Analysis of time to positivity of Mycobacterium tuberculosis in response to treatment for drug susceptible tuberculosis in South African patients

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Background and objectives

- Tuberculosis (TB) disease burden in South Africa is substantial[1]
- Despite relatively high treatment success rates,[1] TB mortality and subsequent complications remain significant
- Identifying factors impacting treatment outcome is imperative

Objective: To characterize mycobacterial clearance from sputum in South African pulmonary TB patients, using Mycobacterium tuberculosis growth indicator tube (MGIT) time to positivity (TTP) as biomarker, and identify influencing factors

Methods

Study design and sample collection

- Observational study (Tuberculosis Treatment and Alcohol Use Study, NCT02840877) in Worcester, South Africa, recruited drug-susceptible pulmonary TB patients
- First-line TB treatment with rifampicin, isoniazid, pyrazinamide and ethambutol using weight-based dosing according to the World Health Organization's guidelines[2]
- Sputum was collected at baseline and weekly for another 11 weeks (Figure 1)

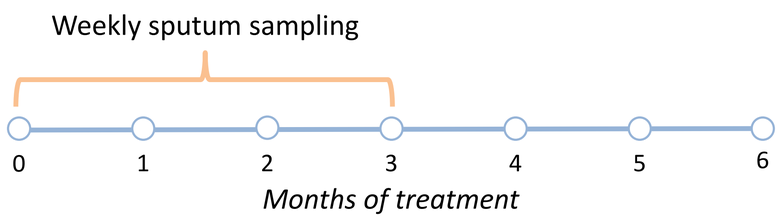

Figure 1: Sample collection

- Bacillary load was quantified using MGIT, capturing TTP
- Contaminated samples were discarded

Population PD modelling

- NONMEM version 7.5.0, using Perl-speaks-NONMEM, was used to describe the relationship between TTP and time on treatment, estimating baseline TTP and response in TTP with time on treatment
- Exponential, linear, and broken-stick models were tested
- Samples remaining TB negative after a 42-day incubation period in the MGIT were treated as above the upper limit of quantification (ULOQ) in the analysis.
- ULOQ data was censored using the M3 method in combination with Laplacian estimation[3]
- Additive, proportional and combination error models were tested to describe the residual variability
- Tested covariates: HIV status and lung cavities

Results: Patient characteristics

Table 1: Participant characteristics (N=316)

Covariate	Median (IQR) or n (%)
Males	191 (60)
Age (years)	38 (27-49)
Weight (kg)	47.3 (42.5-54.2)
BMI (kg/m^2)	17.8 (16.4-19.8)
Living with HIV	87 (28)
Lung cavities	198 (63)

In total 2480 observations were included in the analysis, out of which 49% were above ULOQ.

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Results: Model

- An exponential model estimating baseline TTP and response in TTP with time on treatment fit the data best
- Estimated typical values were 10 days for baseline TTP and 0.38 per treatment week for response in TTP with time on treatment (Table 2) The visual predictive check (VPC) in Figure 2 indicates good model fit.
- Having lung cavities resulted in 32% shorter baseline TTP (dOFV=-48.6, p<0.001) and 29% slower response in TTP with time on treatment (dOFV=-14.9, p<0.001)
- Participants living with HIV had 15% longer baseline TTP than HIV negative participants (dOFV=-4.08, p = 0.04)

Table 2: Final parameter estimates (95% CI)[a]

Parameter	Typical Value	Variability (%CV)
Baseline TTP (days)	9.91 (8.69 – 11.4)	37.5 (31.6 – 43.6)
Response in TTP with time on treatment (per week)	0.374 (0.308 – 0.449)	58.7 (51.2 – 67.1)
Box-cox transformation BSV baseline TTP	1.23 (0.70 – 2.0)	
Effect of lung cavities on baseline TTP (%)	-32.0 (-40.8 – -23.4)	
Effect of lung cavities on response in TTP with time on treatment (%)	-28.6 (-42.5 – -9.15)	
Effect of living with HIV on baseline TTP (%)	15.2 (4.64 – 25.5)	
Proportional error (%)	36.0 (34.3 – 37.6)	

Parameter variability was included as between-subject variability.
[a] Confidence intervals calculated using Sampling Importance Resampling (SIR).

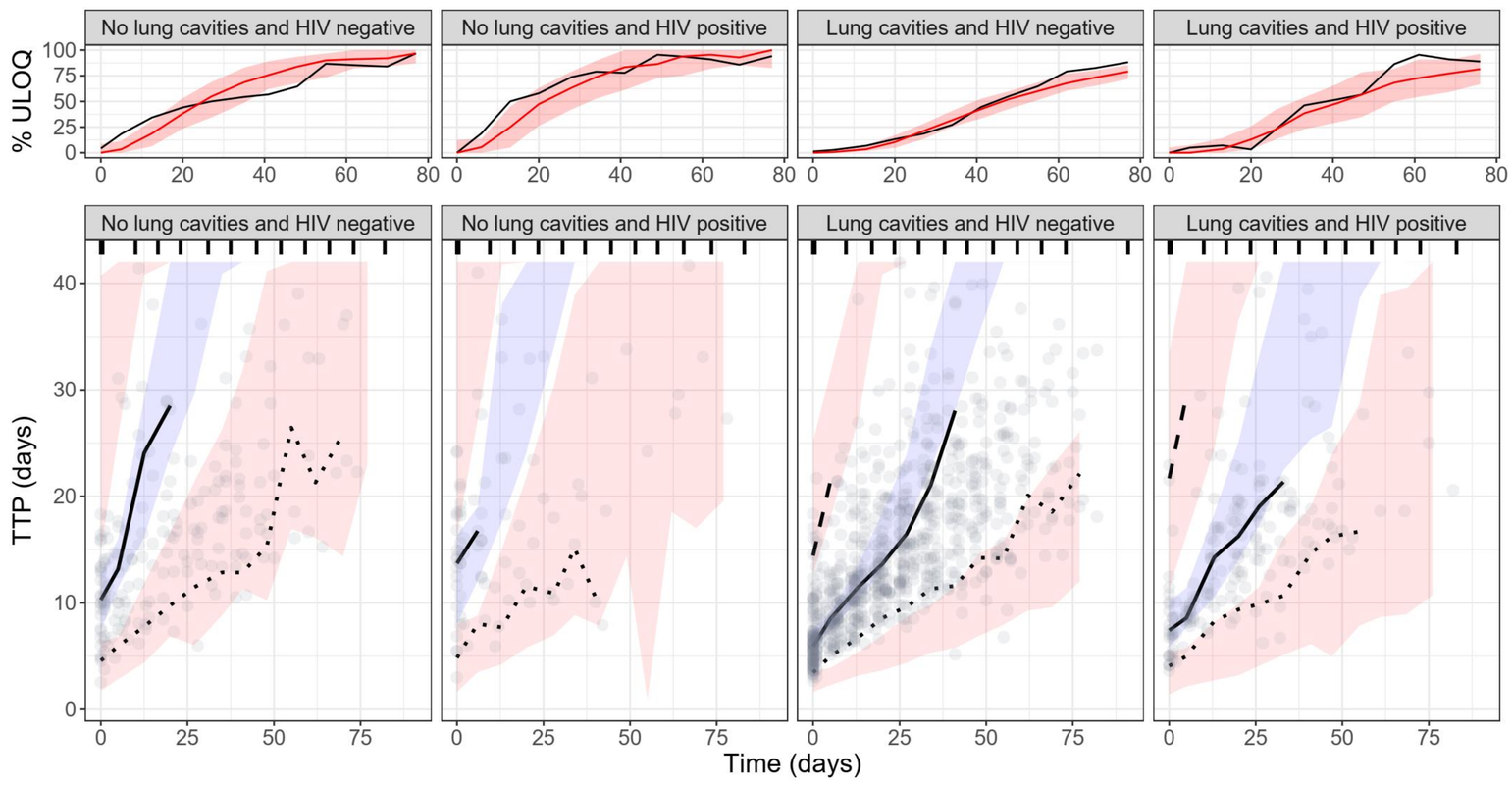

Figure 2: Visual predictive check (VPC). The solid and dashed lines are the 5th, 50th, and 95th percentiles of the observations, while the shaded areas represent the 95% model predicted confidence intervals for the same percentiles.

Discussion and conclusion

- An exponential model parameterized in terms of baseline TTP and response in TTP with time on treatment was developed, similar to previous findings[4]
- Consistent with existing literature,[5-6] individuals with lung cavities displayed higher baseline bacterial load and slower response in TTP with time on treatment in comparison to those without lung cavities, and participants living with HIV had a lower baseline bacterial load compared to participants not living with HIV
- Longitudinal analysis of TTP data is a more robust approach compared to the customary focus on time to culture conversion[7]

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