# Elvitegravir/Cobicistat Pharmacokinetics in Pregnancy and Postpartum


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## Introduction

- Elvitegravir (EVG) is an integrase strand transfer inhibitor (INSTI) coformulated with cobicistat (COBI), a pharmacokinetic enhancer, and two nucleos(t)ides.
- During pregnancy, physiological changes cause decreased exposure to many antiretrovirals.
- EVG is metabolized by CYP 3A and UGT 1A1/3; COBI is metabolized by CYP 3A (major) and 2D6 (minor).
- No data are available on the pharmacokinetic behavior of EVG/COBI during pregnancy, nor on infant washout pharmacokinetics.

## Methods

- IMPAACT P1026s (ClinicalTrials.gov ID NCT00042289) is an ongoing, nonrandomized, open-label, parallel-group, multi-center phase-IV prospective study of antiretroviral pharmacokinetics and safety in HIV-infected pregnant women that includes an arm for EVG/COBI.
- Samples were collected at 20-28 weeks gestation, 30-38 weeks gestation and between 3 to 12 weeks following delivery. Maternal samples were drawn at pre-dose, 1, 2, 4, 6, 8,12 and 24 hours post-dose.
- Infant washout samples were collected, if birth weight was > 1,000 grams and there were no severe malformations or medical conditions, at 2-10 hours, 18-28 hours, 36-72 hours and 5-9 days post delivery.
- EVG/COBI were measured using validated LC/MS/MS (quantitation limit: 10 ng/mL).
- PK parameters were calculated with standard non-compartmental methods. Two-tailed Wilcoxon signed rank tests compared within-subject PK parameters with a two-sided p-value < 0.10.

## Results

**Maternal Pharmacokinetics**

- Data were available for 2nd trimester (2T, n = 16), 3rd trimester (3T, n = 20), postpartum (PP, n = 16) and infant washout (n = 16). [Table 1]
- EVG AUC and C24 were 43 – 50% and 86 – 87% lower in 2T and 3T compared to paired PP. [Table 2, Figures 1, 2]
- COBI AUC and C24 were 54 – 57% and 72 – 76% lower in 2T and 3T versus PP. [Table 2, Figures 3, 4]
- 8/16 (50%) women in 2T, 9/20 (45%) women in 3T and 14/16 (88%) women PP had an EVG AUC above the 10th percentile (23 mcg*hr/mL) of non-pregnant adults.

**Infant Pharmacokinetics**

- Washout pharmacokinetic data were available for 16 infants; COBI was undetectable in all infant samples. [Figure 5]

**Maternal and Infant Safety**

- One maternal AE was possibly treatment related: preterm labor and delivery.
- Congenital anomalies reported in 2/26 infants: one infant with amniotic band syndrome, microcephaly, and intrauterine growth restriction; one infant with ulnar postaxial polydactyly (supernumerary digit).

## Results

Figure 1. Median Elvitegravir Concentrations

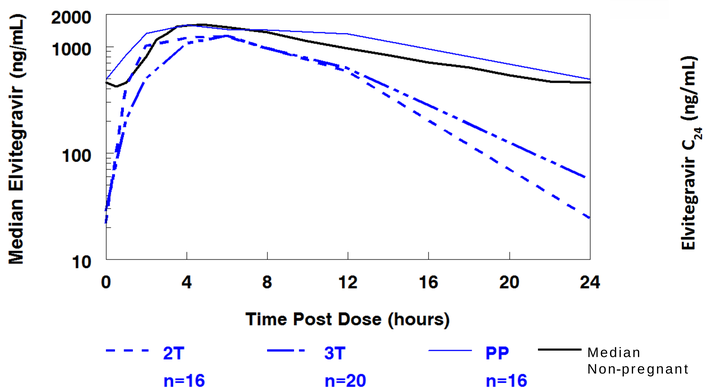


Figure 2. Elvitegravir $C_{24}$ Ante- and Postpartum

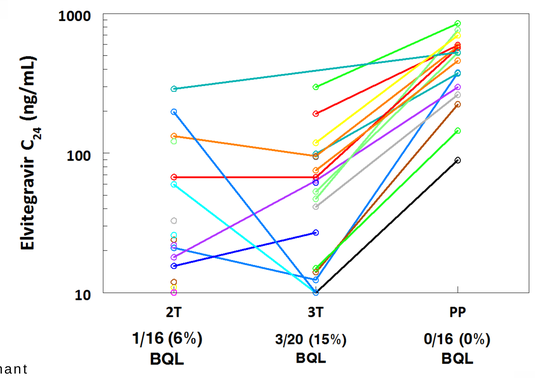


Figure 3. Median Cobicistat Concentrations

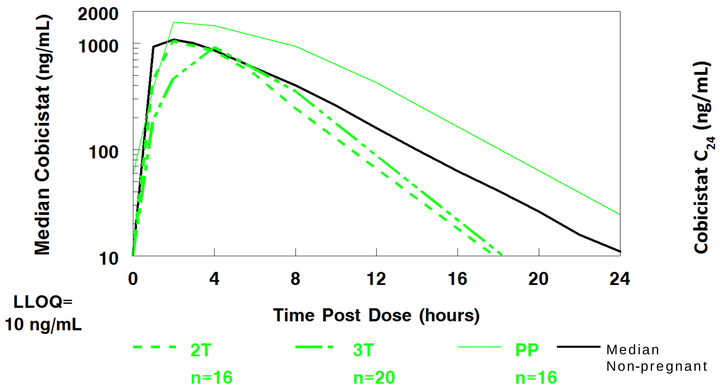


Figure 4. Cobicistat $C_{24}$ Ante- and Postpartum

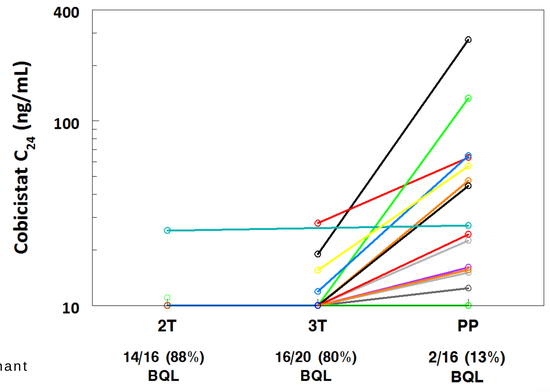


Table 1. Clinical Characteristics (n = 29)

| Maternal Demographics | N (%) or Median (Range) |
|---|---|
| Age at Delivery (years) | 32 (19 – 47) |
| Weight at Delivery (kg) | 86 (58 – 132) |
| Race/Ethnicity - White; Black; Hispanic; Asian/Pac. Islander | 3 (10%); 19 (66%); 6 (21%); 1 (3%) |
| Concomitant ARVs FTC; TDF; TAF; ZDV; MVC | 29 (100%); 28 (97%); 1 (3%); 3 (10%); 1 (3%) |
| Country: United States | 29 (100%) |
| 2T: HIV-1 RNA ≤ 50 copies/mL | 13/16 (81%) |
| 2T: CD4 (cells/mm$^3$) | 701 (253 – 1267) |
| 3T: HIV-1 RNA ≤ 50 copies/mL | 12/15 (80%) |
| 3T: CD4 (cells/mm$^3$) | 728 (145 – 1285) |
| Delivery: HIV-1 RNA ≤ 50 copies/mL | 14/19 (74%) |
| Delivery: CD4 (cells/mm$^3$) | 658 (129 – 1590) |
| PP: HIV-1 RNA ≤ 50 copies/mL | 11/16 (69%) |
| PP: CD4 (cells/mm$^3$) | 956 (247 – 1576) |
| **Pregnancy Outcomes** | |
| Gestational Age (weeks) | 38.8 (34.6 – 41.3) |
| Birth Weight (grams) | 3076 (1885 – 4050) |
| Infection Status: Uninfected / Pending | 20 (77%) / 6 (23%) |

Figure 5. Infant Elvitegravir Concentrations

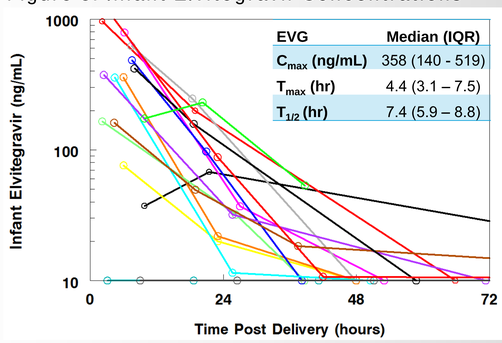


Table 2. Maternal Elvitegravir/Cobicistat Pharmacokinetic Parameters, Median (IQR)

| Parameter | 2T n = 16 | 3T n = 20 | PP n = 15 | GMR (90% CI): 2T/PP | GMR (90% CI): 3T/PP |
|---|---|---|---|---|---|
| **Elvitegravir** | | | | | |
| $AUC_{0-24}$ (ng*hr/mL) | 15,742 (11,601-19,238)* | 14,454 (9,523-19,443)* | 26,767 (17,931-34,191) | 0.51 (0.33-0.78) | 0.58 (0.48-0.69) |
| $C_{max}$ (ng/mL) | 1,463 (1,090-1640) | 1,455 (692-1,703)* | 1,876 (1,056-2,366) | 0.68 (0.46-1.03) | 0.74 (0.60-0.91) |
| $C_{24}$ (ng/mL) | 24.9 (17.3-80.7)* | 57.2 (14.7-94.1)* | 491 (289-584) | 0.14 (0.06-0.34) | 0.13 (0.09-0.17) |
| CL/F (L/hr) | 9.5 (7.8-13.0)* | 10.4 (7.7-15.8)* | 5.6 (4.4-8.4) | 1.98 (1.28-3.05) | 1.73 (1.45-2.07) |
| $T_{1/2}$ (hr) | 3.1 (2.6-4.1)* | 3.5 (3.1-4.8)* | 8.9 (7.3-13.4) | 0.42 (0.30-0.60) | 0.39 (0.33-0.46) |
| **Cobicistat** | | | | | |
| $AUC_{0-24}$ (ng*hr/mL) | 6,775 (4,630-8,523) | 7,142 (4,104-10,111)* | 15,404 (12,582-20,631) | 0.46 (0.22-0.96) | 0.43 (0.34-0.55) |
| $C_{max}$ (ng/mL) | 1,095 (891-1,626) | 1,170 (724-1,836)* | 1,778 (1,285-2,491) | 0.70 (0.39-1.26) | 0.64 (0.50-0.82) |
| $C_{24}$ (ng/mL) | <10 (<10-<10) | <10 (<10-<10)* | 25.7 (15.5-58.6) | 0.28 (0.08-1.0) | 0.24 (0.16-0.36) |
| CL/F (L/hr) | 22.2 (17.9-32.4) | 21.0 (14.8-36.8)* | 9.8 (7.3-11.9) | 2.17 (1.04-4.50) | 2.32 (1.82-2.95) |
| $T_{1/2}$ (hr) | 2.0 (1.8-2.6) | 2.0 (1.8-2.6)* | 3.0 (2.8-3.4) | 0.74 (0.54-1.01) | 0.64 (0.56-0.73) |

GMR (90% CI): Geometric Mean Ratio (90% Confidence Interval)
*p<0.10, n=5 for 2nd trimester vs. postpartum paired comparison, n=15 for 3rd trimester vs. postpartum paired comparison

## Conclusions

- EVG and COBI exposure are substantially lower during pregnancy compared to postpartum; standard doses may not be adequate for sustained viral suppression.
- EVG readily crosses the placenta and has a half-life in newborns similar to non-pregnant adults; COBI was not detectable in neonates.

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