I-021

Pyrazinamide population pharmacokinetics in adults with drug resistant tuberculosis: The role of allometric scaling

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UCT Pharmacometrics

Background

Pyrazinamide is a cornerstone sterilizing agent incorporated into both first- and second-line tuberculosis (TB) treatment [1].

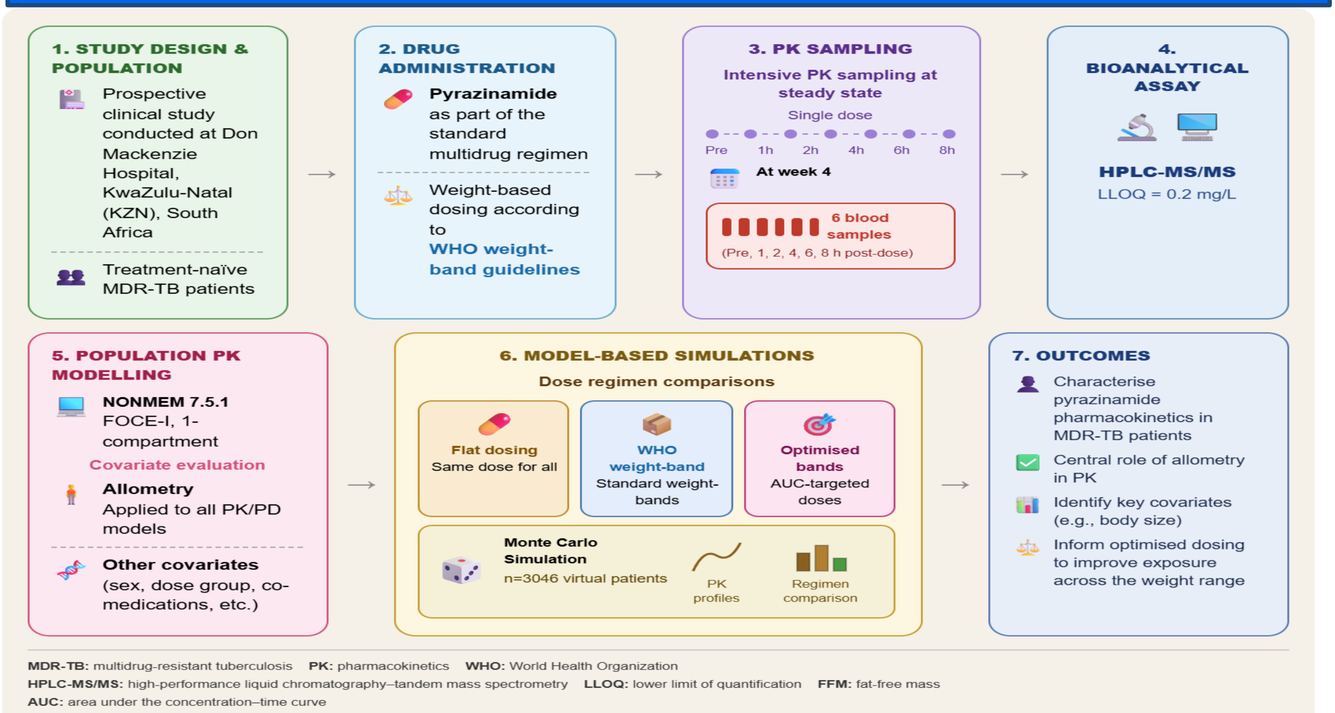
Current WHO guidelines recommend **weight-band dosing of pyrazinamide** [2], with each weight-band receiving on average the same mg/kg dose of 20–30 mg/kg daily.

A recent study [3], reported no **significant effect of body size on pyrazinamide** (elaborate) pharmacokinetics (PK), but observed higher bioavailability in women, lower bioavailability at higher doses, and **recommended flat dosing for pyrazinamide**.

Objectives

- Our study aimed to characterize pyrazinamide **popPK** in a South African multidrug resistant (MDR)-TB population and
- Evaluate the effect of body size via **allometric scaling** in explaining interindividual variability.
- Simulations were used to assess **optimized dosing strategies**.

Methods



MDR-TB: multidrug-resistant tuberculosis **PK:** pharmacokinetics **WHO:** World Health Organization
HPLC-MS/MS: high-performance liquid chromatography–tandem mass spectrometry **LLOQ:** lower limit of quantification **FFM:** fat-free mass
AUC: area under the concentration–time curve

Figure 1. Methodology followed for the PZAP trial

Results

Table 1. Patient's characteristics

Patients Characteristics	Overall N=112
Weight (kg)	54 (50,62)[a]
FFM (kg)	45 (38,49) [a]
Age (years)	35 (30,42) [a]
Sex (female) n(%)	37 (33)
People living with HIV n(%)	91 (81)
ART regimen n(%)	
Efavirenz	8 (7.1)
Lopinavir + Ritonavir	27 (24)
Nevirapine	47 (42)

[a] Continuous variables –Median(Q1,Q3)

Table 2. Parameter estimates

Parameter	Final Model with allometry	
	Typical value (95% CI)[b]	Variability[c] %CV
Clearance (L/h)[a]	2.97 (2.798–3.136)	23.6(22.8-31.3)
Volume of distribution (L)[a]	38.9 (35.4-39.063)	—
Absorption rate constant (1/h)	1.36 (1.25-1.660)	69.4(65.4 – 100)
Absorption lag time (h)	0.104 (0.034-0.155)	128.5(109.5-200.5)
Duration of zero-order abs. (h)	0.485 (0.330-0.661)	126.4 (93.4– 158.0)
Bioavailability, F	1 (FIXED)	28.3 (18.8 – 25.4)
Scaling factor for BOV of pre-dose occasion (fold)[d]	1.27 (0.309-2.069)	—
Proportional error (%)	9.2 (8.51-10.47)	—
Additive error (mg/L)	1.13 (0.917-1.468)	—
Effect of protease inhibitor (PI)	1.25 (1.09-1.38)	—

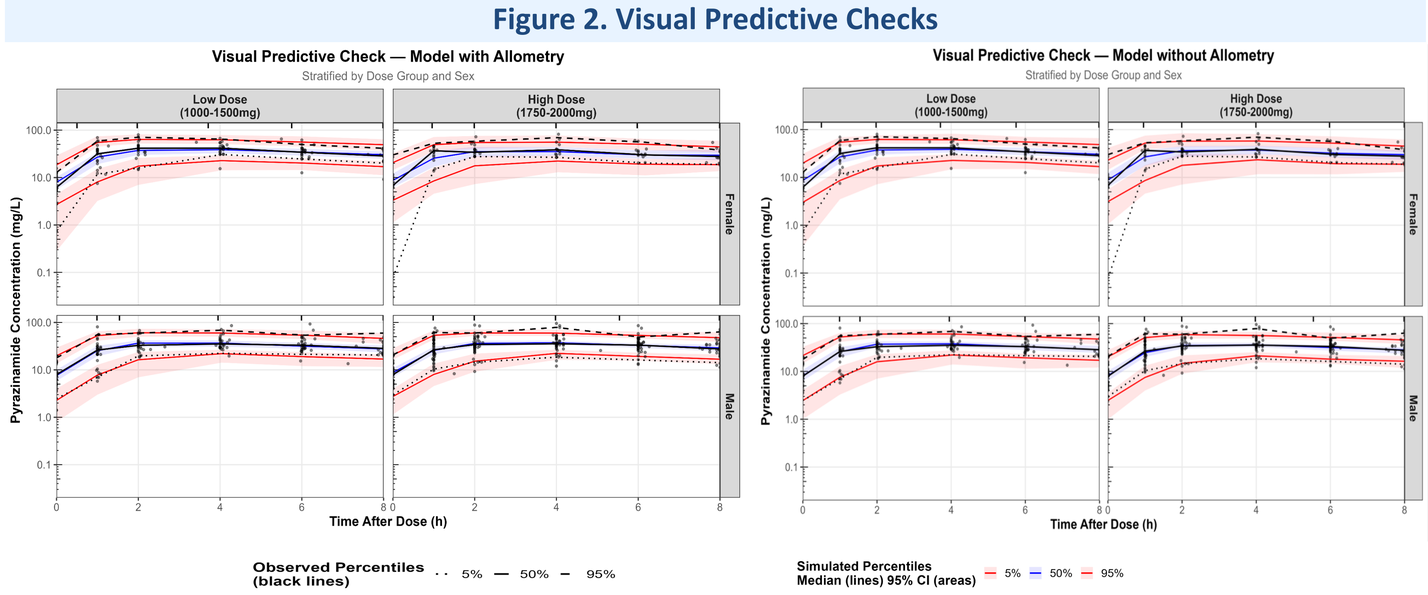
[a] *Standardised to a 54.3 kg individual using allometric scaling (exponent 3/4 for clearance, 1 for volume)*
[b] *95% confidence interval derived from SIR*
[c] *Between subject variability(BSV) & Between-occasion variability (BOV) expressed as %CV = √(exp(ω²) − 1) × 100*
• (0.3%) of the samples were below the limit of quantification.

Table 3. Confounding effect of dose and female_sex

Models	Without Allometry	With Allometry
Dose effect _on BIO	0.804(0.679-0.954)[b]	0.978 (0.88-1.06)[b]
Female sex_associated effects _on BIO	1.04 (0.874-1.240)[b]	1.02 (0.922-1.12)[b]

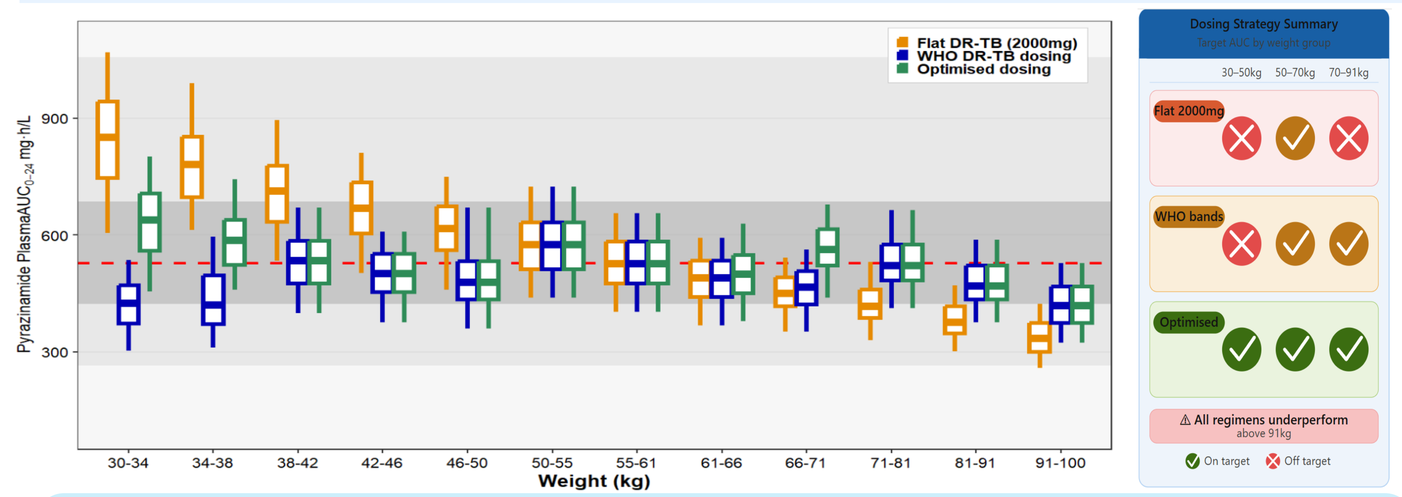
Disposition parameters were best described using allometric scaling with TBW (ΔOFV=-30.2) compared with FFM (ΔOFV=-21.1).. [b] *95% confidence interval derived from SIR*

Figure 2. Visual Predictive Checks



VPCs indicated that both structural models adequately described observed pyrazinamide concentrations across dose groups and sex. In the model without allometry, sex (females: +4% F) and dose group (higher doses: −20% F) were retained as covariates, adding two parameters. With allometric scaling, these effects became non-significant and model fit improved (ΔOFV = −16.5), suggesting they primarily reflect body size. This is consistent with sex–weight correlations and WHO weight-band dosing, where dose group tracks body weight. In oral-only data, incomplete separation of F from CL/F and V/F can generate apparent F effects driven by size. Allometric scaling therefore provides a more mechanistic and parsimonious description of size-related variability than empirical covariates.

Figure 4. Exposure vs weight bands for all dosing regimen



WHO weight-band dosing underexposes lighter DR-TB patients (30–50 kg), with $AUC_{0–24}$ below target, while a fixed 2000 mg dose overexposes this group (>150% of target) despite adequate exposure in mid-range weights. The optimized regimen refers to model-informed weight-band dosing adjusted to achieve target AUC across body weights. This approach maintains $AUC_{0–24}$ within the 80–130% range across 30–91 kg. However, all regimens underperform above ~81 kg, indicating insufficient dose escalation at higher body weights. Overall, current strategies do not adequately capture nonlinear size–exposure relationships.

Conclusion

- The popPK model identified body size as a key determinant of pyrazinamide pharmacokinetics, with weight outperforming fat-free mass.
- Sex and dose effects were only significant without allometric scaling, supporting their interpretation as confounders for body size.
- Lopinavir/ritonavir was associated with increased clearance despite pyrazinamide's non-CYP metabolism-warrants further investigation.
- Flat dosing & Current WHO weight-band dosing compromises exposure for smaller patients, whereas optimized weight-band dosing achieves more consistent exposure across body weights.

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