Timing of TB episodes after the end of isoniazid preventive therapy: reinfection or reactivation?

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Background

- Upsurge in tuberculosis (TB) since advent of HIV epidemic in South Africa
- Isoniazid preventive therapy (IPT) reduces TB incidence among both HIV-infected and uninfected [1,2]
- Durability of protection is limited in high burden settings; mechanism is not well understood (reinfection or reactivation) [3]

The Thibela TB study

- Cluster-randomised trial to investigate impact of community-wide IPT on TB incidence and prevalence compared to standard of care among 15 clusters of gold mine workers in South Africa [4]
- High TB risk population; HIV prevalence estimated at 29% [5]

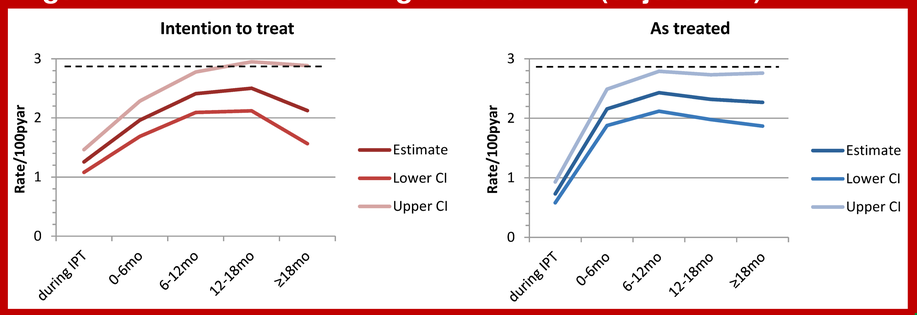
Objectives

1. To investigate the timing of TB incidence during and after IPT
2. To determine (i) risk factors associated with post-IPT TB incidence
   (ii) modifying effects of these factors with follow-up time

Methods

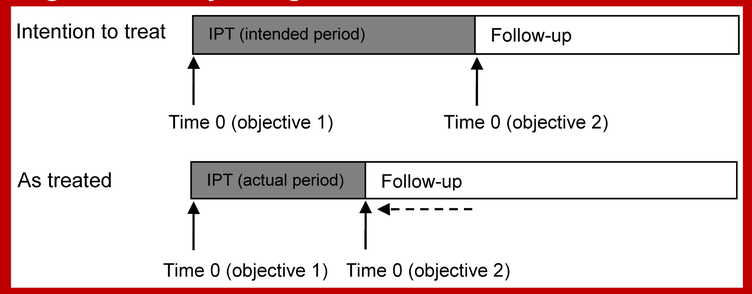
- Post-hoc analysis of IPT arm of Thibela TB study: included all participants prescribed at least one of intended 9 months of IPT
- Crude TB incidence rates were calculated during and after IPT, overall and stratified by follow-up time after end of IPT (per 6 months)
- Cox regression was used to analyse risk factors including cluster as fixed effect (8 intervention clusters)
- Effect modification of risk factors by follow-up time was investigated comparing <12 versus ≥12 months after stopping IPT
- All analyses were done intention to treat (ITT, using end of intended 9 months of IPT) and as treated (AT, using actual end of IPT; Figure 1)

Figure 2. TB incidence during and after IPT (objective 1)



Dashed line: TB incidence rate in control arm of Thibela TB study (2.8/100pyar) [4]; CI, confidence interval; mo, months; IPT, isoniazid preventive therapy; pyar, person years at risk.

Figure 1. Study design



IPT, isoniazid preventive therapy; time 0, start of at risk period.

Table 1. Baseline characteristics

Characteristic (n [col%])	Total n=18520	n (col%)
Gender	Male	17763 (96)
Age (mean [SD])		41 (9)
Years in workforce (median [IQR])		18 (8,26)
Type of work	Surface	1622 (9)
	Underground	16821 (91)
Type of housing	Hostel	10913 (59)
	Other	7606 (41)
Previous TB	No	16294 (88)
	Yes	2212 (12)
Number of INH prescriptions	1-2	5102 (28)
	3-5	2125 (11)
	≥6	11293 (61)

Col, column; INH, isoniazid; IQR, interquartile range; n, number; SD, standard deviation.

Results

- Total 18520 participants (Table 1)
- 708 TB cases during 32371 person-years at risk (pyar)
- ITT: on IPT 1.3/100 pyar (167/13284), off IPT 2.3 541/24037); rate ratio 1.8 (95% CI: 1.5-2.1)
- AT: on IPT rate 0.7/100 pyar (70/9531), off IPT rate 2.30 (638/27790); rate ratio 3.3 (95% CI: 2.5-4.2)
- Increase in rate after cessation of IPT, thereafter no evidence for varying rates over time (Figure 2)
- Well known TB risk factors were associated with post-IPT TB in the ITT analysis (Table 2). AT analysis results were similar (data not shown).
- No effect modification of risk factors by time of follow-up after IPT (data not shown; no evidence for a waning of the protective effect of 3-5 or ≥6 months versus 1-2 months of IPT over time [*P*-value for interaction 0.86]).

Table 2. Factors associated with TB incidence after cessation of IPT (objective 2, ITT)

Risk factor		pyar	TB	aHR (95% CI)[1,6]	*P*-value
Gender	Male	26597	619	1	0.92
	Female	1191	19	0.98 (0.61-1.58)	
Age (years)[2]	≤29	4079	36	1	<0.001
	30-39	7893	159	2.29 (1.59-3.30)	
	40-49	11536	321	2.98 (2.09-4.24)	
	≥50	4280	122	2.92 (1.98-4.29)	
Country of origin	South Africa	16033	330	1	0.16
	Lesotho	7338	223	1.18 (0.98-1.41)	
	Mozambique	2904	53	0.91 (0.68-1.23)	
	Other	1503	32	0.87 (0.60-1.28)	
Type of work	Surface	2511	34	1	<0.001
	Underground	25155	601	1.80 (1.26-2.55)	
Type of housing	Hostel	16392	423	1	0.003
	Other	11396	215	0.76 (0.63-0.91)	
Previous TB	No	24828	498	1	<0.001
	Yes	2939	140	2.05 (1.68-2.50)	
ART use[3]	No	27070	611	1	0.59
	Yes	689	25	1.12 (0.74-1.69)	
Number of INH prescriptions[4,5]	1-2	9517	228	1	<0.001
	3-5	3260	78	0.89 (0.69-1.16)	
	≥6	15013	332	0.66 (0.54-0.79)	

[1]Adjusted for cluster. *P*-value for departure from linearity [2]0.002 and [4]0.65; [3]self-reported; [5]*P*-value for linear trend 0.05; [6]on 17852 individuals. aHR, adjusted hazard ratio; ART, antiretroviral therapy; CI, confidence interval; HR, hazard ratio; INH, isoniazid; pyar, person-years at risk; TB, tuberculosis cases.

Conclusions

- Steep and early increase in TB incidence after stopping IPT, followed by rate stable and similar to rate in control arm [4].
- No evidence of differing risk factors or waning protective effect of INH over time after stopping IPT; some evidence that optimal dose of INH increases protection which is maintained ≥12 months after stopping IPT.
- **Sharp increase may point to reactivation disease, but cannot exclude reinfection with fast progression to active disease in this population with high annual risk of infection and high HIV burden**.

References

1. Smieja, Marchetti, Cook et al, Cochrane Datab Syst Rev 2000(2):CD001363.
2. Akolo et al, Cochrance Datab Syst Rev 2010(1):CD000171.
3. Esmail et al, Drug Discov Today. 2012;17(9-10):514-21.
4. Churchyard et al, NEJM 2014;370(4):301-10.
5. Lewis et al. Am J Respir Crit Care Med. 2009;180(12):1271-8.