The Journal of Clinical Pharmacology
2022, 62(10) 1206–1214

DOI: 10.1002/jcph.2068

Diagnostic Accuracy of Therapeutic Drug Monitoring During Tuberculosis Treatment

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Abstract

Patients with tuberculosis (TB) coinfected 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 (C_{max}) 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 C_{max} 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 C_{max} 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 coinfected 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 (C_{max}) 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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Submitted for publication 7 January 2022; accepted 29 April 2022.

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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[39]

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.[35] 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.[25,36–38] 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.[25,36–38] In brief, the rifampin PK model is a 1-compartment model, with a transit compartment model for oral absorption and first-order elimination.[36] The isoniazid PK model is a 2-compartment model with first-order absorption and elimination.[38] 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).[38] The pyrazinamide PK model is a 1-compartment model with first-order absorption and elimination.[37] 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.[37] The ethambutol PK model is a 2-compartment model with first-order absorption (with a lag time) and first-order elimination.[25] 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.[25]

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.[38] The median age of the patient population was 32 years (range, 20-50 years).[25,36–38] 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,[39] 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 ($AUC_{0\text{-}24}$), based on the intensive 24-hour PK profiles for each drug, provided the gold standard for comparison with the sparse TDM strategies.[26] We performed noncompartmental analysis of the 24-hour PK simulation data to identify the C_{max} and the $AUC_{0\text{-}24}$.

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.[34] 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.[26,40] 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 $AUC_{0\text{-}24}$ 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 $AUC_{0\text{-}24}$ 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 $AUC_{0\text{-}24}$ as the Gold Standard

In contrast to a C_{max} target, the optimal serum concentration threshold corresponding to an $AUC_{0\text{-}24}$ 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 $AUC_{0\text{-}24}$ 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 $AUC_{0\text{-}24}$.[42] The overall diagnostic accuracy is defined by the area under the ROC curve.[35] Due to uncertainty surrounding $AUC_{0\text{-}24}$ 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 $AUC_{0\text{-}24}$ 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. Noncompartmental analysis was performed to determine the PK exposure parameters of interest using the ncappc 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 $AUC_{0\text{-}24}$ 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%),

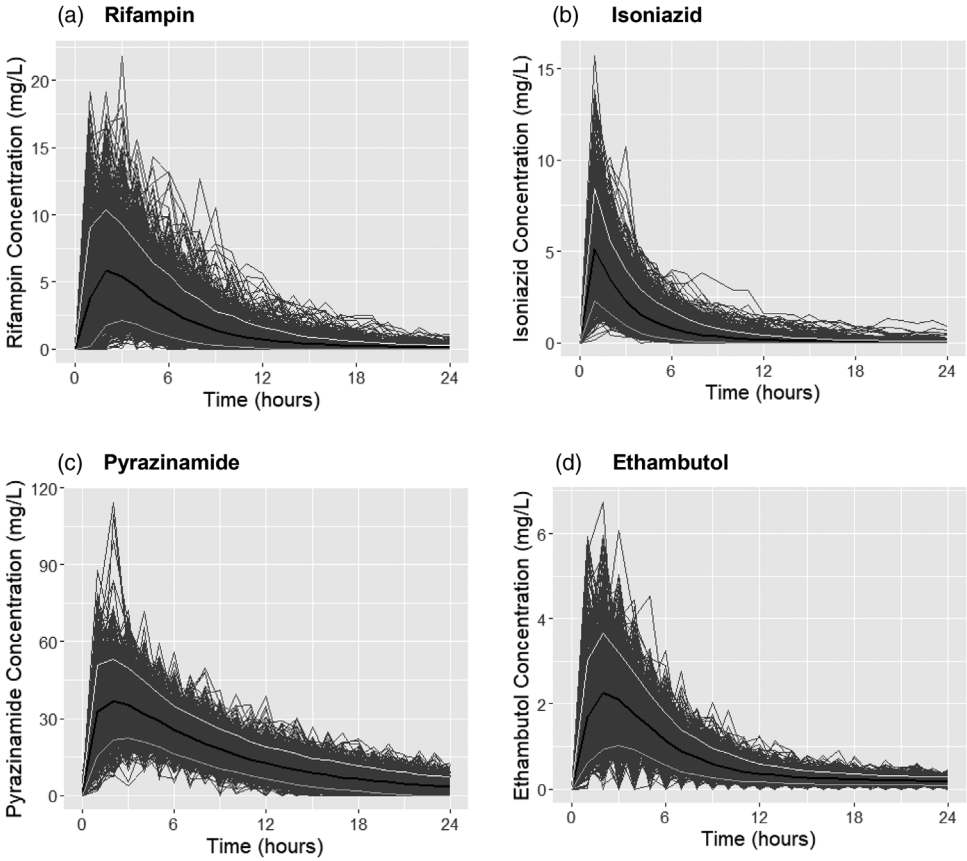

Figure 1. Individual serum concentrations vs time over a 24-hour period in the simulated patient population with HIV/tuberculosis (n = 1000). The black line is the mean line of the concentrations across the 24-hour period. The white line is the 90th percentile of the concentrations across the 24-hour 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_{max} targets.

Diagnostic Performance of Sparse TDM for $AUC_{0\text{-}24}$ Targets

The threshold serum concentration corresponding to an $AUC_{0\text{-}24}$ 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 $AUC_{0\text{-}24}$ exceeding the lowest quartile in the virtual patient population. The ROC curves based on these $AUC_{0\text{-}24}$ thresholds are shown in Figure 4. Notably, the accuracy of a single 2-hour concentration for isoniazid $AUC_{0\text{-}24}$ 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.[39] In this population PK simulation study, we investigated the diagnostic characteristics

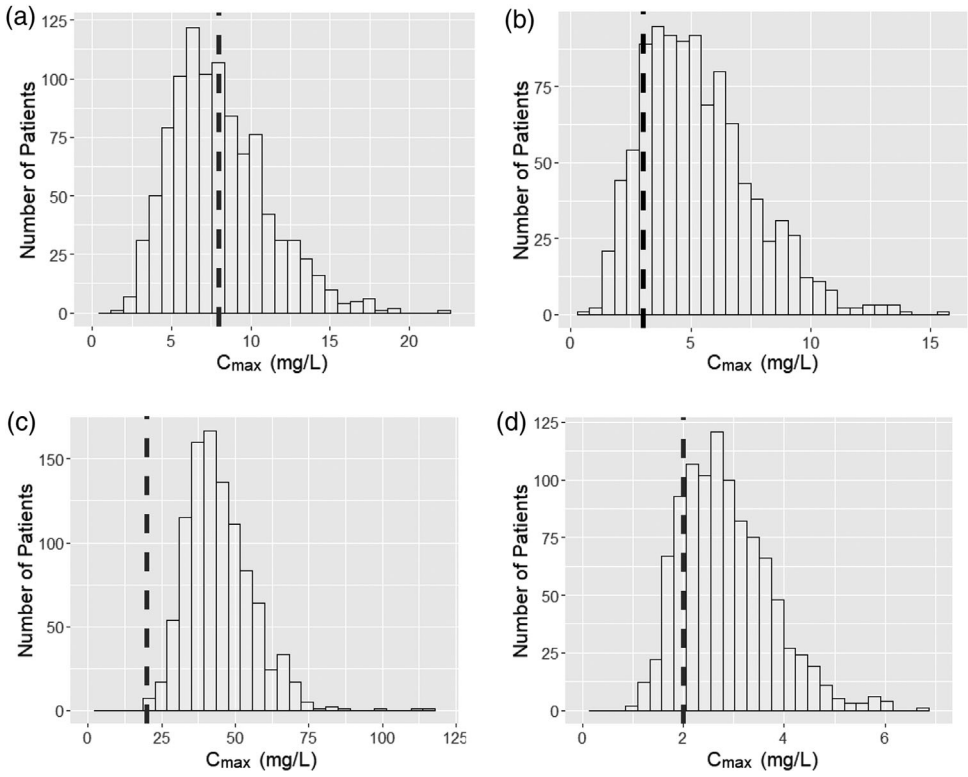

Figure 2. Histogram of distribution of C_{max} (mg/L) for 1000 patients in the simulated patient population with HIV/tuberculosis (n = 1000). (a) Rifampin, (b) isoniazid, (c) pyrazinamide, (d) ethambutol. C_{max}, maximum concentration.

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 $AUC_{0\text{-}24}$ or C_{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_{max} exposures. Thus, we found that nearly half of these virtual patients with HIV/TB with a true rifampin C_{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.[48–51] Similarly for pyrazinamide, clinical studies have provided support for higher doses that do not increase the risk of hepatoxicity.[52] Consistent with the potential for delayed oral rifampin absorption, we found that the sensitivity of sparse TDM for C_{max} targets was lowest for rifampin. Furthermore, we demonstrated that obtaining an additional 6-hour serum samples can help to distinguish between malabsorption and delayed absorption,[26,32] with a statistically significant improvement in diagnostic accuracy for $AUC_{0\text{-}24}$.

Recent publications have provided support for AUC being a better reflection of efficacy compared with C_{max}.[53–59] The modest performance of serum TDM for $AUC_{0\text{-}24}$ 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.[35] Interestingly, we observed a high diagnostic accuracy for a single 2-hour serum concentration of isoniazid with an $AUC_{0\text{-}24}$ target, a reflection of the distinct subpopulations defined by the *NAT-2* genotype and its potent covariate effect on isoniazid clearance. This observation is also a consequence of the half-life of isoniazid (≈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).[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 *NAT-2* genotype and treatment outcomes related to both microbiologic and toxicologic end points.[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_{max} targets evaluated in this simulation

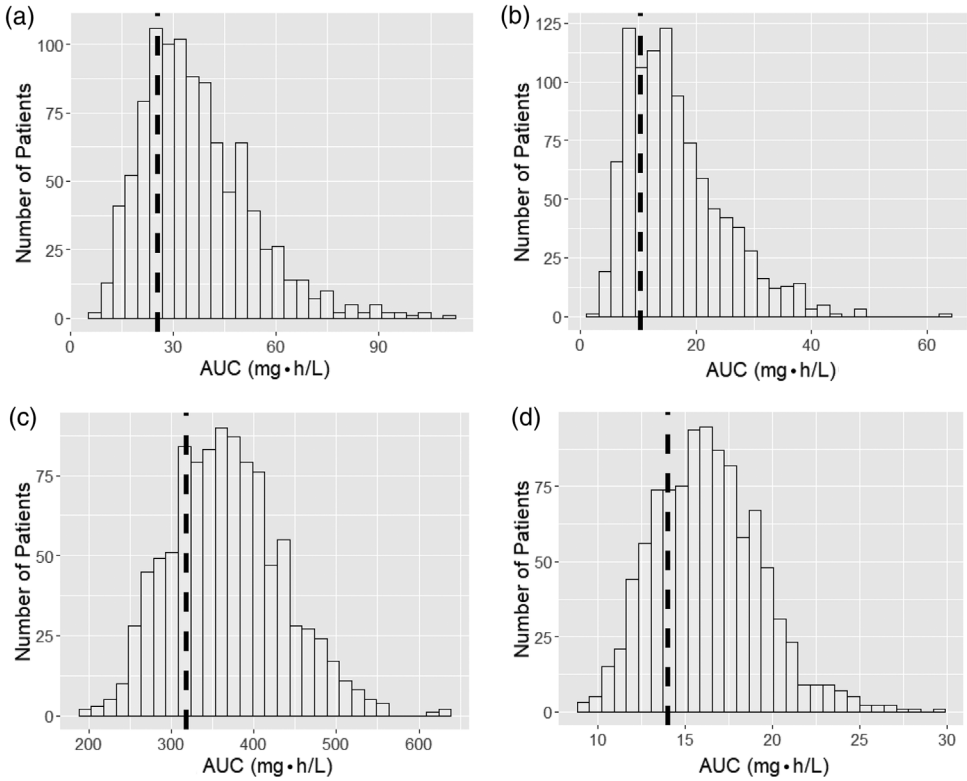

Figure 3. Histogram of distribution of $AUC_{0\text{-}24}$ (mg • h/L) for 1000 patients in the simulated patient population with HIV/tuberculosis (n = 1000). (a) Rifampin, (b) isoniazid, (c) pyrazinamide, (d) ethambutol.

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

	Sensitivity of TDM, % (95%CI)	
Drug	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_{max}, maximum concentration; TB, tuberculosis; TDM, therapeutic drug monitoring.

study are included in clinical guidelines,[26] it is possible that these C_{max} targets will be further adjusted based on ongoing trials.[43,44] Similarly, there are no prospective data in support of $AUC_{0\text{-}24}$ data, and thus our approach was to evaluate the performance of TDM for an $AUC_{0\text{-}24}$ target based on the lowest quartile in the distribution. Our population PK simulations were based on models derived from an patient population with HIV/TB in sub-Saharan Africa, and considerable variability in anti-TB drug PK is observed across settings and populations. Finally, our PK targets were entirely based on summary exposure parameters in serum, recognizing that the tissue concentration relative to the minimum inhibitory concentration (MIC), for example C_{max}/MIC or $AUC_{0\text{-}24}$/MIC, is the underlying driver of microbiologic response. However, our broader objective in this work was to apply the framework of diagnostic test evaluation to the performance of TDM during TB treatment, as an essential toward improving upon the current paradigm. Finally, we did not perform analysis related to intensified dosing regimens, for example, with rifampin or pyrazinamide, which is of great current interest in clinical trials. Should intensified regimens become adopted as standard of care, the diagnostic accuracy of TDM (eg, with the delayed absorption of higher oral rifampin dosing) would require reevaluation in this framework.

Strengths of this study include this study exploring both C_{max} and $AUC_{0\text{-}24}$ 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,[43,44] 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

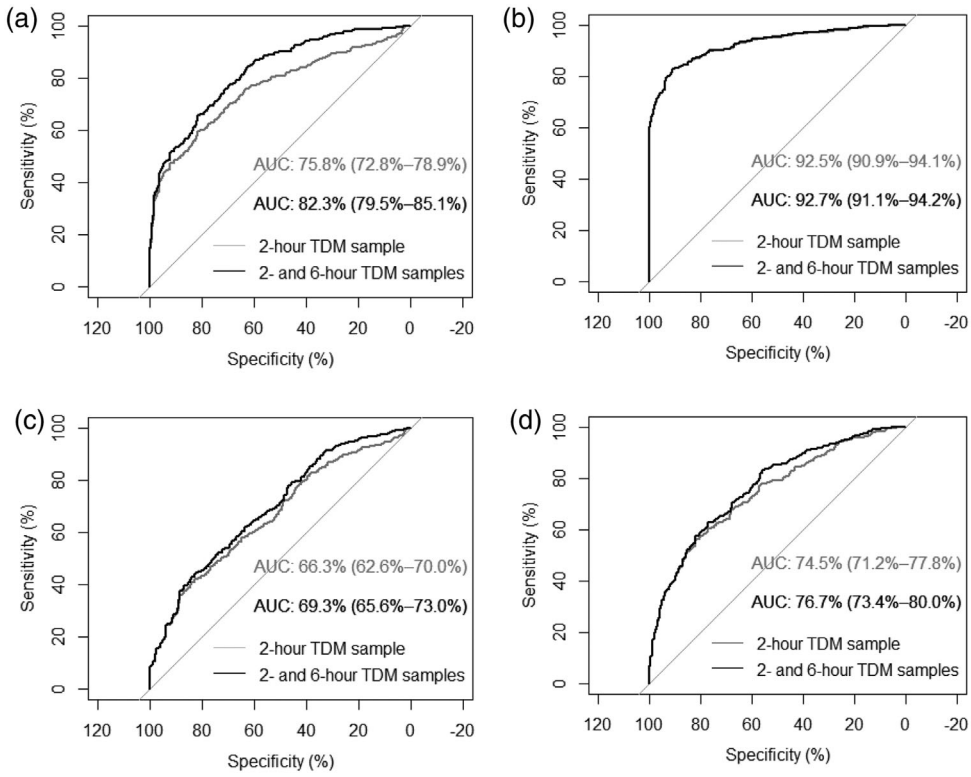

Figure 4. Receiver operating characteristic curves of the diagnostic accuracy of sparse TDM to identify patients with HIV/tuberculosis with adequate serum drug exposures, based on $AUC_{0\text{-}24}$. (a) Rifampin. (b) Isoniazid. (c) Pyrazinamide. (d) Ethambutol. AUC, area under the concentration-time curve; TDM, therapeutic drug monitoring.

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 $AUC_{0\text{-}24}$. 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.

Funding

G.A. received financial support from Rutgers New Jersey Medical School.

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

A portion of these findings were presented in abstract and poster form at IDWeek 2018 in San Francisco, California (October 3-7, 2018). This research is also part of Ginger Anderson's dissertation for partial fulfillment of the requirements for her PhD degree.

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