Low Isoniazid Concentrations in Pregnant and Postpartum Women Treated for Tuberculosis Irrespective of Efavirenz-based ART Co-Treatment

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IMPAACT International Maternal Pediatric Adolescent AIDS Clinical Trials Network

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Disclosures

- I receive salary support from IMPAACT as IMPAACT 2026 Lead Investigator of the 1st line TB drug arms.

Introduction

- HIV-1 infection and concurrent Mycobacterium tuberculosis infection is common in sub-Saharan Africa.

- Active TB rates range from 0.7-7.9% among HIV+ pregnant women in high-burden countries and complicates management.[1]

- Physiologic changes of pregnancy can significantly impact drug metabolism, safety and efficacy through altered pharmacokinetic and pharmacodynamic drug profiles.[2]

[1]Mathad et al. Clin Infect Dis. 2012;55(11):1532–1549
[2]Ansari et al, Anesth Analg. 2016 Mar;122(3):786-804

Introduction

- Drug-drug interactions may further impact on both antiretroviral (ARV) and antituberculosis drug exposure.

- Host genetic polymorphisms may also play a role.

- Aim: We explored the effects of pregnancy gestation on isoniazid (INH) and rifampin (RMP) pharmacokinetics in pregnant women with TB with and without efavirenz (EFV) - based ART.

P1026s - Pharmacokinetic Properties of Antiretroviral and Related Drugs During Pregnancy and Postpartum

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Design: Multi-country, prospective, open-label, opportunistic pharmacokinetic (PK) study. (ClinicalTrials.gov: NCT00042289)

Primary Objective: To assess the bioavailability of ART and 1st line and 2nd line TB drugs in 2nd, 3rd trimester and postpartum

P1026s - recruitment

Inclusions:

- ✓ **Pregnant Women** > 18 yrs, **> 20 and < 37+6** gestation

WITH

- ✓ **TB only (HIV-uninfected)** – on 1st-line TB Rx > 2 weeks

OR

- ✓ **TB and ART** – on 1st-line TB Rx with EFV > 2 weeks

Exclusions:

- × Multi-fetal pregnancy
- × Toxicity requiring change in study drug
- × Taking medication interacting with ART/TB drugs

Methods

- Daily anti-TB fixed-dose combination tablets are given according to WHO-recommended weight-banded dosing guidelines.

- HIV+ women also received daily EFV-based ART.

- Intensive steady-state PK profiles of INH and RMP were performed at time points 0, 1, 2, 4, 6, 8 and 12h at
  - 2nd trimester: 20-26 weeks gestation
  - 3rd trimester: 30-38 weeks gestation
  - Postpartum: 2-8 weeks post delivery

Methods

- INH and RMP exposure was characterized using noncompartmental analysis (AUC, Cmax) and corresponding trimesters were compared between the EFV and non-EFV groups using separate Wilcoxon rank-sum tests.

- A South African non-pregnant comparator cohort with INH and RMP PK data was found in the literature: n= 141, 45% male, 10% HIV+ not on ART.[3]

[3] McIlleron et al, Antimicrob Agents Chemother. 2006 Apr; 50(4):1170-7.

Demographics

Parameter	N % or Median (Range)	
Race		
African	14	56%
Thai	6	24%
Other descent	5	20%
Age at 3rd Trimester (years)	28.7	(23-33)
Weight at 3rd Trimester (kg)	57.7	(54-62)
HIV-infected	11	44%
CD_4 Cell Count (cells/µL)		
2nd trimester	274	(90-316)
3rd trimester	534	(93-708)
Delivery	400	(219-706)
Post-partum	525	(230-746)
Infant		
Gestational Age (weeks)	38.6	(37-40)
Birth Weight (grams)	3040	(2120-3278)

Results

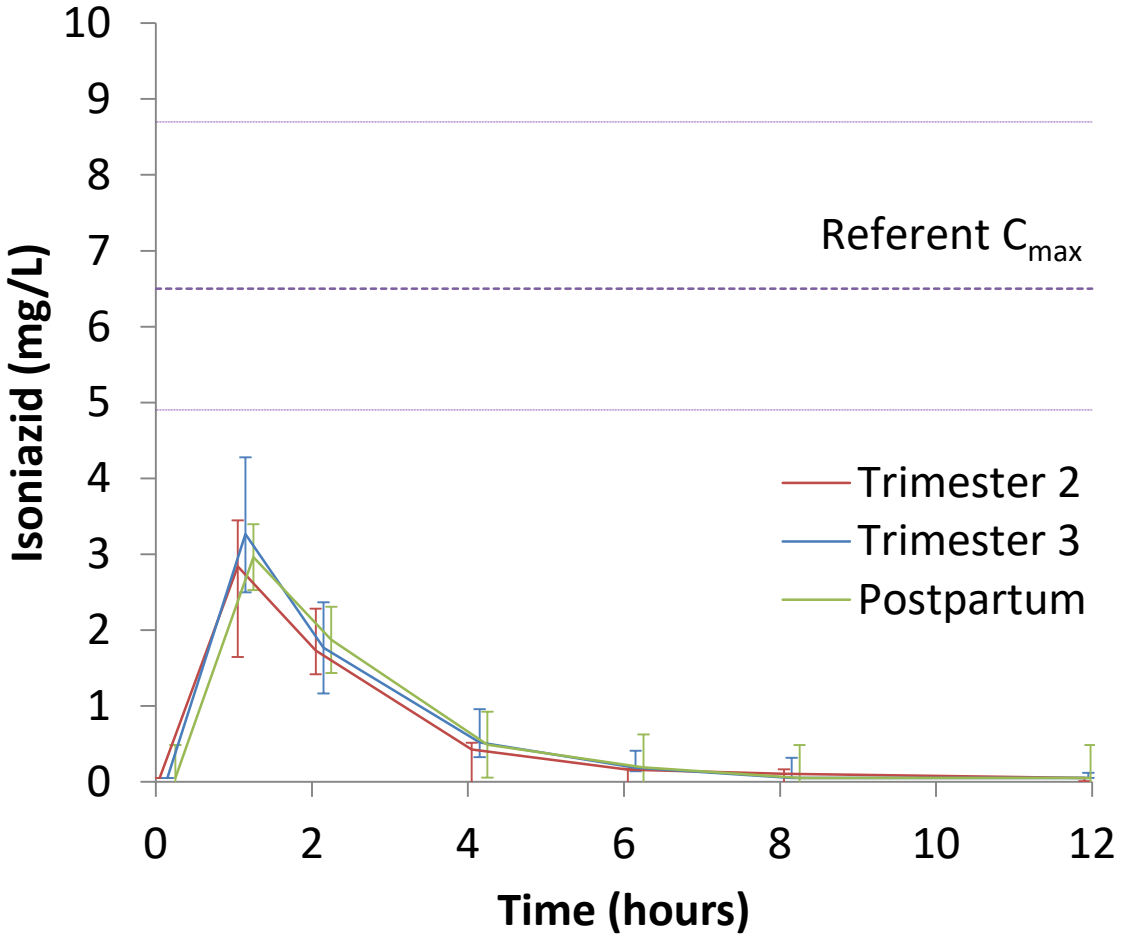
TABLE 1. Isoniazid Pharmacokinetic Parameters, Median (IQR)

Parameter	T2 with EFV	T2 without EFV	T3 with EFV	T3 without EFV	PP with EFV	PP without EFV	Historical Control
N	7	5	10	11	7	8	141
$AUC_{0-\infty}$ (µg·hr/mL)	7.9 (5.4-15.1)	6.2 (5.8-19.4)	8.4 (5.8-12.8)	10.9 (9.4-21.7)	8.7 (6.1-9.7)	14.8 (6.8-24.0)	32.5 (22.5-42.4)
C_{max} (µg/mL)	2.8 (2.2-4.8)	3.0 (1.8-5.1)	3.3 (2.3-4.6)	3.5 (2.1-4.6)	3.0 (2.4-3.7)	3.6 (2.7-5.3)	6.5 (4.9-8.7)

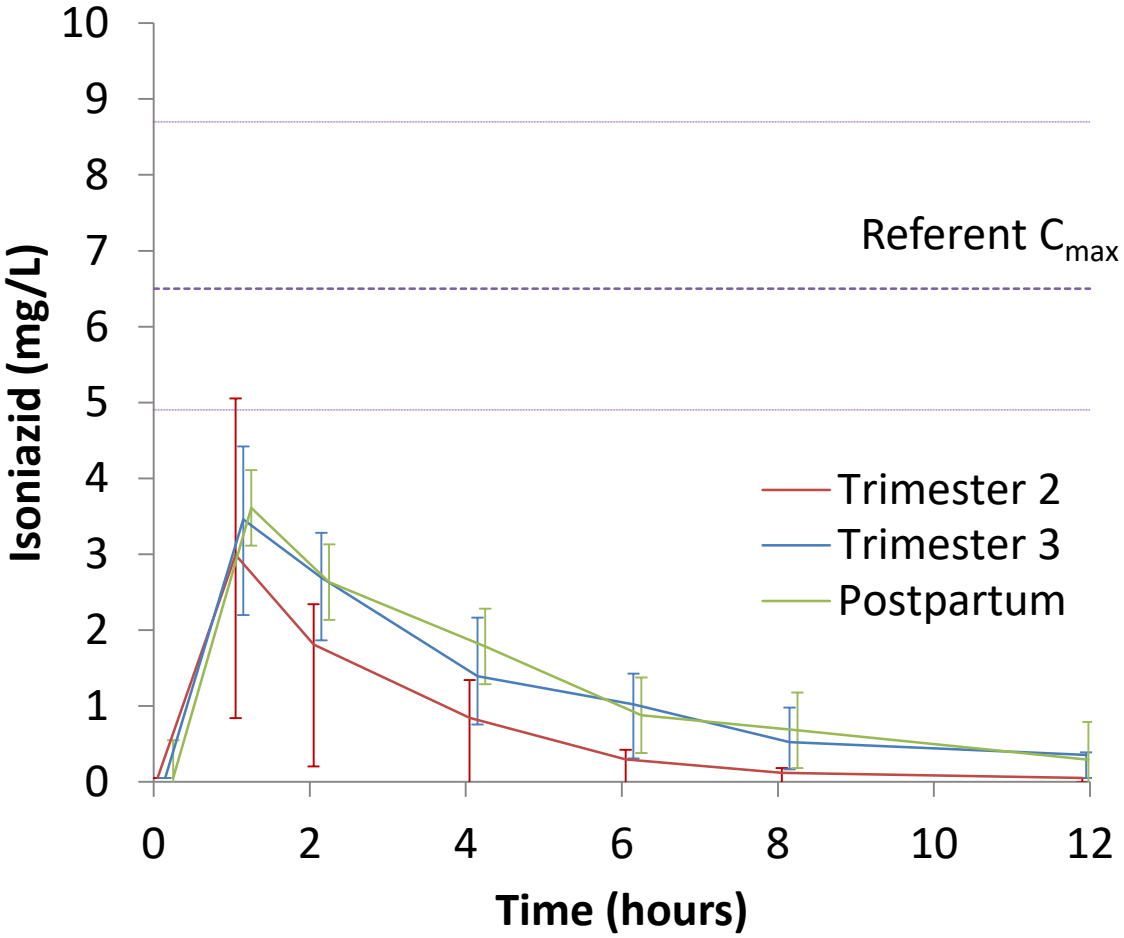
No significant difference between T2, T3 or PP groups but MUCH (≈50%) lower than historical control.

Results

Isoniazid concentrations with EFV

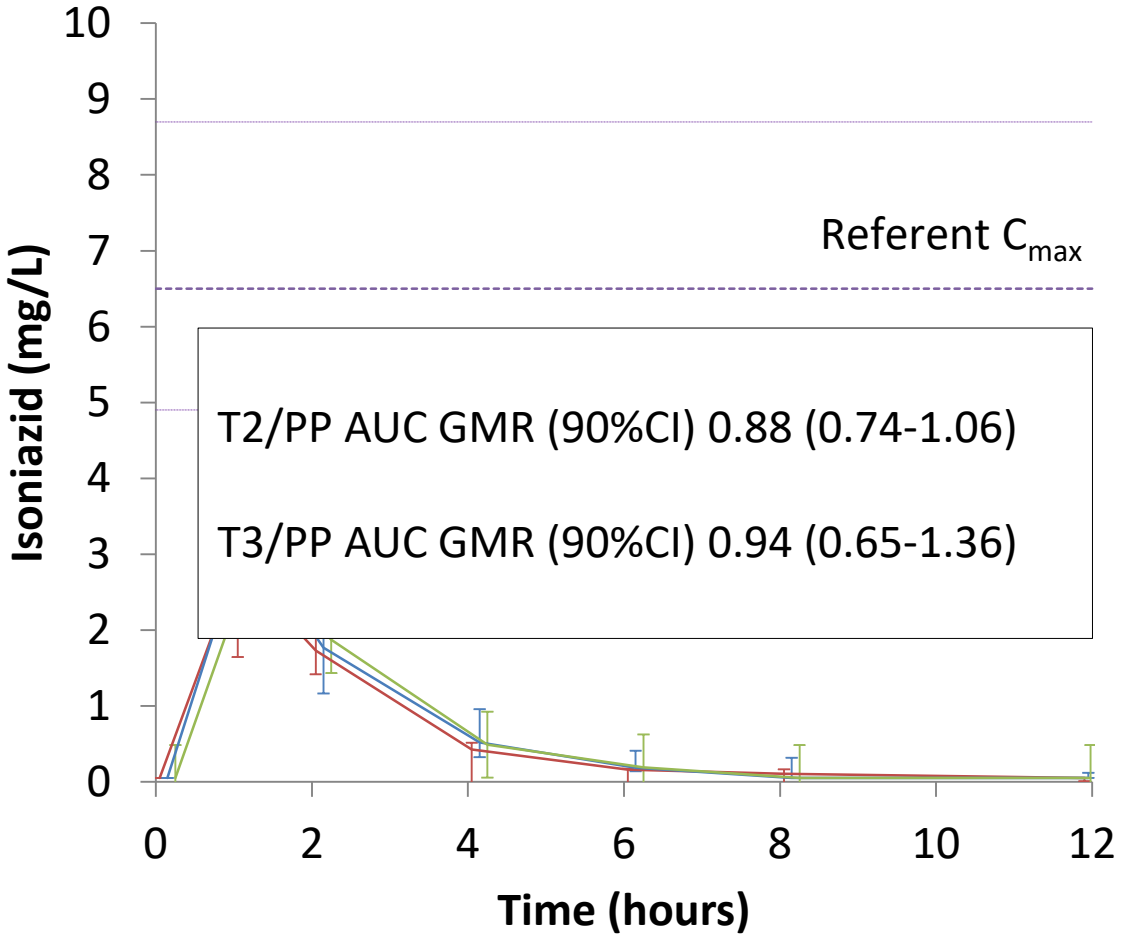


Isoniazid concentrations without EFV

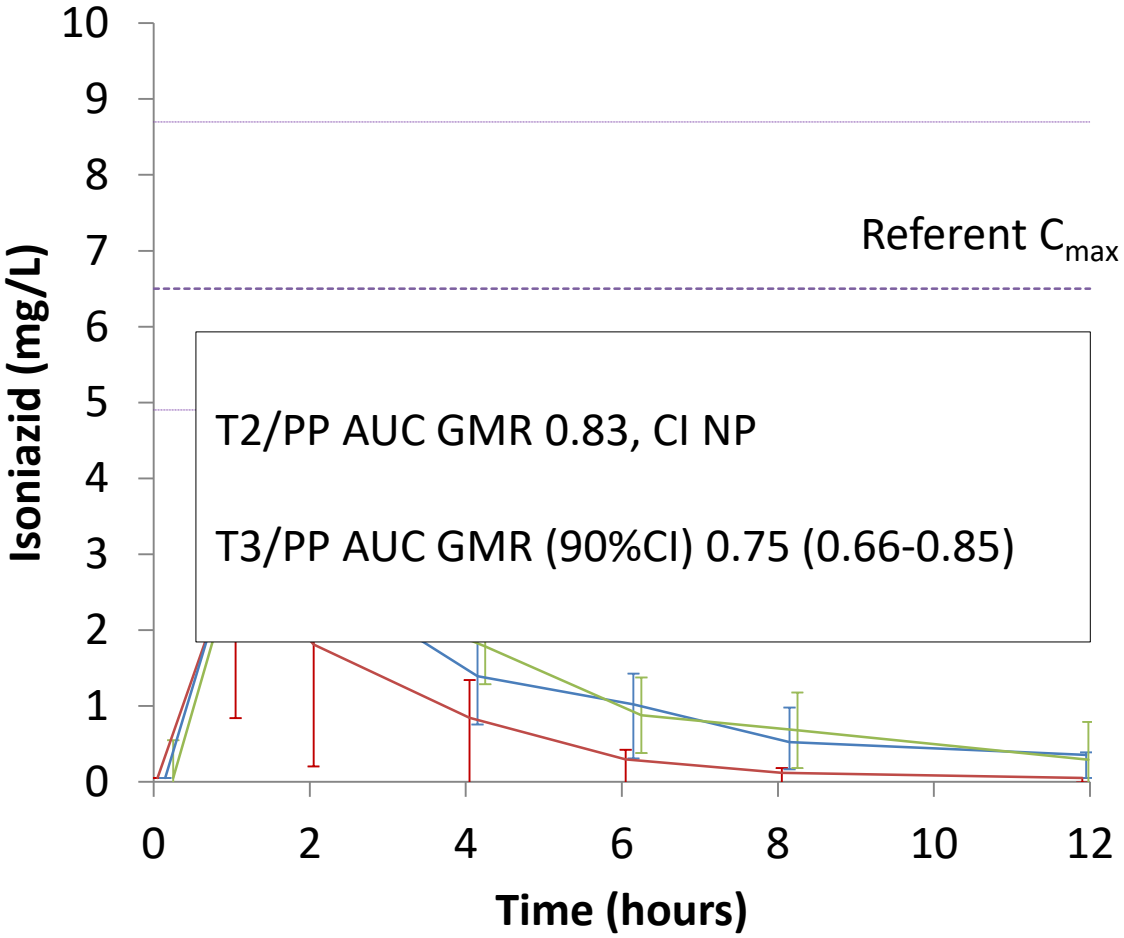


Results

Isoniazid concentrations with EFV



Isoniazid concentrations without EFV



Results

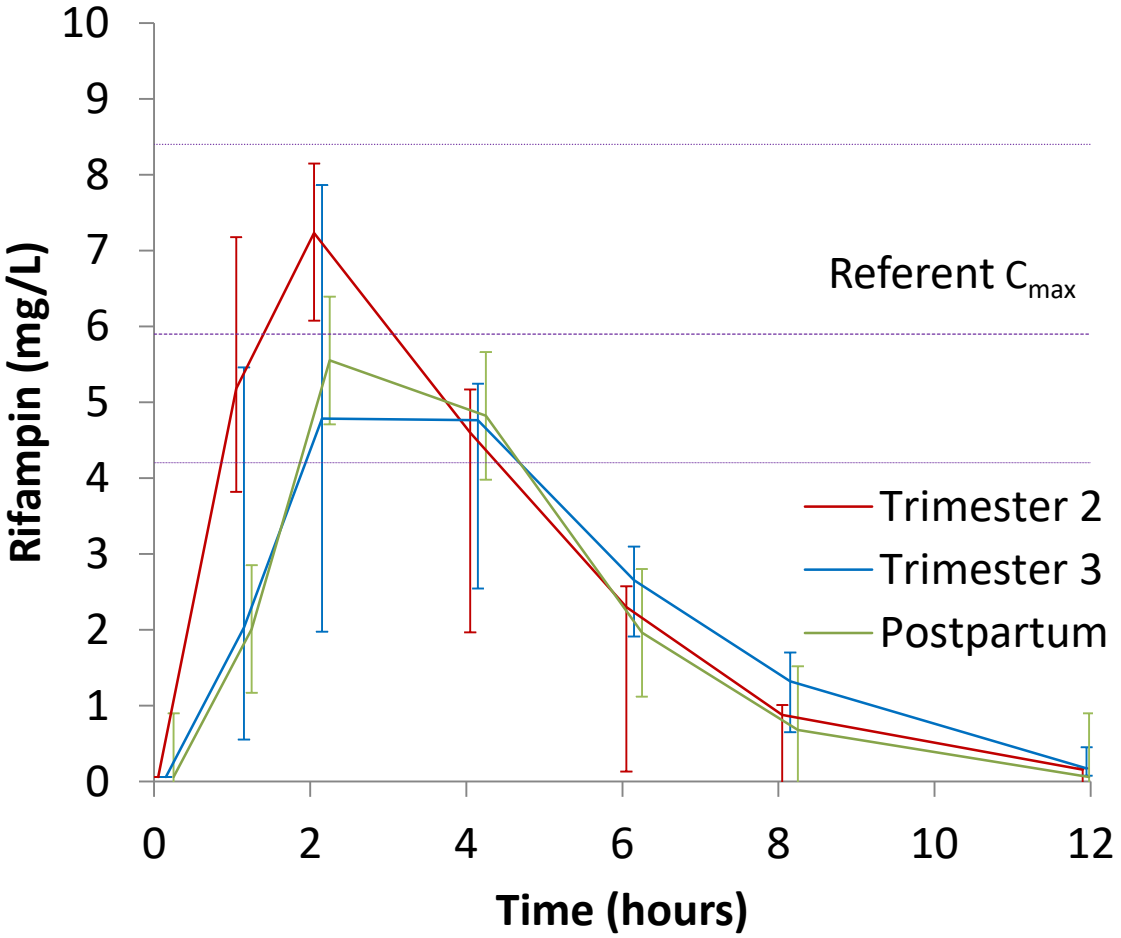
TABLE 2. Rifampin Pharmacokinetic Parameters, Median (IQR)

Parameter	T2 with EFV	T2 without EFV	T3 with EFV	T3 without EFV	PP with EFV	PP without EFV	Historical Control
N	7	5	10	11	7	8	83
$AUC_{0-\infty}$ (µg·hr/mL)	36.8 (28.9-60.6)	30.6 (21.9-38.1)	35.8 (15.6-41.7)	41.4 (26.3-57.0)	31.2 (17.4-43.0)	32.7 (25.8-53.3)	25.6 (16.6-36.0)
C_{max} (µg/mL)	8.4 (6.6-10.0)	4.5 (4.2-6.9)	6.1 (2.8-8.3)	6.9 (5.6-12.1)	6.6 (4.4-12.2)	7.9 (5.7-11.6)	5.9 (4.2-8.4)

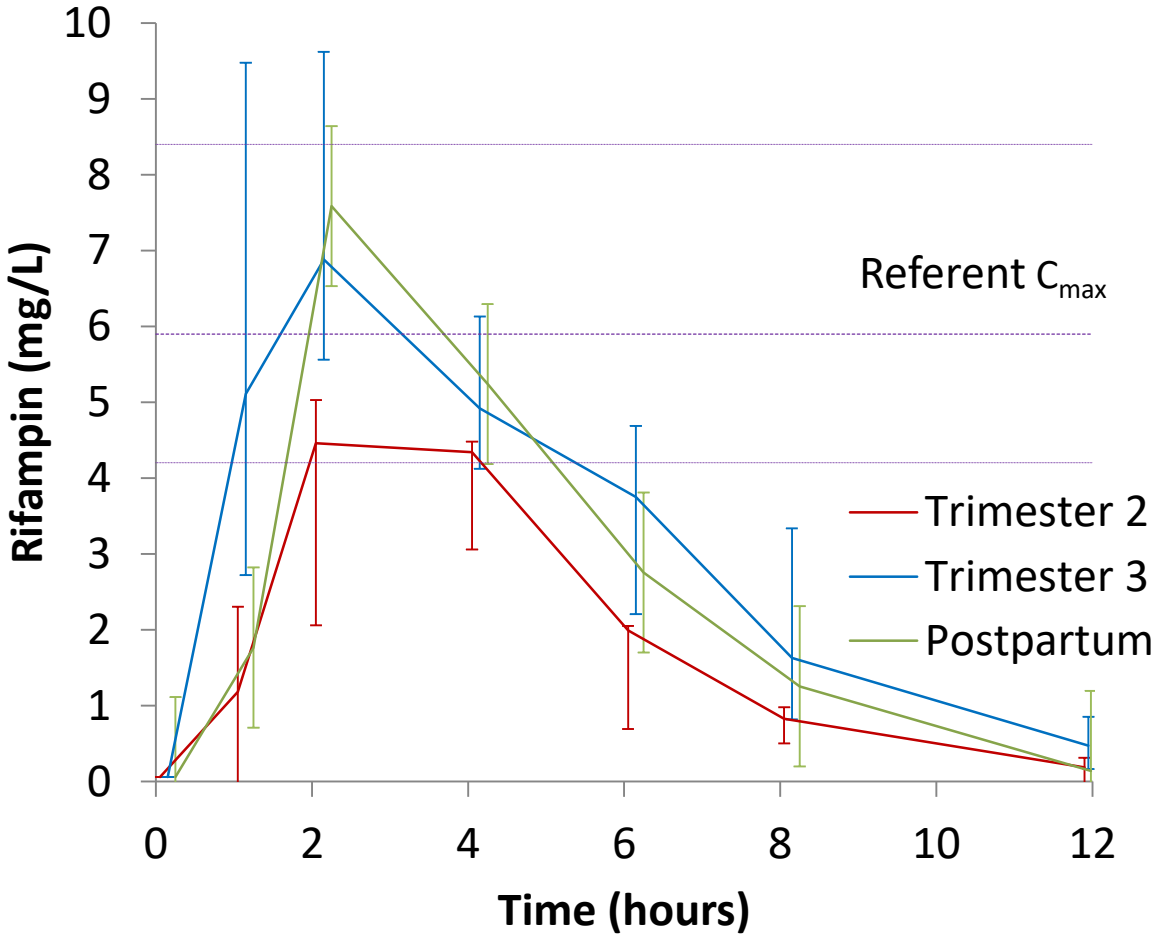
There is no statistical significant difference between the T2 groups, T3 groups or PP groups and concentrations are similar to the control group.

Results

Rifampin concentrations with EFV

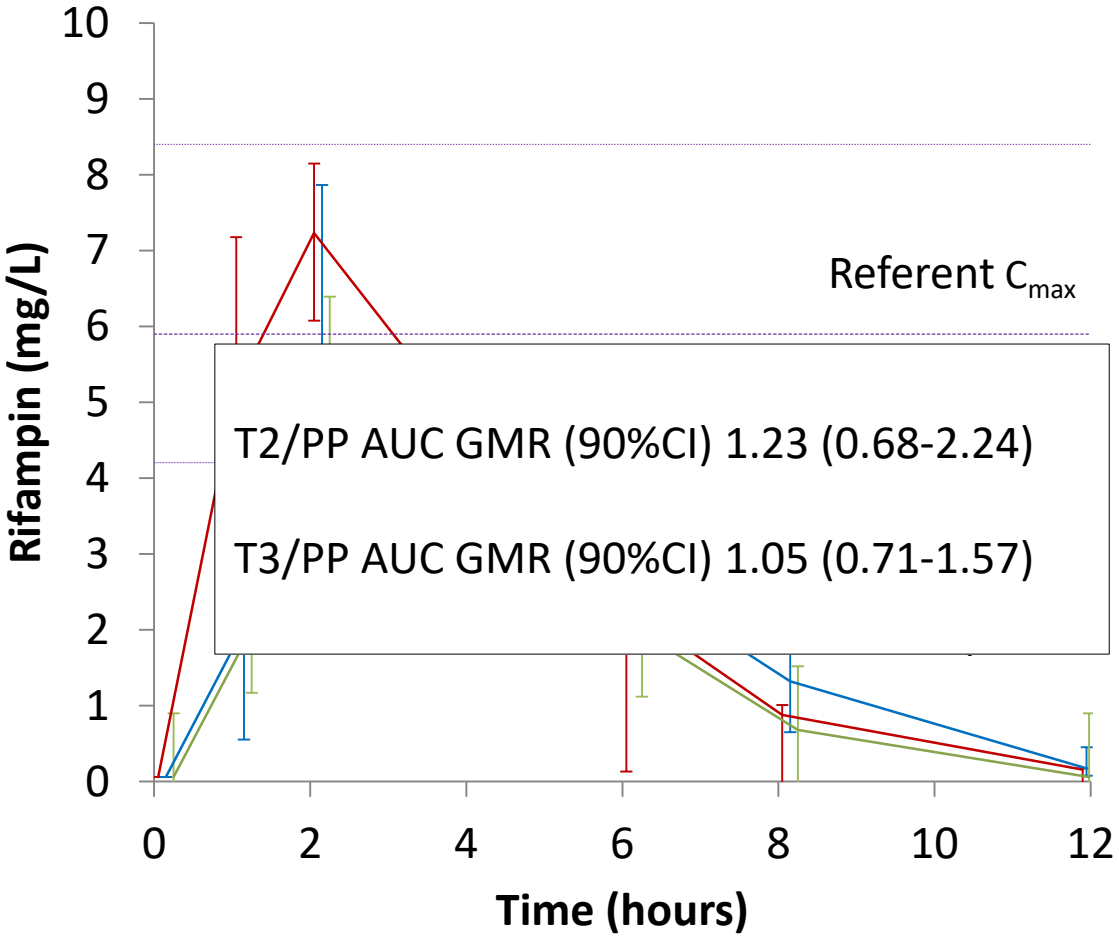


Rifampin concentrations without EFV

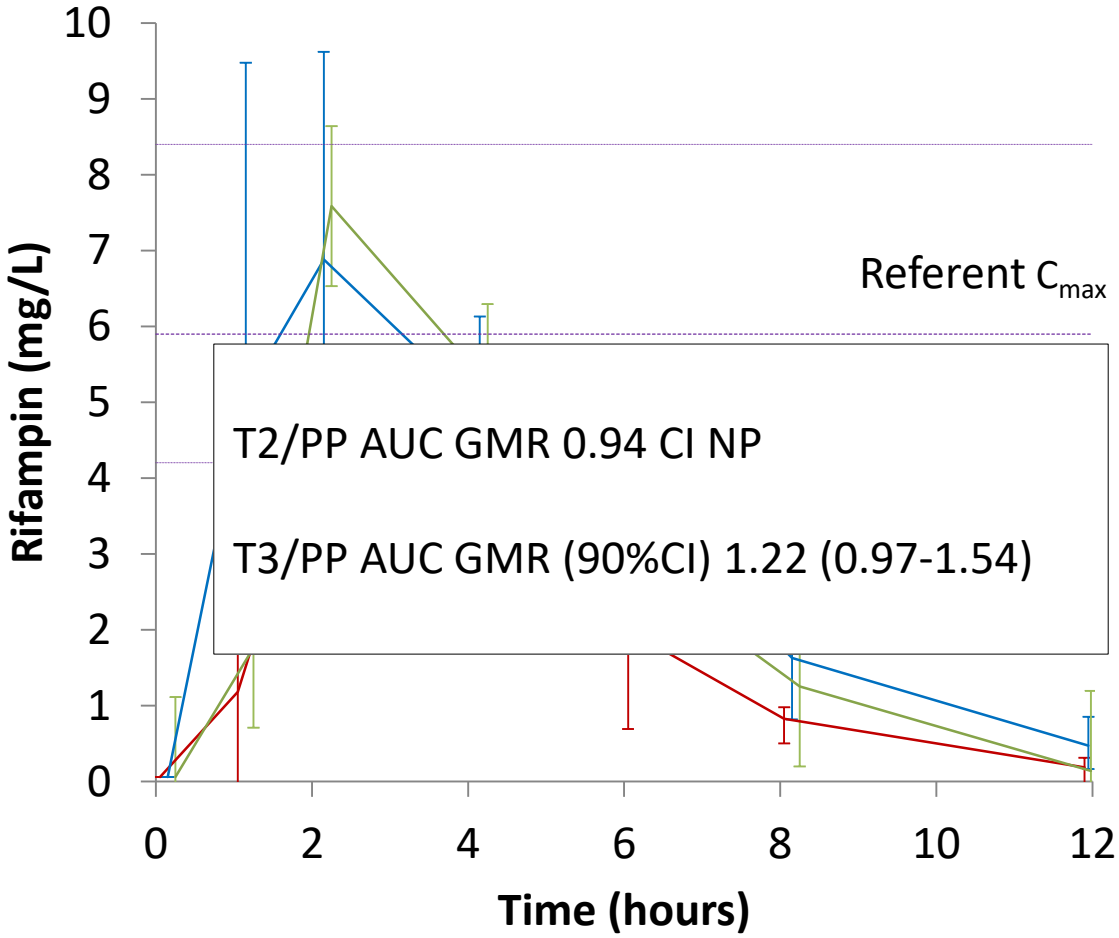


Results

Rifampin concentrations with EFV



Rifampin concentrations without EFV



Conclusions

- Isoniazid exposure was lower across all stages of pregnancy, irrespective of EFV-based ART co-treatment.
- Rifampicin concentrations in pregnancy are similar to non-pregnant concentrations, irrespective of EFV use.
- The clinical relevance of low isoniazid exposure when treating pregnant woman with TB needs to be determined.

References

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3. 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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Enkosi

Dankie

Thank you

Ngiyathokoza

Ke a leboha

Ngiyabonga

Asante

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