Elvitegravir/Cobicistat Pharmacokinetics in Pregnancy and Postpartum

Brookie M. Best[1], Edmund V. Capparelli[1], Alice Stek[2], Edward P. Acosta[3], Elizabeth Smith[4], Nahida Chakhtoura[5], Jiajia Wang[6], Adriane Hernandez[7], Mark Mirochnick[8] on behalf of the IMPAACT 1026s Protocol Team

Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego, CA, US[1], University of Southern California School of Medicine, Los Angeles, CA, US[2], University of Alabama at Birmingham, Birmingham, AL, US[3], Maternal, Adolescent, and Pediatric Research Branch, National Institute of Allergy and Infectious Diseases, Bethesda, MD[4], Maternal and Pediatric Infectious Disease Branch, Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), Bethesda, MD[5], Harvard T.H. Chan School of Public Health, Center for Biostatistics in AIDS Research, Boston, MA, USA[6], Frontier Science Foundation, Amherst, NY, US[7], Boston University School of Medicine, Boston, MA, US[8]

Brookie M. Best
University of California, San Diego
9500 Gilman Drive, MC 0657
La Jolla, CA 92093-0657
Tel: 858-822-5550
E-mail: brookie@ucsd.edu

755

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

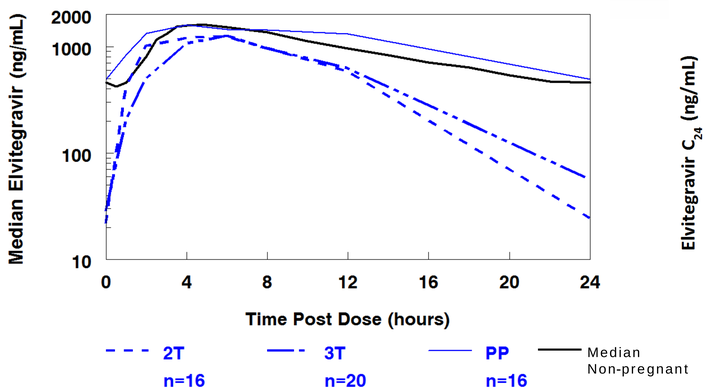

Figure 2. Elvitegravir C_{24} Ante- and Postpartum

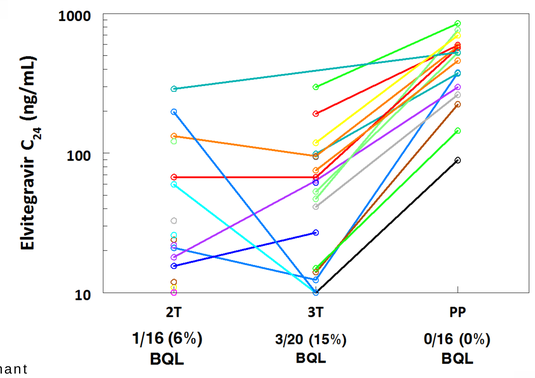

Figure 3. Median Cobicistat Concentrations

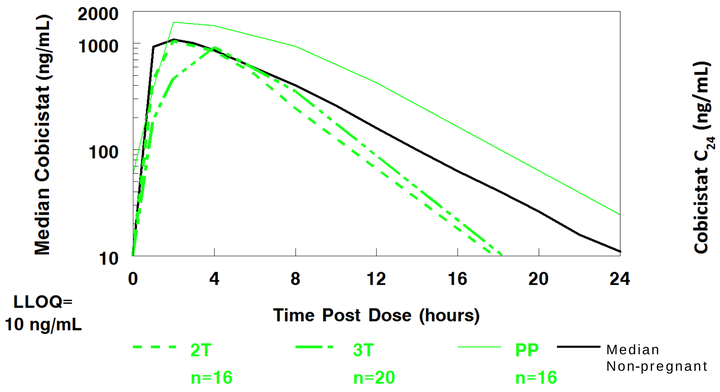

Figure 4. Cobicistat C_{24} Ante- and Postpartum

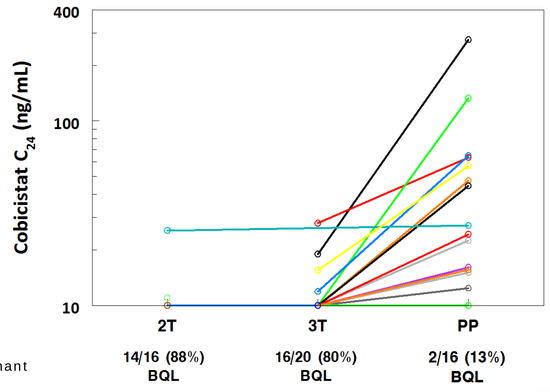

Table 1. Clinical Characteristics (n = 29)

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

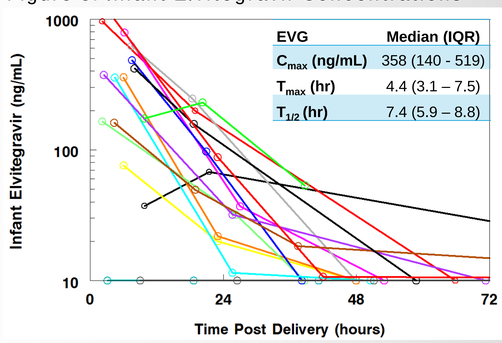

Table 2. Maternal Elvitegravir/Cobicistat Pharmacokinetic Parameters, Median (IQR)

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.

Acknowledgments

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