Pharmacokinetics of Darunavir Boosted with Cobicistat during Pregnancy and Postpartum

Jeremiah D. Momper[1], Brookie Best[1], Jiajia Wang[2], Alice Stek[3], David E. Shapiro[2], Kathleen George[4], Emily Barr[5], Kittipong Rungruengthanakit[6], Elizabeth Smith[7], Nahida Chakhtoura[8], Edmund V. Capparelli[1], Mark Mirochnick[9], for the IMPAACT P1026s Protocol Team

[1]University of California San Diego, La Jolla, CA, USA, [2]Harvard University, Cambridge, MA, USA, [3]University of Southern California, Los Angeles, CA, USA, [4]FHI 360, Durham, NC, USA, [5]Children's Hospital Colorado, Aurora, CO, USA, [6]Chiang Mai University, Chiang Mai, Thailand, [7]NIAID, Bethesda, MD, USA, [8]National Institute of Child Health and Human Development, Bethesda, MD, USA, [9]Boston University, Boston, MA, USA

A-899-0157-06026

Introduction

- Antiretroviral therapy can reduce the risk of perinatal transmission to < 1% and is recommended for all pregnant women.
- During pregnancy, physiological changes may impact drug disposition, often resulting in decreased exposure to many antiretrovirals.
- Darunavir (DRV), an HIV-1 protease inhibitor, is metabolized primarily by CYP3A and must be administered with a pharmacokinetic (PK) booster.
- The PK of DRV co-administered with ritonavir have been described in pregnancy; however, DRV co-formulated with cobicistat (COBI) has not been studied in pregnant women.
- IMPAACT P1026s is an ongoing, nonrandomized, open-label, multi-center, international and domestic, phase-IV prospective study of antiretroviral PK in HIV-infected pregnant women.
- This study described DRV exposure when administered in fixed-dose combination with COBI during pregnancy and postpartum.

Methods

- Intensive steady-state 24-hour PK profiles of DRV following once-daily dosing of 800/150 mg DRV/COBI were performed during the 2nd trimester (2T), 3rd trimester (3T) and postpartum (PP).
- DRV plasma concentrations were measured by a validated HPLC method with a quantitation limit of 0.09 µg/mL.
- PK parameters were calculated with standard non-compartmental methods.
- PK target was AUC of 70 µg*hr/mL, the 10th percentile for non-pregnant adults
- A two-tailed Wilcoxon signed rank test (α = 0.10) was employed for paired within-subject comparison of PK parameters.

References and Acknowledgements

1. Prezcobix (darunavir and cobicistat) [package insert]. Titusville NJ: Janssen Pharmaceuticals 2015.
2. Mirochnick M, Capparelli E. Pharmacokinetics of antiretrovirals in pregnant women. Clin Pharmacokinet 2004; 43(15):1071-1087.
3. Stek A, Best BM, Wang J, Capparelli EV, Burchett SK, Kreitchmann R, et al. Pharmacokinetics of Once Versus Twice Daily Darunavir in Pregnant HIV-Infected Women. J Acquir Immune Defic Syndr 2015; 70(1):33-41.
4. Colbers A, Greupink R, Burger D. Pharmacological considerations on the use of antiretrovirals in pregnancy. *Current Opinion Infectious Disease.* 2013;26(1): 575-88.

The authors wish to thank the women that participated in the protocol and the staff of the participating centers. Overall support for the IMPAACT group was provided by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) under Award Numbers UM1A1068632 (IMPAACT LOC), UM1A1068616 Health (NIMH).

Demographics

Table 1. Clinical Characteristics (n = 29)

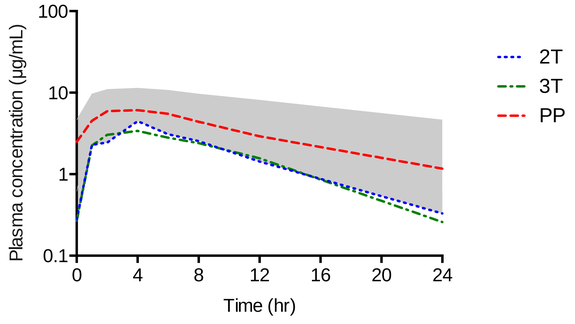
Maternal Demographics	N (%) or Median (Range)
Age at Delivery (years)	27.2 (17.2 – 43.2)
Weight at Delivery (kg)	93.2 (72.5 – 114.8)
Race/Ethnicity Black Non-Hispanic; Hispanic (regardless of race)	18 (62%); 11 (38%)
Concomitant ARVs at 3rd Trimester PK Evaluation (n=25 patients)	3TC: 9 (36%); DTG: 3 (12%); FTC: 14 (56%); LPV:1 (4%); RTV: 1 (4%); TAF: 10 (40%); TDF: 4 (16%); ZDV: 12 (48%)
Country: United States	29 (100%)
2nd Trimester (n=16)	
Gestational Age (wk)	23.5 (20.3 – 26.9)
HIV-1 RNA ≤ 50 copies/mL	11 (68.6%)
CD4 (cells/mm^3)	506.5 (237 – 1596)
3rd Trimester (n=25)	
Gestational Age (wk)	32.6 (30.0 – 36.7)
HIV-1 RNA ≤ 50 copies/mL	20 (83.3%)
CD4 (cells/mm^3)	461 (153 – 1581)
Postpartum (n=18)	
Weeks After Delivery	10.8 (6.6 – 14.9)
HIV-1 RNA ≤ 50 copies/mL	13 (76.5%)
CD4 (cells/mm^3)	596 (322 – 1807)
Pregnancy Outcomes (n=27)	
Gestational Age (weeks)	38.0 (35.9 – 40.9)
Birth Weight (grams)	2875 (2400– 3800)
Infant HIV Infection Status: Uninfected; Indeterminate; Pending	19 (70%); 7 (26%); 1 (4%)

Results

Maternal Pharmacokinetics

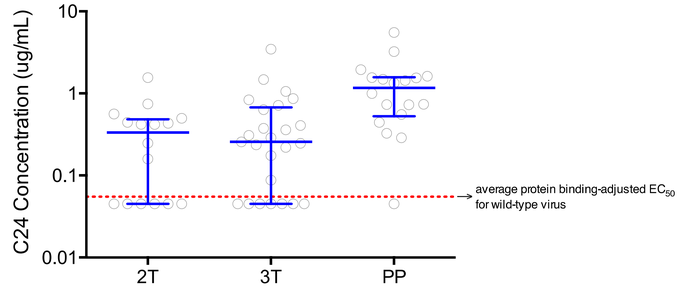
- Data were available for 2nd trimester (n = 16), 3rd trimester (n = 25), and postpartum (n = 18) [Table 1]
- 24-hour DRV trough concentrations (C_{24}) were decreased in the second and third trimester compared to PP. [Table 2]
- DRV $AUC_{0\text{-}24}$, C_{max}, and C_{24} were lower and CL/F was higher in the third trimester compared to PP [Table 2]
- A total of 4/16, 8/25, and 14/18 mothers had $AUC_{0\text{-}24}$ values above the 10th percentile in non-pregnant adult patients at 2T, 3T, and PP, respectively [Figure 1]
- A total of 6/16, 7/25, and 1/18 mothers had C_{24} below quantitation limit at 2T, 3T, and PP, respectively, suggesting concentrations in these women may have been below 0.055 ug/mL, the threshold for the average protein binding-adjusted EC_{50} for wild-type virus [Figure 2]

Figure 1. Median Steady State Darunavir Concentrations following once-daily dosing of 800/150 mg Darunavir/Cobicistat



The shaded area shows the 10th to 90th percentile concentrations in non pregnant adults

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



Concentrations below the limit of quantitation (BLOQ; 0.9 µg/mL) are displayed as ½ the lower limit of quantitation (1.95 ng/mL).

Table 2. Maternal Darunavir Pharmacokinetic Parameters

Parameter	2nd Trimester Median (min-max) n = 16	3rd Trimester Median (min-max) n = 25	Postpartum Median (min-max) n = 18	GMR (90%): 2nd Trimester/ Postpartum	GMR (90%): 3rd Trimester/ Postpartum
$AUC_{0\text{-}24}$ (µg*hr/mL)	47.22 (13.50 – 93.60)	43.62 (12.70 – 89.30)	96.03 (4.50 – 231.78)	0.67 (0.34 – 1.33)	0.52 (0.37 – 0.74)*
C_{max} (µg/mL)	4.61 (1.82 – 9.70)	4.14 (1.98 – 7.01)	7.06 (0.93 – 12.39)	0.74 (0.44 – 1.26)	0.64 (0.50 – 0.82)*
C_{24} (µg/mL)	0.44 (0.05 – 1.55)	0.49 (0.05 – 3.47)	1.45 (0.05 – 5.53)	0.29 (0.10 – 0.81)*	0.25 (0.13 – 0.49)*
CL/F (L/hr)	23.60 (8.55 – 59.26)	22.68 (8.96 – 62.99)	14.24 (2.59 – 133.33)	1.98 (1.01 – 3.90)	2.55 (1.81 – 3.59)*
$T_{1/2}$ (hr)	6.183 (2.199 – 15.536)	7.274 (1.652 – 33.784)	8.037 (1.446 – 18.106)	0.80 (0.42 – 1.52)	0.82 (0.54 – 1.25)

GMR: Geometric Mean Ratio
*p<0.10, n=11 for 2nd trimester vs. postpartum paired comparison, n=17 for 3rd trimester vs. postpartum paired comparison

Maternal and Infant Safety

Table 3. Reported maternal Grade 3 or 4 adverse events

Event	# Participants	Relatedness
Anemia	5	Not related
Preterm delivery	2	Not related
Severe pre-eclampsia	1	Not related
Hypercalcemia	1	Not related
Hyperglycemia	1	Not related
Hyperkalemia	1	Not related

Table 4. Birth Abnormalities

Abnormality	Gest Age TAF begun	Relatedness
Patent Foramen Ovale Ventricular Septal Defect	8 4/7 weeks	Not related Not related
Congenital Tongue Tie	21 1/7 weeks	Not related
Bilateral Undescended Testes and Inguinal Hernias	23 6/7 weeks	Not related
Sacral Dimple	Prior to conception	Normal variant
Lumbosacral Congenital Dermal Melanocytosis	15 6/7 weeks	Normal variant
Congenital Anemia	21 2/7 weeks	Not related

Discussion and Conclusion

- In women taking DRV in fixed-dose combination with COBI, the exposure to DRV was significantly lower in pregnancy compared to postpartum.
- The 25th percentile of plasma concentrations at the end of the dosing interval (C_{24}) during pregnancy was below the lower limit of quantitation of the assay (0.9 µg/mL) suggesting trough concentrations in many women fell below 0.055 ug/mL, the threshold for the average protein binding-adjusted EC_{50} for wild-type virus.
- Cobicistat plasma concentrations from this study are currently being analyzed
- DRV/COBI should be used with caution in pregnant women.