

## Contribution of reinfection to recurrent tuberculosis in South African gold miners

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### SUMMARY

**SETTING:** A gold mine in South Africa.

**OBJECTIVE:** To investigate incidence and risk factors for tuberculosis (TB) recurrence and the relative contribution of reinfection and relapse to recurrence.

**DESIGN:** Prospective cohort study.

**METHODS:** Employees cured of a first episode of culture-positive TB were followed up for recurrence, which was classified as reinfection or relapse by restriction fragment length polymorphism using an insertion sequence (IS) 6110 probe.

**RESULTS:** Among 609 patients, 57 experienced recurrence during a median follow-up period of 1.02 years, corresponding to a recurrence rate of 7.89 per 100 person-years (py). The culture positive recurrence rate was 5.79/100 py, and was higher in human immunodeficiency virus (HIV) infected patients (8.86/100 py in HIV-infected vs. 3.35/100 py in non-HIV-infected). Among HIV-infected

patients, the risk of culture-positive recurrence was higher with decreasing CD4 count (compared with CD4 < 200, hazard ratios for recurrence among individuals with CD4 200–500 and CD4 > 500 were 0.40 [95% CI 0.14–1.09] and 0.14 [95% CI 0.02–1.10], respectively,  $P_{\text{trend}} = 0.01$ ). IS6110 genotyping was available on both the initial and subsequent isolate for 16/42 (38%, 14 HIV-infected) patients with culture-positive recurrence, and showed reinfection in 11 (69%).

**CONCLUSION:** HIV-infected gold miners, particularly those who are more immunosuppressed, are at higher risk of TB recurrence. TB control strategies need to take into account reinfection as an important cause of recurrent TB.

**KEY WORDS:** RFLP; TB recurrence; reinfection; HIV infection; South Africa

THE HUMAN IMMUNODEFICIENCY VIRUS (HIV) pandemic presents a major challenge to tuberculosis (TB) control in sub-Saharan Africa,<sup>1,2</sup> where TB incidence rates continue to increase, driven by the HIV epidemic.<sup>2</sup> Recurrence of TB after cure is common in settings with high TB incidence<sup>3</sup> and HIV prevalence.<sup>4–10</sup> The gold mining industry in South Africa has been affected by a severe TB epidemic, fuelled by HIV infection, silicosis and an aging workforce.<sup>9,11</sup> Identified risk factors for recurrence of TB include HIV infection, residual radiological lesions and drug resistance.<sup>9</sup>

Recurrent TB can be due either to endogenous reactivation (relapse) or exogenous reinfection (reinfection), or both.<sup>12</sup> Understanding the mechanism of recurrence is key to guiding TB control measures. The relative contribution of relapse and reinfection may

differ according to the prevalence of TB and HIV, but studies show conflicting results, even in areas with similar TB incidence.<sup>13–16</sup> Restriction fragment length polymorphism studies carried out in Cape Town,<sup>17</sup> a metropolitan area with very high TB incidence but lower HIV prevalence,<sup>18</sup> indicate that a large proportion (77%) of recurrent TB may be attributable to reinfection. Among gold miners in South Africa, HIV-infected persons were more likely to have recurrence due to reinfection, while relapse was more likely in non-HIV-infected individuals.<sup>16</sup>

This prospective cohort study aimed to investigate incidence and risk factors for recurrence and to distinguish relapse from reinfection using insertion sequence (IS)6110 genotyping among gold miners in South Africa.

## STUDY POPULATION AND METHODS

### Study setting

The study was conducted in a single mining health service in Free State Province, South Africa, between 1999 and 2002. In 1999, TB case notification rates in this section of the workforce exceeded 4000 per 100 000.<sup>19</sup> Ninety per cent of employees were underground workers, mostly migrants living in single-sex hostels. The mine hospital was the sole source of tertiary care for mine employees and it managed the TB control programme, which included directly observed rifampicin (RMP) based short-course chemotherapy regimens, use of combination tablets and active case detection using miniature chest radiographs (CXR) at least once annually.

### Study population

Patients completing an episode of culture-confirmed TB between 1 January 1999 and 30 June 2001 were eligible for the study if their treatment outcome was cure, defined as treatment completion with two negative sputum smears during or at the end of treatment. Enrolment was restricted to patients cured of a first-ever TB episode, to make the study population more homogeneous with respect to risk of subsequent recurrence on the basis that patients with recurrent TB episodes would be more likely to have drug resistance and hence more prone to relapse. Patients were excluded if they were not mining company employees or if they had extra-pulmonary TB with no concomitant pulmonary disease. Enrolled patients were followed for recurrence until 31 March 2002 (earlier than was initially expected due to the sale of the mine).

### Definitions

All TB episodes were considered to start on the TB treatment start date. A recurrent TB episode was defined as a second episode of TB treated within the follow-up period with either 1) a positive result from sputum microscopy or culture at the start of treatment or 2) a radiographic response to treatment after 2 months. If *Mycobacterium tuberculosis* was cultured at the second episode, this defined a culture-positive recurrence.

### Risk factor data

Information about age, residence, job location and duration of employment were collected as part of the routine TB programme. Patients were classified as HIV-positive if they had a positive HIV test result either before or up to 4 months after the start of the initial TB episode, and as HIV-negative if they had a negative HIV test result either after or up to 4 months before the initial TB episode. For HIV-positive patients, the CD4 count closest to the treatment start date of the initial TB episode (within 4 months) was used.

Mini CXRs taken at least 6 months prior to the

initial TB episode were graded for silicosis (using a 6-point scale modified from the International Labour Organization guidelines)<sup>20</sup> by an independent experienced reader unaware of the recurrence status. For the purposes of the study, silicosis was characterised as absent (0/0), early (0/1 or 1/0) and advanced (1/1 and above). Post-treatment scarring was determined using CXRs obtained at completion of treatment for the initial TB episode, dividing the lung on each side into three equal zones and allocating a score according to the number of zones involved.

### Laboratory methods

Microscopy was performed using auramine staining of concentrated sputum and fluorescent microscopy. Sputum was cultured on Löwenstein-Jensen (LJ) slopes and incubated for up to 6 weeks. A colorimetric ribosomal RNA hybridisation test (Accuprobe *M. tuberculosis*, followed by *M. kansasii* complex probe kit, Gen-Probe, San Diego, CA, USA, if not positive for *M. tuberculosis*) was used for initial species identification for LJ slopes with more than five colonies. Drug susceptibility testing (DST) for isoniazid (INH) and RMP was routinely carried out using the direct proportional method.<sup>21</sup>

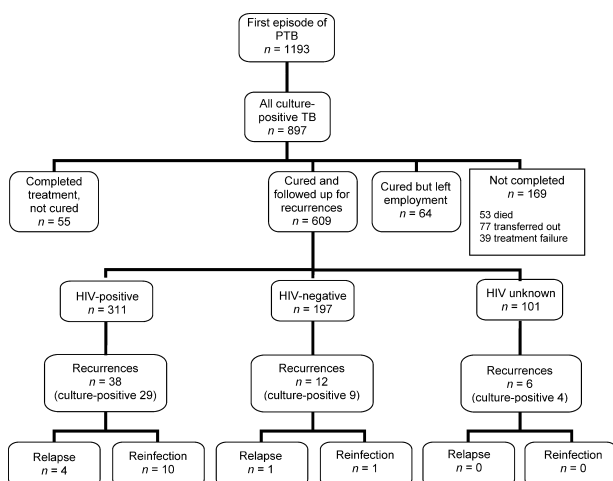
Positive cultures were transferred to 1.8 ml cryovials and frozen at  $-70^{\circ}\text{C}$ . For patients who experienced a recurrence, isolates were recultured on LJ slopes and transported to Stellenbosch University for IS6110 genotyping analysis.<sup>22</sup> Recurrent TB episodes were classified as reinfection if strains of the paired episodes differed by more than one band, or relapse if they were identical or differed by one band only.

Correlation between microscopy readers was determined every 3 months, and contamination and culture positivity rates were audited to minimise laboratory cross-contamination. All positive sputum smears and 10% of the negative smears were re-read at the reference laboratory. We stored duplicate cultures to confirm strain typing.

### Data analysis

Data were analysed using STATA 7.0 (Stata Corporation, College Station, TX, USA). For the survival analysis, patients entered the study on the date of documentation of completion of treatment for the initial episode of TB. Patients exited the study either when a recurrence occurred, when lost to follow-up or on 31 March 2002, whichever was earliest.

The primary analysis looked at risk factors for culture-positive TB recurrence. Secondary analyses were carried out stratified by HIV status. Cox regression was used to calculate unadjusted and adjusted hazard ratios (HRs) for potential risk factors, with *P* values based on the likelihood ratio test. We adjusted for age group and silicosis because of an a priori assumption that both are associated with increased risk of TB.



**Figure 1** Patient participation in the study. PTB = pulmonary tuberculosis; TB = tuberculosis; HIV = human immunodeficiency virus.

Ethics approval for this study was obtained from the ethics committees of the AngloGold Health Service, Welkom, South Africa and the London School of Hygiene and Tropical Medicine, London, UK.

## RESULTS

From 1 January 1999 to 30 June 2001, 1193 employees started treatment for their first episode of TB classified as pulmonary, of whom 897 had *M. tuberculosis* isolated on sputum culture. Figure 1 illustrates patient participation in the study. Six hundred and nine (311 HIV-infected) patients with a first-ever episode of culture-confirmed TB who were classified as cured and were still in employment at end of treatment formed the study cohort. Characteristics of study participants at the time of the first TB episode are shown in Table 1. Of 545 (89%) with DST data available, 34 (6%) had resistance to any drug and nine (1.6%) had multidrug resistance (to at least INH and RMP). The only baseline factor associated with HIV infection was less cavitation on the CXR at the end of the initial treatment.

Of the 609 patients, 56 (9%) experienced TB recurrence: 42 (75%) were sputum culture-positive. Of the culture-positive cases, 34 (81%) had more than one positive culture or were smear-positive. Due to problems with regrowth from frozen specimens, IS6110 genotyping on both the initial and subsequent isolate was available for only 16/42 (38%) pairs of specimens, 14 from HIV-infected and two from non-HIV-infected patients. IS6110 genotyping showed relapse in five (31%) cases (four HIV-infected, one non-HIV-infected) and reinfection in 11 (68%) cases (10 HIV-infected, one non-HIV-infected). Of the two patients with drug-resistant TB on the initial episode who had recurrence, only one had both strains fingerprinted and was found

**Table 1** Characteristics of participants at time of initial TB episode\*

	Non-HIV-infected n (%)	HIV-infected n (%)	HIV unknown n (%)	P value†
Total	197 (32)	311 (51)	101 (17)	
Age, years (n = 588)				0.178
<35	24 (13)	52 (17)	17 (18)	
35-44	94 (50)	156 (52)	46 (47)	
≥45	72 (38)	93 (31)	34 (35)	
Employment duration, years (n = 545)				0.300
<10	14 (8)	42 (14)	22 (25)	
10-19	59 (36)	104 (36)	30 (34)	
20-24	43 (26)	68 (23)	21 (24)	
≥25	49 (30)	78 (27)	15 (17)	
Residence (n = 530)				0.437
Hostel	122 (76)	207 (73)	63 (73)	
Other	38 (24)	77 (27)	23 (27)	
Microscopy (n = 609)				0.436
Negative	35 (18)	64 (21)	19 (19)	
Positive	162 (82)	247 (79)	82 (81)	
Drug resistance (n = 545)‡				0.473
Fully susceptible	163 (92)	260 (94)	88 (96)	
Any drug resistance	14 (8)	16 (6)	4 (4)	
Silicosis (n = 496)				0.654
Absent	107 (71)	201 (76)	62 (77)	
Early	19 (13)	27 (10)	10 (12)	
Advanced	23 (15)	38 (14)	9 (11)	
Scarring at treatment completion (n = 504)				0.308
No zones	6 (4)	16 (6)	4 (5)	
One zone	92 (58)	159 (61)	55 (65)	
Two or more zones	62 (39)	85 (33)	25 (30)	
Cavitation at treatment completion (n = 503)				<0.001
No	124 (78)	234 (90)	69 (82)	
Yes	36 (23)	25 (10)	15 (18)	

\* Measures at start of treatment unless otherwise indicated.

† P value is using a  $\chi^2$  test and comparing HIV-infected with non-HIV-infected.

‡ Any first-line TB drug resistance.

HIV = human immunodeficiency virus; TB = tuberculosis.

to have reinfection. In all five paired samples for which duplicate cultures were available, strain typing of the duplicates confirmed the original classification as relapse or reinfection.

Among 609 individuals, there were 56 recurrences over 709.6 person-years (py) (median follow-up 1.02 years), giving overall and culture-positive recurrence rates of 7.9/100 py (95% confidence interval [CI] 6.1-10.3) and 5.9/100 py (95% CI 4.4-8.0) respectively. By HIV status, the culture-positive recurrence rate was 8.7/100 py (95% CI 6.0-12.5) and 3.5/100 py (95% CI 1.8-6.8) for HIV-infected and non-HIV-infected patients, respectively. The median time to recurrence was 1.1 years in non-HIV-infected and 0.9 years in HIV-infected patients.

In the univariate analysis (Table 2), HIV infection was strongly associated with an increased rate of recurrence (HR 2.5, 95% CI 1.2-5.3,  $P = 0.01$ ), but age, employment duration, presence of silicosis and characteristics of the initial TB episode, such as TB cavitation and scarring at the end of the episode, were

**Table 2** Univariate and multivariate analysis of risk factors for culture-positive tuberculosis recurrence

	Events	py	Rate/100 py	HR (95%CI)	aHR (95%CI)*	P value
Overall	42	7096	5.9			
HIV						$P = 0.01$
Negative	9	2551	3.5	1	1	
Positive	29	3341	8.7	2.5 (1.2–5.3)	3.0 (1.3–7.0)	
Age, years						$P^T = 0.71$
<35	8	1167	6.9	1	1	
35–44	22	3467	6.4	0.9 (0.4–2.1)	1.6 (0.6–4.3)	
≥45	12	2115	5.7	0.9 (0.4–2.1)	1.6 (0.5–4.9)	
Employment duration, years						$P^T = 0.31$
<10	5	920	5.4	1	1	
10–19	13	2172	6.0	1.1 (0.4–3.2)		
20–24	12	1545	7.8	1.5 (0.5–4.2)		
≥25	12	1477	8.1	1.5 (0.5–4.4)		
Silicosis						$P^T = 0.31$
Absent	32	4232	7.6	1	1	
Early	4	661	6.1	0.8 (0.3–2.3)	0.6 (0.2–2.0)	
Advanced	3	707	4.2	0.6 (0.2–1.9)	0.6 (0.2–2.0)	
Drug-resistant TB <sup>†</sup>						$P = 0.76$
No	36	5927	6.1	1	1	
Yes	2	406	4.9	0.8 (0.2–3.4)		
Post-treatment scarring						$P = 0.40$
No zones	2	233	8.1	1	1	
One zone	22	3539	6.2	0.7 (0.2–2.9)		
Two or more zones	16	1785	9.0	1.0 (0.2–4.4)		
Cavitation at end of treatment						$P = 0.85$
No	33	4648	7.1	1	1	
Yes	7	901	7.7	1.1 (0.5–2.5)		

\* Multivariate model included silicosis, age and HIV status.

<sup>†</sup> Any first-line TB drug resistance.

py = person-years; HR = hazard ratio; CI = confidence interval; aHR = adjusted HR; HIV = human immunodeficiency virus;  $P^T$  =  $P$  value based on  $\chi^2$  test for linear trend; TB = tuberculosis.

not. In the multivariate model, HIV infection remained associated with increased rate of recurrence after adjustment for age group and silicosis (HR 3.0, 95%CI 1.3–7.0). Figure 2 shows a Kaplan Meyer graph for time to recurrence by HIV status.

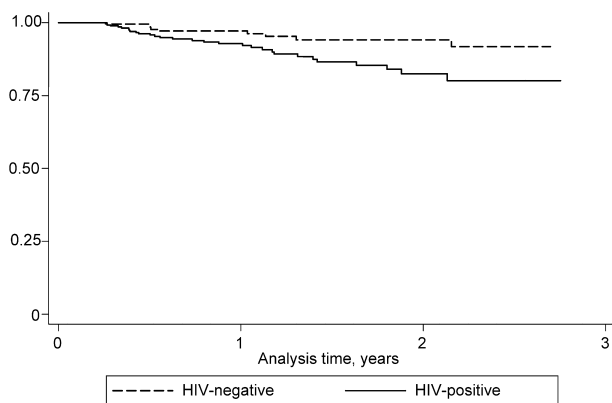
Among HIV-infected patients (Table 3), lower CD4 count was associated with increased risk of recurrence (taking CD4 <200 as the reference group, CD4 200–500 HR 0.4 [95%CI 0.1–1.1] and CD4 >500

HR 0.1 [95%CI 0.0–1.1],  $P_{\text{trend}} = 0.01$ ), as was employment duration ( $P_{\text{trend}} = 0.03$ ). In the non-HIV-infected group, the only risk factor associated with increased recurrence (although not statistically significant) was cavitation at completion of treatment (HR 3.3, 95%CI 0.9–12.3).

## DISCUSSION

The study documents very high rates of TB recurrence amongst gold miners in South Africa, with a substantial proportion due to reinfection, and HIV infection as the strongest risk factor for recurrence. The decreasing rate of recurrence associated with higher baseline CD4 count observed in HIV-infected individuals is consistent with previous work.<sup>23</sup> The absolute number of recurrences with genotype results was too small to show an association specifically between reinfection and CD4 count, but given that reinfection is the predominant cause of recurrence, such an association would be consistent with increasing risk of rapid progression to disease after a new TB infection with advancing immunosuppression.

A previous study in a different South African gold mine similarly showed high rates of recurrence, with reinfection as the predominant mechanism, in HIV-



**Figure 2** Kaplan Meyer graph of time to recurrence by HIV status among 963 individuals with known HIV status. HIV = human immunodeficiency virus.

**Table 3** Univariate analysis of culture-positive recurrences in HIV-infected patients

	Events	Rate/ 100 py	HR (95%CI)	P value
Overall	29	8.7		
Age, years				<i>P</i> = 0.48
<35	4	5.8	1	
35–44	16	10.2	1.8 (0.6–5.5)	
≥45	9	9.9	1.8 (0.6–5.9)	
Employment duration, years				<i>P<sub>T</sub></i> = 0.03
<10	2	3.8	1	
10–19	8	7.5	2.1 (0.4–9.9)	
20–24	8	10.7	3.0 (0.6–14.0)	
≥25	11	14.2	4.0 (0.9–17.9)	
Silicosis				<i>P</i> = 0.97
Absent	22	10.7	1	
Early	3	9.6	0.9 (0.3–3.0)	
Advanced	3	9.1	0.9 (0.3–3.0)	
Drug-resistant TB*				<i>P</i> = 0.63
No	25	9.0	1	
Yes	2	12.6	1.4 (0.3–6.1)	
Scarring at end of treatment				<i>P</i> = 0.56
No zones	2	14.4	1	
One zone	17	10.0	0.7 (0.2–2.8)	
Two or more zones	8	10.6	0.7 (0.2–2.6)	
Cavitation at end of treatment				<i>P</i> = 0.22
No	26	11.1	1	
Yes	1	3.9	0.4 (0.1–2.6)	
CD4 count, cells/μl†				<i>P<sub>T</sub></i> = 0.01
<200	9	16.5	1	
200–500	7	7.2	0.4 (0.1–1.1)	
>500	1	2.5	0.1 (0.0–1.1)	

\* Any TB drug resistance.

† CD4 counts available for 171 patients.

py = person years; HR = hazard ratio; CI = confidence interval; *P<sub>T</sub>* = likelihood ratio test for trend; TB = tuberculosis.

infected compared with non-HIV-infected persons.<sup>16</sup> The absolute rate of recurrence was lower in our study, perhaps because we only included individuals with a first-ever episode of TB. Reinfection was also an important mechanism of recurrence among non-HIV-infected persons in another setting of epidemic TB incidence.<sup>15</sup>

The predominance of reinfection as the cause of recurrence underlines the need to reduce TB transmission as part of the TB control strategy in this community. Active TB case finding is already conducted in gold mine workforces by means of a radiological screening programme, and ways to strengthen this should be considered. Infection control measures also need strengthening, particularly in health care settings in the light of the emergent threat of multi- and extensively drug-resistant TB.<sup>10</sup> As HIV infection is the strongest risk factor for recurrence and individuals with advanced immunosuppression are at highest risk, effective anti-retroviral treatment (ART) should reduce the risk of recurrence, as it does the risk of incident TB.<sup>24,25</sup> TB preventive treatment also reduces the risk of recurrence among HIV-infected individuals.<sup>7,23</sup> In settings of very high TB incidence, community-wide screening for TB followed by treatment of those with active disease and

TB preventive treatment for those without active disease may be the most rapid way to reduce TB transmission. This is currently being tested in South African gold mines. A key issue will be the durability of such an intervention.

Estimates of the proportion of relapse and reinfection are affected by study design issues. We recruited TB cases who achieved cure at the end of treatment, resulting in a population with a lower than average risk of relapse, which may partially explain the predominance of reinfection.<sup>26</sup> Conversely, the relatively short median follow-up period, because of the downsizing of the workforce and subsequent sale of the mine, would be likely to increase the proportion of recurrences due to relapse, as relapses would tend to occur fairly early whereas reinfection could continue indefinitely.<sup>16,26</sup>

Neither of these should affect the comparison between HIV-infected and non-HIV-infected individuals. Recurrences due to reinfection may be underestimated if there is little genotype diversity in *M. tuberculosis*, such that reinfection with the same strain may be misinterpreted as relapse. Previous studies in a similar population indicate that heterogeneity was sufficient to make the risk of reinfection with the same organism small.<sup>27</sup>

We assigned HIV status as determined at the time of the initial TB episode, but some initially HIV-negative participants may have become infected during follow-up. This is unlikely to affect our results, as median follow-up was short; any such misclassification would result in an underestimation of differences between HIV-infected and non-HIV-infected participants. HIV-infected individuals are more likely to experience rapid progression from new infection to disease,<sup>28</sup> and hence reinfections in HIV-negative individuals could take longer to become apparent and may thus be underestimated over a short follow-up period.

Gold miners have a relatively high prevalence of silicosis, which is associated with an increased risk of TB<sup>29</sup> but inconsistently associated with TB recurrence,<sup>9,16</sup> and was not a significant risk factor for recurrence in this study. Other factors associated with TB recurrence in similar settings, such as post-tuberculous scarring<sup>9</sup> and cavitation,<sup>16</sup> also did not emerge as risk factors for recurrence in our study.

Our study was limited by the failure of frozen isolates to grow after thawing, such that fingerprints were only available for 16 of 42 culture-positive recurrences (38%). There were no important differences in baseline characteristics between recurrent episodes with and without fingerprint results.

## CONCLUSION

This study highlights the importance of reinfection as a mechanism of recurrent TB, especially in HIV-infected individuals. This suggests an urgent need to

reduce TB transmission by improved infection control measures, a strong TB treatment programme and early detection of infectious cases in high HIV prevalence settings. Individuals at highest risk of progression to rapid disease after new infection require interventions to reduce their susceptibility, such as ART and TB preventive treatment, and further work is needed to determine how to combine these interventions most effectively.

#### Acknowledgements

The authors thank the participants and the staff of Aurum Institute for Health Research and Ernest Oppenheimer Hospital, AngloGold Health Services, particularly those from the TB laboratory, the radiology department, the TB clinic and the Prevention Clinic. A grant is supported by a UK Department of Health Public Health Career Scientist award. R Chaisson is supported by NIH Grant AI01637. Funding body: AngloGold Pty Ltd.

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**CONTEXTE :** Une mine d'or d'Afrique du sud.

**OBJECTIF :** Investiguer l'incidence et les facteurs de risque de récurrence de tuberculose (TB) ainsi que la contribution respective de la réinfection et de la rechute dans ces récurrences.

**SCHÉMA :** Enquête prospective de cohorte.

**MÉTHODES :** Les membres du personnel guéris après un premier épisode de TB à culture positive ont été suivis pour une éventuelle récurrence qui a été classifiée comme réinfection ou comme rechute grâce au test de polymorphisme de longueur des fragments de restriction utilisant une sonde IS6110.

**RÉSULTATS :** Sur 609 patients, une récurrence de TB est survenue chez 57 au cours d'un suivi médian de 1,02 années, correspondant à un taux de récurrence de 7,89 pour 100 années-personne (ap). Le taux de récurrence avec culture positive a été de 5,79/100 ap et s'est avéré plus élevé chez les patients infectés par le virus de l'immunodéficience humaine (VIH) (8,86/100 ap chez les sujets infectés vs.

3,35/100 ap chez les non-infectés). Parmi les patients infectés par le VIH, le risque de récurrence avec culture positive a été le plus élevé chez ceux dont le décompte de CD4 était plus bas (par comparaison avec les décomptes de CD4 < 200, les ratios de risque de récurrence parmi les individus dont les CD4 étaient entre 200 et 500 ou > 500 ont été respectivement de 0,40 [IC95% 0,14–1,09] et de 0,14 [IC95% 0,02–1,10] ;  $P_{\text{tendance}} = 0,01$ ). Le génotypage par IS6110 a été disponible à la fois dans les isolats initiaux et ultérieurs chez 16 des 42 patients où la récurrence s'accompagnait d'une culture positive (38%, 14 infectés par le VIH). La réinfection a été démontrée dans 11 cas (69%).

**CONCLUSION :** Chez les mineurs d'or infectés par le VIH, en particulier ceux dont l'immunodépression est la plus marquée, le risque de récurrence de la TB est plus élevé. Les stratégies de lutte antituberculeuse doivent tenir compte de la réinfection comme étant une cause importante de reprise de la TB.

**MARCO DE REFERENCIA :** Una mina de oro en Sudáfrica.

**OBJETIVO :** Investigar la incidencia y los factores de riesgo de recurrencia de tuberculosis (TB) y la contribución relativa de la reinfección y la recaída en la recurrencia.

**MÉTODO :** Estudio prospectivo de cohortes. Se practicó un seguimiento de los empleados curados después de un primer episodio de TB con cultivo positivo, en busca de casos de recurrencia, la cual se clasificó como reinfección o recaída mediante el polimorfismo de longitud de los fragmentos de restricción usando una sonda IS6110.

**RESULTADOS :** De los 609 pacientes, 57 presentaron recurrencia durante un período de seguimiento cuya mediana fue 1,02 años, lo cual corresponde a un índice de recurrencia de 7,89 por 100 años-persona (ap). El índice de recurrencia de cultivos positivos fue de 5,79 por 100 ap, más alto en pacientes infectados por el virus de la inmunodeficiencia humana (VIH) (8,86 por 100 ap comparado con 3,35 por 100 años-persona en pacientes

exentos de infección por el VIH). En los pacientes infectados por el VIH, el riesgo de recurrencia con cultivo positivo fue más alto entre más bajo fue el recuento de células CD4 (comparados con pacientes con recuentos de CD4 < 200, el cociente de riesgos instantáneos de recurrencia en personas con recuentos de CD4 entre 200 y 500 células fue de 0,40 [IC95% 0,14–1,09] y el de individuos con recuentos de CD4 > 500 fue de 0,14 [IC95% 0,02–1,10] ; la tendencia de  $P = 0,01$ ). Se obtuvo el genotipado con el segmento de inserción IS6110 en el aislado clínico inicial y en el segundo episodio en 16 de los 42 pacientes (38%, 14 de ellos infectados por el VIH) con recurrencia y cultivo positivo y se demostró reinfección en 11 casos (69%).

**CONCLUSIÓN :** Los trabajadores de las minas de oro infectados por el VIH, en particular aquellos con una mayor inmunodepresión, presentan un riesgo más alto de recurrencia de TB. Las estrategias de control de la TB deben tener en cuenta la reinfección como una causa importante de TB recurrente.