Estimating Optimal Anti-TB Drug Concentrations in a Prospective, Observational Cohort in Brazil

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BACKGROUND

- Individual drug pharmacokinetics (PK) can affect tuberculosis (TB) treatment effectiveness and safety[1]
- TB drug levels are not routinely performed
- Need for studies to evaluate TB drug levels based on minimizing drug toxicity and maximizing treatment efficacy

OBJECTIVE

- To compute a therapeutic range in which concentration of the four standard TB drugs (isoniazid [INH], rifampin [RIF], ethambutol [EMB], and pyrazinamide [PZA]) were effective and safe, in a large prospective cohort of TB cases in Brazil

METHODS

- Machine learning methods (e.g., Extreme Gradient Boosting, [XGBoost]) were used to create individual drug concentration curves over time and study visits, for each standard TB drug.[2]
- We used 10-fold cross-validation, adjusting for several baseline variables: sex, BMI, HIV status, smoking and alcohol status, illicit drug use, HbA1c, ancestry informative markers, directly observed therapy assigned at baseline, and NAT2 acetylator status.
- Maximum drug concentrations (Cmax) were extracted from each PK curve and later correlated to the probability of having grade 3 or higher adverse drug reaction (ADR) and to the probability of having treatment failure or recurrence.
- With the fitted model, we calculated the safety and effectiveness bounds, which were defined as drug concentrations that would lead to probabilities of toxicity or treatment failure/recurrence of at most 5%, respectively.
- Confidence intervals were obtained via bootstrapping, with 999 replicates
- We also computed individual drug percentiles; these were obtained from a quantile regression model in which the observed drug concentration was regressed against the timing of the most recent TB dose (via restricted cubic splines); patient-percentiles were later correlated to main outcomes and had the respective therapeutic bounds computed.

Estimated therapeutic range for **isoniazid** was **higher** than the currently recommended range

Estimated therapeutic range was **much lower** for **rifampin**.

	Cmax		Patient-percentile		
	Estimated effectiveness bound (95% CI)	Estimated safety bound (95% CI)	Estimated effectiveness bound (95% CI)	Estimated safety bound (95% CI)	Current recommend therapeutic drug range[3]
INH	2.2 (0; 3.7)	9.7 (7.9; 14.5)	0 (0; 0.2)	8.4 (7.9; 9.1)	3-6
RIF	0.8 (0; 21.6)	8.8 (7.4; 16.2)	0 (0; 0)	7.7 (7.1; 8.6)	8-24
EMB	0.3 (0; 0.7)	3.5 (2.6; 5.6)	0 (0; 0)	2.6 (2.2; 3.2)	2-6
PZA	11.7 (0; 17.6)	61.6 (38.9; 64.2)	0 (0; 0)	58.9 (35.5;∞)	20-60

Estimated therapeutic drug range (µg/ml)

Table 1. Estimated therapeutic drug range for the four main TB drugs, using patient-percentile and XGBoost. Abbreviations: Cmax: Maximum drug concentration; CI = confidence interval

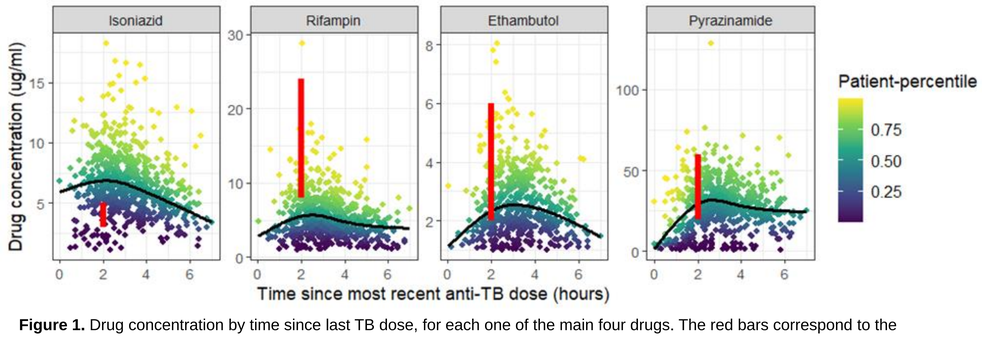

Figure 1. Drug concentration by time since last TB dose, for each one of the main four drugs. The red bars correspond to the recommended therapeutic drug range[1]

RESULTS

- A total of 466 participants (96% received DOT) with 819 plasma samples assayed. (**Figure 1**); a large proportion of patients had low RIF concentration
- Estimated therapeutic ranges were comparable using either patient-percentile or machine learning methods (**Table 1**)
- RIF and INH were associated with higher odds of having ADR in both approaches (**Table 2**);
- Low concentrations of EMB and PZA were protective against ADR using machine learning methods, but not using the patient-percentile approach (**Table 2**).

	Adverse Drug Reaction (N = 11) OR (95%CI)		Failure/recurrence (N = 13) OR (95%CI	
	Cmax	Patient-percentile	Cmax	Patient-percentile
INH	8.2 (0.9; 74.8)	1.4 (1.2; 1.8)	0.5 (0.2; 0.9)	0.9 (0.8; 1.0)
RIF	12.9 (3.5; 47.1)	1.5 (1.1; 2.0)	0.8 (0.3, 1.9)	0.9 (0.8; 1.1)
EMB	3.5 (0.5, 23.8)	1.1 (0.8; 1.3)	0.6 (0.4; 1.0)	1.0 (0.8; 1.2)
PZA	1.9 (0.3 12.0)	1.0 (0.9; 1.2)	0.4 (0.2; 0.8)	1.0 (0.8; 1.2)

Table 2. Associations of drug concentrations with grade 3+ adverse drug reaction, using patient-percentile and XGBoost. Abbreviations: Cmax: Maximum drug concentration; OR: odds ratio; CI = confidence interval

CONCLUSIONS

- Estimated therapeutic ranges differed substantially to recommend ranges for INH and RIF; value for RIF were substantially lower than recommended ranges.
- Effectiveness bounds (minimum dose) were unreliable or even unable to be computed due to the lack of association between drug concentration and failure/recurrence outcomes
- Limitations: small number of events, sparse PK data, self-reported time to last TB dose.

ADDITIONAL KEY INFORMATION

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