Pharmacokinetics of Rifampin in TB/HIV Co-Infected Women – Does Pregnancy Matter?

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Background and Objectives

Pregnant women are at high risk of progression from latent to active TB. They are typically treated with the same regimen as non-pregnant adults.

Pregnancy induces physiological changes that may impact drug exposures and the effects on the pharmacokinetics (PK) of rifampin – mainstay of TB treatment – are unknown.

Population PK modelling was used to investigate rifampin PK during pregnancy.

Methods

Prospective cohort of pregnant, HIV/TB co-infected women taking standard first-line TB treatment in Soweto, South Africa.

PK sampling at 37 weeks' gestation or delivery, and then at around **6 weeks postpartum**.
Blood samples generally collected pre-dose, 2, 4, and 6-8 hours post-dose. Cord blood was also collected.

Rifampin was quantified using LC-MS/MS, with lower limit of quantification (LLOQ) 0.117 mg/L.

Population PK model developed in NONMEM [1].
Initial structural model previously reported [2].
Allometric scaling [3] of clearance (CL) and volume (V) based on body weight (WT).

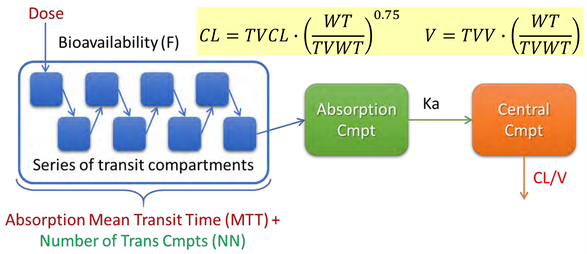

Figure 1: Structural model. Rifampicin absorption delay is modelled through a series of transit compartments. Elimination is from central compartment with first-order kinetics

Results - Study population

48 women, median age 28 yrs and weight 67 kg.
Most women were concomitantly receiving efavirenz-based HAART. Summary of characteristics in Table 1.

The sampling schedule was designed for the PK of ARVs, so some PK curves could not be used for rifampin PK.
After exclusion of profiles with no detectable rifampin levels or inconsistent with the self-reported dosing times, **the modelling analysis included 33 participants, 48 PK visits, and 183 samples**.

Results – PK model

Table 1 Patient characteristics

Patient Characteristics (N=48)	
Age in years at enrollment, median (IQR)	28 (25-31)
CD4 cells/mm^3 at enrollment, median (IQR)	301 (195-439)
Site of TB infection, N (%)	
Pulmonary	45 (94)
Extra-pulmonary	3 (6)
Infant weight in grams at delivery, median (IQR)	3000 (2575-3370)
Mothers weight in kg at delivery, median (IQR)	**67 (60-76)**
Gestational age at delivery (weeks), median (IQR)	38 (37-40)
Weeks of TB treatment at time of delivery, median (IQR)	9 (7-17)
TB treatment outcome, N (%)	
Cured	2 (4)
Treatment completed	40 (83)
Death	0 (0)
Default	1 (2)
Failure	0 (0)
Lost to follow up	3 (6)
Ongoing treatment	2 (4)
Concomitant ART:	
EFV-based HAART	41 (85)
NVP-based HAART	1 (2)
LPV/r-based HAART	1 (2)
AZT until delivery + single dose NVP at delivery	5 (10)

The final model structure was one-compartment model with first-order elimination, transit compartment absorption.
Parameter estimates: Table 2, visual predictive check: Figure 2.

After adjusting for the differences in dose and the effect of body weight, **pregnancy reduced rifampicin clearance by 14%.**

Based on the model individual Bayesian estimates, the median (interquartile range) rifampicin area under the concentration-time curve ($AUC_{0\text{-}24}$) during pregnancy or intra-partum was 40.8 mg·h/L (27.1-54.2), compared to 37.4 (26.8-50.3) post-partum. Maximum concentration during pregnancy and postpartum were 8.4 mg/L (7.1-10.0) vs. 9.0 (6.6-11.9), respectively.

Table 2 Final parameter estimates

Parameter	Typical Value	Parameter variability[a] – (Shrinkage)
Clearance[b] – CL [L/h]	16.2 [13.8, 19.1]	BSV: 30.4% [15.7%, 44.3%] - (4%)
Volume of distribution[b] – V [L]	43.3 [35.6, 48.5]	
Absorp. rate constant - ka [1/h]	1.67 [1.01, 2.75]	BOV: 78.2% [35.2%, 114.5%] - (54%)
Absorp. mean transit time – MTT [h]	1.31 [1.04, 1.56]	BOV: 34.4% [18.8%, 50.8%] - (47%)
Number of abs. transit cmpts – NN [ ]	54.6 [27.2, 108.5]	
Bioavailability – F [ ]	1 FIXED	BOV: 28.0% [19.4%, 35.5%] - (36%)
Proportional Error [%]	13.1% [6.9%, 16.7%]	
Additive Error[c] [mg/L]	0.0585 FIXED	
Pregnancy effect on CL [%]	-14.0% [-28.7%, -2.8%]	

Values in brackets are 95% confidence interval, obtained with a 500-sample nonparametric bootstrap.
[a] The parameter variability was included either as between-subject (BSV) or between-occasion (BOV). It is reported here as approximate %CV.
[b] The values of CL and V were allometrically scaled, so the typical values reported here refer to the median body weight of the cohort included in the PK model, 66 kg.
[c] The estimate of the additive component of the error was not significantly different from its lower boundary of LLOQ/2, so it was fixed to this value.

Results – Cord blood

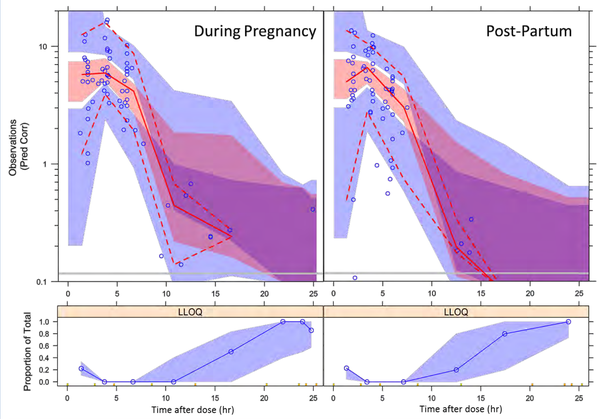

Figure 2: Visual predictive check. Prediction-corrected visual predictive check [4] of the final model, stratified by pregnancy status.
The **upper panels** refer to the **concentrations above the limit of quantification (LLOQ)**: the solid and dashed lines are the 5th, 50th, and 95th percentiles of the observations, while the shaded areas represent the 95% model-predicted confidence intervals for the same percentiles.
The **lower panels** show the **proportion of data below the limit of quantification (BLQ)**: the solid line is the proportion observed, while the shaded area is the proportion predicted by the model.

Rifampicin was measured in 22 cord blood samples (7 collected with maternal PK samples) and 14 had concentration BLQ.

Two of the matched cord/mother samples were excluded due to implausibly low maternal rifampin levels (all samples with concentrations BLQ shortly after a self-reported dose).

The cord blood concentrations are plotted versus time after maternal dose intake in Figure 3.

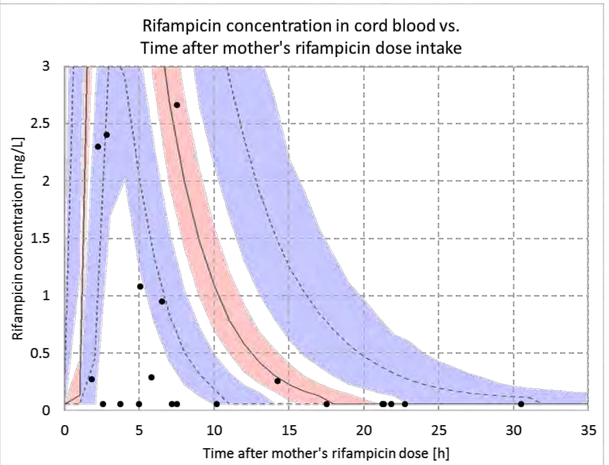

Figure 3: Cord blood concentrations. Rifampin cord blood concentration vs. time after mother's rifampicin dose intake. The black dots are the rifampicin concentrations observed in cord blood, while the solid and dashed lines represent the model-simulated 5th, 50th and 95th percentiles of rifampicin concentration in this cohort of pregnant women. The shaded areas are the 95% confidence intervals of the same percentiles.

Results

Cord blood concentrations were generally detectable when delivery happened shortly after maternal rifampicin dosing.

88% (42/48) of women had successful tuberculosis treatment outcomes. There was one case of perinatal TB.

Discussion

Rifampicin exposures were very modestly increased during the last trimester of **pregnancy**, seemingly due to decreased clearance. Dose adjustment is not needed.

Rifampicin was detected in cord blood samples when delivery occurred soon after dosing.

Consequences of exposure to this potent inducer of metabolizing enzymes among HIV-exposed infants are unclear.

References

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