**Title:** Population pharmacokinetic modelling of pyrazinamide in plasma and cerebrospinal fluid from HIV-associated tuberculosis meningitis adults

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**Introduction:**

Tuberculosis meningitis (TBM) is a devastating manifestation of infection by *Mycobacterium tuberculosis*. Pyrazinamide achieves excellent brain concentrations in animal models and may have an important role in TBM therapy. Although well-studied in patients with pulmonary TB, plasma pharmacokinetics (PK) and cerebrospinal fluid (CSF) penetration of pyrazinamide in TBM still requires further research. We aimed to describe the plasma and CSF pharmacokinetics of pyrazinamide in adults with HIV-associated TBM.

**Methods:**

This study was nested in a randomised controlled trial to evaluate the safety of intensified antituberculosis therapy among adults with HIV-associated TBM in South Africa. All participants received pyrazinamide 25 mg/kg daily as part of standard TBM therapy and those randomised to the intervention arms were provided additional rifampicin (35 mg/kg as opposed to 10 mg/kg daily) plus linezolid with or without high-dose aspirin, for the first 56 days of treatment. Blood samples were intensively collected at day 3 of study enrolment, at pre-dose and 0.5, 1, 2, 3, 6, 8-10, and 24 hours post-dose. Sparse sampling was performed on day 28 at pre-dose, 2, and 4 hours post-dose. One lumbar CSF sample was collected after drug administration at each visit, with sample timing randomized to one of the intervals 1-3, 3-6, 6-10, and 24 hours. Pyrazinamide concentrations were assayed using LC-MS/MS. Data were analysed with nonlinear mixed-effects modelling in NONMEM. The CSF concentrations were linked to the central compartment using a hypothetical effect compartment, which estimates the plasma-to-CSF equilibrium half-life and the CSF-to-plasma partition coefficient. These parameters describe the delay in the equilibrium between the CSF and plasma concentrations and the extent of pyrazinamide penetration into the CSF, respectively.

**Results:**

A total of 414 plasma and 44 CSF concentrations were available from 49 participants, with median (range) age of 39 (25–78) years, weight of 60 (30–107) kg, and fat-free mass (FFM) of 45.2 (30.3–59.4) kg. Plasma pharmacokinetics of pyrazinamide was best described by a one-compartment model with first-order elimination and transit compartments absorption. The typical values of clearance and volume of distribution, allometrically scaled by FFM, were 4.19 L/h and 45.0 L, respectively. Clearance was 30% higher at day 28 compared with day 3 of the study. The CSF concentrations were linked to the plasma concentrations with an equilibration half-life of 0.66 h and a CSF-to-plasma partition coefficient of 1.05. No statistically significant differences were observed between the intervention arms receiving the high dose of rifampicin (with and without aspirin) and the one receiving the standard regimen.

**Conclusions:**

We developed a model describing the pharmacokinetics of pyrazinamide in plasma and CSF in adults with TBM. Our model confirms that pyrazinamide quickly reaches the CSF and achieves concentrations similar to plasma, supporting further efficacy evaluations in TBM. Our results on plasma PK are in line with previous reports in pulmonary TB patients. Consistently with Chirehwa *et al*., we observed an increase in pyrazinamide clearance over treatment duration. The reasons for this are unclear, but possible explanations are induction of drug-metabolising enzymes by rifampicin, or the recovery of clearance processes with treatment.