

Are people living with HIV (PLWH) more prone to relapse?

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Are People Living with HIV (PLWH) more prone to relapse?

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CONFLICT OF INTEREST DISCLOSURE FORM

I have no Conflict of Interest to report.

OUTLINE OF PRESENTATION

- Definitions
- What do we know about the extent of recurrence, relapse and re-infection?
- What do we know about the extent of relapse in PLWH?
- What are the implications for health services?

DEFINITIONS

Recurrent infection: A second episode of TB occurring after a first episode had been successfully treated.

Relapse: Reactivation of the 1st infection

Reinfection: Infection with another strain of TB.

Recurrence = relapse + reinfection

RELAPSE VS REINFECTION

- The question whether recurrent tuberculosis is due predominantly to relapse or reinfection has been a subject of debate for decades.
- Recent advances in genotyping technologies have made it possible to discriminate between relapse with the same strain that had caused previous TB episode and reinfection by a different strain.
- Efforts to distinguish relapse and reinfection are of great importance to formulate effective control strategies to address the burden of TB.

THE EXTENT OF RECURRENT TB, RELAPSE AND RE-INFECTION

- The pooled estimate of recurrent TB incidence across 145 studies was 2.26 per 100 person-years at risk (95% CI 1.88 – 2.72).
 - Low TB incidence settings: recurrence rates 1.47 per 100 person years
 - High TB incidence settings: recurrence rates 4.10 per 100 person years
 - Background HIV prevalence, treatment drug regimen, sample size and duration of follow-up were confounders.
 - HIV infection a strong risk factor for recurrence
- Recurrences = 71% relapses and 29% reinfections
 - Low TB incidence settings: Relapses 83% of the recurrences and reinfection 17%
 - High TB incidence settings: Relapses 59% of the recurrences and reinfection 41%
- In multivariate analysis only background TB incidence had a significant effect on the odds ratio for reinfections.
- HIV prevalence, study design, molecular method used, sample size and study quality, were all confounders.
- Study limitations include the limited power of meta-regression and the small number of studies included.

Vega V, Rodríguez S, Van der Stuyft P, Seas C, Otero L. Recurrent TB: a systematic review and meta-analysis of the incidence rates and the proportions of relapses and reinfections. *Thorax* 2021;76:494-502.

THE EXTENT OF RECURRENT TB, RELAPSE AND RE-INFECTION

Across 25 studies:

- Relapse: Time spanning less than two years was a risk factor (RR = 1.56, 95% CI: 1.33-1.85)
- Reinfection: Risk factors included:
 - Coinfection with HIV (RR = 0.72, 95% CI: 0.63-0.83)
 - Beijing family genotype (RR = 0.46, 95% CI: 0.32- 0.67)
 - History of imprisonment (RR = 0.36, 95% CI: 0.16-0.81)
 - Immigration (RR = 0.66, 95% CI: 0.53- 0.82)

Qiu B, Wu Z, Tao B, et al. Risk factors for types of recurrent tuberculosis (reactivation versus reinfection): A global systematic review and meta-analysis. *Int J Infect Dis* 2022;116:14-20.

WIDE DISPARITY ACROSS STUDIES

- Definitions
 - Reinfection with the same strain.
 - Timing of second episode.
- Different genotyping methods
- Length of follow-up
- Infectious environment (background incidence of TB)
- HIV incidence in study population

RISK FACTORS FOR RELAPSE AND REINFECTION

Individual risk factors

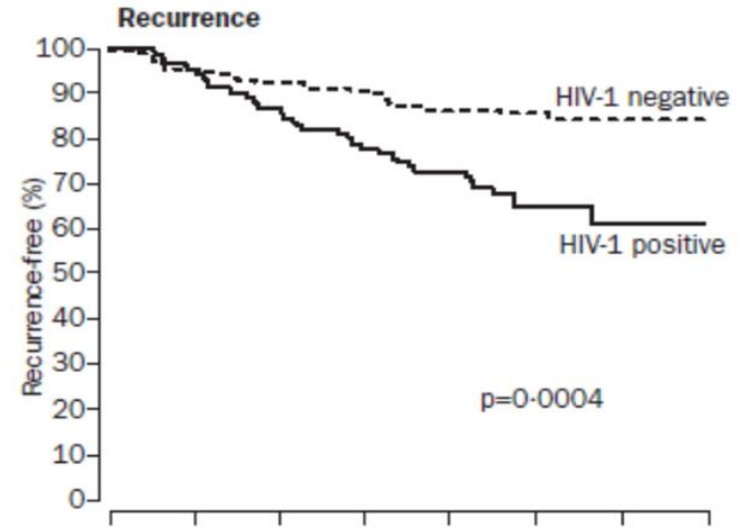
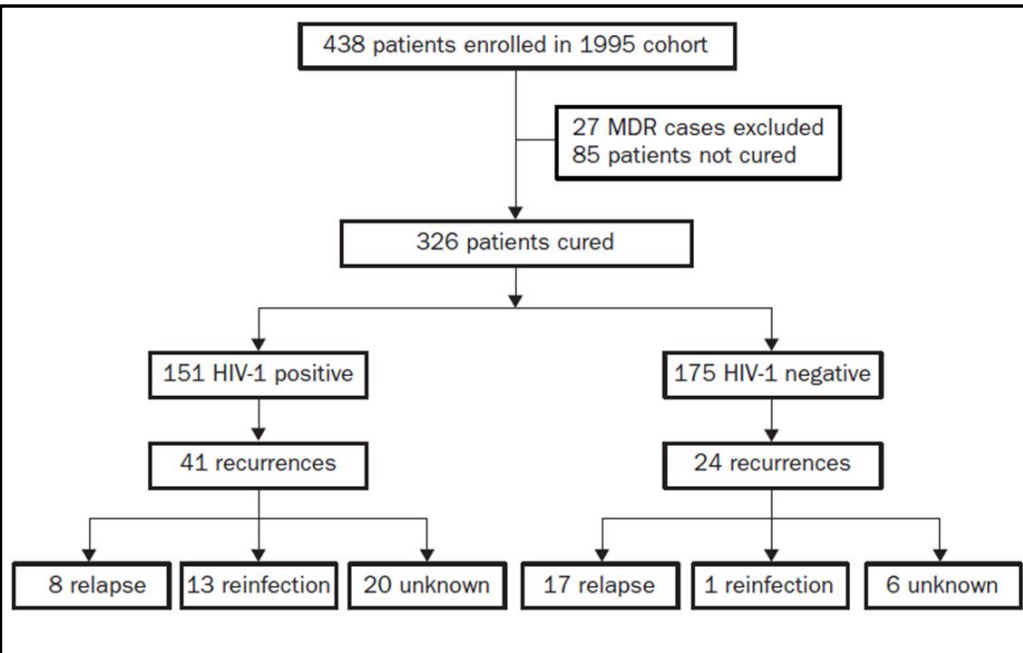
- Genetic predisposition
- Risk of individuals progression to active disease
- HIV and ART status
- Extent of lung damage or immunological deficiency caused by previous TB episode
- Cavitory disease
- Pre-existing chronic conditions e.g. COPD

Treatment related risk factors

- Inadequate treatment (older studies)
- Undetected pre-existing drug resistance
- Poor adherence to treatment
- Response to treatment:
 - smear positive at 2 months
- Treatment completion vs cure

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

Pamela Sonnenberg, Jill Murray, Judith R Glynn, Stuart Shearer, Bupe Kambashi, Peter Godfrey-Faussett



A recurrence rate of 10.3 episodes per 100 PYAR:

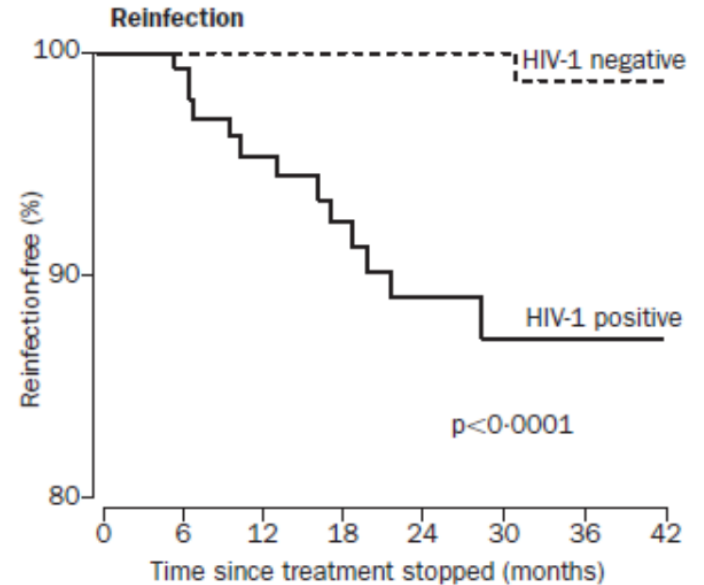
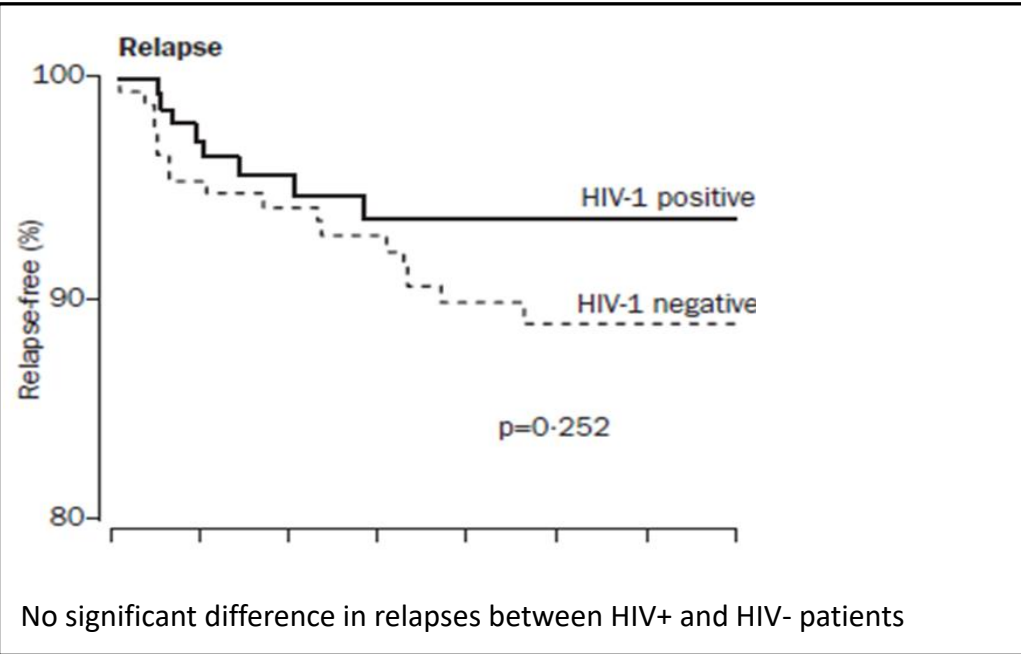
- 16.0 per 100 PYAR in HIV-positive miners
- 6.4 per 100 PYAR in HIV-negative miners

The unadjusted HR of TB recurrence in HIV+ compared with HIV- miners was 2.4 (1.5–4.0).

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

Virtual Event November 8-11

Pamela Sonnenberg, Jill Murray, Judith R Glynn, Stuart Shearer, Bupe Kambashi, Peter Godfrey-Faussett



62% recurrences in HIV+miners due to reinfection vs 6% in HIV-miners.

- HIV-infection was a risk factor for recurrence (HR 2.4) due to its strong association with reinfection (18.7) but not relapse (0.58).
- 93% recurrences within first 6 months due to relapse vs 48% of later recurrences.

SYSTEMATIC REVIEW 2003

Table 2. Estimated incidence of recurrences due to reinfection, and relapse, per 100 person years (95% confidence intervals)²⁰

Recurrences due to	HIV-	HIV+
Reinfection	0.35 (0.06–1.9)	11.0 (7.6–15.9)
Relapse	5.9 (3.9–9.0)	5.3 (3.1–9.0)

Table 3. Reinfection as the cause of recurrence, according to the estimated background tuberculosis incidence, and HIV status

Country of study	Reinfections among recurrences with fingerprinting results (%)		Odds ratio for recurrence due to reinfection HIV+/- (95% CI)
	HIV+	HIV-	
<i>Low tuberculosis incidence (<50/100 000/year)</i>			
Italy ²⁶	1/10 (10)	4/22 (18)	0.50 (0.02–6.40)*
Gran Canaria ²⁷	2/3 (67)	4/5 (80)	0.50 (0.01–34.8)*
USA ²²	1/1 (100)		
USA ²⁴	0/7 (0)		
<i>High tuberculosis incidence (50–499/100 000/year)</i>			
Kenya ¹⁹	1/3 (33)		
Uganda ¹²	0/3 (0)	0/1 (0)	
Hong Kong ²⁸		5/42 (12)†	
India ²¹		3/13 (27)†	
India ²²		9/29 (31)†	
Brasil ²⁵	3/3 (100)		
Kenya ²⁰	1/5 (20)		
<i>Very high tuberculosis incidence (>500/100 000/year)</i>			
South Africa ²⁵		12/15 (80)	
South Africa (miners) ⁷	13/21 (62)	1/18 (6)	27.63 (2.72–683)

Lambert ML, Hasker E, Van Deun A, Roberfroid D, Boelaert M, Van der Stuyft P. Recurrence in tuberculosis: relapse or reinfection? *Lancet Infect Dis* 2003;3:282-7.

OTHER AFRICAN STUDIES

Malawian studies (High TB and HIV incidence)^{1,2}

- Reinfection responsible for 44% of recurrent TB
- Rate of reinfection disease 2.2/ 100 person years in HIV-positives and 0.4/100 in HIV-negatives.
- Almost all relapses occurred in 1st 2 years.
- HIV infection associated with reinfection but not relapse.

Ugandan study (Moderately high TB and HIV incidence)³

Relapses higher than reinfections – 79% of recurrences in HIV-positive and 85% in HIV-negative.

BUT

- Short follow-up period (mean 1.24 years)
- Recurrence with same strain considered a relapse

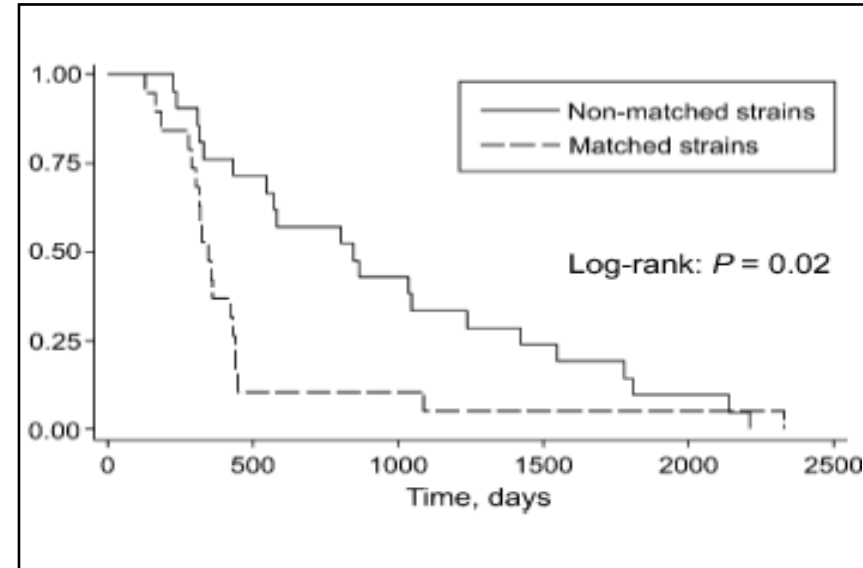
¹ Crampin AC, Mwaungulu JN, Mwaungulu FD, et al. Recurrent TB: relapse or reinfection? The effect of HIV in a general population cohort in Malawi. *Aids* 2010;24:417-26.

² Houben RM, Glynn JR, Mboma S, et al. The impact of HIV and ART on recurrent tuberculosis in a sub-Saharan setting. *Aids* 2012;26:2233-9.

³ Luzze H, Johnson DF, Dickman K, et al. Relapse more common than reinfection in recurrent tuberculosis 1-2 years post treatment in urban Uganda. *Int J Tuberc Lung Dis* 2013;17:361-7.

RECURRENT TB IN SOUTH AFRICA: THE ROLE OF RE-INFECTION, HIV AND ART

- In patients who interrupted their 1st course of treatment/failed treatment recurrence more likely due to relapse ($P = 0.04$).
- Re-infection predominated in patients who had completed their initial TB treatment and was associated with a longer time interval between episodes.
- HIV-positive patients and HIV-positive patients on ART were more likely to have a reinfection ($P = 0.01$ and $P = 0.03$). HIV-negative patients were more likely to have a relapse ($P < 0.001$).
- Patients with matching strains had shorter time intervals between episodes than patients with non-matching strains ($P = 0.02$).
- With increasing time from first episode, an increasing proportion of retreatment cases were due to re-infection:
 - 29% in the first year after the first episode
 - 44% in the second year
 - 83% in the third year
 - 88% >3 years after the first episode



Middelkoop K, Bekker LG, Shashkina E, Kreiswirth B, Wood R. Retreatment tuberculosis in a South African community: the role of re-infection, HIV and antiretroviral treatment. *Int J Tuberc Lung Dis* 2012;16:1510-6.

CONCLUSION

PLWH

- Higher rates of recurrence
- Higher rates of reinfection – associated with HIV status
- Relapse – Similar relapse rates documented in HIV-infected and uninfected people. But relapse rates not associated with HIV status

PLWH are at risk of relapse

- Immunosuppression
- Continuous exposure to health services

IMPLICATIONS FOR HEALTH SERVICES

- High rates of recurrent TB need to be addressed to address the global TB burden.
- TB programs should implement measures to ensure effective treatment of the first episode of TB:
 - Universal drug susceptibility testing to ensure adequate treatment is given
 - Adherence
 - Successfully cured TB patients should be followed up for a year post treatment
- Identify patients at risk of recurrence:
 - Treatment completion
 - Coinfection with HIV
 - Beijing family isolates
 - Imprisonment
 - Immigration.

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