Impact of isoniazid and pregnancy on efavirenz pharmacokinetics in women living with HIV

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Background and Objectives

Efavirenz (EFV) is the backbone of first-line antiretroviral therapy (ART) for HIV-1 infection in most low- and middle-income countries (LMIC)

WHO guidelines recommend >6 months of **isoniazid** (INH) preventive therapy for people living with HIV from LMIC where TB is endemic, including pregnant women.

While mainly cleared by CYP2B6, a secondary metabolic pathway for EFV is ***CYP2A6***, which is inhibited by **INH**, creating a potential **drug-drug interaction.**

Objective: Evaluate the **interaction of EFV and INH during pregnancy and postpartum.**

Methods

HIV infected pregnant women at 14 to 34 weeks of gestation were recruited and
ARM A immediately initiated **INH 300-mg daily for 28 weeks then switched to placebo.**
ARM B started on placebo then **switched to INH at 12 weeks postpartum.**

Intensive PK sampling (**pre-dose,1, 2, 4, 6, 8 and 12 hours** after INH dosing), sparse PK sampled (**around 2** hours after INH dose) once at ≥ 2 weeks after recruitment and again at 12-21 weeks after delivery. EFV was frequently dosed at night and sample were drawn the next day after INH dose.

CYP2B6 and ***CYP2A6*** genotype information was captured, categorizing patients into **extensive, intermediate or slow** metaboliser groups[1].

Population PK modelling in NONMEM [2] was used to interpret the data.

- 2-compartment model, transit compartment absorption [3], and hepatic clearance and first-pass metabolism due to hepatic extraction E_h.
- Allometric scaling [4] of all clearances based on fat-free mass (FFM) and volumes based on body weight (WT).
- **Model assumption**: The free fraction of efavirenz (f_u) in plasma was assumed 0.5% [5].

$$CL_{int}, Q, Qh = TVpar \cdot \left(\frac{FFM}{TVFFM}\right)^{0.75} \qquad V, Vp = TVpar \cdot \left(\frac{WT}{TVWT}\right)$$

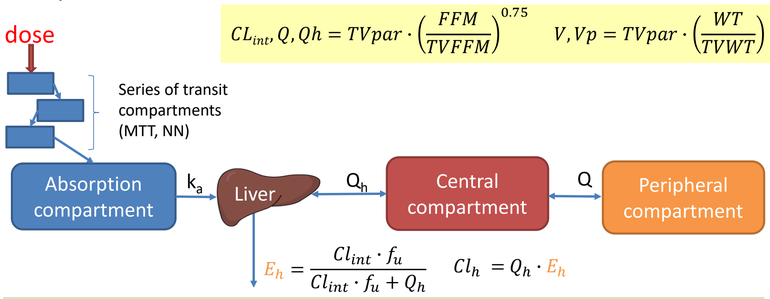

Figure 1: Structural model. Absorption is modelled through a series of transit compartments. The hepatic extraction (E_h) is responsible for both first-pass metabolism and the systemic elimination with first-order kinetics

Results - Study population

EFV concentrations from 21 intensively PK-sampled and 767 sparsely PK-sampled women were included. 596 women have PK data **both** during pregnancy and postpartum
Summary of characteristics in Table 1.

Table 1 Patient characteristics.

Characteristics	Pregnancy (n=712)	Postpartum (n=670)
Age in years, median (range)	29 (18 - 45)	29 (18 - 45)
Weight in kg, median (range)	67 (41 - 166)	61 (37 - 165)
Fat-Free Mass in kg, median (range)	40 (25 - 65)	38 (25-59)
Gestation/postnatal age in weeks, median (range)	26 (14 - 34)	16 (7 - 23)
Concomitant drugs, N(%)		
Isoniazid	352 (49)	540 (80)
Duration on EFV regimen (days)	125 (18 - 3800)	408 (1 - 4228)
Baseline Viral load (copies/mL)	<40 (<40 - 237332)	<40 (<40 – 465894)
Genotype Frequency for *CYP2B6*, N (%)		
Fast	168 (23%)	146 (22%)
Intermediate	299 (42%)	264 (39%)
Slow	119 (17%)	104 (16%)
Missing	126 (18%)	156(23%)
Genotype Frequency for *CYP2A6*, N (%)		
Fast	501 (70%)	439(65%)
Intermediate	81 (11%)	71(11%)
Slow	4 (1%)	4(1%)
Missing	126 (18%)	156(23%)

Results

Parameter estimates: Table 2, visual predictive check: Figure 2.

As expected, the **effect of *CYP2B6* genotype on EFV clearance was significant.** Each phenotype had a specified estimated clearance.

After adjusting body size (with allometry) and *CYP2B6* genotype effect, **pregnancy increased isoniazid clearance by 16%.**

INH decreased the clearance of EFV by 7% in the fast metabolizers and 14% in the intermediate and slow metabolizer.

No significant effect of *CYP2A6* on the clearance. This might be due to the small sample size of slow metabolizers (1%) as shown in table 1.

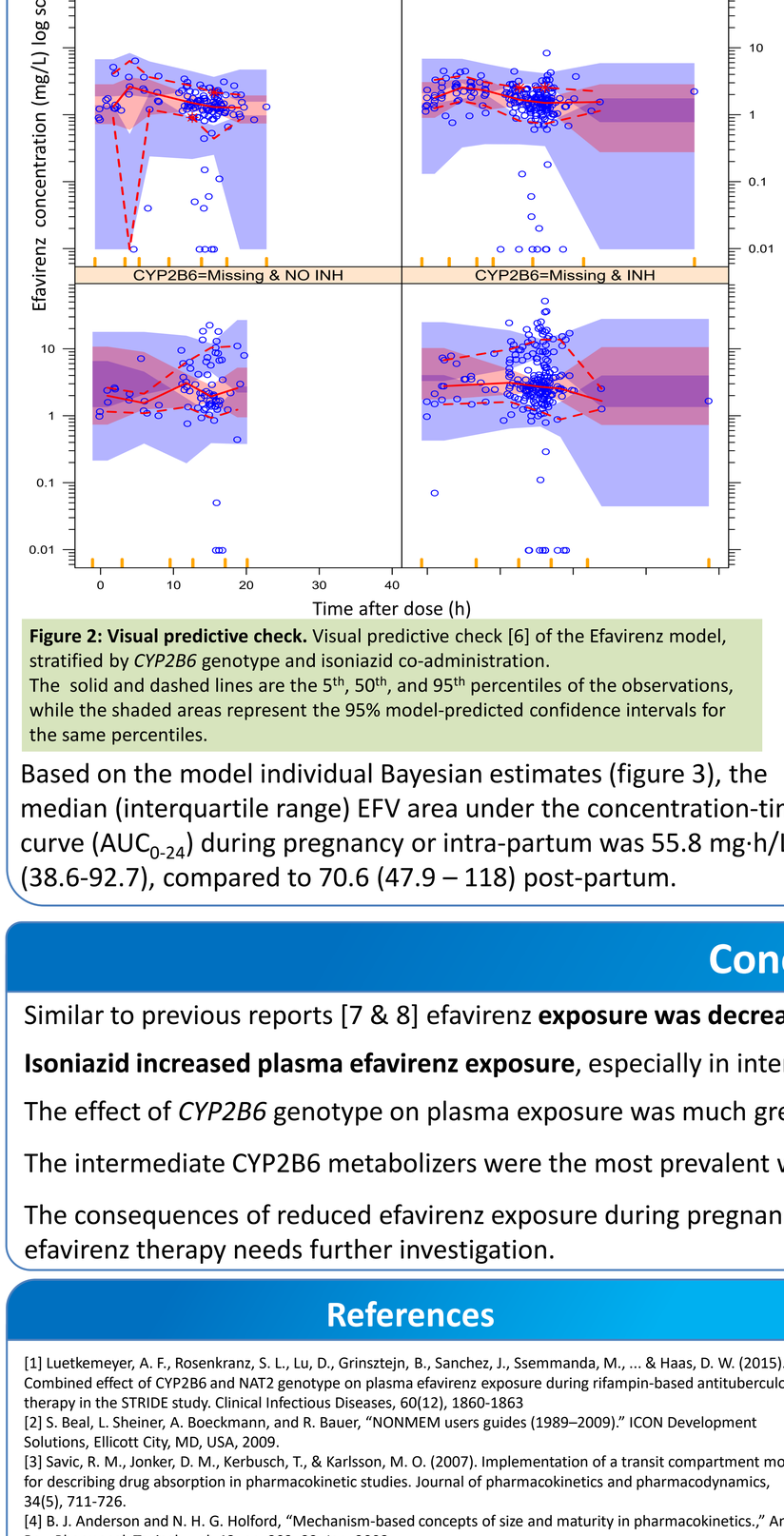

Figure 2: Visual predictive check. Visual predictive check [6] of the Efavirenz model, stratified by *CYP2B6* genotype and isoniazid co-administration.
The solid and dashed lines are the 5th, 50th, and 95th percentiles of the observations, while the shaded areas represent the 95% model-predicted confidence intervals for the same percentiles.

Based on the model individual Bayesian estimates (figure 3), the median (interquartile range) EFV area under the concentration-time curve (AUC_{0-24}) during pregnancy or intra-partum was 55.8 mg·h/L (38.6-92.7), compared to 70.6 (47.9 – 118) post-partum.

Table 2 Final parameter estimates

Parameter	Typical Value (95%CI[a])	Variability[c], %CV (95% CI[a])
CLint[b] [L/h] *CYP2B6* Fast	2690 (2300 – 3030)	BSV: 53.8 (48.9 – 59.2)
CLint[b] [L/h] *CYP2B6* Intermediate	1940 (1790 – 2100)	
CLint[b] [L/h] *CYP2B6* Slow	545 (487 – 624)	
Central Vol of distribution[b] – V [L]	135 (109 – 165)	
Peripheral Vol of distribution[b] – V [L]	512 (487 – 623)	
Intercompartmental clearance[b] – Q [L/h]	26.9 (19.8 – 36.5)	
Absorp. rate constant - ka [1/h]	1.75 Fixed	BOV: 180 (114.9- 227)
Absorp. mean transit time – MTT [h]	1.78 (1.20 – 2.39)	BOV: 131 (103- 166))
Number of abs. transit cmpts – NN [ ]	48.4 (11.3 – 64.7)	
Bioavailability – F [ ]	1 FIXED	BOV: 23.2 (20.7 – 26.1)
Proportional Error [%]	6.91 (4.72 – 9.45)	
Additive Error [mg/L]	0.353 (0.303 – 0.408)	
INH effect on CL for fast *CYP2B6* (%)	**-6.87 (-12.1 – -1.13)**	
INH effect on CL for intermediate or slow *CYP2B6* metabolizer (%)	**-13.4 (-17.3 – -9.06)**	
Pregnancy effect on CL [%]	+15.6 (9.82-23.6)	

[a] 95% confidence intervals (CIs) obtained with the SIR procedure
[b] The values of clearances and volumes of distribution were allometrically scaled, so the typical values reported here refer to the typical body size in the cohort included in the PK model (67 kg body weight for volumes of distribution and 38 kg fat-free mass for clearances).
[C] The parameter variability was included either as between-subject (BSV) or between-occasion (BOV) assuming a lognormal distribution. It is reported here as approximate %CV.

Table 3 Efavirenz clearance

CYP2B6 Phenotype status	Intrinsic Clearance – Clint(L/h)	Hepatic Clearance – CLh (L/h)	Extraction Ratio - Eh (fraction)	Bioavailability after first pass – Fh (fraction)	Oral Clearance - CL/F (L/h)
Fast	2690	9.89	26%	74%	13.4
Intermediate	1940	7.70	21%	79%	9.70
Slow	545	2.54	7%	93%	2.73

For a typical individual (67kg), liver hepatic plasma flow (Q_h) 37.4 L/h and scaled to each patient's size using individual FFM.

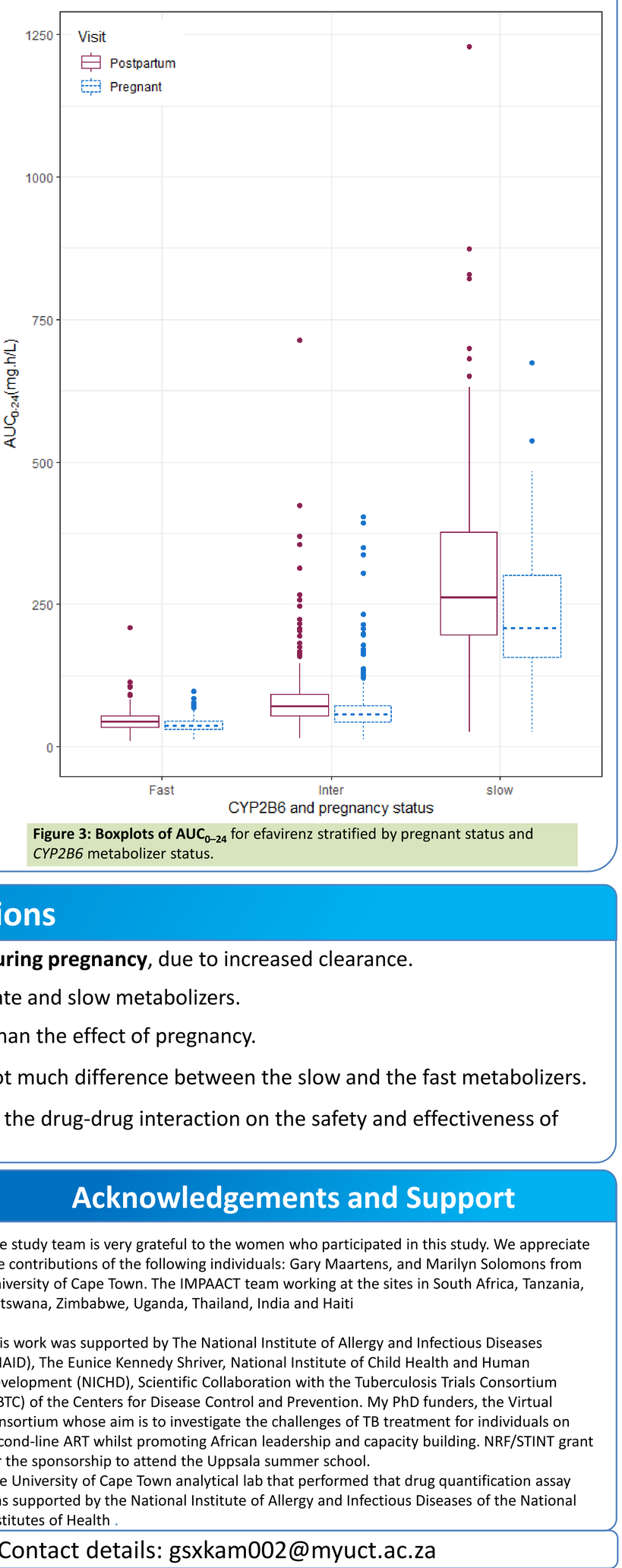

Figure 3: Boxplots of AUC_{0-24} for efavirenz stratified by pregnant status and *CYP2B6* metabolizer status.

Conclusions

Similar to previous reports [7 & 8] efavirenz **exposure was decreased during pregnancy**, due to increased clearance.

Isoniazid increased plasma efavirenz exposure, especially in intermediate and slow metabolizers.

The effect of *CYP2B6* genotype on plasma exposure was much greater than the effect of pregnancy.

The intermediate CYP2B6 metabolizers were the most prevalent with not much difference between the slow and the fast metabolizers.

The consequences of reduced efavirenz exposure during pregnancy and the drug-drug interaction on the safety and effectiveness of efavirenz therapy needs further investigation.

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