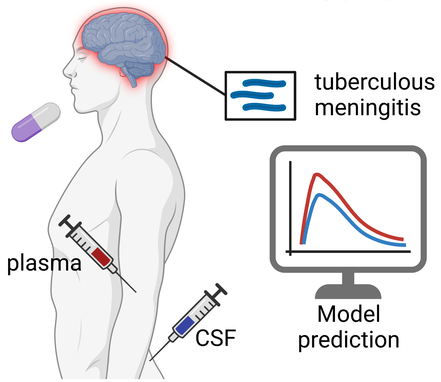
Linezolid reaches the target site in patients with TB meningitis and HIV co-infection

752

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BACKGROUND

- Tuberculous meningitis (TBM) is a devastating TB form[1-2].
- Anti-TB drugs penetrate the cerebrospinal fluid (CSF) poorly, but linezolid has good CSF penetration[3].
- We quantified plasma and CSF pharmacokinetics (PK) and pharmacodynamics (PD) for preliminary data of the Phase 2 ALTER trial[4] of adjunctive linezolid with high (35 mg/kg) or standard (10 mg/kg) dose rifampin in TBM patients.

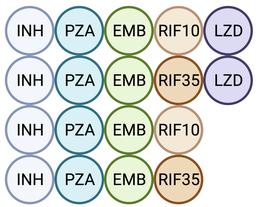


Table 1. Participant demographics

	Total
Total participants	n = 15
Female	8 (53 %)
Age (yr)	37 (25.7-61.3)
Weight (kg)	50 (37.4-65.8)
Living with HIV	15 (100 %)

Figure 1. ALTER clinical trial design. INH: isoniazid, PZA: pyrazinamide, EMB: ethambutol, RIF: rifampin (with dose in mg/kg), LZD: linezolid

METHODS

- Adult participants in Uganda were randomized to high vs. standard dose rifampin, and then to linezolid 1200 mg vs. no linezolid **(Fig 1, Table 1)**.
- CSF and plasma were sampled on days 2, 14, and/or 28.
- We quantified linezolid population PK in CSF and plasma, testing demographics and rifampin dose as covariates[5].
- Clinical trials (n=80 per trial, 50 trials) were simulated to get the proportion of participants reaching CSF PKPD targets, extrapolated from plasma targets assuming similar binding: time above MIC (85% of 24h interval) and $AUC_{0\text{-}24,ss}$/MIC (100)[6].

Linezolid reaches the target site in TB meningitis patients irrespective of standard or high rifampin dose

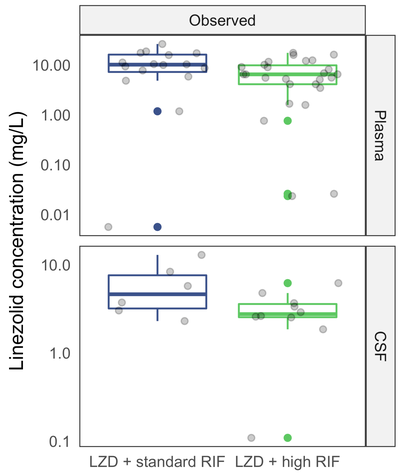


Figure 2. Observed linezolid concentrations stratified by dose of rifampin comedication shows a trend towards lower concentrations in both plasma (top) and CSF (bottom).

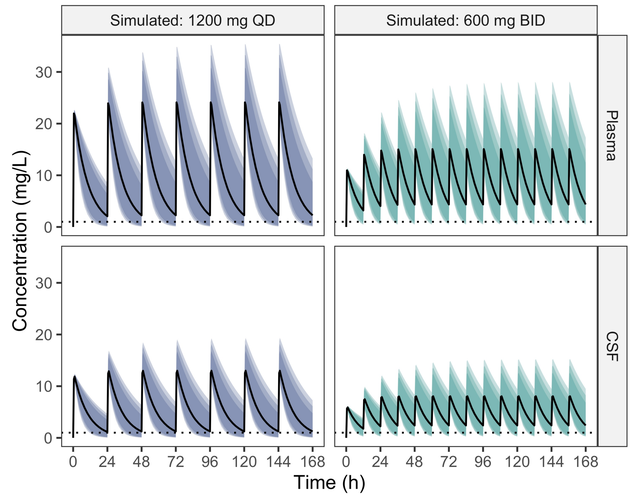


Figure 3. Clinical trial simulation for once daily (QD) 1200 mg or twice daily (BID) 600 mg linezolid shows concentrations in plasma (top) and CSF (bottom) above MIC (1 mg/L, dotted line). Median and 80, 90, and 95% confidence interval (line, areas) for 50 simulations.

RESULTS

- Median linezolid CSF and plasma peak concentrations were 3.20 and 11.0 mg/L, respectively **(Fig 2)**.
- PK was best described by a one compartment (distribution volume 46.1 L) model with first-order absorption (6.86 h^{-1}), and allometrically scaled clearance (7.95 L/h) with inter-individual variability.
- Women had 36% lower clearance than men. Plasma-to-CSF rate was fast, with a partition coefficient of 55%. A trend towards an effect of high dose rifampin on linezolid PK in both CSF and plasma was observed (**Fig 2**).
- Extrapolated CSF efficacy targets for linezolid (1200 mg QD/600 mg BID) were achieved in 63%/87% for time above MIC and 65%/55% for $AUC_{0\text{-}24,ss}$/MIC in simulated clinical trials **(Fig 3-4)**

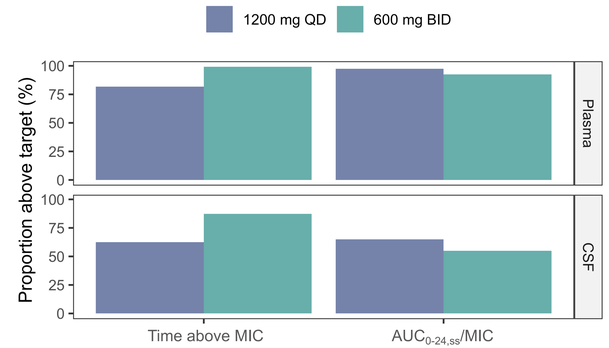


Figure 4. Proportion of participants in clinical trial simulations above the PKPD target. Bars show median from 50 simulations.

CONCLUSIONS

- Linezolid reached the target site in patients with TBM and HIV co-infection as quantified by our model-based approach of the preliminary trial data, and clinical trial simulations indicated extrapolated targets were achieved in a moderate to major proportion of simulated patients.
- This workflow will be used to confirm these results once data are available from the fully enrolled trial, including the effect of rifampin dosing on linezolid PK, and support therapeutic recommendations.

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