Diagnostic Accuracy of Therapeutic Drug Monitoring During Tuberculosis Treatment

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Abstract

Patients with tuberculosis (TB) coinfect with HIV are more likely to have low blood concentrations of the first-line anti-TB drugs (associated with poor outcomes). Therapeutic drug monitoring (TDM) is recommended for certain patient populations with TB at increased risk for a poor outcome. Our objective was to estimate the diagnostic accuracy of a 2-hour TDM serum sample for the first-line anti-TB drugs among patients with HIV/TB and evaluate the information gained by an additional 6-hour sample. We created a virtual (n = 1000) HIV/TB patient population and performed pharmacokinetic simulations using published population models for isoniazid, rifampin, pyrazinamide, and ethambutol. We performed receiver operating characteristic analysis to compare the diagnostic performance of a single 2-hour serum sample with samples obtained at 2 and 6 hours after dosing. The sensitivity of a single 2-hour serum concentration to identify patients with HIV/TB with adequate serum exposures was lowest for rifampin (54.9%; 95%CI, 50.79%-59.41%) and highest for ethambutol (70.8%; 95%CI, 66.06%-72.61%) for maximum concentration (Cmax) targets. Diagnostic accuracy of a single 2-hour serum sample for the area under the concentration-time curve (AUC) from time 0 to 24 hours target was highest for isoniazid (93%; 95%CI, 90.9%-94.1%) and lowest for pyrazinamide (66.3%; 95%CI, 62.6%-70.0%). In summary, the diagnostic performance of TDM for Cmax and AUC from time 0 to 24 hours targets demonstrated variability across the first-line anti-TB drugs. The addition of a 6-hour serum sample led to the highest statistically significant improvement (P < .001) and highest increase in diagnostic accuracy (area under the receiver operating characteristic curve) for rifampin for Cmax and AUC. The other first-line drugs had modest/negligible increases in diagnostic accuracy.

Keywords
HIV, pharmacokinetic modeling, pharmacokinetic simulations, receiver operating characteristic (ROC), therapeutic drug monitoring, tuberculosis

Interpatient variability in antituberculosis drug pharmacokinetics (PK) is increasingly recognized as a major contributor to variability in tuberculosis (TB) treatment outcomes.¹ Patients with TB coinfect with HIV in all settings are more commonly found to have low anti-TB drug concentrations in blood,²⁻⁻¹⁶ leading to lower tissue exposures at the site of infection, typically the lung granuloma or cavity in pulmonary TB.¹⁷ The exact mechanism(s) for decreased systemic anti-TB drug exposure in the setting of HIV coinfection remains poorly understood and may be due to several factors, including an HIV-related gut condition or drug interactions due to cytochrome P450 enzymes.¹⁸⁻⁻²³ Poor nutritional status may have a prominent role,²⁴ and some improvement of systemic anti-TB drug exposure following the initiation of antiretroviral therapy has been observed.²⁵

Dose adjustments of anti-TB drugs based on therapeutic drug monitoring (TDM) results are performed to speed the time to sputum sterilization (shortening the period of infectiousness),²⁶ decrease the risk of treatment failure and relapse,²⁶⁻⁻²⁸ and reduce the danger of developing drug-resistant mutants.²⁹ In resource-rich settings, TDM is performed by measuring serum drug concentrations in patients undergoing anti-TB therapy when poor absorption is suspected clinically.³⁰,³¹ TDM during TB therapy is performed by estimating the peak blood concentration (Cmax) using blood samples obtained 2 and 6 hours after dosing.²⁶,³² 2- and 6-hour postdosing samples are recommended but not always obtained due to logistical constraints.³³ Despite the increasing use of TDM in the clinic, reflected in its inclusion in recent TB treatment guidelines,³⁴ surprisingly little is known about the diagnostic performance of sparse TDM strategies. We sought to determine the diagnostic characteristics of TDM for the first-line anti-TB drugs (isoniazid, rifampin, pyrazinamide, and ethambutol) among a patient population with HIV/TB in sub-Saharan

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Table 1. World Health Organization Tuberculosis Treatment Weight-Based Dosing Guidelines During the Initial Phase of Treatment, Administered as Fixed-Dose Combinations

| Body Weight (kg) | Rifampin Daily (mg) | Isoniazid Daily (mg) | Pyrazinamide Daily (mg) | Ethambutol Daily (mg) |
|------------------|---------------------|----------------------|-------------------------|-----------------------|
| 30-37            | 300                 | 150                  | 800                     | 550                   |
| 38-54            | 450                 | 225                  | 1200                    | 825                   |
| 55-70            | 600                 | 300                  | 1600                    | 1100                  |
| ≥71              | 750                 | 375                  | 2000                    | 1375                  |

Africa, using the receiver operating characteristic (ROC) framework for diagnostic test evaluation. In this framework, the sparse TDM sample represented the “diagnostic test,” and the summary PK exposure parameters determined from the 24-hour concentration-vs-time profile represented the “gold standard.” Our objective was to estimate the diagnostic accuracy of a 2-hour TDM serum sample for the first-line anti-TB drugs among patients with HIV/TB and evaluate the information gained by an additional 6-hour sample.

**Methods**

**Population PK Simulations of the First-Line Anti-TB Drugs in a Patient Population With HIV/TB**

Population simulations were performed using previously published population PK models that were derived from a cohort of patients with HIV/TB. The overall objective of this prior study was to evaluate the potential covariate effects of HIV-associated immune activation and gut damage on the PK of anti-TB drugs. The patients enrolled in the PK study (n = 40) were naive to antiretroviral therapy and treated with first-line anti-TB regimens that included isoniazid, rifampin, pyrazinamide, and ethambutol, and the population PK models for each drug have been previously published.

The rifampin PK model is a 1-compartment model, with a transit compartment model for oral absorption and first-order elimination. The isoniazid PK model is a 2-compartment model with first-order absorption and elimination. Covariate effects on clearance included N-acetyltransferase 2 (NAT-2) genotype (fast, intermediate, slow) and cellular immune activation effect (measured as the percentage of CD8+ T cells coexpressing human leukocyte antigen–DR isotype and CD38). The pyrazinamide PK model is a 1-compartment model with first-order absorption and elimination. Covariates in the pyrazinamide PK model included a weight effect on both clearance and volume of distribution, a sex effect on clearance, and a cellular immune activation effect on clearance. The ethambutol PK model is a 2-compartment model with first-order absorption (with a lag time) and first-order elimination. A weight effect was included on the model parameters for the volumes of the central and peripheral compartments, as well as clearance and intercompartment flux.

For each drug, we introduced a virtual population of adult patients with HIV/TB (n = 1000), with PK model covariates sampled from underlying observed distributions, including body weight, sex, NAT-2 genotype, and HIV-associated immune activation. The median age of the patient population was 32 years (range, 20-50 years). The virtual patient population with HIV/TB was then treated with the first-line anti-TB regimen of rifampin, isoniazid, pyrazinamide, and ethambutol, with drug dosing according to the weight-based dosing bands defined by World Health Organization TB treatment guidelines, as shown in Table 1. For each virtual patient with HIV/TB, we simulated an intensive 24-hour PK profile for each drug.

**Noncompartmental Analysis of 24-Hour PK Profiles to Determine “Gold Standard” Serum Exposures**

The summary PK measures of C_max and area under the concentration-time curve (AUC) from time 0 to 24 hours (AUC_0-24), based on the intensive 24-hour PK profiles for each drug, provided the gold standard for comparison with the sparse TDM strategies. We performed noncompartmental analysis of the 24-hour PK simulation data to identify the C_max and the AUC_0-24.

**Simulation of Sparse TDM in the Virtual Patient Population With HIV/TB**

To simulate sparse TDM using our intensive PK data set, we selected the 2- and 6-hour drug concentrations (after dosing) for each virtual patient with HIV/TB for each drug. In the first TDM approach, the 2-hour sample alone was used as the “diagnostic test” for comparison with the gold standard in the ROC analysis. In the second approach, we used the higher of the 2- and 6-hour concentrations as the diagnostic test, in accordance with clinical guidelines. The rationale for including an additional 6-hour sample is based on an improvement in TDM performance for rifampin, where delayed oral absorption is a concern. Thus, while the rifampin C_max occurs nearly 2 hours after...
dosing for most patients, the additional 6-hour concentration may distinguish between delayed absorption and malabsorption.26

Receiver Operating Characteristic Analysis of Serum Targets
We next evaluated the diagnostic accuracy of both of these TDM approaches (ie, a single 2-hour concentration, vs 2- and 6-hour concentrations). Given that clinical data have supported both C max and AUC0-24 as predictors of TB treatment outcome, we performed separate analyses using each of these summary PK measures as the gold standard. In both sets of analyses, we defined a “true success” virtual patient as one having either C max or AUC0-24 exceeding the target threshold, corresponding to an adequate PK exposure that does not require a dose increase. On the other hand, a “true failure” corresponds to a virtual patient with a serum PK exposure below the target, who would likely benefit from a dose increase. In this manner, an increasing diagnostic test threshold (corresponding to the sparse TDM concentration value) is directly related to an increasing sensitivity to identify a patient with sufficient PK serum exposures, who would not require an increase in drug dose based on this TDM result. Details of the thresholds are stated in the next 2 following sections.

Blood Anti-TB Drug C max as the Gold Standard
The sparse TDM concentration is used directly to estimate the C max from the concentration-vs-time curve. By definition, a sparse TDM concentration that exceeds the C max threshold is 100% specific for defining C max target attainment. Thus, the key criterion for evaluation of sparse TDM for a C max target will be its sensitivity to identify patients with TB with adequate PK exposures. We examined C max targets that have been recommended in the clinical performance of sparse TDM, including a serum rifampin concentration of 8 mg/L, a serum isoniazid concentration of 3 mg/L, a serum ethambutol concentration of 2 mg/L, and a serum pyrazinamide concentration of 20 mg/L.26,41 Based on the observed percentage of target attainment at this threshold, this study was also extended to include a serum pyrazinamide concentration of 35 mg/L.41

Blood Anti-TB Drug AUC0-24 as the Gold Standard
In contrast to a C max target, the optimal serum concentration threshold corresponding to an AUC0-24 target has not been defined in clinical practice guidelines, which supports the use of an ROC framework to examine diagnostic performance over a range of potential AUC0-24 thresholds. The ROC curve displays the graphical relationship between sensitivity and 1-specificity, with an increasing threshold corresponding to an increasing likelihood of attaining the desired AUC0-24.42 The overall diagnostic accuracy is defined by the area under the ROC curve.33 Due to uncertainty surrounding AUC0-24 targets for first-line TB drugs, we defined the lowest-quartile AUC as the group of patients with serum drug concentrations “below” the target. The upper three quartiles represent patients who have serum drug concentrations “above” the target. An advantage of this framework will be the flexibility to incorporate subsequent serum AUC0-24 targets that become identified and prospectively validated in ongoing clinical trials.43,44

Simulation and Statistical Packages
Phoenix NLME 7.0 (Certara, Princeton, New Jersey) was used to perform population PK simulations. Non-compartmental analysis was performed to determine the PK exposure parameters of interest using the naccpp package in R (R Foundation for Statistical Computing, Vienna, Austria).45 and ROC analysis was performed using the pROC package.46 Bootstrapping (n = 1000) was performed to identify 95% CIs for the area under the ROC curve.47 Statistical significance was declared for P values <.05 under a 2-sided alternative.

Results
Population PK Simulations of Anti-TB Drug Concentrations in Blood
For each virtual patient (n = 1000), an intensive 24-hour concentration-time profile was simulated from the population PK model for each drug. The spaghetti plots of the individual blood concentration-vs-time for each of the first-line anti-TB drugs are shown in Figure 1. The observed C max for each drug was directly obtained from these intensive concentration-vs-time curves, with observed distributions shown in Figure 2. The median and interquartile range for C max was 7.6 mg/L (5.8-9.8 mg/L) for rifampin, 5.0 mg/L (3.6-6.6 mg/L) for isoniazid, 43.0 mg/L (36.6-51.1 mg/L) for pyrazinamide, and 2.7 mg/L (2.18-3.39 mg/L) for ethambutol. The serum AUC0-24 for each drug was calculated by noncompartmental analysis from the intensive concentration-vs-time curves, with the distributions shown in Figure 3.

Diagnostic Performance of Sparse TDM for C max Targets
Given that nearly all of the virtual patients with HIV/TB had attained the pyrazinamide C max target of 20 mg/L, we also explored a pyrazinamide C max target concentration of 35 mg/L, which has also been clinically validated in patients with TB.41 In identifying patients with HIV/TB with a C max exceeding the target threshold, a single serum concentration obtained 2 hours after dosing was 54.9% sensitive for rifampin (95% CI, 50.34%-59.64%), 65.5% sensitive for isoniazid (95% CI, 62.41%-69.09%), 96.3% sensitive for pyrazinamide for 20 mg/L (95% CI, 95.18%-97.49%),
Figure 1. Individual serum concentrations vs time over a 24-hour period in the simulated patient population with HIV/tuberculosis (n = 1000). The black line is the mean line of the concentrations across the 24-hour period. The white line is the 90th percentile of the concentrations across the 24-hour period. The gray line is the 10th percentile of the concentrations across the 24-hour period. (a) Rifampin, (b) isoniazid, (c) pyrazinamide, (d) ethambutol.

64.9% sensitive for pyrazinamide for 35 mg/L (95%CI, 61.35%-68.1%), and 70.8% sensitive for ethambutol (95%CI, 65.82%-72.73%), as shown in Table 2. The addition of a 6-hour serum sample led to modest or negligible increases in diagnostic accuracy (area under the ROC curve) for the majority of first-line drugs for these C\text{max} targets.

Diagnostic Performance of Sparse TDM for AUC\textsubscript{0-24} Targets

The threshold serum concentration corresponding to an AUC\textsubscript{0-24} target has not been defined in clinical practice, supporting the use of an ROC framework that can incorporate emerging clinical data regarding exposure targets. In this analysis, we defined a “true success” as having an AUC\textsubscript{0-24} exceeding the lowest quartile in the virtual patient population. The ROC curves based on these AUC\textsubscript{0-24} thresholds are shown in Figure 4. Notably, the accuracy of a single 2-hour concentration for isoniazid AUC\textsubscript{0-24} was high, with an area under the ROC curve of 0.93 (95%CI, 90.9%-94.1%). The accuracy of this approach for pyrazinamide and ethambutol was modest, with an area under the ROC curve of 0.66 (95%CI, 62.6%-70.0%) and 0.75 (95%CI, 71.2%-77.8%), respectively.

Consistent with our hypothesis that the 6-hour sample would distinguish between malabsorption and delayed absorption of rifampin, we observed an increase in diagnostic accuracy when the 6-hour serum rifampin concentration was included, as defined by the area under the ROC curve, increasing from 0.76 (95%CI, 72.8%-78.9%) to 0.82 (95%CI, 79.5%-85.1%), and reaching the threshold of statistical significance (P = .001). The addition of a 6-hour serum sample led to modest or negligible increases in diagnostic accuracy (as defined by the area under the ROC curve) for the other first-line drugs for these AUC targets.

Discussion

Updated clinical practice guidelines for the management of drug-susceptible TB highlight the role of sparse serum sampling as the optimal approach for TDM in select patient populations, including patients with TB coinfected with HIV.\textsuperscript{39} In this population PK simulation study, we investigated the diagnostic characteristics
of sparse TDM to identify patients with adequate PK exposures, as defined by the gold standard of intensive PK sampling during a 24-hour dosing interval (either $\text{AUC}_{0-24}$ or $C_{\text{max}}$). By using this approach, we consider TDM sampling as a diagnostic test, which reflects its use in the TB clinic to “diagnose” patients with low serum drug exposures. While TDM results must be interpreted alongside other data to inform clinical decision making, the TB clinician is ultimately provided with a TDM test result and the corresponding target value.

In the current simulation study, we observed median sensitivity ranging between 55% for rifampin to 71% for ethambutol in identifying patients with HIV/TB with adequate $C_{\text{max}}$ exposures. Thus, we found that nearly half of these virtual patients with HIV/TB with a true rifampin $C_{\text{max}}$ above the target of 8 mg/L would be “missed” by a 2-hour sparse TDM sampling strategy. For rifampin, recent studies suggest that higher doses are well tolerated and might improve clinical outcomes.\textsuperscript{48–51} Similarly for pyrazinamide, clinical studies have provided support for higher doses that do not increase the risk of hepatotoxicity.\textsuperscript{32} Consistent with the potential for delayed oral rifampin absorption, we found that the sensitivity of sparse TDM for $C_{\text{max}}$ targets was lowest for rifampin. Furthermore, we demonstrated that obtaining an additional 6-hour serum sample can help to distinguish between malabsorption and delayed absorption,\textsuperscript{26,32} with a statistically significant improvement in diagnostic accuracy for $\text{AUC}_{0-24}$.

Recent publications have provided support for AUC being a better reflection of efficacy compared with $C_{\text{max}}$.\textsuperscript{53–59} The modest performance of serum TDM for $\text{AUC}_{0-24}$ targets, for each drug except isoniazid, lends support to efforts under way to develop alternative methods for TDM during TB treatment, for example, using saliva or urine.\textsuperscript{35} Interestingly, we observed a high diagnostic accuracy for a single 2-hour serum concentration of isoniazid with an $\text{AUC}_{0-24}$ target, a reflection of the distinct subpopulations defined by the $\text{NAT}-2$ genotype and its potent covariate effect on isoniazid clearance. This observation is also a consequence of the half-life of isoniazid ($\approx 1.5$ hours for fast acetylators and 4 hours for slow acetylators), which is shorter than ethambutol (2–4 hours for the initial phase) or pyrazinamide (9 hours).\textsuperscript{32} The potential for sparse TDM to provide highly accurate discrimination of isoniazid exposures is intriguing and worthy of further study, given the relationship between $\text{NAT}-2$ genotype and treatment outcomes related to both microbiologic and toxicologic end points.\textsuperscript{38,60–62}

There were several important limitations of this study. Foremost, there are not yet prospectively validated PK targets for the treatment of TB overall, or specifically among patient populations with HIV/TB. While the $C_{\text{max}}$ targets evaluated in this simulation

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**Figure 2.** Histogram of distribution of $C_{\text{max}}$ (mg/L) for 1000 patients in the simulated patient population with HIV/tuberculosis ($n = 1000$). (a) Rifampin, (b) isoniazid, (c) pyrazinamide, (d) ethambutol. $C_{\text{max}}$, maximum concentration.
Figure 3. Histogram of distribution of $AUC_{0-24}$ (mg · h/L) for 1000 patients in the simulated patient population with HIV/tuberculosis ($n = 1000$). (a) Rifampin, (b) isoniazid, (c) pyrazinamide, (d) ethambutol.

Table 2. Sensitivity of TDM to Identify Patients With HIV/TB With Serum Drug Exposures Above the Threshold Concentration for $C_{\text{max}}$ Targets

| Drug            | Sensitivity of TDM, % (95%CI) |
|-----------------|--------------------------------|
|                 | 2-h Concentration | 2- and 6-h Concentrations |
| Rifampin        | 54.9 (50.79-59.41) | 58.05 (53.74-62.81) |
| Isoniazid       | 65.5 (62.41-69.09) | 65.5 (62.41-68.86) |
| Pyrazinamide (20 mg/L) | 96.3 (95.08-97.59) | 98.5 (97.89-99.5) |
| Pyrazinamide (35 mg/L) | 64.9 (61.72-68.1) | 69.20 (66.26-72.52) |
| Ethambutol      | 70.8 (66.06-72.61) | 71.76 (68.72-75.15) |

$C_{\text{max}}$, maximum concentration; TB, tuberculosis; TDM, therapeutic drug monitoring.

Strengths of this study include this study exploring both $C_{\text{max}}$ and $AUC_{0-24}$ for first-line anti-TB drugs while also reflecting how clinicians approach treating drug-susceptible TB, evaluating the 4 first-line anti-TB drugs rather than focusing on a single drug. An advantage of our approach with the ROC framework is the flexibility in defining the target, which can be informed by future studies of PK/clinical response relationships among TB patients, and reflects how clinicians are trained to approach diagnostic tests as one component of clinical decision making. Future applications of this framework could be applied to studies...
of intensified dose regimens for rifampin. Importantly, recent studies have provided support for higher doses of rifampin than what is used in current standard of care to improve outcome of patients with TB or shorten treatment.48–51,63

**Conclusion**

Sparse serum TDM displayed modest diagnostic performance characteristics for the first-line anti-TB drugs, with the exception of isoniazid AUC$_{0-24}$. This work provides a benchmark for evaluation of alternate approaches to TDM based on saliva or urine assays, with the long-term goal of understanding the tools available to clinicians to individually optimize anti-TB drug dosing for select patient populations.

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**Author Contributions**

G.A. performed the computational analysis. Both authors contributed to writing the manuscript and read and approved the final manuscript.

**Conflicts of Interest**

The authors declare no conflicts of interest.

**Data Sharing Statement**

All code, data sets, and R library associated with the current study are available from the corresponding author upon reasonable request at ginger.anderson@rutgers.edu. The code and code word output files for each drug are provided as Supplemental Information.

**Disclaimer**

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**References**

1. Gumbo T. New susceptibility breakpoints for first-line anti-tuberculosis drugs based on antimicrobial pharmacokinetic/pharmacodynamic science and population pharmacokinetic variability. *Antimicrob Agents Chemother.* 2010;54(4):1484-1491.
2. Burhan E, Ruesen C, Ruslamı R, et al. Isoniazid, rifampin, and pyrazinamide plasma concentrations in relation to
treatment response in Indonesian pulmonary tuberculosis patients. *Antimicrob Agents Chemother.* 2013;57(8):3614-3619.

3. Chideya S, Winston CA, Peloquin CA, et al. Isoniazid, rifampin, ethambutol, and pyrazinamide pharmacokinetics and treatment outcomes among a predominantly HIV-infected cohort of adults with tuberculosis from Botswana. *Clin Infect Dis.* 2009;49(12):1685-1694.

4. Choudhri SH, Hawken M, Gathua S, et al. Pharmacokinetics of antituberculosis drugs in patients with tuberculosis, AIDS, and diarrhoea. *Clin Infect Dis.* 1997;25(1):104-111.

5. Gurumurthy P, Ramachandran G, Hemanth Kumar AK, et al. Decreased bioavailability of rifampin and other antituberculosis drugs in patients with advanced human immunodeficiency virus disease. *Antimicrob Agents Chemother.* 2004;48(11):4473-4475.

6. Kimerling ME, Phillips P, Patterson P, et al. Low serum antitubercular drug 64s in non-HIV-infected tuberculosis patients. *Chest.* 1998;113(5):1178-1183.

7. Peloquin CA, Nitta AT, Burman WJ, et al. Low antituberculosis drug concentrations in patients with AIDS. *Ann Pharmacother.* 1996;30(9):919-925.

8. Sahai J. Reduced plasma concentrations of antituberculosis drugs in patients with HIV infection. *Ann Intern Med.* 1997;127(4):289-93.

9. Saleri N, Dembele SM, Villani P, et al. Systemic exposure to rifampicin in patients with tuberculosis and advanced HIV disease during highly active antiretroviral therapy in Burkina Faso. *J Antimicrob Chemother.* 2012;67(2):469-472.

10. Gordon SM, Horsburgh CR, Peloquin CA, et al. Low serum levels of oral antitubercular agents in patients with disseminated Mycobacterium avium complex disease. *J Infect Dis.* 1993;168(6):1559-1562.

11. Berning SE, Huitt GA, Iseman MD, et al. Malabsorption of antituberculosis medications by a patient with AIDS. *N Engl J Med.* 1992;327(25):1817–1818.

12. Gurumurthy P, Ramachandran G, Hemaanth Kumar AK, et al. Malabsorption of rifampin and isoniazid in HIV-infected patients with and without tuberculosis. *Clin Infect Dis.* 2004;38(2):280-283.

13. Patel KB, Belmonte R, Crowe HM. Drug malabsorption and resistant tuberculosis in HIV-infected patients. *N Engl J Med.* 1995;332(5):336-337.

14. Zhu M, Burman WJ, Starke JR, et al. Pharmacokinetics of ethambutol in children and adults with tuberculosis. *Int J Tuberc Lung Dis.* 2004;8(11):1360–1367.

15. Daskapan A, Idrus LR, Postma MJ, et al. A Systematic review on the effect of HIV infection on the pharmacokinetics of first-line tuberculosis drugs. *Clin Pharmacokinet.* 2019;58(6):747–766.

16. Esposito S, Codecasa LR, Centis R. The role of therapeutic drug monitoring in individualised drug dosage and exposure measurement in tuberculosis and HIV co-infection. *Eur Respir J.* 2015;45(2):571-574.

17. Gaohua L, Wedagedera J, Small Bg, et al. Development of a multicompartiment permeability-limited lung PBPK Model and its application in predicting pulmonary pharmacokinetics of antituberculosis drugs. *CPT Pharmacometrics Syst Pharmacol.* 2015;4(10):605-613.

18. Brenchley JM, Douek DC. HIV infection and the gastrointestinal immune system. *Mucosal Immunol.* 2008;1(1):23–30.

19. Vinnard C, Manley I, Scott B, et al. A pilot study of immune activation and rifampin absorption in HIV-infected patients without tuberculosis infection: a short report. *Tuberc Res Treat.* 2017;2017:2140974.

20. Brenchley JM, Price DA, Douek DC. HIV disease: fallout from a mucosal catastrophe? *Nat Immunol.* 2006;7(3):235-239.

21. Abdool Karim SS, Naidoo K, Grobler A, et al. Integration of antiretroviral therapy with tuberculosis treatment. *N Engl J Med.* 2011;365(16):1492-1501.

22. Burman WJ, Jones BE. Treatment of HIV-related tuberculosis in the era of effective antiretroviral therapy. *Am J Respir Crit Care Med.* 2001;164(1):7–12.

23. McIlreron H, et al. Complications of antiretroviral therapy in patients with tuberculosis: drug interactions, toxicity, and immune reconstitution inflammatory syndrome. *J Infect Dis.* 2007;196(Suppl 1):S63-S75.

24. Bekker L-G, Wood R. The changing natural history of tuberculosis and HIV coinfection in an urban area of hyperendemica. *Clin Infect Dis.* 2010;50 (Suppl 3):S208-S214.

25. Mehta K, Ravimohan S, Pasipanodya JG, et al. Optimizing ethambutol dosing among HIV/tuberculosis co-infected patients: a population pharmacokinetic modelling and simulation study. *J Antimicrob Chemother.* 2019;74(10):2994–3002.

26. Alsultan A, Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis: an update. *Drugs.* 2014;74(8):839-854.

27. Kim HY, Ulbricht E, Ahn YK, et al. Therapeutic drug monitoring practice in patients with active tuberculosis: assessment of opportunities. *Eur Respir J.* 2020;57(1):2002349.

28. Mårtton A-G, Burch G, Ghimire S, Alffenaar J-WC, Peloquin CA. Therapeutic drug monitoring in patients with tuberculosis and concurrent medical problems. *Expert Opin Drug Metab Toxicol.* 2021;17(1):23-39.

29. Sotgiu G, Alffenaar J-WC, Centis R, et al. Therapeutic drug monitoring: how to improve drug dosage and patient safety in tuberculosis treatment. *Int J Infect Dis.* 2015;32:101-104.

30. Nwobodo N. Therapeutic drug monitoring in a developing nation: a clinical guide. *JRSM Open.* 2014;5:205427041435112.

31. Ghimire S, Bolhuis MS, Sturkenboom MGG, et al. Incorporating therapeutic drug monitoring into the World Health Organization hierarchy of tuberculosis diagnostics. *Eur Respir J.* 2016;47(6):1867-1869.

32. Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis. *Drugs.* 2002;62(15):2169-2183.

33. Heyssell SK, Moore JL, Keller SJ, Houpt ER. Therapeutic drug monitoring for slow response to tuberculosis treatment in a state control program, Virginia, USA. *Emerg Infect Dis.* 2010;16(10):1546-1553.

34. Nahid P, Dormann SE, Alipanah N, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: treatment of drug-susceptible tuberculosis. *Clin Infect Dis.* 2016;63(7):e147-e195.

35. Zentner I, Modongo C, Zetola NM, et al. Urine colorimetry for therapeutic drug monitoring of pyrazinamide during tuberculosis treatment. *Int J Infect Dis.* 2018;68:18–23.

36. Vinnard C, Ravimohan S, Tamuhla N, et al. Markers of gut dysfunction do not explain low rifampicin bioavailability in HIV-associated TB. *J Antimicrob Chemother.* 2017;72(7):2020–2027.

37. Vinnard C, Ravimohan S, Tamuhla N, et al. Pyrazinamide clearance is impaired among HIV/tuberculosis patients with high levels of systemic immune activation. *PLoS One.* 2017;12(11):e0187624.

38. Vinnard C, Ravimohan S, Tamuhla N, et al. Isoniazid clearance is impaired among human immunodeficiency virus/tuberculosis patients with high levels of immune activation. *Br J Clin Pharmacol.* 2017;83(4):801–811.

39. World Health Organization. *Treatment of Tuberculosis Guidelines.* World Health Organization; 2010.
40. Dekkers BGJ, Akkerman OW, Alffenaar JWC. Role of therapeutic drug monitoring in treatment optimization in tuberculosis and diabetes mellitus comorbidity. *Antimicrob Agents Chemother*. 2019;63(2).
41. Tappero JW, Bradford WZ, Agerton TB, et al. Serum concentrations of antimycobacterial drugs in patients with pulmonary tuberculosis in Botswana. *Clin Infect Dis*. 2005;41(4):461-469.
42. MS P. *The Statistical Analysis of Medical Tests for Classification and Prediction*. New York, NY: Oxford University Press;2003.
43. Tuberculosis Drug Levels in Diabetics. NCT04242511. Not yet recruiting (No Results Available): p. Tuberculosis|Diabetes Mellitus.
44. Feasibility of Centralized Therapeutic Drug Monitoring of Fluoroquinolones in Multi-Drug Resistant Tuberculosis Patients. NCT03409315. Recruiting (No Results Available): p. Tuberculosis. Multidrug-Resistant.
45. Acharya C, Hooker AC, Türkyilmaz GY, Jönsson S, Karlsson MO. A diagnostic tool for population models using non-compartmental analysis: the ncappc package for R. *Comp Methods Programs Biomed*. 2012;106:83–93.
46. Robin X, Turck N, Hainard A, et al. pROC: an open-source package for R and S+ to analyze and compare ROC curves. *BMC Bioinformatics*. 2011;12(1):77.
47. Carpenter J, Bithell J. Bootstrap confidence intervals: when, which, what? A practical guide for medical statisticians. *Stat Med*. 2000;19(9):1141-1164.
48. Seijger C, Hoefsloot W, Bergsma-De Guchteneire I, et al. High-dose rifampicin in tuberculosis: experiences from a Dutch tuberculosis centre. *PLoS One*. 2019;14(3):e0213718.
49. Steingart KR, Joblud S, Robsky K, et al. Higher-dose rifampin for the treatment of pulmonary tuberculosis: a systematic review. *Int J Tuberc Lung Dis*. 2011;15(3):305–316.
50. Milstein M, Lecca L, Peloquin C, et al. Evaluation of high-dose rifampin in patients with new, smear-positive tuberculosis (HRIF): study protocol for a randomized controlled trial. *BMC Infect Dis*. 2016;16(1):453.
51. Ruslami R, Nijland HMJ, Alisjahbana B, Parwati I, Van Crevel R, Aarnoutse RE. Pharmacokinetics and tolerability of a higher rifampin dose versus the standard dose in pulmonary tuberculosis patients. *Antimicrob Agents Chemother*. 2007;51(7):2546-2551.
52. Pasipanodya JG, Gumbo T. Clinical and toxicodynamic evidence that high-dose pyrazinamide is not more hepatotoxic than the low doses currently used. *Antimicrob Agents Chemother*. 2010;54(7):2847-2854.
53. Srivastava S, Masuka S, Sherman C, Meek C, Leff R, Gumbo T. Efflux-pump-derived multiple drug resistance to ethambutol monotherapy in Mycobacterium tuberculosis and the pharmacokinetics and pharmacodynamics of ethambutol. *J Infect Dis*. 2010;201(8):1225-1231.
54. Magis-Escurra C, Later-Nijland HMJ, Alffenaar JWC, et al. Population pharmacokinetics and limited sampling strategy for first-line tuberculosis drugs and moxifloxacin. *Int J Antimicrob Agents*. 2014;44(3):229-234.
55. Gumbo T, Siyambalapitiyage Dona CSW, Meek C, Leff R. Pharmacokinetics-pharmacodynamics of pyrazinamide in a novel in vitro model of tuberculosis for sterilizing effect: a paradigm for faster assessment of new antituberculosis drugs. *Antimicrob Agents Chemother*. 2009;53(8):3197-3204.
56. Gumbo T, Louie A, Deziel MR, et al. Concentration-dependent Mycobacterium tuberculosis killing and prevention of resistance by rifampin. *Antimicrob Agents Chemother*. 2007;51(11):3781-3788.
57. Gumbo T, Louie A, Liu W, et al. Isoniazid bactericidal activity and resistance emergence: integrating pharmacodynamics and pharmacogenomics to predict efficacy in different ethnic populations. *Antimicrob Agents Chemother*. 2007;51(7):2329-2336.
58. Jayaram R, Gaonkar S, Kaur P, et al. Pharmacokinetics-pharmacodynamics of rifampin in an aerosol infection model of tuberculosis. *Antimicrob Agents Chemother*. 2003;47(7):2118-2124.
59. Jayaram R, Shandil RK, Gaonkar S, et al. Isoniazid pharmacokinetics-pharmacodynamics in an aerosol infection model of tuberculosis. *Antimicrob Agents Chemother*. 2004;48(8):2951-2957.
60. Azuma J, Ohno M, Kubota R, et al. NAT2 genotype guided regimen reduces isoniazid-induced liver injury and early treatment failure in the 6-month four-drug standard treatment of tuberculosis: a randomized controlled trial for pharmacogenetics-based therapy. *Eur J Clin Pharmacol*. 2013;69(5):1091-1101.
61. Alffenaar J-WC, Tiberi S, Verbeeck RK, Heysell SK, Grobusch MP, Therapeutic drug monitoring in tuberculosis: practical application for physicians. *Clin Infect Dis*. 2017;64(1):104-105.
62. Verbeeck RK, Günther G, Kibule D, Hunter C, Rennie TW. Optimizing treatment outcome of first-line anti-tuberculosis drugs: the role of therapeutic drug monitoring. *Eur J Clin Pharmacol*. 2016;72(8):905-916.
63. Velásquez GE, Brooks MB, Coit JM, et al. Efficacy and safety of high-dose rifampin in pulmonary tuberculosis. A randomized controlled trial. *Am J Respir Crit Care Med*. 2018;198(3):657-666.

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