EFFECT OF METFORMIN ON THE PHARMACOKINETICS OF RIFAMPICIN, ISONIAZID, AND PYRAZINAMIDE IN ADULTS WITH TB AND HIV

II-021

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UCT Pharmacometrics

Background

Tuberculosis burden: ~131 cases per 100,000 globally; ~5.8% occur in people living with HIV. In the WHO African Region, the burden is substantially higher.[1]

Exposure matters: Low rifampicin and other first-line TB drug concentrations are linked to poorer outcomes. [2]

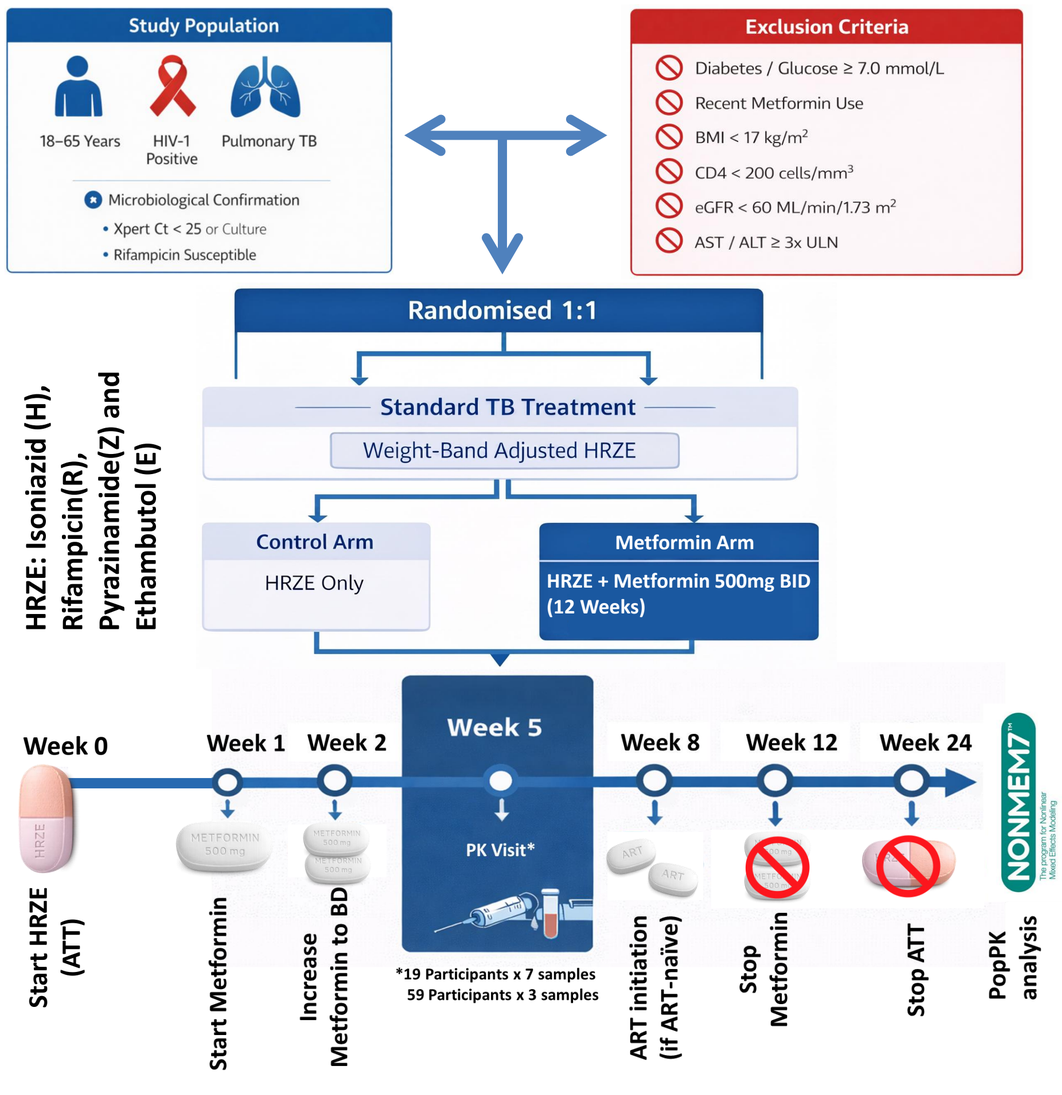
Knowledge gap: Metformin is widely co-administered and is a candidate host-directed TB therapy, but its pharmacokinetic impact on TB drugs is uncertain. [3,4]

Whether a clinically meaningful drug-drug interaction exists and warrants dose adjustment remains to be established.

Objective:
To assess **metformin-associated** pharmacokinetic **interactions** with isoniazid, rifampicin, and pyrazinamide in **HIV-associated pulmonary TB in non-diabetics,** through **population PK modelling.**

Methods

METHOD Study: NCT0490744; Study ID: AUR1-1-199



Intensive PK sample (n = 399)
(pre-dose, 1, 2, 4, 6, 8, 10 h post-dose)
Sparse PK sampling (n = 531)
(pre-dose, 2 and 6 h post-dose)

Lower limit of quantification:
Isoniazid: 0.117 mcg/ml
Rifampicin: 0.105mcg/ml
Pyrazinamide: 0.2 mcg/ml

→ **BLQ Handling Method:** M7+[10]

Population PK modelling done in NONMEM 7.5.1 with **FOCE-I**

For isoniazid, rifampicin, and pyrazinamide, 68 (21.5%), 72 (23.2%), and 5 (1.6%) plasma observations were **BLQ –** Majority of those were pre-dose samples

Patient Characteristics

Characteristic	No Metformin N = 35	Metformin N = 43	Overall N = 78
No. of males	23 (66%)	26 (60%)	49 (63%)
Age (Years)	42 (37, 49)	43 (34, 49)	43 (35, 49)
Weight (kg)	63.0 (56.6, 71.5)	59.3 (52.2, 64.7)	60.8 (53.9, 67.8)
Height (cm)	166 (160, 175)	165 (159, 172)	166 (160, 172)
Fat-Free Mass (kg)[a]	47.2 (41.8, 53.2)	45.9 (40.3, 51.1)	46.8 (41.0, 51.9)
Body mass index (kg/m²)	22.4 (20.0, 26.3)	21.3 (19.0, 23.3)	21.8 (19.6, 24.0)
Creatinine clearance (mL/min)[b]	104 (85.0, 130)	111 (86.6, 122)	110 (86.6, 123)
Bilirubin (µmol/L)	6.0 (4.0, 7.0)	5.5 (4.0, 7.0)	5.5 (4.0, 7.0)
Antiretroviral therapy			
Not on antiretroviral therapy	3 (8.6%)	12 (29%)	15 (19%)
Efavirenz-based Treatment	1 (2.9%)	0 (0%)	1 (1.3%)
Dolutegravir-based Treatment	31 (89%)	30 (70%)	61 (78%)

[a] Fat-free mass was calculated according to Janmahasatian et al.[5]
[b] Creatinine clearance was calculated using the Cockcroft–Gault method [6]

Results

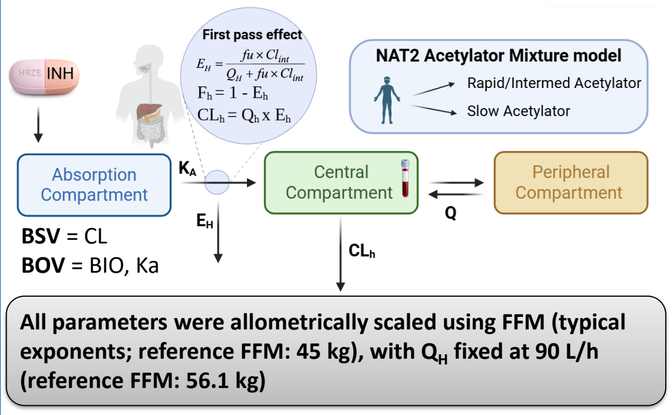


Figure 2: Isoniazid. Left panel: Final two-compartment model with first-order absorption and hepatic first-pass extraction. **Right panel:** Simulation of a typical individual stratified by metformin and no-metformin arms and acetylator status.

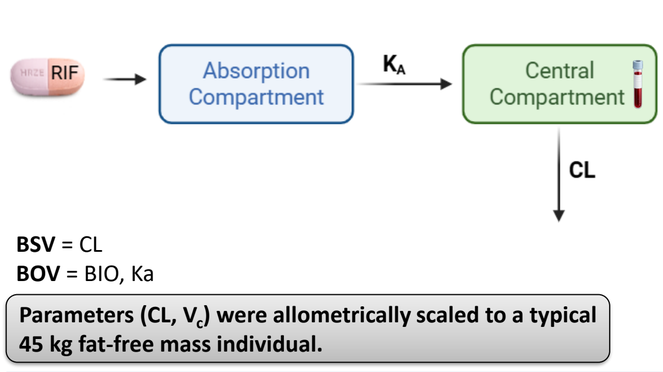


Figure 3. Rifampicin. Left panel: Final one-compartment model with first-order absorption and clearance. **Right panel:** Simulation of a typical individual stratified by metformin and no-metformin arms.

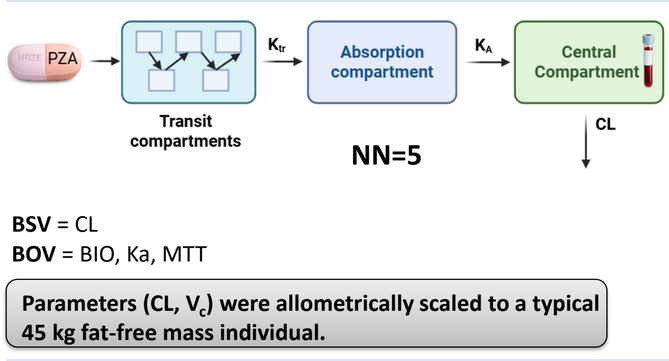


Figure 4. Pyrazinamide. Left panel: Final one-compartment transit model with first-order absorption and clearance. **Right panel:** Simulation of a typical individual stratified by metformin and no-metformin arms.

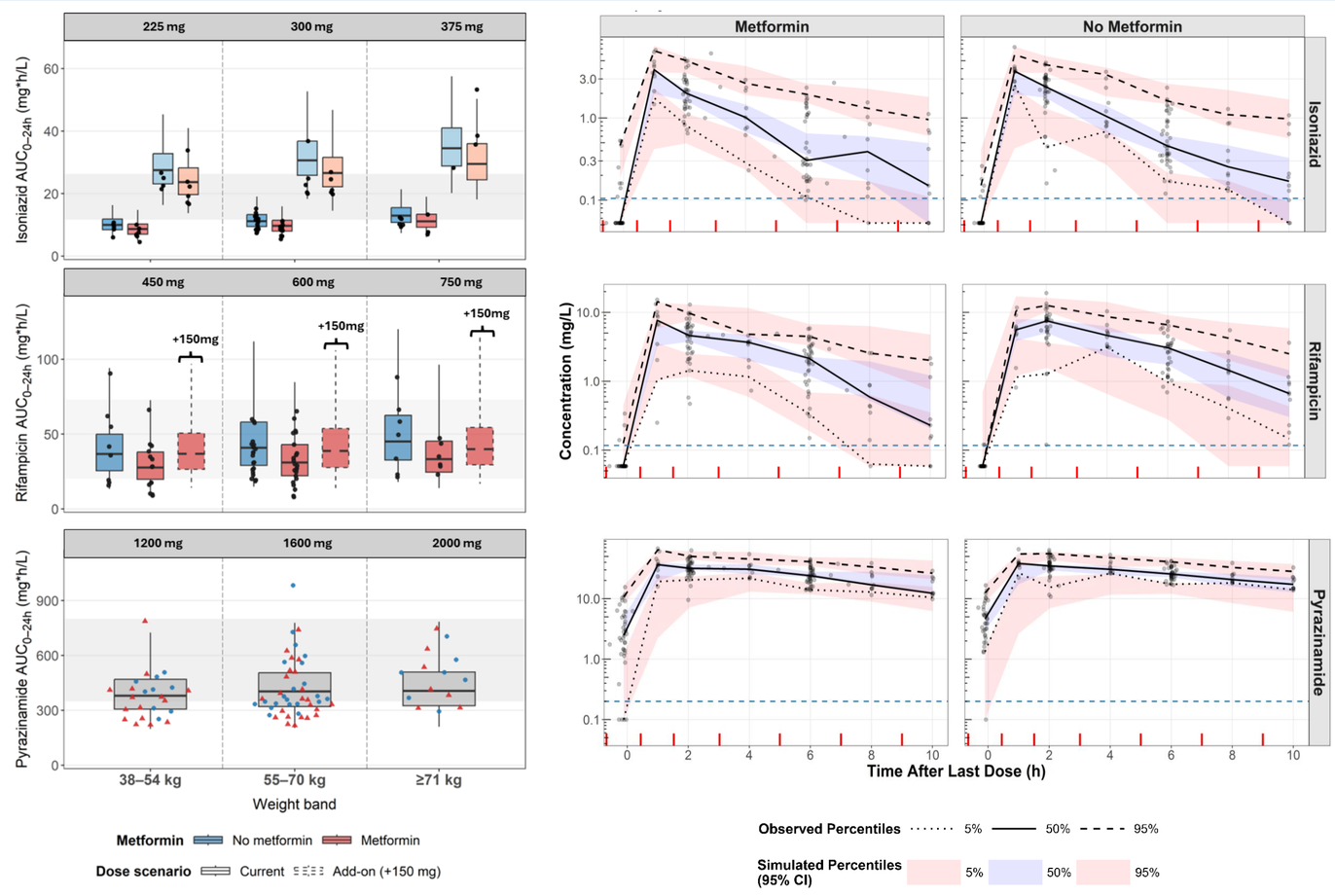


Figure 5: Model-predicted AUC_{0-24h} distributions with GMR between Metformin vs No Metformin arms for isoniazid (top), rifampicin (middle) and pyrazinamide (bottom) in a virtual cohort of 1,000 individuals. The dotted line boxplot represents a **simulated cohort that received an extra Rifampicin dose (+150mg).** Boxes and whiskers show the median and 95% prediction interval, points represent observed participant AUC estimates, and grey shaded bands indicate historical adult reference exposure ranges at standard dosing[7,8].

Figure 6: : Visual predictive checks (VPCs) of steady-state plasma concentration–time profiles for isoniazid, rifampicin, and pyrazinamide stratified by metformin co-administration. Points indicate observed concentrations, while concentrations below the lower limit of quantification (LLOQ) are shown as dashed blue lines (LLOQ/2) for both observed and simulated data for visualization purposes. Isoniazid, rifampicin and pyrazinamide lower limits of quantification are **0.117**, **0.105**, and **0.200 mg/L**, respectively.

Conclusion

Primary finding: Lower rifampicin and isoniazid exposure in metformin arm, consistent with prior reports.[9]
Pyrazinamide: No statistically significant difference between arms in this study.
Rifampicin exposure: Simulations showed that one additional 150 mg virtual capsule restored exposure towards the non-metformin group.

Acknowledgements

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NIH National Institute of Allergy and Infectious Diseases

NRF National Research Foundation

FULL MODEL PARAMETERS AND ADDITIONAL GRAPHS AND TABLES
Full model parameters
Additional graphs and figures
Summary tables and outputs
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