Pharmacokinetics of Increased Dose Darunavir during Late Pregnancy and Postpartum

Alice Stek[1], Brookie M. Best[2], Edmund V. Capparelli[2], Jiajia Wang[3], David E. Shapiro[3], Tim Cressey[3,4], Elizabeth Smith[5], Regis Kreitchmann[6], Nahida Chakhtoura[7], Mark Mirochnick[8] for the IMPAACT 1026s Protocol Team

University of Southern California School of Medicine, Los Angeles, CA, US[1], Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego, CA, US[2], Harvard T.H. Chan School of Public Health, Center for Biostatistics in AIDS Research, Boston, MA, US[3] ,Chiang Mai University, Chiang Mai, Thailand[4], Maternal, Adolescent, and Pediatric Research Branch, National Institute of Allergy and Infectious Diseases, Bethesda, MD, US[5], Irmandade da Santa Casa de Misericordia de Porto Alegre, Porto Alegre, Brazil[6], Maternal and Pediatric Infectious Disease Branch, Eunice Kennedy Shriver National Institute of Child Health and Human Development , Bethesda, MD, US[7], Boston University School of Medicine, Boston, MA, US[8]

Alice Stek
Dep't of Obstetrics and Gynecology
Univ. of Southern California
LAC+USC Medical Center
2020 Zonal Ave, IRD room 220
Los Angeles, CA 90033
E-mail: stek@usc.edu

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Introduction

- Combination antiretroviral therapy is recommended for all pregnant women with HIV to reduce the risk of perinatal transmission and for maternal health.[1]
- Darunavir (DRV), dosed twice daily, is one of two preferred protease inhibitor regimens during pregnancy, per the US DHHS perinatal guidelines.[1]
- During pregnancy, physiological changes cause decreased exposure to many antiretrovirals.
- IMPAACT 1026s describes the pharmacokinetics of ARVs in pregnant women in comparison to post-partum kinetics.
- The IMPAACT P1026s protocol and other studies have demonstrated that standard doses of protease inhibitors result in lower maternal drug levels during late pregnancy.
- The IMPAACT P1026s and PACTG 353 studies demonstrated that increased doses of lopinavir, atazanavir, and nelfinavir achieved targets for maternal drug exposure.
- IMPAACT P1026s previously demonstrated that during pregnancy DRV exposure was reduced by 26% compared to postpartum with DRV/ritonavir (RTV) 600/100 mg bid.[2]
- We hypothesized maternal plasma DRV exposure during pregnancy would increase with DRV/RTV 800/100 mg bid.

Methods

- IMPAACT P1026s is an ongoing nonrandomized, open-label, international multi-center phase 2/3 prospective study in HIV-infected pregnant women. All DRV participants were in the US and took DRV 800 mg and RTV 100 mg BID.
- Medications were chosen and prescribed by the participants' clinicians, who also managed any toxicities and adverse events
- Intensive steady-state 12 hour PK profiles were performed during the 2nd trimester , 3rd trimester and 2-6 weeks postpartum. Serial blood collection was drawn at pre-dose, 1, 2, 4, 6, 8 and 12 hours post-dose.
- Paired maternal and cord blood and infant wash-out PK samples were obtained; analysis is in progress.
- DRV and RTV plasma concentrations were measured using HPLC; detection limit was 0.09 mcg/mL for both.
- Target DRV exposure was ≥ 70% (43.6 mcg*hr/mL) of median AUC (62.3) in non-pregnant adults on 600/100 mg.
- 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.

References

1. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health *and* Interventions to Reduce Perinatal HIV Transmission in the United States. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf. Accessed 2.16.16
2. A Stek, BM Best, J Wang, EV Capparelli, SK Burchett, R Kreitchmann, K Rungruengthanakit, TR Cressey, LM Mofenson, E Smith, D Shapiro, M Mirochnick: Pharmacokinetics of Once Versus Twice Daily Darunavir in Pregnant HIV-Infected Women. JAIDS 05.2015

Participant Characteristics

Table 1. Subject characteristics and outcomes (n = 18)

Maternal Characteristics	N (%) or Median (Range)
Age at Delivery (years)	26.4 (18.6 – 41.9)
Weight at Delivery (kg)	89.6 (54.4 – 135.5)
Race/Ethnicity Black non-Hispanic Hispanic	 10 (56%) 8 (44%)
Concomitant ARVs	FTC 11; TDF 11; ZDV 3; 3TC 2; RAL 5; RPV 2; DTG 2;T20 1
2nd Trimester	
Gestational Age (weeks)	23.6 (22.4 – 23.9)
HIV-1 RNA ≤ 50 copies/mL	3 (75%)
CD4 (cells/mm^3)	277 (128 – 1061)
3rd Trimester	
Gestational Age (weeks)	33.3 (30.1 – 34.9)
HIV-1 RNA ≤ 50 copies/mL	16 (94%)
CD4 (cells/mm^3)	376 (128 – 1140)
Delivery	
HIV-1 RNA ≤ 50 copies/mL	14 (82%) [16 (94%) <400)]
CD4 (cells/mm^3)	423 (198 – 1123)
Postpartum	
Weeks After Delivery	7.3 (6 – 12)
HIV-1 RNA ≤ 50 copies/mL	11 (73%)
CD4 (cells/mm^3)	469 (220 – 1164)
Pregnancy Outcomes	
Gestational Age (weeks)	39.0 (32.6 – 41.0)
Birth Weight (grams)	3390 (950 – 3970)
Infection Status:	12 uninfected / 6 pending

Results

Maternal Pharmacokinetics

- Data were available for 2nd trimester (n = 4), 3rd trimester (n = 17) and postpartum (n =15) [Table 1].
- Median DRV AUC with 800 mg dose during 3rd trim was 36% lower than with 600 mg dose postpartum (NS; p=0.14) [Table 2, Fig. 1, 2].
- Geometric mean of the individual women's 3rd trimester/postpartum DRV ratios was 0.65 (90% CI 0.54-0.78; p<0.001). [Table 2, Fig. 2]
- While 65% (95% CI 35-85%) met our AUC target in 3rd trim, 93% (95% CI 68-100%) met the target postpartum (NS).
- Cmin, C12 and Cmax were significantly lower in 3rd trim than postpartum and CL/F was higher.
- DRV PK data from our prior DRV cohort on 600/100 mg BID are included for comparison.

Figure 1. Median Darunavir Concentrations

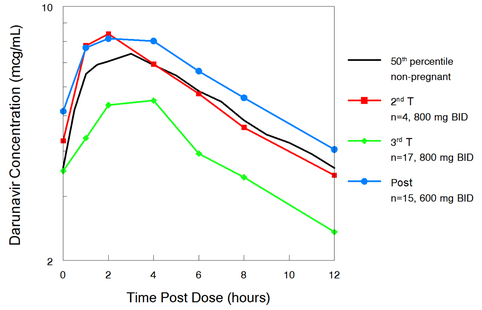
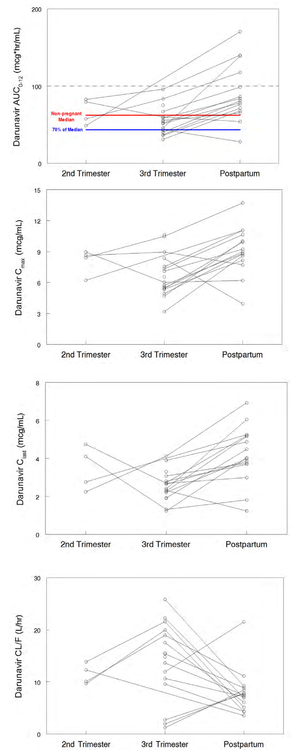


Figure 2. Darunavir Ante- and Postpartum



Maternal and Infant Safety

- Four maternal adverse events were possibly treatment related: moderately increased ALT, proteinuria, oligohydramnios and IUGR.
- Four infants had abnormalities; none were thought to be related to DRV or RTV: short frenulum, sacral Mongolian spot, G6PD deficiency, hyperbilirubinemia

Table 2. Maternal Darunavir and Ritonavir Pharmacokinetic Parameters

	DRV 800 mg BID			RTV 100 mg BID			DRV 600 mg BID (from prior cohort P1026)	
Parameter Median (IQR)	2nd trim	3rd trim	PP (600 BID)	2nd trim	3rd trim	PP	3rd trim	PP
	n = 4	n=17	n=15	n = 4	n=17	n=15	n = 34	n = 27
AUC_{0-12} (µg*hr/mL)	68.6 (55.5- 80.2)	52.1 * (42.3-60.1)	80.9 (69.6-108.1)	7.5 (5.4-10.0)	5.4 (3.8-8.1)	5.9 (5.5-11.2)	45.9 * (29.3-50.5)	61.7 (49.7-80.6)
Met AUC target	4/4 (100%)	11/17 (65%)	14/15 (93%)	-	-	-	19/34 * (56%)	22/27 (81%)
C_0 (µg/mL)	4.3 (1.8-7.1)	3.5 (2.8-4.5)	5.1 (2.1-5.8)	0.55 (0.33-0.77)	0.37 (0.22-0.55)	0.53 (0.14-0.69)	-	-
C_{max} (µg/mL)	8.5 (7.9 - 8.7)	6.0 * (5.4-7.5)	8.8 (7.9-10.3)	0.81 (0.62-1.23)	0.78 (0.56-0.91)	0.88 (0.71-1.43)	5.5 * (4.4-7.1)	7.8 (6.4-9.5)
C_{12} (µg/mL)	3.4 (0.8-2.0)	2.4 * (2.2-2.8)	4.0 (3.3-5.2)	0.48 (0.31-0.56)	0.30 (0.10-0.41)	0.37 (0.12-0.64)	2.2 (1.7-3.3)	2.5 (2.0-3.3)
T_{max} (hr)	1.5 (0.8-2.0)	2.0 (2.0-4.0)	2.0 (2.0-3.0)	3.0 (2.0-4.0)	4.0 (2.0-4.0)	4.0 (2.0-5.0)	-	-
CL/F (L/hr)	11.2 (10.0-12.7)	15.4 * (13.3-18.9)	7.4 (5.6-8.6)	13.8 (10.3-20.1)	18.5 (14.8-27.3)	14.6 (9.0-17.7)	13.1 * (11.4-20.5)	9.5 (7.4-11.7)
$T_{1/2}$ (hr)	9.6 (7.5-12.9)	8.0 (5.6-10.7)	7.7 (5.3-21.8)	17 (12.5-19.5)	6.9 (2.7-18.7)	5.0 (3.1-6.7)	-	-

* $p<0.05$ 3rd trimester compared with postpartum; Wilcoxon signed-rank test

Discussion and Conclusions

- These data confirm that DRV exposure is decreased during pregnancy.
- Increasing the DRV dose to 800 mg during pregnancy failed to significantly increase DRV exposure compared to 600 mg. This is in contrast to our findings with other protease inhibitors, where increased dosing did achieve target drug levels.
- While viral suppression was fairly good in our participants, if achieving DRV exposure during pregnancy equivalent to that in non-pregnant adults is desired, other strategies, such as increasing the RTV dose or using an alternative booster, should be investigated.

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