

Plasma pharmacokinetics of high dose oral versus intravenous rifampicin in patients with tuberculous meningitis: a randomised controlled trial

SUPPLEMENTARY MATERIAL

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IMPUTATION STRATEGY

Concentration-time profiles were inspected for each participant to compare pre-dose and 24-hour concentrations. In cases where the 24-hour concentration was missing, these were imputed as pre-dose concentrations if two prior observations were available in the elimination phase. The 24-hour concentration was considered highly unlikely to represent the true trough value where it exceeded the pre-dose concentration and was > 50% of the concentration at the prior sampling time point. This was based on the published elimination half-life of rifampicin,¹⁶ and the assumption that the 24-hour concentration would therefore fall below the 6- or 8-hour concentration in the absence of additional dosing. In these cases, the 24-hour concentration was imputed from the pre-dose concentration. Where the pre-dose concentration exceeded the 24-hour concentration by > 2-fold, indicating late dosing prior to the PK visit, the pre-dose concentration was replaced by $C_{24} \cdot K_e$ to adjust for contribution to AUC. Concentrations reported as below the limit of assay quantification (BLQ) were imputed as 50% of the lower limit of detection (i.e. 0.585 µg/mL).

FIGURES

Figure S1. Trial schema

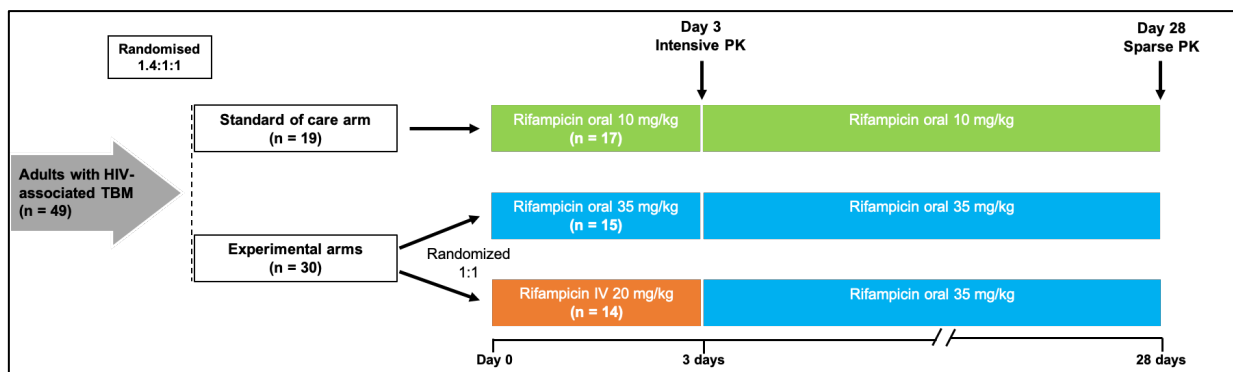


Figure S2. Simulations showing balanced exposures across weight bands with LASER-TBM dosing table

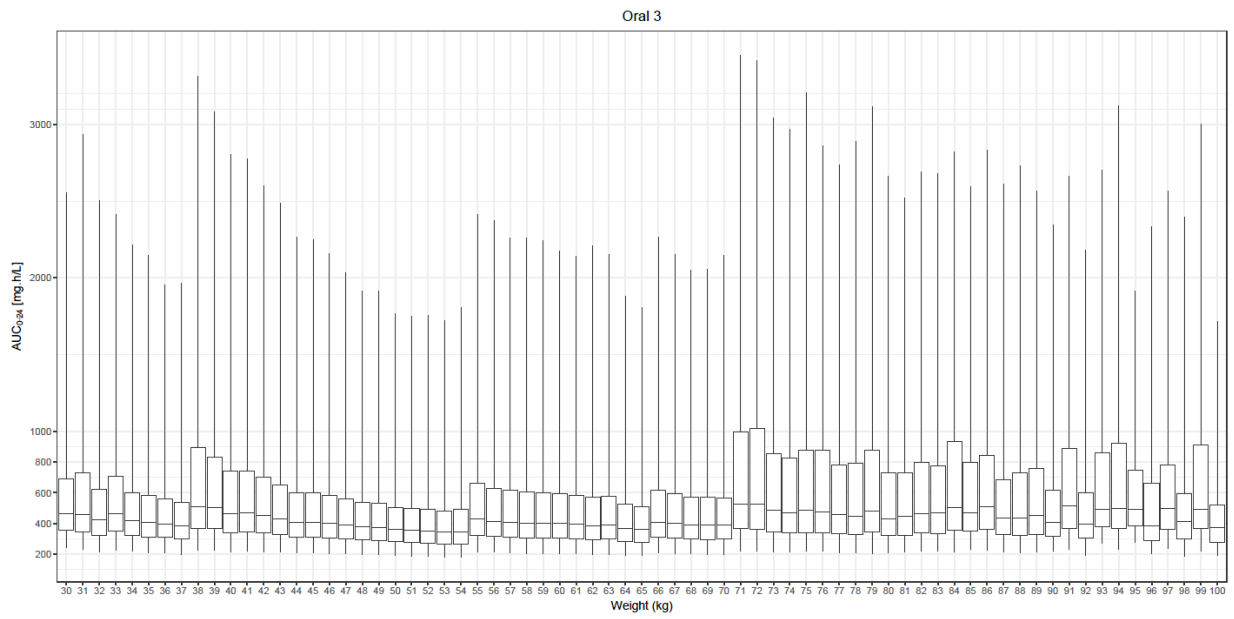


Figure S3. Exposures from swallowed versus crushed administration of rifampicin tablets for oral 35 mg/kg (Fig. S3A) and 10 mg/kg (Fig. S3B).

Fig S3A

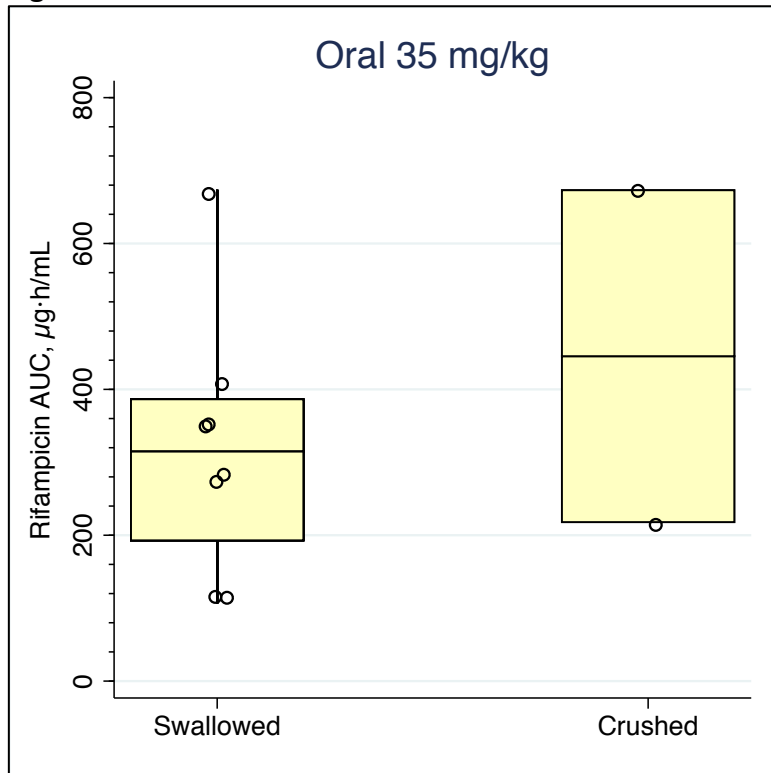
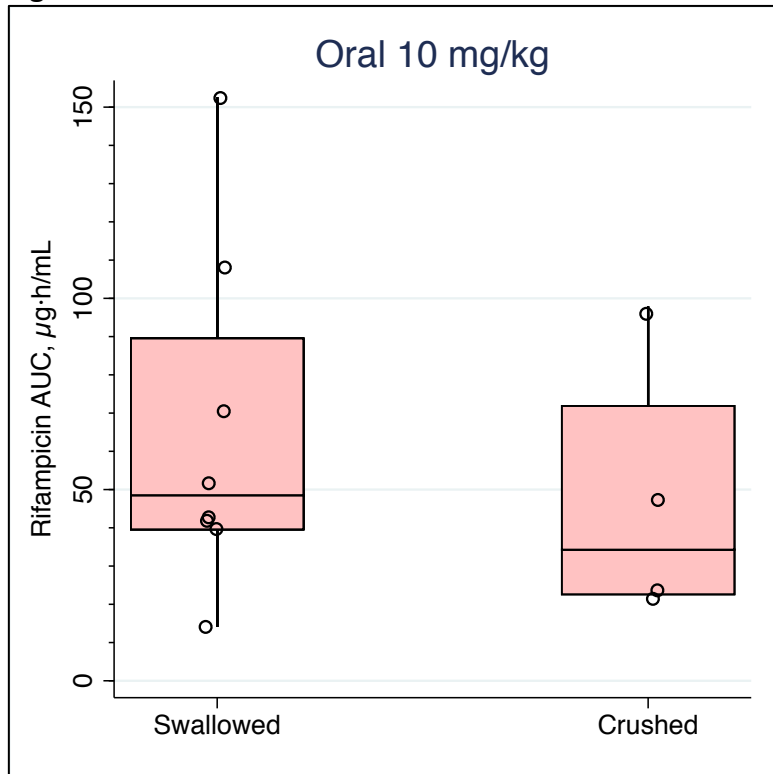


Fig S3B



TABLES

Table S1. Weight bands for oral rifampicin dosing

LASER-TBM bands	Band 1	Band 2	Band 3	Band 4	Band 5
Weight range	30 – 37 kg	38 – 54 kg	55- 65 kg	66 - 70	> 70 kg
R₁₀HZE (WHO)	300	450	600	600	750
R₂₅ additional	1200	1350	1500	1650	1950
Total RIF (~35 mg/kg)	1500	1800	2100	2250	2700

Table S2. Weight bands for intravenous rifampicin dosing

	Band 1	Band 2	Band 3	Band 4	Band 5	Band 6
Weight range	30 – 33 kg	34 - 37 kg	38 – 54 kg	55- 65 kg	66 - 70 kg	> 70 kg
HZE tabs	2	2	3	4	4	5
R₂₀ IV	900	1050	1200	1350	1500	1650
Total Rif	900	1050	1200	1350	1500	1650