Decreased Serum Drug Levels of Second-Line Antimycobacterial Agents in People With HIV

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Felipe Ridolfi[1]*, Prerna R. Arora[2]*, Yilan Gao[3], Valeria C. Rolla[4], Timothy R. Sterling[1], Vidya Mave[5], Sanjay Gaikwad[5], Sonali Sarkar[6], Padma Priyadarsini[7], Tester F. Ashavaid[2], Camilla Rodrigues[2], Zarir F. Udwadia[2], Jeffrey A. Tornheim[8], Nicole F. Maranchick[9], Rifa Khan[10], Amita Gupta[11], Charles A. Peloquin[9], Charles R. Horsburgh[3], and the Predictors of Resistance Emergence Evaluation in Multidrug Resistant-Tuberculosis Patients on Treatment (PREEMPT) study group

[1]Department of Medicine, Division of Infectious Disease, Vanderbilt University Medical Center, Nashville, USA; [2]P. D. Hinduja National Hospital and Medical Research Centre, Mumbai, India; [3]Department of Global Health, Boston University School of Public Health, Boston, USA; [4]Clinical Research Laboratory on Mycobacteria, National Institute of Infectious Disease, Fiocruz, Rio de Janeiro, Brazil; [5]BJ Medical College and Sassoon General Hospitals, Maharashtra, India; [6]Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India; [7]National Institute for Research in Tuberculosis, Chennai, India; [8]Center for Clinical Global Health Education, Johns Hopkins School of Medicine, Baltimore, USA; [9]Department of Pharmacotherapy and Translational Research, University of Florida, Gainesville, USA; [10]Y.R. Gaitonde Centre for AIDS Research and Education, Chennai, India; [11]Division of Infectious Diseases, Johns Hopkins School of Medicine, Baltimore, USA; * These authors share the first authorship

BACKGROUND

- HIV is associated with higher odds of multidrug-resistant tuberculosis (MDR-TB), and an increased risk of acquiring additional drug resistance during treatment [1-3]
- Persons with HIV (PWH) and TB frequently have lower or subtherapeutic serum concentrations of first-line anti-TB drugs which may contribute to the emergence of resistance during therapy [4-6]
- **AIM**: to compare exposure to second-line antimycobacterial drugs between persons with and without HIV receiving treatment for MDR-TB

METHODS

- Participants from PREEMPT study, a multicenter cohort study (enrolled 2019–2023) of adults with confirmed pulmonary MDR-TB in Brazil and India, with one-year post-treatment follow-up
  - MDR-TB was defined as resistance to rifampin and isoniazid
  - MDR-TB treatment followed the Brazilian national guideline and, in India, the P. D. Hinduja Hospital and Medical Research Centre's guideline
  - In India, high dose isoniazid is used as a second-line drug for MDR-TB
- Plasma concentrations of levofloxacin, moxifloxacin, ethionamide, isoniazid, and pyrazinamide were measured using liquid chromatography mass spectrometry
- Samples with undetectable drug levels were excluded
  - Samples with detectable vs undetectable levels, by HIV status → mixed-effects logistic regression (random intercept for participant)
- Pharmacokinetic sampling: 14–28 days after treatment initiation
  - Intensive sampling: blood collection at 0, 1-, 2-, 4-, and 6-hours post-dose
  - Sparse sampling: collections at 2- and 6-hours post-dose
- Maximum observed concentration (C_{max}) → Phoenix WinNonlin
- Area under the concentration–time curve (AUC) 0-6h and 0-24h → Noncompartmental analysis
- C_{max} values: continuous and categorical (below and not below), according to drug-specific lower ranges (**Table 1 legend**)
- C_{max} and AUC were compared by HIV status using the Mann–Whitney U test. C_{max} proportions (below vs not below) were compared using Firth's penalized logistic regression to account for sparse data
- Per-patient analyses used Mantel–Haenszel methods, stratified by number of drugs assayed

Compared to persons without HIV, persons with HIV were more likely to have samples with undetectable drug levels and to have more samples with C_{max} below the normal range

Table 1. MDR-TB drug samples below the lower range for C_{max}, according to HIV-status

Antimycobacterial drug	N samples below C_{max}/ Total number of samples (%)		*p*-value	OR (95% CI)
	Persons without HIV N =571 (87%)	PWH N =87 (13%)		
Ethionamide	18/112 (16)	2/13 (15)	0.89	1.11 (0.20-4.20)
Isoniazid[1]	6/75 (8)	3/8 (38)	**0.03**	**6.80 (1.33-32.81)**
Pyrazinamide	15/170 (9)	2/16 (13)	0.48	1.73 (0.32-6.40)
Levofloxacin	12/101 (12)	10/44 (23)	0.10	2.18 (0.86-5.43)
Moxifloxacin	13/113 (12)	1/6 (17)	0.49	2.03 (0.20-11.32)
All drugs combined	64/571 (12)	18/87 (22)	**0.02**	**2.09 (1.15-3.66)**

Legend. [1] High dose isoniazid (900mg/day). Abbreviations: OR: odds ratio; 95% CI: 95% confidence interval. PWH: persons with HIV. Lower reference cutoff values for each drug: ethionamide: 1 mcg/mL; isoniazid: 3 mcg/mL; pyrazinamide: 20 mcg/mL; levofloxacin: 8 mcg/mL; moxifloxacin: 3 mcg/mL

PLAIN LANGUAGE SUMMARY

We showed that people with HIV tended to have lower amounts of medicines used to treat drug-resistant tuberculosis. The clearest example was isoniazid. The highest level of this drug in their system was lower compared to persons without HIV.

RESULTS

- 365 participants enrolled (PWH 23%, N=85), 834 samples
  - Overall, detectable samples: 658 (79%); undetectable: 176 (21%)
- Compared to participants without HIV, PWH were older (p=0.008), with negative baseline sputum smear (p<0.001), and more likely to have samples with undetectable drug concentrations (33% vs 19%, OR 2.08 95%CI 1.25-3.47, p=0.005), mainly for ethionamide (p=0.027), pyrazinamide (p<0.001), and moxifloxacin (p=0.005)
  - Detectable samples: 87 for PWH (67%), 571 for persons without HIV (81%)
- PWH had lower median C_{max} values for all drugs (except levofloxacin), with significant difference only for isoniazid (median 5.91 vs 9.62 mcg/mL; p=0.027).
- The median C_{max} for levofloxacin was higher among PWH (14 vs 13 mcg/ml, p=0.82)
- PWH were more likely to have samples with C_{max} values below the expected range, with significant differences for isoniazid (OR 6.80, 95% CI 1.33-32.81, p=0.03), and for all drug samples combined (22% vs 12%; OR 2.09, 95% CI 1.15–3.66; p=0.02) (**Table 1**)
- AUC_{0-24} and AUC_{0-6} did not differ significantly according to HIV status
- PWH were more likely to have at least one C_{max} below the reference range (Mantel–Haenszel Risk Ratio 1.6, 95% CI 1.0–2.5)

LIMITATIONS

- 176 samples had undetectable drug levels despite reported intake
- 24% (n=157) of samples had 6-hour concentrations higher than 2-hour values, limiting accurate AUC_{0-24} estimation
  - this was not associated with HIV status

CONCLUSIONS

- PWH were more likely to have samples with undetectable drug levels
- PWH also had a higher proportion of samples with C_{max} below the reference range, except for levofloxacin
- AUCs did not differ according to HIV status

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felipe.ridolfi@vumc.org