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Pharmacodynamic Biomarkers for Quantifying the Mycobacterial Effect of High Doses of Rifampin in Patients with Rifampin-susceptible Pulmonary Tuberculosis

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Abstract

Background—Suboptimal drug exposure in patients with drug-susceptible tuberculosis (DS-TB) can drive treatment failure. Pharmacodynamics (PD) biomarkers such as the plasma TB drug-activity (TDA) assay may guide dose finding studies and predict microbiological outcomes differently than conventional indices.

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Ethical clearance
A waiver of informed consent was obtained from Scientific and Ethics Review Committee (SERC) of Centre for Innovative Drug Development and Therapeutic Trials for College of Health Sciences, Addis Ababa University.

Conflicts of interest
There are no conflicts of interest.

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Methods—A study was nested from phase 2b randomized double-blind controlled trial of Tanzanian patients who received a 600 mg, 900 mg, or 1200 mg with a standard dose for DS-TB. Serum at 6 weeks collected over 24-h at 2-h intervals was collected for rifampin area under the concentration–time curve relative to minimum inhibitory concentration (AUC_{0-24}/MIC) or peak concentration and MIC (C_{max}/MIC). TDA was the ratio of time-to-positive growth of the patient's *Mycobacterium tuberculosis* isolates with and without coculture of patient's plasma collected at C_{max}. Spearman's rank correlation (r) between PD parameters and culture convention on both liquid and solid culture media.

Results—Among 10 patients, 600 mg (3), 900 mg (3), and 1200 mg (4) of rifampin dosages. The mean ± standard deviation (SD) of AUC_{0-24}/MIC for patients on 600 mg was 168 ± 159 mg·h/L, on 900 mg was 169 ± 166 mg·h/L, and on 1200 mg was 308 ± 238 mg·h/L. The mean-TDA (SD) was 2.56 (±0.75), 1.5 (±0.59), and 2.29 (±1.08) for patients on 600 mg, 900 mg, and 1200 mg rifampin doses, respectively. Higher TDA values correlated with faster time to culture convention on both liquid (r =–0.55, P = 0.099) and solid media (r =–0.65, P = 0.04).

Conclusions—TDA and rifampin AUC_{0-24}/MIC did not trend as expected with rifampin dose, but TDA better predicted the time to sputum culture conversion. TDA may provide additional discrimination in predicting treatment response for some regimens distinct from plasma exposure relative to MIC or mg/kg dose.

Keywords

Mycobacterial activity; pharmacodynamic biomarkers; tuberculosis; tuberculosis drug activity

Introduction

Tuberculosis (TB) is still a major chronic infectious disease of humankind, caused by *Mycobacterium tuberculosis*.[1] For the past 10 years, the annual estimates of TB incidence rate remained at 10 million people worldwide.[2] TB remains the leading cause of death from a single bacteria accounting for approximately 1.4 million deaths in 2019.[3–5] In resource-limited settings like Tanzania, TB is treated based on an adapted "one-size fits all" regimen for all patients with weight-based stratifications of dosages.[6] Such strategies may not account for the considerable pharmacokinetic (PK) variability observed in people with common comorbidities such as human immunodeficiency virus (HIV), diabetes mellitus, or malnutrition, which can impact drug absorption, distribution, metabolism, and excretion. PK variability, particularly failure to reach minimal exposure targets, may result in unfavorable TB treatment outcomes including clinical or microbiological treatment failures, relapse of disease after treatment completion, and acquired drug resistance.[7,8]

Globally, unfavorable treatment outcomes occur in 15% of all cases.[3,9] Most anti-TB drugs are concentration dependent in their activity, whereby higher concentrations relative to the *M. tuberculosis* minimum inhibitory concentration (MIC) result in improved killing.[10–12] Improving exposures, such as with higher milligram per kilogram (mg/kg) dosages, may not only prevent treatment failure but also lead to regimens of significantly shorter treatment duration.[13]

Conventional pharmacodynamics (PD) indices such as the 24-hour area under the concentration–time curve (AUC_{0-24}) or maximum achieved concentration (C_{max}) can be measured in the serum, and for some critical anti-TB drugs such as rifampin, have been associated with declines in sputum *M. tuberculosis* bacterial count over time on treatment.[14] In addition, bacterial killing can also be measured by coculture of *M. tuberculosis* with a patient's whole blood or plasma while on TB treatment.[13] The use of plasma collected at the time of estimated C_{max} for an anti-TB drug has been termed the TB drug activity (TDA) assay and calculated as the ratio of the time to detection (TTD) of plasma cocultured with a standardized inoculum of the patient's own *M. tuberculosis* to the TTD of *M. tuberculosis* inoculum alone without first coculturing with plasma.[15] TDA values >1 indicate killing of bacteria with drug present in the plasma. To date, TDA has been performed in observational settings in people treated with traditional doses of rifampin at the minimal efficacious dose (~10 mg/kg or 600 mg maximum). To compare TDA to other conventional PD indices, we studied a subset of patients enrolled in a trial of higher dosages of rifampin in Tanzania.

Subjects And Methods

Designs and patients

This was a secondary data analysis for patients who were consented to participate in a clinical phase trial IIb of 600 mg, rifampin at 900 mg, or 1,200 mg with a standard background regimen of isoniazid, pyrazinamide, and ethambutol for streptomycin, in a drug- susceptible pulmonary TB patients from July 2010 to September 2013 in Tanzania. The study was approved by the Kilimanjaro Christian Medical College Research Ethics and Review Committee (CRERC), the Ifakara Health Institute Institutional Review Board (IHI-IRB), and the Tanzanian National Health Research Ethics Subcommittee (NatHREC). The trial was registered at ClinicalTrials.gov under identifier NCT00760149(https://clinicaltrials.gov/ct2/show/NCT00760149). This secondary analysis was additionally approved by the Scientific and Ethics Review Committee of CDT-Africa by ref no. CDT/0278/21 and the administrations of the study sites including the Kibong'oto Infectious Diseases Hospital and Mawenzi Regional Hospital in the Kilimanjaro region and IHI/Bagamoyo Research and Training Centre.

Source data and variables collected

Datasets for this secondary analysis were sought from the corresponding author of the primary study.[16] From these datasets, we abstracted (i) clinical and demographic data such as gender, age, weight, and height and (ii) 6-week PK/PD data including drug dosage, rifampin C_{max}, rifampin time to maximum concentration (T_{max}), rifampin AUC_{0-24}, and TDA. Plasma samples for TDA were collected at 2 h after a directly observed dose. C_{max} and T_{max} were observed values, and AUC_{0-24} was calculated. All were using non-compartmental analysis with software WinNonLin version 6.3 software (Pharsight Corp, Mountain View, CA, USA). PK performed from samples collected at 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 24 hours after the directly observed dose. Plasma was separated within 1 h of collection of blood and was frozen at 20°C, transferred to 80°C within 72 h, and transported on dry ice to the Radboud University Medical Center, Nijmegen, the Netherlands, for bioanalysis by ultraperformance liquid chromatographic. TDA was performed onsite at the

Kilimanjaro Clinical Research Institute. Sputum culture results of both solid Lowenstein-Jensen (LJ) and liquid media in the mycobacteria growth indicator tube (MGIT, Bactec), from pretreatment, 4, 6, 8, 10, and 12 weeks were used to determine the time to sputum culture conversion to negative (no growth). The MIC for rifampin from the *M. tuberculosis* pretreatment isolate was measured by Sensititre MycoTB MIC plate as described previously using serial 2-fold dilutions of antibiotics.[17] The *M. tuberculosis* H37Rv strain was included as an internal control in MGIT, and the MIC of a drug was considered the lowest concentration able to inhibit visible growth.

Data management and statistical analysis

Variables were recorded in Excel and involved constructing conventional PD parameters ($AUC_{0\text{-}24\ h}$/MIC, C_{max}/MIC), by dividing PK values by the rifampin MIC. For continuous data, mean and standard deviation (SD) among the three rifampin arms were compared using ANOVA. Nonparametric data variables were presented using median and interquartile range (IQR). PD parameters ($AUC_{0\text{-}24\ h}$/MIC or C_{max}/MIC) were compared among the different drug dosage groups using Kruskal–Wallis test. Spearman's rank correlation tested correlation coefficient (r) between plasma drug activity (TDA) and sputum culture conversion on both MGIT and LJ and correlation between TDA and rifampin C_{max}/MIC. All statistical calculations were performed using R version 4.0.5 (2021-03-31) (https://www.r-project.org/).

Results

Patients characteristics

In total, 37 patients were enrolled and had plasma collected for PK testing at 6 weeks. However, of these, only 10 patients met full inclusion criteria with MIC testing available [Figure 1]. Of the 10 patients, 3 received 600 mg, 3 received 900 mg, and 4 received 1200 mg of rifampin. In total, 9 (90%) of the patients were male and had a mean (± SD) age of 40.1 ± 7.9 years. All patients were above 50 kg and their mean body weight was 55.6 ± 3.3. The mean C_{max} concentration for patients receiving the standard dosage of 600 mg of rifampin was below the recommended minimum reference value of at least 8 mg/liter, but there was a significant increase in C_{max} concentration ($P = 0.04$) and $AUC_{0\text{-}24}$ ($P = 0.02$) with dose increase [Table 1].

The overall mean ± SD $AUC_{0\text{-}24}$/MIC was 224.7 ± 188.4, which only increased in the 1200 mg rifampin dosage group [Table 2]. Furthermore, the overall median (interquartile-range) rifampin of C_{max}/MIC was 37.7 (1.2 – 75.9) and it showed a non-statistically significant increase in median value ($p = 0.689$), with 26.7(13.4 – 52.1) for those receiving 600 mg rifampin, 38.5 (19.7 – 57.2) for those receiving 900 mg, and 57.5 (36.8 –91.0) for receiving 1200 mg [Table 2, $P = 0.762$]. Table 2 demonstrates the importance of MIC whereby C_{max} and $AUC_{0\text{-}24}$ increased significantly with dose category [Table 1]; this was also observed slightly when including MIC [Table 2] for which even a two-dilution μg/mL increase in MIC within an otherwise susceptible range can dramatically lower the $AUC_{0\text{-}24}$/MIC value.

Pharmacodynamic indices and sputum culture conversion

While the mean TDA values did not consistently increase with increasing dose category from 600mg, 900 to 1200mg (2.2 ±0.75, 1.36 ± 0.59, 3.2 ±1.05) [Table 2] ($P = 0.855$), this did not mirror the rifampin $AUC_{0\text{-}24}$/MIC changes within the dose categories but both the lowest $AUC_{0\text{-}24}$/MIC and TDA values were observed for the patients in the 600 and 900 mg dosage categories. Previously, a TDA value of 1.5 or greater indicated a non-stasis degree of killing, and in this study 7 (78%) of patients had TDA values of 1.5 or greater (regardless of dosage category). However, we did observe a significant linear correlation with higher 6-week TDA values and faster time to sputum culture conversion in both MGIT and LJ ($R = -0.55$, $P = 0.099$) and ($R = -0.65$, $P = 0.04$) by Spearman's-rank correlation test in [Figure 2]. This is contrary to the lack of correlation of rifampin $AUC_{0\text{-}24}$/MIC and time to sputum culture conversion in both MGIT and LJ ($R = 0.24$, $P = 0.5$) and ($R = 0.0098$, $P = 0.79$) by Spearman's-rank correlation test in [Figure 3]. A similar lack of correlation of rifampin C_{max}/MIC and time to sputum culture conversion in MGIT ($R = 0.045$, $P = 0.9$) and LJ ($R = 0.086$, $P = 0.81$).

Discussion

In this study of PD biomarkers (C_{max}/MIC, $AUC_{0\text{-}24}$/MIC) and TDA with different rifampin dosages, while PK exposure generally increased with increased dose, the effect was blunted when considering MIC. TDA appeared to correlate better with sputum culture conversion in both MGIT and LJ at 12 weeks than with conventional PD biomarkers.

In strains of *M. tuberculosis* that are susceptible to rifampin, TDA determinations can offer some proof for dose adjustment through increases in Cmax/MIC and enhanced killing by rifampin.[18] The current study included a minimal number of subjects in each dosing and given this small number of participants, there was no significant correlation of rifampin C_{max}/MIC and TDA, as would otherwise have been expected. Furthermore, the TDA assay includes plasma containing all administered drugs (rifampin, isoniazid, pyrazinamide, and ethambutol), and therefore individual variability of another drug peak concentration besides rifampin may have accounted for more of the bacterial killing in a given TDA assay that could have obscured trends across rifampin dosage group. Plasma drug concentrations other than rifampin were not available. Patients in the 600 mg and 1200 mg groups did have the highest mean TDA, which were well above the cutoff of 1.5, which previously had been associated with bacterial killing above stasis.[19]

It was identified that concentration not constantly varying as expected in subjects initiating drug-susceptible TB (DS-TB) treatment at different rifampin drug dosages when measured at 6 weeks of treatment, which reinforced prior observations that even with dose increase, rifampin exhibits considerable PK variability.[20] Despite inter-individual PK variability and expected variability of MIC with so few participants, there was still a slightly mean increase in $AUC_{0\text{–}24}$/MIC and at the highest increase in rifampin dosage of the 1200 mg arm there was increase of 1.8-fold above the conventional 600 mg arm (from 168 to 308 mg h/liter), which reflects a dose-proportional increase in the level of exposure with the dose. Other studies have found a greater exposure ($AUC_{0\text{-}24}$) response relative to dose doubling for rifampin and may indicate that in this subset of the population, that 1200 mg may even

be on the lower end of the dose–response curve. Further studies should follow the PK-PD guidelines for the development of antimicrobial medicinal products by the Committee for Medicinal Products for Human Use (CHMP).[21]

The main objective of this study was to compare PD parameters for rifampin that describe the mycobactericidal effect of high rifampin dose. In the hollow fiber model, an *in vitro* system used for dose finding and novel regimen development, rifampin AUC_{0-6}/MIC ratios >24.14 (96.56 in 24 h) were associated with improved killing capacity against *M. tuberculosis* [22] The overall mean rifampin AUC_{0-24}/MIC in this study was 254 (63.5 in 6 h), thus exceeding the *in vitro* system threshold. In line with these findings, a study model demonstrated by Kloprogge *et al.* of MIC-adjusted PK estimates (C_{max}/MIC or AUC_{0-24}/MIC) found association with those indices and sterilizing effect of anti-TB drugs at month 2 during treatment.[23] In contrast, our study did not find a correlation with rifampin C_{max}/MIC or AUC_{0-24}/MIC and time to sputum culture conversion. It is possible that measurement of a single day of drug exposure at 6 weeks as was done in this study does not fully capture the PD dynamics over the entire 2 months of treatment.

Instead, this study demonstrated the important differences among PD parameters, such as the difference in individual drug AUC_{0-24}/MIC (for in this case, rifampin) and total drug plasma PD (in this case, TDA) in predicting microbiological outcome.[24–27] The superiority of TDA in predicting time to sputum culture conversion may not only be reflective of the multiple drug concentrations in the plasma but also contributed by the variability of growth mechanisms for the *M. tuberculosis* plasma co-cultured. While these PD parameters can serve as important targets for dose finding studies and development of novel drug regimens, they may also be used to target individual dose optimization in routine clinical care. Unfortunately, chromatography or mass spectrometry for the measurement of drug concentrations from plasma is not currently available in most TB endemic settings, and MIC testing requires a cultured *M. tuberculosis* isolate and additional weeks of time for incubation in the presence of drugs. Thus, for some settings, a TDA procedure may be more practical to perform. More definitively, though this study highlights the need to scale up capacity for alternative forms of PK testing such as with dried blood spot which bypasses plasma collection and the cold chain,[28] or spectrophotometric assays which have been performed on saliva and urine.[24,25] With closer to the point-of-care PK testing coupled with rapid sequencing techniques of *M. tuberculosis* from direct specimens with an improved bioinformatics pipeline such that specific drug resistance mutations can better predict MIC change, prior equipment intensive procedures may ultimately be rendered unnecessary.

The overall mean value of TDA did not consistently increase with rifampin drug dosages, which is different from previous studies that showed that TDA assay was mainly found to measure the concentration-dependent activity of the rifampin levels and thus TDA values increase as concentrations increase.[18,26] However, our lack of increase was only observed between the 600 and 900 mg doses and reflected higher MIC values in the few patients in the 900 mg dose category. TDA increased considerably in the 1200 mg category from 600mg doses, and this poses expectation of more consistent trend of TDA increase with all increasing doses that would have been observed with a larger sample size.

Higher doses of up to 32–35 mg/kg of rifampin have shown to be potential for shortening the total duration of the regimen.[27,29] In this study the highest dose category (1200mg) of rifampin total dose was closer to 20 mg/kg in and given that most patients attained sputum culture conversion relatively early, the 10mg/kg dose may have been too low to observe differences from the conventional 600 mg category. Further studies of dosages of 30 mg/kg or above may also be better designed to measure PD indices over time. For example, in a study by Ndusilo *et al.* evaluating a regimen for drug-resistant TB,[30] the majority of patients had a significant increase in TDA from 2 weeks to 4 weeks, and TDA increase was associated with a favorable treatment outcome.

The number of participants in this study is the main limitation and it may be difficult to make more generalized conclusions based on only few cases with available plasma PK, MIC, and TDA results. Second, other host comorbidities that could have influenced drug absorption or metabolism were not considered in comparison of PD parameters and the clinical outcome of time to sputum culture conversion. It may be possible with a larger sample size, for instance, that a PD parameter such as TDA performs differently among people with HIV or another comorbidity. Furthermore, while TDA has been studied for other anti-TB drugs including in MDR-TB regimens with drugs such as the fluoroquinolones,[30] this current study was restricted to different dosages of rifampin.

Conclusion And Recommendation

In a small subset of people with pulmonary TB in Tanzania, a 1200 mg dosage of rifampin produced significantly higher rifampin plasma Cmax and $AUC_{0\text{-}24}$ at 6 weeks of treatment, with improved AUC0-24/MIC and TDA. Plasma TDA, a biomarker of all drug activity, demonstrated the greatest bacterial killing for patients in the 1200 mg rifampin dose category and importantly correlated with time to sputum culture conversion, whereby the patients with the highest TDA values demonstrated the fastest time to microbiological cure. The rifampin dose of 1200 mg appears to be an appropriate starting dose for further studies of higher dose and PK target attainment. TDA may provide further discrimination for understanding multiple drug PD interactions. Larger sample sizes among patients with diverse comorbidities should be employed to further study TDA for not only dose finding studies but practical implementation of individualized dosing in routine practice.

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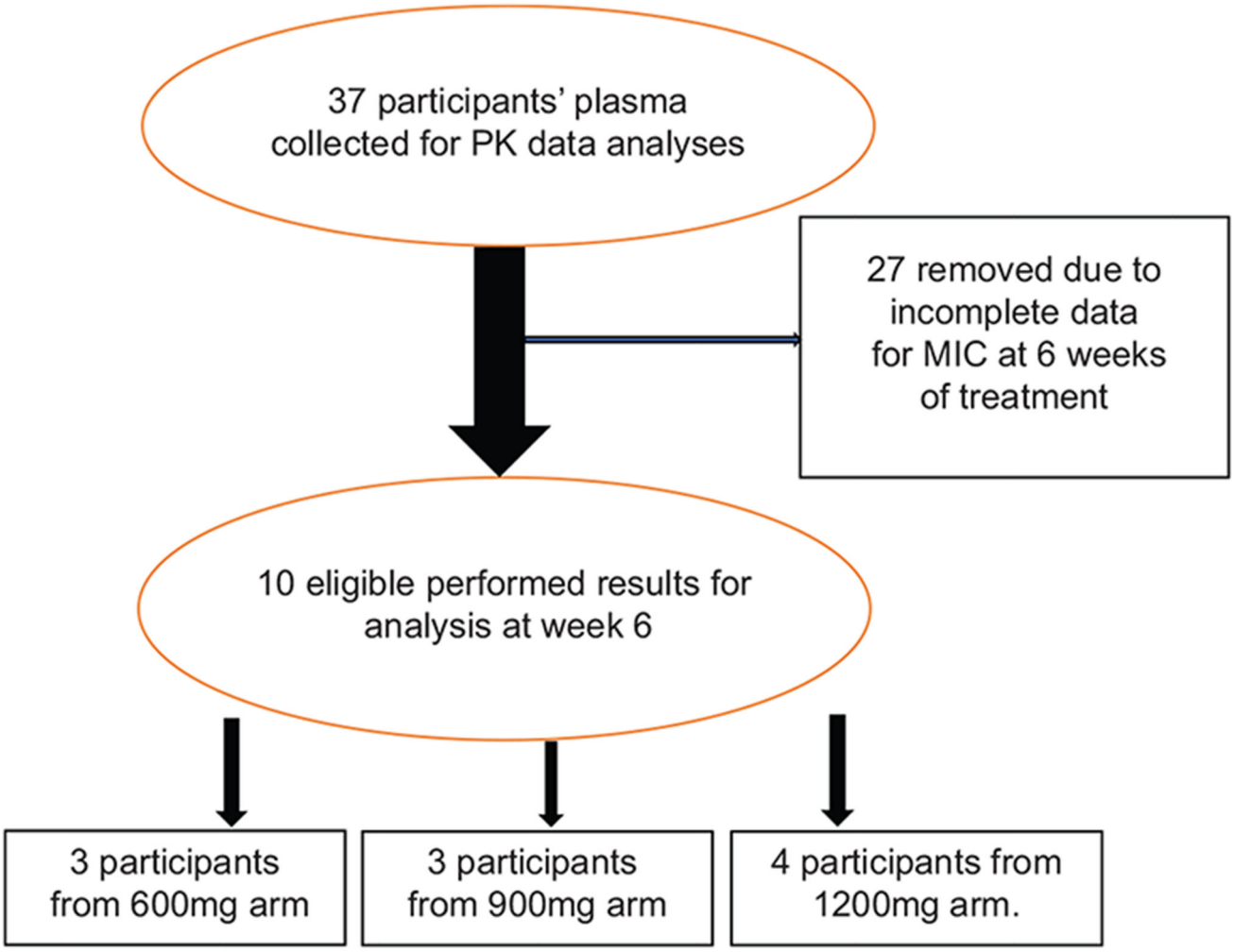

Figure 1. Study flow diagram showing the participants selection during extraction of data from the main database

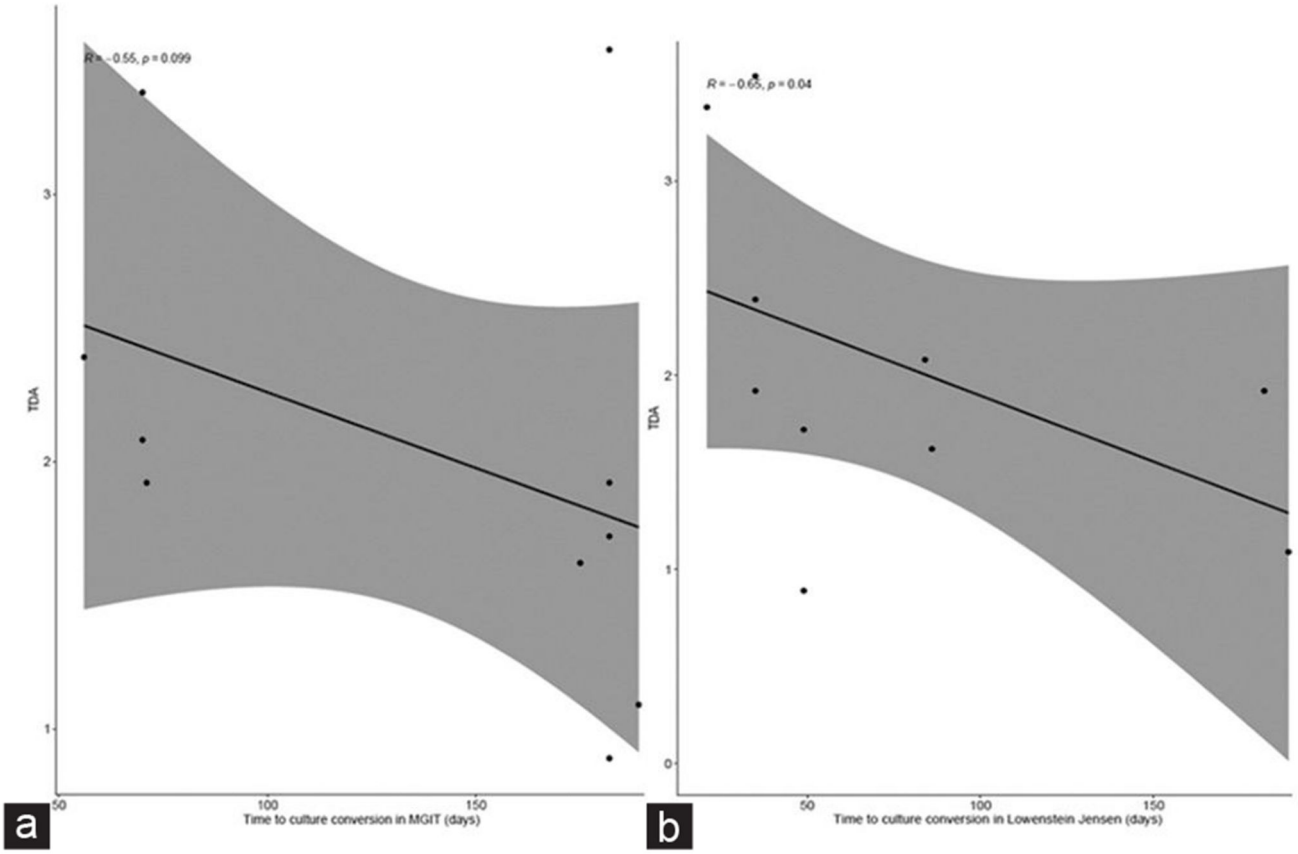

Figure 2. (a) Tuberculosis drug-activity versus Time to culture conversion in mycobacteria growth indicator tube and (b) Time to culture conversion in Lowenstein-Jensen

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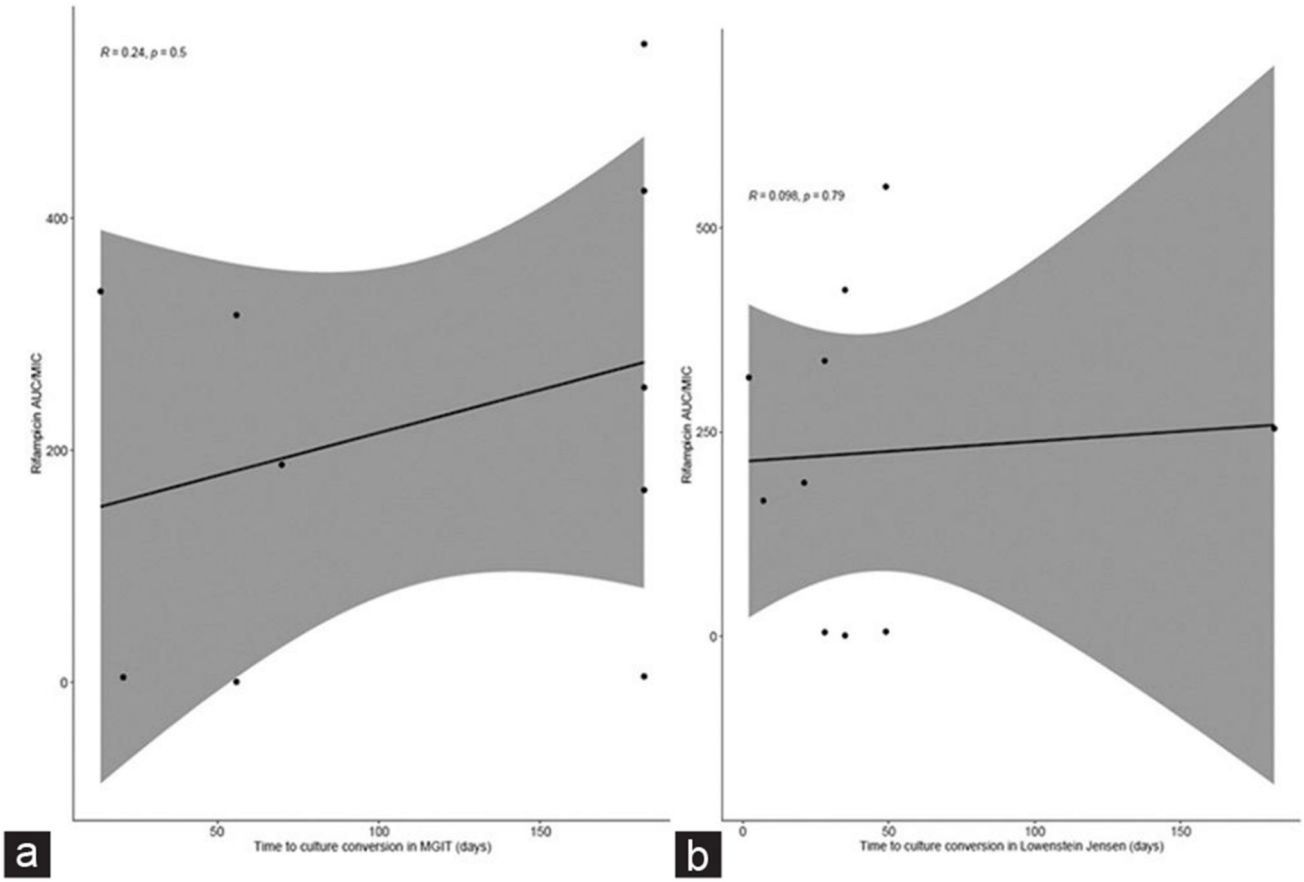

Figure 3. (a) Rifampin $AUC_{0\text{-}24}$/MIC versus Time to culture conversion in mycobacteria growth indicator tube and (b) Time to culture conversion in Lowenstein-Jensen

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Table 1

Demographic and pharmacokinetic values within the rifampin dose categories for participants with pulmonary tuberculosis after 6 weeks of treatment

Characteristics	Overall mean (mean±SD)/median (IQR)	600 mg (*n*=3)	Rifampin dose 900 mg (*n*=3)	1200 mg (*n*=4)	*P*
Age (years)	40.1±7.9	41.3±3.21	39.3±1.53	39.8±13.3	0.822
Weight (kg)	55.6±3.3	54.3±2.89	55±2.65	57±4.24	0.306
Rifampin (mg/kg) *	16.7±4.53	11.1±0. 61	16.4±0.81	21.1±1.60	<0.00l
T_{max} (h)	3.62±1.51	3.38±2.27	4.02±2.06	3.51±0.57	0.949
C_{max} (mg/L)	11.8.9±5.65	6.8±2.93	10.4±4.37	16.9±3.46	0.04
AUC_{0-24}	56.4±27.92	32±18.8	53±28.2	77.3±19.60	0.021

* Mean rifampin dosages at different dosages per kilogram each arm received pharmacodynamics of rifampin. SD: Standard deviation, IQR: Interquartile range

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Table 2
Pharmacodynamics parameters on different rifampin dosages

PD parameters	Overall	600 mg (*n*=3)	Rif dosages 900 mg (*n*=3)	1200 mg (*n*=4)	*P*
AUC_{0-24}/MIC, mean±SD	224.7±188.4	168±159	169±166	308±238	0.546
C_{max}/MIC, median (IQR)	37.7 (2.6-73.6)	26.7 (13.4-52.1)	38.5 (19.7-57.2)	57.5 (36.8-91.0)	0.689
TDA [a], mean±SD	2.05±0.9	2.2±0.75	1.36±0.59	3.2±1.05	0.855
		n=3	*n*=2	*n*=2	

[a] *n*=7. SD: Standard deviation, IQR: Interquartile range, PD: Pharmacodynamics, MIC: Minimum inhibitory concentration, TDA: Tuberculosis drug-activity