Population pharmacokinetics of rifampin and pyrazinamide in patients with TB: the role of HbA1c and HIV

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BACKGROUND

- Exposure to first-line anti-tuberculosis (TB) drugs varies widely between individuals[1,2]
- Persons with HIV (PWH) and individuals with diabetes mellitus (DM) frequently exhibit reduced drug exposure, particularly to rifampin[3,4]
- **AIM:** to develop population pharmacokinetic (PopPK) models, using real-world data from individuals with TB receiving first-line fixed-dose combination (FDC) TB treatment in the outpatient setting

METHODS

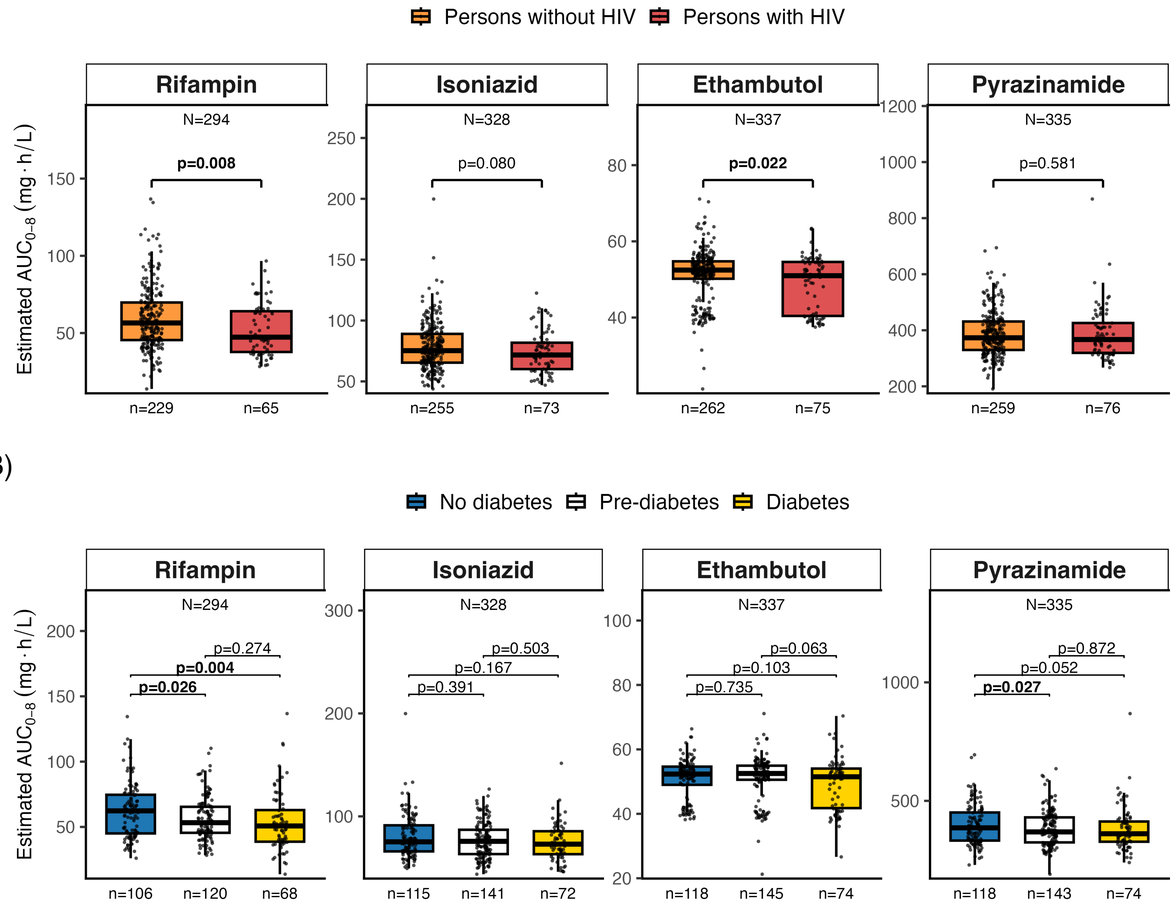
- RePORT-Brazil study participants with drug-susceptible, culture-confirmed pulmonary TB
- FDC: two-month intensive phase of rifampin (RIF), isoniazid (INH), and pyrazinamide (PZA), and ethambutol (ETB), followed by four (or more) months maintenance phase of RIF and INH.
- Participants were sparsely sampled on month 1, with one sample per participant
  - drug concentration: liquid chromatography-mass
- Age, sex, weight (scaled), glycated hemoglobin (HbA1c), and HIV status, and *NAT2* acetylator profiles for INH were used in the covariate model building
  - DM categories were defined based on baseline HbA1c: non-DM (HbA1c ≤5.7%), pre-DM (HbA1c 5.8–6.4%), and DM (HbA1c ≥6.5%)
- Time since last dose was recorded in hours
- Samples >8 h post-dose and with undetectable drug levels were excluded
- Stochastic approximation of the expectation maximization (SAEM) algorithm in Monolix® was used for structural and covariate model building and individual parameters estimations
  - Lowest Bayesian Information Criterion for model selection
- Estimated Area Under the Curve (AUC, mg·h/L), calculated as dose/CL, was compared by DM and HIV status (Mann–Whitney U test)

RESULTS

- 339 participants included
- Undetectable concentrations were most frequent for RIF (n=45, 13%)

- HIV was associated with lower rifampin and ethambutol exposures
- Pre-diabetes was associated with lower rifampin and pyrazinamide exposure
- Diabetes was associated with lower rifampin exposure

Figure 1. Model-derived drug exposure according to **(A)** HIV and **(B)** DM-status, for each anti-TB drug



RESULTS (Cont.)

- Drug-specific one-compartment PopPK model, with oral administration, first-order absorption and linear elimination adequately described all four drugs, estimating clearance (CL), volume of distribution (Vd), and absorption rate constant (ka)
  - Adequate model fit, but with residuals variability not fully captured by the model
- CL and ka were estimated with precision on all models (Residual Standard Error [RSE] <30%), but Vd was not (RSE>30%)
- Lower RIF (p=0.008), ETB (p=0.022), and marginally lower INH (p=0.08) exposure among PWH compared to HIV-negative participants (**Figure 1A**)
- Lower RIF exposure among participants with pre-DM and DM, compared to normoglycemia (p=0.026 and p=0.004, respectively). Participants with pre-DM were additionally associated with lower PZA exposure (p=0.027) (**Figure 1B**)

LIMITATIONS

- Samples with undetectable drug levels were not included
- Self-reported time since last dose

CONCLUSIONS

- Four drug-specific PopPK models developed, with reliable parameter estimations and performance
- Key findings:
  - Lower RIF and ETB, and trend lower INH exposures in PWH
  - Lower RIF exposure in persons with pre-DM and DM
  - Lower PZA exposure in persons with pre-DM
- **NEXT STEP: e**xposure–response analysis for TB outcomes and adverse reactions

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PLAIN LANAGUAGE SUMMARY: we showed that people with HIV, pre-diabetes, and diabetes have lower levels of certain tuberculosis medications in their bodies

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