Efavirenz Pharmacokinetics in Pregnancy and Postpartum With and Without First-line Tuberculosis Drugs.

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BACKGROUND

- Efavirenz (EFV) pharmacokinetics (PK) may be influenced by both pregnancy-related physiological changes and concurrent treatment for drug-sensitive tuberculosis (DS-TB) in pregnant women living with HIV (PWLHIV) with TB.
- As EFV might be preferred over dolutegravir to avoid double dosing during DS-TB treatment, more EFV PK data in PWLHIV on DS-TB treatment are needed.

Study objective: to evaluate EFV PK in a prospective observational cohort of PWLHIV on EFV-based antiretroviral therapy (ART) alongside first-line DS-TB medications rifampin and isoniazid, with or without ethambutol and pyrazinamide.

METHODS

- IMPAACT P1026s was a multicenter, nonrandomized study that enrolled PWLHIV at >20 weeks' gestation and on daily WHO-recommended EFV-based ART and first-line TB drugs.
- Intensive PK samples were collected pre-dose and at 1, 2, 4, 6, 8, 12 and 24 hours post-dose in the 2nd (2T) and 3rd (3T) trimesters of pregnancy and at 2-8 weeks postpartum (PP).

TABLE 1. Maternal and Infant Demographics

	n (%) or Median (range)	n (%) or Median (range)	P-value
Maternal demographics	**TB-group (n=22)**	**Non-TB-group (n=27)**	
Age (years) at delivery	31.6 (20.7–38.0)	30.9 (20.8–43.6)	0.70
Weight (kg)			
2T	57.3 (48.0–96.5) (n=12)	70.5 (54.2–128.5) (n=14)	*0.01*
3T	59.3 (46.9–99.4) (n=21)	72.3 (54.5–127.7) (n=26)	*<0.001*
PP	54.3 (42.7–68.9) (n=13)	67.5 (47.3–126.0) (n=24)	*<0.001*
Country	Brazil (n=1) South Africa (n=9) Thailand (n=2) USA (n=1) Uganda (n=9)	Argentina (n=1) Brazil (n=12) South Africa (n=3) USA (n=11)	
CD4 (cells/mm^3)			
2T	274 (46–695)	421 (129–1,012)	*0.03*
3T	284 (51–999)	564 (169–1,188)	*0.01*
Delivery	290 (35–735)	540 (166–975)	*0.01*
PP	268 (42–1,133)	620 (244–1,725)	*0.02*
HIV-1 RNA ≤ 400 cps/mL			
2T	10 (83)	13 (93)	0.58
3T	18 (86)	25 (96)	0.31
Delivery	17 (77)	26 (96)	*0.08*
PP	9 (69)	23 (96)	*0.04*
Infant demographics			
Gestational age (weeks)	38.9 (26.9–41.7)	38.4 (33.6–41.4)	0.63
Birth weight (grams)	2,895 (830–4,400) (n=21)	3,005 (1,875–4,365)	0.23

METHODS

- EFV plasma concentrations were determined using validated LCMS (quantitation limits 0.02-0.1 µg/mL).
- Noncompartmental methods estimated EFV PK parameters.
- Minimum targets were $AUC_{0\text{-}24}$= 40 µg·h/mL and C_{min}= 1.0 µg/mL
- Within-study paired comparisons used geometric mean ratios (GMR) with 90% confidence intervals (CI).
- Comparisons to a previously published P1026s cohort of 27 PWLHIV on EFV without TB (non-TB-group) used univariate mixed effects models with EFV PK as the dependent variable and treatment group as the independent variable.

Late pregnancy combined with first-line TB treatment is associated with lower EFV exposure in pregnant women with HIV.

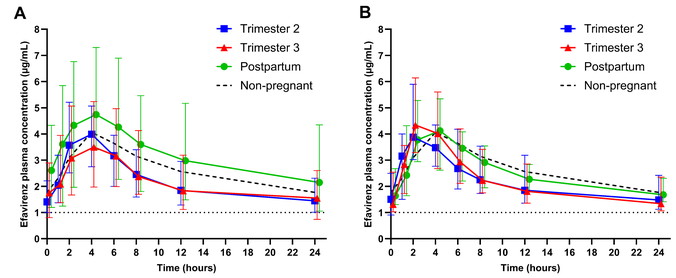
RESULTS

- 22 participants enrolled in the TB-group; demographics of both groups are shown in **Table 1.**
- EFV concentrations vs. time after dose are shown in **Figure 1.**
- In the TB-group **3T EFV exposure was lower than PP: $AUC_{0\text{-}24}$ was 19% lower, C_{max} 16% lower, C_{min} 25% lower, and apparent oral clearance (CL/F) 24% higher** (Table 2).
- 2T GMRs were similar to 3T, but not significantly different.
- Although median EFV parameters in the TB-group exceeded therapeutic thresholds in all sampling windows, **25% of participants did not meet target $AUC_{0\text{-}24}$ and C_{min} in 2T and 38% not in 3T.**
- **In contrast, in the non-TB-group, the EFV $AUC_{0\text{-}24}$ and C_{max} in pregnancy were similar to PP.**
- EFV $AUC_{0\text{-}24}$ and C_{min} were similar between the treatment groups and 3T EFV $AUC_{0\text{-}24}$ depended on the CYP2B6 metabolizer type in both treatment groups.
- Less viral suppression at delivery was noted in the TB-group but no infants had acquired HIV.

TABLE 2. TB-group Maternal Efavirenz Pharmacokinetic Parameters and Target Attainment

	2T	3T	PP	2T/PP GMR [90% CI]	3T/PP GMR [90% CI]	3T/PP *P*-value
	n=12	n=21	n=13	n=4	n=13	n=13
$AUC_{0\text{-}24}$ (µg·h/mL)	53.7 (38.0–71.0)	49.3 (31.8–84.5)	78.4 (41.8–115.6)	0.79 [0.57–1.09]	0.81 [0.69–0.95]	*0.008*
CL/F (L/h)	11.2 (8.5–16.0)	12.2 (7.1–18.9)	7.7 (5.2–14.3)	1.26 [0.92–1.74]	1.24 [1.06–1.46]	0.057
$T_{½}$ (h)	23.1 (18.1–35.5)	25.6 (19.3–36.6)	34.0 (24.4–53.7)	0.69 [0.48–1.00]	0.80 [0.65–0.99]	0.244
C_{max} (µg/mL)	4.5 (3.3–5.2)	4.0 (2.4–5.3)	5.3 (3.9–7.0)	0.93 [0.80–1.09]	0.84 [0.76–0.94]	*0.033*
C_{min} (µg/mL)	1.3 (1.0–2.1)	1.4 (0.7–2.5)	2.2 (1.1–4.0)	0.65 [0.41–1.04]	0.75 [0.63–0.90]	*0.003*
n (%) C_{min} < 1.0 µg/mL	3 (25%)	8 (38%)	2 (15%)			
n (%) $AUC_{0\text{-}24}$ < 40 µg·h/mL	3 (25%)	8 (38%)	3 (23%)			

FIGURE 1. Median plasma concentration-time profiles of efavirenz (600 mg once daily) in the TB-group (A) and the non-TB-group (B) during 2T, 3T and PP (error bars indicate the IQR). The dashed curve represents the reference 50th percentile concentrations in historical non-pregnant patients. The minimum target C_{min} is represented by the horizontal dotted line.



CONCLUSIONS

- With first-line TB treatment, EFV exposure during late pregnancy is reduced compared to postpartum, more so than in pregnancy without TB treatment.
- While standard dosing achieved adequate exposure in most participants, a significant subset — particularly those with extensive CYP2B6 metabolizer genotypes — did not reach target $AUC_{0\text{-}24}$ or C_{min} concentrations.
- EFV dose optimization or therapeutic drug monitoring may be beneficial for those co-treated for tuberculosis in pregnancy.

PLAIN LANGUAGE SUMMARY

Pregnant women on efavirenz-based antiretroviral treatment together with standard TB treatment had lower efavirenz exposure in the 3rd trimester compared to postpartum with almost 40% of participants not reaching minimum target concentrations.

Although the clinical implications are unclear, we advise to monitor HIV viral load frequently in pregnant women on efavirenz and concurrent TB treatment.

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