies have investigated the proportion of recurrence due to these mechanisms in more than five patients.[2–8] In countries with a low incidence of tuberculosis, recurrence seems to be attributable to relapse in most cases.[5,7] Studies from settings with a high incidence are conflicting because the proportion of cases attributable to reinfection varies from 12% to 75%.[3,4,6,8] Risk factors for relapse and reinfection, especially the effect of HIV-1 infection, have not been explored.

Although mortality from tuberculosis is high in patients coinfected with HIV-1, treatment failure rates are similar in HIV-1-positive and HIV-1-negative tuberculosis patients.[9–12] The relative risk of recurrence in these groups, however, is not clear. The results of some studies show closely similar recurrence rates in individuals positive and negative for HIV-1.[9,13,14] However, the results of other studies show a higher rate of recurrence in HIV-1-positive patients than in HIV-1-negative patients,[10,12,15–18] especially when regimens containing thioacetazone are used,[10,16,18,19] and in patients with low levels of immunity.[15,20] The varied estimates of the relative risk of recurrence could be attributable to differences in the risk of new *Mycobacterium tuberculosis* infection and influence of HIV-1 on relapse and reinfection.

We investigated recurrence of tuberculosis in a cohort of South African gold-mine workers, some of whom were HIV-1 positive and some of whom were HIV-1 negative, and who had all successfully completed treatment for pulmonary tuberculosis in 1995. The prevalence of tuberculosis in gold miners is high (1536 per 100 000 in 1995),[11] and we estimate that half of the cases of tuberculosis in this community can be attributed to ongoing transmission.[21] We aimed to find out whether recurrent disease was due to relapse or reinfection, and analysed risk factors for these two mechanisms.

Patients and methods

Patients

The setting for our study was a hospital serving four gold mines in Gauteng province, South Africa. The study population, tuberculosis control programme, study design, laboratory methods, and chest radiography have been previously described.[11] Ethical approval was obtained from the Committee for Research on Human Subjects at the University of the Witwatersrand, South Africa, and the London School of Hygiene and Tropical Medicine ethics committee, UK.

We included patients in our study if their initial tuberculosis episode (in 1995) was proven by culture, if they did not have multidrug-resistant tuberculosis (resistant to at least isoniazid and rifampicin), and if they were cured of tuberculosis (figure 1). All patients

completed at least 6 months of treatment (2 months with isoniazid, rifampicin, pyrazinamide, and ethambutol followed by 4 months with isoniazid and rifampicin). Radiography, clinical assessment by a doctor, and sputum examination confirmed cure. All patients had at least two negative sputum examinations during the course of treatment; at 6 months they either had a negative culture (n=317) or were unable to produce sputum (9). We enrolled patients into our study on the date they completed anti-tuberculosis treatment.

Procedures

Patients were examined and radiographed at a dedicated tuberculosis clinic 3 months and 6 months after cure, and sputum was sent for microscopy and culture. Thereafter, they were continually monitored by routine tuberculosis surveillance, which includes an annual chest radiograph and, if unwell, presentation to free medical facilities. No patient received antiretroviral therapy. We obtained employment and mortality details from hospital records, the mines' personnel departments, and the Employment Bureau of Africa. Recurrent pulmonary tuberculosis was diagnosed if *M tuberculosis* was grown from cultures of sputum in the follow-up period and the patient had symptoms of tuberculosis.

IS*6110* DNA fingerprints were made according to internationally agreed guidelines.[22] Isolates from the initial 1995 episode have been fingerprinted and were classified as unique or clustered with Gelcompar software (Applied Maths, Kortrijk, Belgium).[21] Initial and recurrent isolates were compared directly. If the fingerprint patterns were identical (number and position of bands), recurrence was classified as relapse; if the pattern was different, recurrence was classified as reinfection.

Statistical analysis

Data were analysed with EpiInfo (version 6.04) and STATA (version 5.1). Survival analysis methods were used in univariate and multivariate analyses to account for losses to follow-up attributable to death and loss to the cohort. Information on tuberculosis recurrence in miners who had moved home was not available. We followed up every patient until Dec 31, 1998, or until they left the mine or died, whichever occurred first. We did separate analyses to estimate risk factors for recurrence overall, relapse, and reinfection. In the analysis of risk factors for relapse, patients whose disease recurred because of reinfection or unknown mechanism were censored on the date of recurrence. Similarly, in the analysis of risk factors for reinfection, patients whose tuberculosis recurred because of relapse or unknown mechanism were censored on the date of recurrence.

For every analysis, we looked at several risk factors: demographics (age, home region), lifestyle (smoking, alcohol consumption), and occupational (years in mine employment, years at current mine, years working underground, silicosis). We also looked at clinical, laboratory, and radiological features on enrolment to the initial cohort: tuberculosis history, sputum smear, drug resistance, DNA fingerprints, HIV-1 status (all patients consented to HIV-1 testing), CD4 count, and chest radiograph appearance (typical or atypical, extent of changes, cavitation, fibrosis).

Radiographs were judged to be typical of tuberculosis if there was predominantly upper zone infiltrates/fibrocavitation or miliary disease. A radiograph was judged atypical if changes, including cavitation, were present predominantly in the lower lung fields, if there was isolated hilar and/or mediastinal lymphadenopathy, if there was lobar consolidation, or if there were no changes.

Other characteristics studied were adherence to treatment during the initial episode (any directly observed therapy missed, tuberculosis clinic missed, leave), and clinical, laboratory, and radiological features at cure (symptomatic, confirmation of cure bacteriologically, HIV-1, CD4 count, chest radiograph improvement, extent of changes, residual cavitation, fibrosis).

We calculated an unadjusted hazard ratio for every potential risk factor, with a p value for the log-rank test. Variables with $p<0{\cdot}1$ were tested for the proportional hazards assumption and, when valid, were included in a Cox's regression model. Age and HIV-1 status at enrolment were included in the model a priori. Adjusted hazard ratios with 95% CIs were estimated. Interaction was determined with likelihood ratio tests and, if present, results are reported separately.

Results

We investigated the cohort for 629·3 person-years, with a median follow-up of 25·1 months (IQR 13·2–33·4).

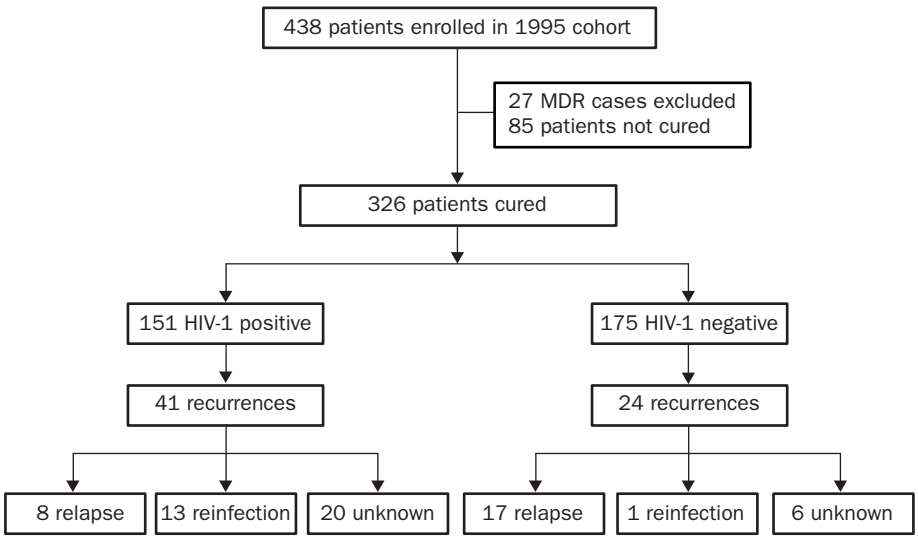
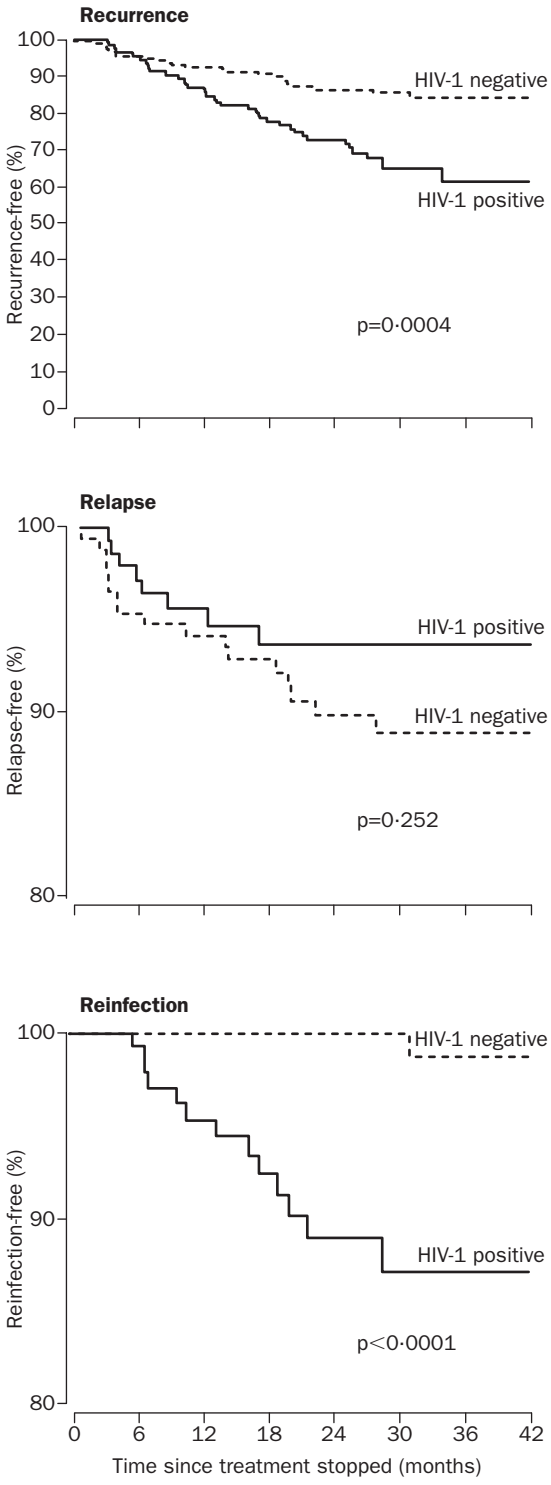


Figure 1: **Study profile and outcomes**
MDR=multidrug resistant.



Numbers at risk

HIV-1 negative	175	160	146	131	106	84	34	34
HIV-1 positive	151	131	104	87	66	39	15	15

Figure 2: **Kaplan-Meier curves**
Showing risk of recurrence, relapse, and reinfection in 151 HIV-1-positive and 175 HIV-1-negative tuberculosis patients.

The 151 HIV-1-positive tuberculosis patients were studied for a shorter period than the 175 HIV-1-negative tuberculosis patients (median 21·2 months [10·2–30·3] *vs* 29·5 months [17·8–35·2]). A closely similar proportion of

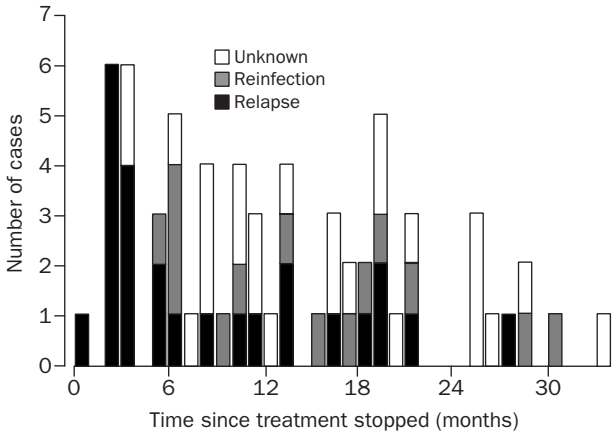


Figure 3: **Mechanism of recurrence in 65 patients according to time interval between cure and recurrence**

patients had left employment (53 [49%] *vs* 74 [44%], p=0·5), but HIV-1-positive patients were more likely to have died than HIV-1-negative patients (42 [28%] *vs* seven [4%], p<0·0001). 65 of 326 patients (20%) had a subsequent episode of tuberculosis during follow-up (figure 1). The rate of recurrence was 10·3 per 100 person-years at risk (PYAR; 95% CI 8·1–13·2). 41 HIV-1-positive (16·0 per 100 PYAR; 11·8–21·7) and 24 HIV-1-negative patients (6·4 per 100 PYAR; 4·3–9·6) had a recurrence of tuberculosis. The unadjusted hazard ratio of tuberculosis recurrence in HIV-1-positive patients compared with HIV-1-negative patients was 2·4 (1·5–4·0). Kaplan-Meier curves for recurrence according to HIV-1 status showed that patients negative for HIV-1 were less likely to have recurrence than HIV-1-positive patients (figure 2).

DNA fingerprints from the initial and subsequent episodes of tuberculosis were available for comparison in 39 of 65 recurrences (60%); 25 fingerprints were identical (relapse) and 14 were different (reinfection). In all cases of reinfection, the two fingerprints differed by at least three bands. 93% (13/14) of recurrences within the first 6 months were attributable to relapse versus 48% (12/25) of later recurrences (figure 3). Exclusion of patients whose disease recurred or who were censored in the first 6 months (n=36) had little effect on the hazard ratios for factors associated with recurrence, relapse, or reinfection.

On univariate analysis, several potential risk factors for relapse and reinfection were identified (table 1). Kaplan-Meier curves show that HIV-1-positive patients were more likely to have recurrence attributable to reinfection than HIV-1-negative patients (figure 2). For relapse, we found no significant difference between HIV-1-positive and HIV-1-negative patients (figure 2). 62% (13/21) of recurrences in HIV-1-positive patients were attributable to reinfection versus 6% (1/18) in those who were HIV-1 negative (p=0·0003). The one HIV-1-negative individual with reinfection was still HIV-1 negative at the time of recurrence. On multivariate analysis we identified increasing years in employment and residual cavitation as significant risk factors for relapse, and HIV-1 infection as the only significant risk factor for reinfection. There were no significant interactions in the analysis of risk factors for relapse and reinfection (table 2).

39 recurrent cases with paired fingerprints were closely similar—with respect to age and occupational history—to 26 patients for whom the initial or recurrent isolate was not available. All 39 cases were assessed as cured on the basis of a negative culture, whereas two of the 26 patients

Risk factor	Number of patients in cohort (n=326)	Relapse		Reinfection	
		Number of relapses (n=25)	Hazard ratio (95% CI)	Number of reinfections (n=14)	Hazard ratio (95% CI)
Age (years)					
<30	35	1 (3%)	0·29 (0·04–2·2%)	1 (3%)	0·72 (0·09–6·0)
30–39	163	15 (9%)	1·0	6 (4%)	1·0
40–49	84	7 (8%)	0·93 (0·38–2·3)	6 (7%)	2·1 (0·67–6·5)
⩾50	44	2 (5%)	0·55 (0·13–2·4)	1 (2%)	0·81 (0·10–6·8)
Employment (years)					
0–9	59	1 (2%)	1·0	2 (3%)	1·0
10–15	167	17 (10%)	6·4 (0·85–48·0)	7 (4%)	1·4 (0·28–6·6)
>15	100	7 (7%)	4·7 (0·57–38·0)	5 (5%)	1·9 (0·36–9·6)
Tuberculosis category					
New tuberculosis	252	16 (6%)	1·0	11 (4%)	1·0
Previous tuberculosis	74	9 (12%)	2·1 (0·93–4·8)	3 (4%)	1·1 (0·30–3·8)
Sputum smear					
Negative	84	6 (7%)	1·0	2 (2%)	1·0
Positive	242	19 (8%)	1·1 (0·43–2·7)	12 (5%)	2·0 (0·44–8·8)
Drug resistance					
Sensitive	291	23 (8%)	1·0	13 (4%)	1·0
Resistant*	32	2 (6%)	0·82 (0·19–3·5)	1 (3%)	0·72 (0·09–5·5)
HIV-1 status					
Negative	175	17 (10%)	1·0	1 (1%)	1·0
Positive	151	8 (5%)	0·61 (0·26–1·4)	13 (9%)	18·9 (2·5–145)
CD4+ in HIV-1-positive patients					
>28%	24	2 (8%)	1·0	3 (13%)	1·0
14–28%	61	2 (3%)	0·36 (0·05–2·6)	6 (10%)	0·73 (0·18–2·9)
<14%	60	4 (7%)	0·83 (0·15–4·5)	3 (5%)	0·49 (0·10–2·4)
Missed directly observed therapy					
No	246	16 (7%)	1·0	10 (4%)	1·0
Yes	80	9 (11%)	1·8 (0·78–4·0)	4 (5%)	1·3 (0·40–4·1)
Chest radiograph at presentation					
Typical of tuberculosis	278	20 (7%)	1·0	11 (4%)	1·0
Atypical of tuberculosis	47	4 (9%)	1·4 (0·47–4·0)	3 (6%)	2·1 (0·58–7·5)
Silicosis					
None	284	21 (7%)	1·0	12 (4%)	1·0
Possible	38	3 (8%)	1·06 (0·32–3·6)	2 (5%)	1·3 (0·29–5·7)
Confirmed	3	0		0	
Cavitation at cure					
None	256	12 (5%)	1·0	9 (4%)	1·0
Residual	69	12 (17%)	4·1 (1·8–92)	5 (7%)	2·5 (0·84–7·5)

*Isoniazid (n=27), streptomycin, no recurrences (3), isoniazid and streptomycin, no recurrences (2).

Table 1: **Risk factors for relapse or reinfection in 326 patients (univariate analysis)**

had been unable to produce sputum at the end of treatment. Patients not fingerprinted were more likely to be HIV-1 positive than HIV-1 negative (20/26 *vs* 21/39; p=0·06) and to have an atypical chest radiograph (12/26 *vs* 7/38; p=0·02), although other radiological features, including the proportion of patients with cavitation, were similar.

We estimated risk factors for recurrence separately for patients positive and negative for HIV-1 (table 3), since there were significant interactions between HIV-1 infection and residual cavitation (p=0·003, test for interaction) and previous tuberculosis treatment (p=0·01). Patients treated for previous tuberculosis (n=74) include those with previous recurrent tuberculosis (15/54 recurred; 16·8/100 PYAR) and those whose treatment had failed on enrolment to the study and who were assessed as cured 6 months later (5/20 recurred; 12·6/100 PYAR). Of 69 patients with residual cavitation, 26 had recurrence, a rate of 22·9 per 100 PYAR (95% CI 15·6–33·7). The rate of recurrence in patients with residual cavitation was 23·5 per 100 PYAR (14·1–38·9) and 22·3 per 100 PYAR (12·3–40·2) in HIV-1-positive and HIV-1-negative patients, respectively. Thus, HIV-1 infection was not a risk factor for recurrence in those with cavitation (hazard ratio 0·97, 0·44–2·1), but was a strong risk factor for recurrence in those without cavitation (4·7, 2·2–10·0). Age, positive sputum smear, drug resistance, extent of radiographical changes at cure, residual fibrosis, silicosis, and CD4 count in HIV-1-positive patients were not associated with recurrence. Of 22 patients who had recurrence and who had missed directly observed therapy, 18 had missed less than 7 days.

Risk factor	Relapse*	Reinfection
HIV-1 positive	0·58 (0·24–1·4)	18·7 (2·4–143)
Employment (years)		
10–19 *vs* 0–9	9·2 (1·1–75·7)	2·1 (0·35–11·9)
⩾20 *vs* 0–9	12·4 (0·99–156)	3·2 (0·29–35·4)
Residual cavitation	4·3 (1·9–9·7)	2·6 (0·86–8·0)

Data are hazard ratio (95% CI) adjusted for age and other risk factors. *24 relapses included in the multivariate analysis, since chest radiograph missing for one patient.

Table 2: **Adjusted hazard ratios for risk factors for relapse or reinfection in 326 patients**

61 of 65 recurrent cases had tuberculosis caused by a fully sensitive organism on their initial episode and four cases had isoniazid resistance. At recurrence, four sensitive cases had developed isoniazid resistance (one relapse, one reinfection, two unknown) and two had developed multidrug resistance (one reinfection, one unknown). Of the four with initial isoniazid resistance,

Risk factor	HIV-1 positive			HIV-1 negative		
	Number of recurrent cases/total	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)*	Number of recurrent cases/total	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)*
Chest radiograph at cure						
No cavitation	29/119	1·0	1·0	9/137	1·0	1·0
Residual cavitation	11/31	1·6 (0·80–3·2)	2·4 (1·1–5·1)	15/38	7·4 (3·2–17·0)	7·1 (2·7–18·5)
Chest radiograph at presentation						
Typical of tuberculosis	23/113	1·0	1·0	22/165	1·0	1·0
Atypical of tuberculosis	17/37	2·7 (1·4–5·0)	3·1 (1·6–6·1)	2/10	1·7 (0·40–7·2)	5·7 (1·2–27·8)
Tuberculosis category						
New tuberculosis	33/120	1·0	1·0	12/132	1·0	1·0
Previous tuberculosis	8/31	0·94 (0·43–2·0)	0·68 (0·29–1·6)	12/43	3·7 (1·7–8·3)	2·7 (1·1–6·7)
Missed directly observed therapy						
No	29/116	1·0	1·0	14/130	1·0	1·0
Yes	12/35	1·3 (0·66–2·6)	1·2 (0·61–2·4)	10/45	2·2 (0·98–5·0)	3·2 (1·3–7·7)

*Adjusted for age and other risk factors.

Table 3: **Unadjusted and adjusted hazard ratios according to HIV-1 status for risk factors for recurrent tuberculosis in 326 patients**

two relapsed with the same drug susceptibility pattern and two had sensitive tuberculosis on the subsequent episode (one reinfection, one unknown).

Discussion

We combined classic and molecular epidemiology to estimate rates of recurrent tuberculosis, the proportion of recurrent cases attributable to relapse or reinfection, and risk factors for these mechanisms. HIV-1 infection was a risk factor for recurrence (hazard ratio 2·4) because HIV-1 was strongly associated with disease caused by reinfection (adjusted hazard ratio 18·7) but not with relapse (0·58). Thus, even in regimens containing rifampicin, recurrence can be more common in patients with HIV-1 than in those without HIV-1 if exposure to *M tuberculosis* remains high.

Although a gold-mining community might not be typical of African societies, the stable population, good medical records, and high quality of healthcare provide an opportunity to understand the natural history of *M tuberculosis* infection. Miners are all adult males and are exposed to silica dust in the mines; HIV-1-positive and HIV-1-negative men are likely to be at similar risk of exposure to *M tuberculosis* and silica dust. A mining community is therefore a useful setting in which to explore the effect of HIV-1 on the pathogenesis of recurrence.

HIV-1-positive individuals infected with *M tuberculosis* might rapidly progress to disease;[23,24] they might also be at high risk of developing infection after exposure to *M tuberculosis*. After active disease, HIV-1-positive patients might have low immunity to subsequent infection. The estimate of HIV-1 as a risk factor for recurrence was based on HIV-1 status on entry to the study, which was available for all patients. In patients who seroconverted since enrolment, immunosuppression is unlikely to have a large effect, because these patients would have been infected, at most, 3 years previously. We did not find that the level of immunosuppression increased the risk of overall recurrence, relapse, or reinfection. This might be because patients with advanced immunosuppression die from other causes before development of recurrent tuberculosis. A single CD4 lymphocyte count at tuberculosis diagnosis might be an insensitive marker of immune depletion; however, closely similar results were obtained by analysing CD4 counts at cure.

Concordant fingerprints in recurrent isolates from an individual are unlikely to arise by chance. IS*6110* fingerprint patterns were sufficiently heterogeneous to make the risk of reinfection with a strain of *M tuberculosis* with the same pattern as the original infection small. We do not know the distribution of circulating strains at the time of recurrence, but the commonest strain circulating in 1995 was strain 1A (10% of all tuberculosis cases);[21] this strain also caused three of 14 reinfections, which suggests that it was still prevalent in the follow-up period. Strain 1A was found in four patients who subsequently recurred and had paired fingerprints available. In all these cases, the same strain was found again at recurrence. Of the remaining 21 patients who relapsed, seven had strains which were unique in 1995 and 14 had strains which were in clusters, each representing less than 7% of tuberculosis cases.

Different fingerprints can arise from true reinfection or misclassification. Since the proportion of HIV-1-negative patients with reinfection is low, and only 2·3% (10/429) of all isolates in 1995 were found to be false positives,[21] laboratory or clerical error does not seem to be a likely explanation for our results. Over time, mutations or transpositions can alter the fingerprint pattern of a strain, resulting in overestimation of reinfection. No cases classified as reinfection in this study differed by fewer than three bands. Heterogeneity could also be caused by mixed infections at the initial episode, but this phenomenon seems to be rare.[6,21]

Findings from studies comparing DNA fingerprints from original and recurrent episodes have shown that when a diagnosis is based on an isolated positive culture with a negative smear, fingerprints were likely to be different, whereas among recurrences confirmed on more than one positive sample, the original and recurrent isolates were likely to have identical fingerprints.[4,6] In our study, seven patients had recurrence diagnosed by an isolated positive culture, and these specimens were not fingerprinted. Of the 39 patients with paired fingerprints, three had an isolated positive culture on their initial episode—of these, two subsequently relapsed and one was reinfected.

We obtained paired fingerprints from recurrent episodes of tuberculosis in 60% of recurrent patients. Of those without a paired fingerprint, four did not have the initial isolate fingerprinted and 20 of 22 did not have an isolate forwarded from the diagnostic tuberculosis laboratory to the DNA fingerprinting laboratory. These 26 patients did not differ from those included in the study with respect to the risk factors identified for relapse or reinfection, except that they were more likely to be HIV-1 positive than patients with paired fingerprints. The hazard ratios for relapse and reinfection are unlikely to be biased, and the proportion of recurrence attributable to reinfection by HIV-1 should be valid.

Comparison of studies that estimate the proportion of recurrence attributable to relapse or reinfection should consider study setting and differences in selection of patients, diagnosis of disease and cure, and duration of follow-up. Our results suggest the proportion of tuberculosis patients coinfected with HIV-1 will also determine the relative proportion of recurrence caused by relapse or reinfection. Moreover, long follow-up could increase the proportion of cases attributable to reinfection and thus increase the relative risk of recurrence between HIV-1-positive and HIV-1-negative patients.

Early studies have shown that patients with extensive disease, measured by initial bacterial count, smear positivity, time to sputum conversion, radiological severity of disease, and cavitation, are more likely to have recurrence than those without extensive disease.[25–28] Recent studies have been less likely to identify significant risk factors for recurrence, partly because of improvements in chemotherapy and low relapse rates, which result in limited statistical power.[14,19,29] Risk factors for recurrence overall are a combination of those for relapse and reinfection, two very different mechanisms, and the risk factors identified would thus depend on the proportion of recurrent disease attributable to each of these mechanisms. For example, cavitation at diagnosis[25] or at the end of chemotherapy[25–28] has been identified as a strong risk factor for recurrence. We found that residual cavitation was a significant risk factor for relapse but not reinfection, and this finding explains the apparent difference in relative risk of overall recurrence associated with cavitation between HIV-1-positive and HIV-1-negative individuals. Similarly, increasing years of employment, a possible marker of exposure to silica dust, was a risk factor for relapse, but not for recurrence overall.

Since active disease does not seem to confer immunity to tuberculosis in HIV-1-positive patients, the development of a vaccine to prevent tuberculosis in these individuals might be difficult. Conversely, since the risk of reinfection is low in HIV-1-negative patients, the prospect of a vaccine in these patients is promising. Our findings also have implications for the assessment of clinical trials that test new regimens. In settings with a high prevalence of HIV-1 infection and tuberculosis, rates of relapse rather than recurrence might be a more appropriate measurement of treatment efficacy, and fingerprinting data might be needed.[1,24]

The findings of our study lend support to the underlying principles of tuberculosis control. Patients with active tuberculosis need to be diagnosed early and treated effectively to be cured and to reduce the risk of transmission to others. Early diagnosis could also prevent extensive disease, often associated with cavitation, which is a strong risk factor for relapse. Patients with residual cavitation could benefit from extended treatment.

Chemotherapeutic options to reduce the high recurrence rate in HIV-1-positive patients include intensification of therapy for the initial episode and secondary chemoprophylaxis. Aggressive primary chemotherapy would probably result in fewer relapses, since patients are more likely to be cured than those who do not undergo chemotherapy. Additionally, strategies to improve adherence, such as the introduction of dosage cards signed by both health worker and patient,[30] would reduce relapse. Secondary chemoprophylaxis for up to 1 year reduces the risk of recurrent disease.[12,15,20] The mechanism is likely to be a reduction in the rates of both relapse and reinfection. In settings with a high risk of tuberculous infection, lifelong chemoprophylaxis for cured tuberculosis patients who are known to be HIV-1 positive might therefore be an appropriate intervention. The possibility of selecting for resistant strains would need to be considered. Secondary chemoprophylaxis might be easier logistically than primary prophylaxis, since the patients' HIV-1 status is known, active tuberculosis has been excluded, and the patient is already used to regular treatment and follow-up.

Contributors

P Sonnenberg helped with the study design, patient management, data collection, analysis of fingerprints and data, and wrote the report. J Murray and S Shearer helped with the study design, data collection, analysis, and wrote the report. J Glynn helped with data analysis and wrote the report. B Kambashi helped make and analyse the fingerprints. P Godfrey-Faussett helped with the study design, made and analysed the fingerprints, analysed data, and wrote the report. All authors reviewed and approved the final manuscript.

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