Pharmacokinetics of Rifampin and Isoniazid during Pregnancy and Postpartum in South African Women

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Introduction

HIV-1 infection and concurrent Mycobacterium tuberculosis infection is common in South Africa.[1] Dual disease occurs in pregnant women and presents management challenges to treating clinicians. Antituberculosis drugs used during pregnancy should be safe for both mother and fetus and efficacious in treating tuberculosis disease.

Pregnancy is known to impact drug distribution through altered pharmacokinetic and pharmacodynamic drug profiles. While antituberculosis therapy is generally prescribed using weight-banding World Health Organization (WHO) tables, pregnancy might alter dynamics considerably during the progression of trimesters and increase and decrease of weight. Concurrent treatment with antiretroviral drugs and subsequent drug interaction may further impact on both antiretroviral and antituberculosis drug exposure.

There is paucity of data on pharmacokinetics of both antiretroviral and first line antituberculosis drugs during pregnancy. Trimester differences in rifampin (RMP) and isoniazid (INH) exposure have not been described. We explored the effects of pregnancy gestation on RMP and INH pharmacokinetics in tuberculosis-infected women with and without antiretroviral treatment.

Methods

P1026s is an ongoing, non-blinded, phase IV, prospective study of antiretroviral and antituberculosis pharmacokinetics in HIV-infected and uninfected pregnant women. It is an opportunistic study that does not provide the study drugs involved, but actively observes clinical and safety outcomes. The data were collected from the enrolling TB treatment arms of the study, comprising of co-administered efavirenz (EFV) or lopinavir/ritonavir (LPV/r) or no concurrent antiretroviral treatment.

Daily antituberculosis fixed-dose combination tablets were given according to WHO-recommended weight-banded dosing guidelines. The study enrolled participants that received a daily dose of rifampin between 8-12mg/kg (max. 600 mg) and isoniazid between 4-6 mg/kg (max. 300 mg). Daily antiretroviral tablets, where possible fixed-dose combinations, were given according to South African National HIV Treatment Guidelines for adult dosing.

Pharmacokinetic sampling was planned in the second trimester between 20-26 weeks gestation and in the third trimester between 30-38 weeks gestation. Between 2-8 weeks post-partum intensive pharmacokinetic sampling was repeated, using the same ARV and/or TB drug dose when still on treatment.

Steady-state plasma samples were collected for an intensive 12 hour pharmacokinetic curve (t = 0, 1, 2, 4, 6, 8, 12 ± 24h) after supervised intake of the studied medication in the second and third trimester. At least 2 weeks post-partum intensive PK sampling was repeated, using the same antiretroviral and/or antituberculosis drug dose.

High Performance Liquid Chromatography (HPLC) was used to measure RMP and INH plasma concentrations with a lower limit of quantification of 0.117 µg/ml and 0.098 µg/ml, respectively.

The pharmacokinetic parameters of RMP and INH were characterized using non-compartmental analysis and compared to published non-pregnant South African adult data.[2]

Results

Preliminary pharmacokinetic data are available for 11 South African participants. Demographics are presented below in Table 1.

Table 1. Participant Demographics

Parameter	N % or Median (Range)	
Race		
Black	9	81.8%
Mixed	1	9.1%
Indian	1	9.1%
Age at 3rd Trimester (years)	28.4	(21-40)
Weight at 3rd Trimester (kg)	59.5	(49-99)
HIV-infected	7	63.6%
On EFV	6	54.5%
On LPV/r	1	9.1%
HIV RNA (copies/mL)		
2nd trimester	LDL§	(LDL-165)
3rd trimester	LDL	(LDL-2533)
Delivery	LDL	(LDL-400)
Post-partum	LDL	(LDL-126)
CD_4 Cell Count (cells/µL)		
2nd trimester	98	(46-316)
3rd trimester	186	(60-999)
Delivery	372	(35-800)
Post-partum	505	(64-746)
Infant		
Gestational Age (weeks)	39	(36-41)
Birth Weight (grams)	3170	(1875-3845)

§ LDL = Lower than Detectable Level, < 40 copies/mL

RMP and INH pharmacokinetic data were available in 6, 11 and 6 women in 2T, 3T and PP. See Tables 2 and 3 respectively. Median concentration curves for RMP and INH with the Referent C_{max} as target indicator are shown in Figures 1 and 2 respectively.

Table 2. Rifampin Pharmacokinetic Parameters, Median (IQR)

Parameter	2nd Trimester	3rd Trimester	Postpartum	Historical Control[2]
No. evaluated / No. HIV-infected	6 / 5	11 / 7	6 / 3	87 / 9
AUC_{0-8} (µg·hr/mL)	26.6 (23.4-33.7)	29.7 (18.4-36.5)	24.5 (16.2-33.1)	21.5 (15.3-31.7)
C_{max} (µg/mL)	6.9 (6.0-8.4)	6.3 (4.6-8.3)	6.7 (4.9-7.9)	5.9 (4.2-8.4)

Figure 1. Rifampin concentration curve

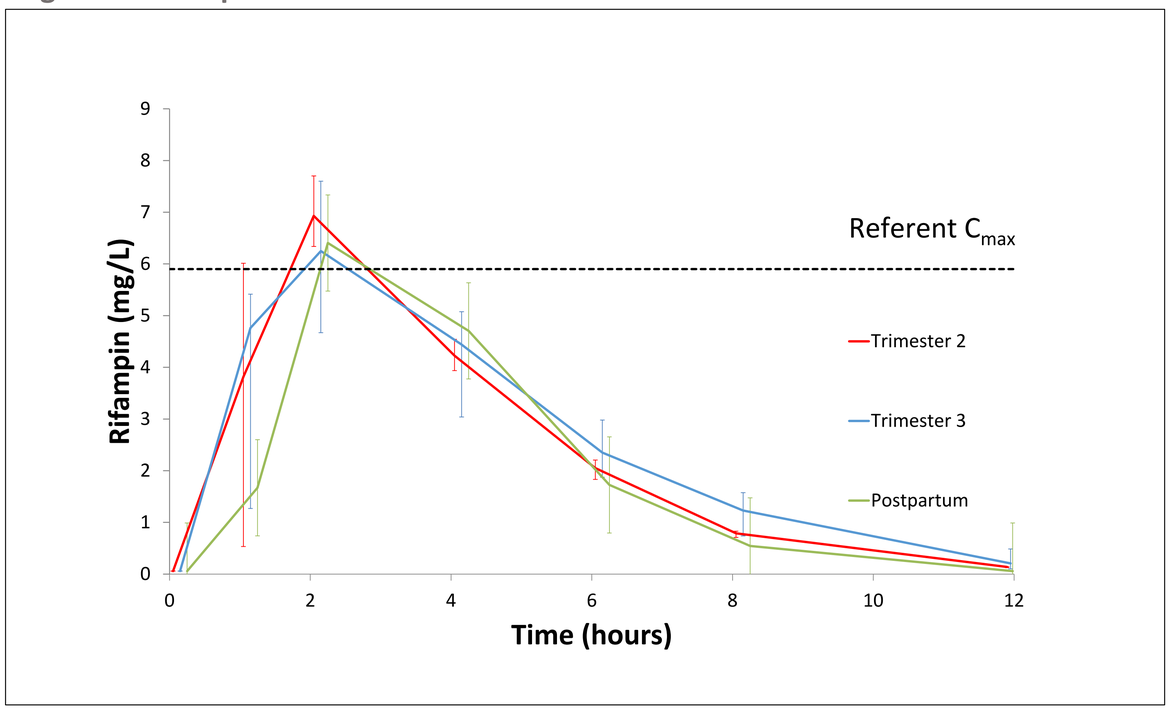
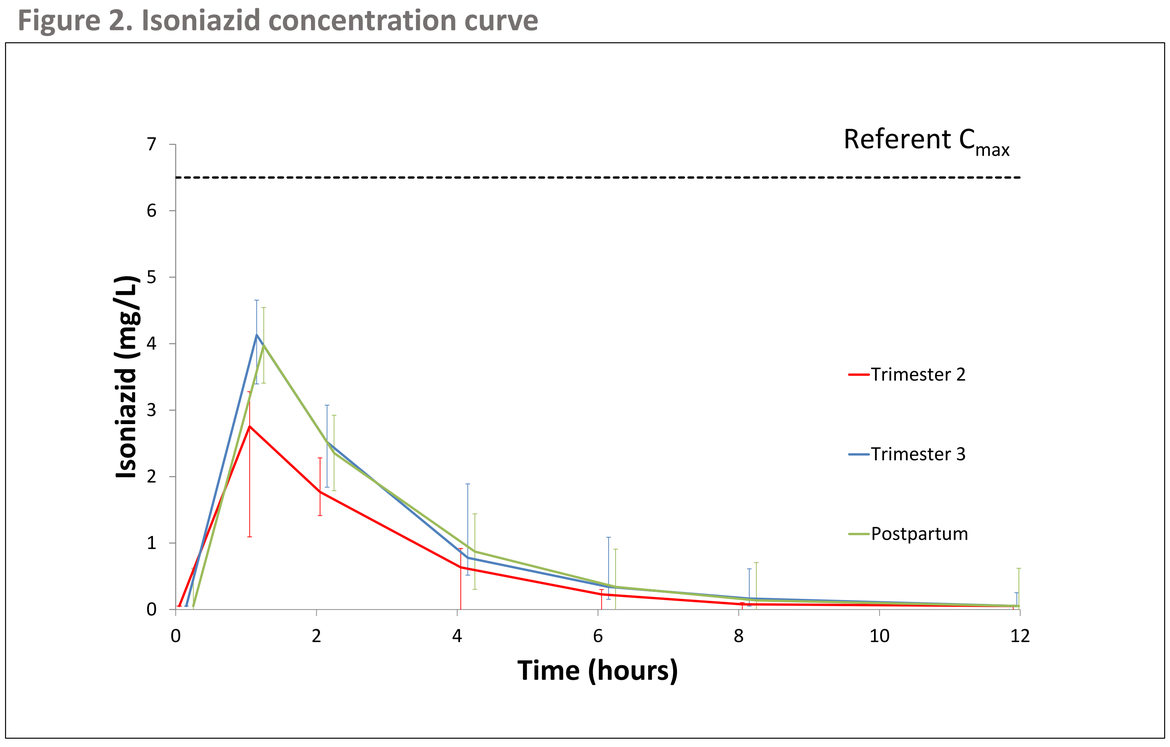


Table 3. Isoniazid Pharmacokinetic Parameters, Median (IQR)

Parameter	2nd Trimester	3rd Trimester	Postpartum	Historical Control[2]
No. evaluated / No. HIV-infected	6 / 5	11 / 7	6 / 3	141 / 14
AUC_{0-8} (µg·hr/mL)	6.6 (4.9-13.0)	10.5 (7.7-18.9)	9.9 (8.2-20.5)	25.0 (18.9-32.8)
C_{max} (µg/mL)	2.8 (2.2-4.8)	4.1 (3.4-4.7)	4.0 (3.7-5.6)	6.5 (4.9-8.7)

Figure 2. Isoniazid concentration curve



Compared to a non-pregnant South African adult cohort (45% male, 10% HIV-infected not receiving antiretrovirals, McIlleron et al. 2006[2]), RMP exposure was similar or higher in 2T and 3T. INH exposure was below the 25th percentile across all stages of pregnancy. Small sample size and unavailable comparator raw dataset prohibited formal statistical testing.

Discussion and Conclusions

- Rifampin concentrations in pregnancy compared well to non-pregnant concentrations.
- Isoniazid exposure was reduced throughout all stages of pregnancy.
- Possible explanation for the lower isoniazid concentrations includes a higher proportion of phenotypical fast acetylators (n=7) compared to phenotypical slow acetylators (n=4) in our sample selection. This will be further evaluated once genotyping has been processed during the progress of the study.
- More data are needed on isoniazid and rifampin in pregnancy to make dosing recommendations. Forthcoming pharmacokinetic data from P1026s constituting a larger sample size will inform dosing strategy in pregnancy.

References

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2. McIlleron H, Wash P, Burger A, Norman J, Folb PI, Smith P. Determinants of rifampin, isoniazid, pyrazinamide, and ethambutol pharmacokinetics in a cohort of tuberculosis patients. Antimicrob Agents Chemother. 2006 Apr; 50(4):1170-7. PubMed PMID: 16569826; PubMed Central PMCID: PMC1426981.

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