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 g, 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 86–100% lower in 2T and 3T compared to paired PP, [Table 2, Figures 1, 2]
• COBI AUC and C24 were 57–72% 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).

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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