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

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Introduction: Tuberculosis is the primary cause of death by an infectious agent globally. In South Africa, the burden of tuberculosis is substantial, and over half of tuberculosis patients are living with HIV. Despite relatively high treatment success rates, tuberculosis mortality and subsequent complications remain significant, and identifying factors affecting treatment outcome is crucial. The sterilization of tuberculosis is associated with both treatment outcome and relapse, and early sterilization might indicate improved treatment outcomes. This work aimed to characterize mycobacterial clearance from sputum in South African patients with drug-susceptible pulmonary tuberculosis and identify influencing factors.

Methods: Within an observational study conducted in Worcester, South Africa, pulmonary tuberculosis patients received first-line tuberculosis treatment with weight-based dosing: rifampicin (8-12 mg/kg), isoniazid (4-6 mg/kg), pyrazinamide (20-30 mg/kg), and ethambutol (15-25 mg/kg). Sputum samples were collected at baseline and weekly for 12 weeks. Bacillary load was quantified using the growth detection system Mycobacterium tuberculosis (Mtb) growth indicator tube (MGIT), capturing time to positivity (TTP). Samples not yielding a positive result within a 42-day incubation period in the MGIT were considered negative and treated as above the upper limit of quantification (ULOQ) in the analysis. Samples showing contamination were discarded. We utilized nonlinear mixed effects modelling in NONMEM to describe the relationship between TTP and time on treatment. Exponential, linear and broken-stick models were evaluated, estimating baseline TTP and response in TTP with time on treatment. Interindividual variability was assumed to be log-normally distributed and additive, proportional and combination error models were tested to describe the residual variability. Covariates tested included the effect of HIV status, lung cavities and other patient characteristics.

Results: The analysis included 305 participants, with a majority being male (60%). 27% were living with HIV, and 64% displayed lung cavities. Median age was 38 years (range 15-77), and median weight was 47.1 kg (range 29.6-97.7). A total of 2364 samples were available, of which 49% were

ULOQ. The relationship between baseline TTP and response in TTP with time on treatment was best described by an exponential model, with residual variability described by a proportional error model. The M3 method, in conjunction with Laplacian estimation, was used to censor ULOQ data. Estimated typical values were 10 days for baseline TTP and 0.38 per treatment week for the response in TTP with time on treatment. Having lung cavities resulted in a 32% shorter baseline TTP (dOFV = -48.6, $p < 0.001$), meaning a higher initial bacterial load, and a 35% slower response in TTP with time on treatment (dOFV = -14.9, $p < 0.001$). Participants living with HIV had a 12% longer baseline TTP compared to HIV-negative participants (dOFV = -4.08, $p = 0.04$).

Conclusion: We developed an exponential model to estimate baseline TTP and response in TTP with time on treatment, similar to previous findings. Consistent with existing literature, individuals with lung cavitation displayed a higher baseline bacterial load and slower response in TTP with time on treatment in comparison to those without lung cavitation, and participants living with HIV had a lower baseline bacterial load.