Population Pharmacokinetics (PK) of Lopinavir During Pregnancy and Postpartum

Justin T. Hoffman, PharmD[1], Brookie M Best, PharmD[1], Mark Mirochnick, MD[2], Alice Stek, MD[3], Jiajia Wang, MS[4], David Shapiro, PhD[4], Tim R. Cressey, PhD[5], Edmund Capparelli, PharmD[1].

[1]University of California, San Diego, Skaggs School of Pharmacy & Pharmaceutical Sciences and School of Medicine, San Diego, CA, USA; [2]Boston University School of Medicine, Boston, MA, USA; [3]Los Angeles County and USC Medical Center, Los Angeles, CA, USA; [4]Harvard School of Public Health, Boston, MA, USA; [5]Chang Mai University, Muang, Chiang Mai, Thailand.

Oral Abstract Presentation
SCDMDG 10/22/2012
Presented by:
Justin Hoffman PharmD MS
Former UCSD-Pfizer Post-Doctoral Fellow

Introduction

- The protease inhibitor Lopinavir (LPV) has an unfavorable pharmacokinetic (PK) profile, due primarily to extensive first pass metabolism and rapid systemic clearance by intestinal and hepatic CYP3A.[1-3]

- To boost systemic exposure LPV is administered as a fixed-dose combination with the potent CYP3A inhibitor Ritonavir (RTV) at doses of 400/100mg twice a day.

- Antiretroviral treatment during pregnancy in HIV-infected women is critical to reduce viral load and prevent mother-to-child transmission of the virus.

- Several independent evaluations have indicated reduced LPV drug concentrations during the third trimester of pregnancy increasing the risk of perinatal transmission and virologic resistance.[4-9]

- Pregnant women experience physiological changes that can result in clinically significant alterations in drug PK including increased gastrointestinal transit time, changes in body composition, decreased circulating albumin and alpha-1-acid glycoprotein concentrations, increased hepatic and renal blood flow, and increased expression of metabolic enzymes including CYP3A.[4-9]

IMPAACT Study 1026s Dataset

- 3 Arms of IMPAACT Study 1026s were combined providing 182 intensive, steady-state 12-hour PK profiles for LPV and RTV from 92 distinct HIV-positive female patients.

- PK Profiles Summary:

  - **Formulation:**

    soft gel capsule (n=94) vs melt extrusion tablet (n=88)

  - **State of pregnancy:**

    2nd trimester (n=29), the 3rd trimester (n=82), and 2-8 weeks postpartum (n=71).

  - **Dose:**

    3rd trimester LPV doses ranged from 400-600mg twice a day.

- A total of 1267 and 1215 plasma LPV and RTV concentrations above LLOQ were available for   POP-PK modeling

Methods

Population Pharmacokinetic (POP-PK) Modeling

- LPV and RTV POP-PK analyses were conducted by nonlinear mixed effects modeling using NONMEM version 6.2 with first order conditional estimation with interaction (FOCE-I) method.

- Both LPV and RTV were modeled using a 1-compartment, 1st order absorption, 1st order elimination models

- Between-subject variability was modeled using an exponential error model

- Pregnancy covariates were included as dichotomous categorical power models

- Modeling the effect of [RTV] on CL_{LPV} was attempted using a median normalized power model and a direct response I_{max} model.

- Model performance was evaluated by review of diagnostic plots, bootstrapping, and via visual predictive check using the programs PsN, Xpose, R, and RfNM.

Model Building Strategy

Build population pharmacokinetic base models for Lopinavir (LPV). Choose best model to obtain pharmacokinetic parameters.

1. 1 compartment, 1st order absorption, 1st order elimination
2. Add parameters for between-subject variability (BSV)
3. Account for differential bioavailability of the two formulations (F_Tab)

Expand on base model by accounting for state of pregnancy as a categorical covariate on base model parameters.

1. Using postpartum as reference add covariate of pregnancy on base model parameters CL/F and V/F.
2. Using postpartum as reference, add separate covariates for 2nd and 3rd trimester on Cl/F (2T_CL, 3T_CL)
3. Using postpartum as reference, add separate covariates for 2nd and 3rd trimester on V/F (2T_V, 3T_V)

Expand model to account for [Ritonavir]$_{plasma}$ on LPV CL/F, and choose best fit model.

1. Attempt to add observed [Ritonavir]$_{plasma}$ as a direct continuous covariate on LPV Cl/F and F.
2. Add effect of [Ritonavir]$_{plasma}$ as a maximum inhibitory (I_{max}) direct response model on LPV Cl/F. IC_{50} and I_{max} for effect fixed to literature values.
3. Unfix IC_{50} and I_{max} values for RTV inhibition of LPV CL/F.

Summary of Key Models

LPV POP-PK Model*	COVARIATES	OBJ FUNC
1-Compartment Base Model	F_Tab	4240.747
Pregnancy Covariate Model	F_Tab, 3T_CL, 3T_V, 2T_CL, 2T_V	3559.628
Fixed RTV I_{max} Covariate Model	F_Tab, 3T_CL, 3T_V, 2T_CL, 2T_V, Imax, IC50	3505.401
RTV I_{max} Covariate Model	F_Tab, 3T_CL, 3T_V, 2T_CL, 2T_V, Imax, IC50	3427.786

*All models contain the following PK parameters: CL/F, V/F, k_a, and BSV n's on each
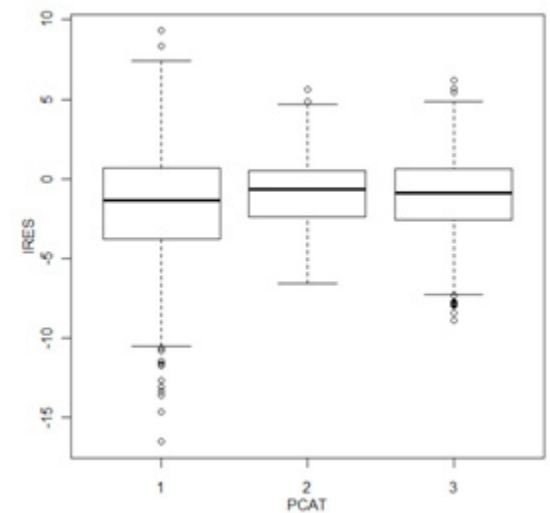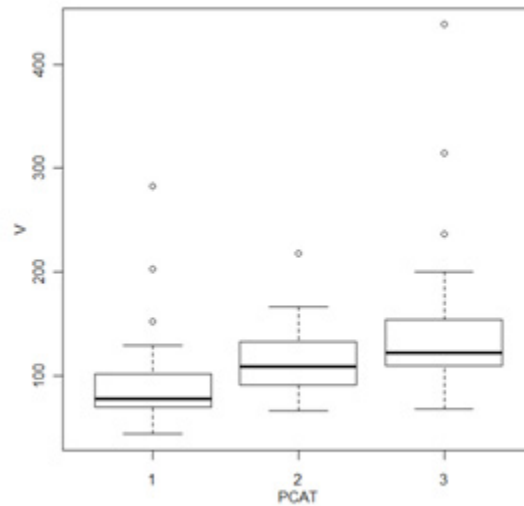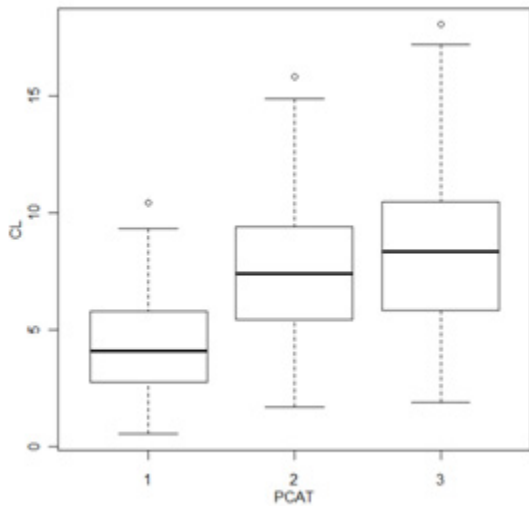
PCAT: 1= POST-PARTUM, 2= 2ND TRIMESTER, 3= 3RD TRIMESTER

Final Covariate Model

$$TVV = \theta_V \cdot (\theta_{3T\_V})^{PCAT3} \cdot (\theta_{2T\_V})^{PCAT2}$$

$$V/F = TVV \cdot e^{BSV_{V/F}}$$

$$TVCL = \theta_{CL} \cdot (\theta_{3T\_CL})^{PCAT3} \cdot (\theta_{2T\_CL})^{PCAT2} \cdot (RTV\_CL)$$

$$Cl/F = TVCL \cdot e^{BSV_{Cl/F}}$$

$$RTV\_CL = 1 - \left(\frac{I_{max} \cdot [RTV]_{obs}}{IC_{50} + [RTV]_{obs}} \right)$$

$$TVK_a = \theta_{Ka}$$

$$K_a = TVK_a \cdot e^{BSV_{Ka}}$$

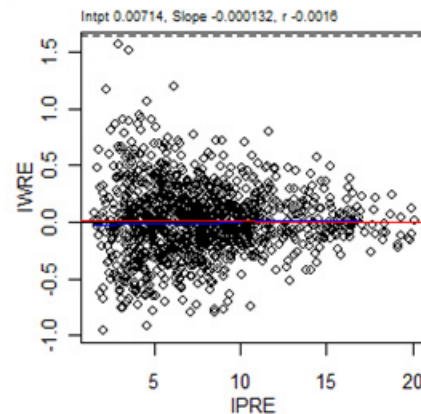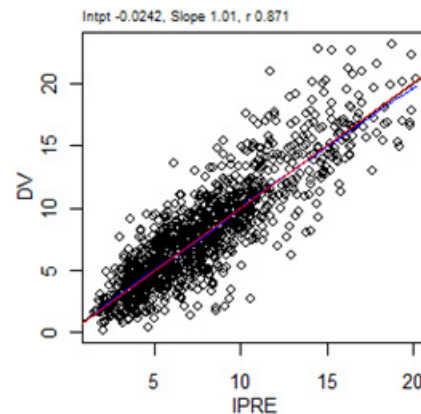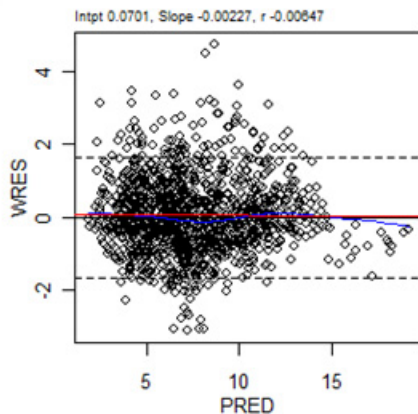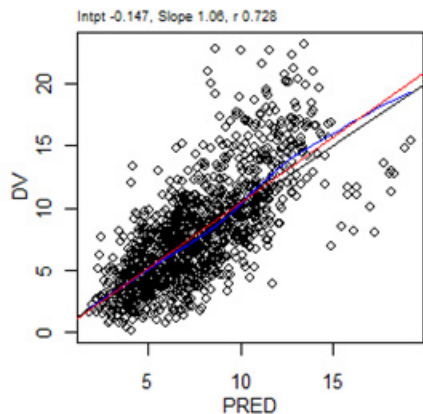$$F1 = 1 \cdot (\theta_{F\_TAB})^{(Form-1)}$$

Dichotomous Variables

(1 = Yes, 0 = No)

PCAT2 = 2nd trimester

PCAT3 = 3rd trimester

Form = Melt Extrusion Tablet

Intpt -0.147, Slope 1.06, r 0.728

Intpt 0.0701, Slope -0.00227, r -0.00647

Intpt -0.0242, Slope 1.01, r 0.871

Intpt 0.00714, Slope -0.000132, r -0.0016

Evaluation of Model Performance

Visual Predictive Check
Stratified by State of Pregnancy
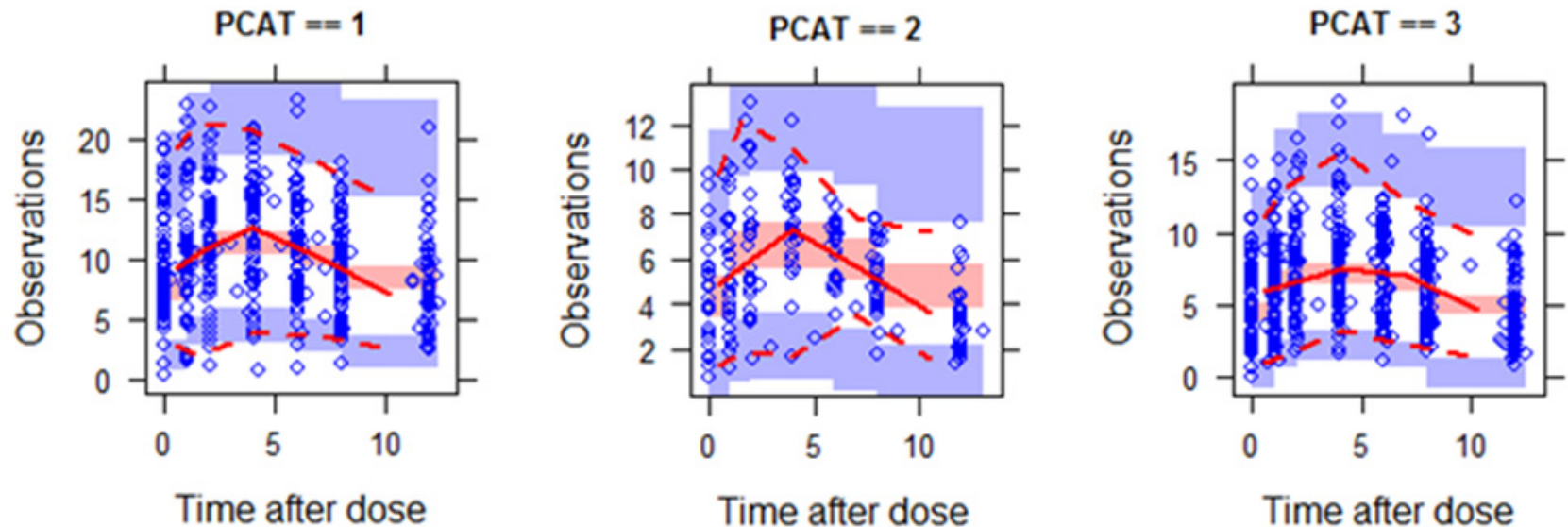
PCAT: 1= POST-PARTUM, 2= 2ND TRIMESTER, 3= 3RD TRIMESTER

RTV-Pregnancy Final Covariate Model Parameter Estimates Compared to Bootstrapping of 1200 Sample Runs

Parameter	Estimate	Bootstrap Mean	95% CI
OBJ FUNCTION	3427.786	3401.475	(3069.026, 3786.546)
CL/F (L/hr)	6.91	7.05	(5.14, 8.68)
BSV CL/F (%)	26.6	26.4	(17.1, 33.4)
V_2/F (L)	85	84.5	(60.4, 109.6)
BSV V/F (%)	42.7	42.1	(0, 62.1)
k_a (hr^{-1})	0.656	0.646	(0.440, 0.871)
BSV k_a (%)	39.6	43.4	(0, 67.0)
F_TAB	1.35	1.35	(1.21, 1.48)
3T_CL	1.73	1.72	(1.51, 1.95)
3T_V	1.55	1.62	(0.87, 2.23)
2T_CL	1.52	1.51	(1.26, 1.78)
2T_V	1.43	1.49	(0.64, 2.22)
RTV_CL Imax	1	0.999	(0.998, 1.001)
RTV_CL IC50	0.419	0.439	(0.155, 0.682)
Proportional Residual Variability (%)	19.8	19.6	(11.8, 25.4)
Additive Residual Variability	1.48	1.47	(0.92, 1.88)

Summary

- The melt extrusion tablet formulation of LPV/RTV had a relative lopinavir bioavailability 1.35-fold that of the soft gel capsule formulation.

- The effect of RTV plasma concentration on LPV CL/F was best modeled as a maximum inhibitory effect (I_{max}) direct response model. The IC50 for RTV inhibition of LPV clearance was 0.419 mcg/mL.

- The best fit LPV POP-PK model included stage of pregnancy covariates on LPV CL/F and V/F, as well as an I_{max} RTV covariate on LPV CL/F.

- Using the median plasma RTV concentrations from each cohort, the population predicted LPV apparent plasma clearances were:

  5.84 (2nd trimester) and 6.74 (3rd trimester) and 3.24 (postpartum) L/hr.

- The population predicted LPV apparent volumes of distribution were:

  122 (2nd trimester) and 132 (3rd trimester) and 85 (postpartum) L.

Conclusion

Altered LPV PK during pregnancy appears to be driven directly by pregnancy stage and indirectly by the effect of pregnancy on RTV PK.

References

1. Ter Heine, R et al. "An Integrated Pharmacokinetic Model for the Influence of CYP3A4 Expression on the In Vivo Disposition of Lopinavir and Its Modulation by Ritonavir." J Pharm Sci. 2011;100(3): 2508-2515.
2. Van Waterschoot, R et al. Br J Pharmacol. "Effects of Cytochrome P450 3A and the Drug Transporters P-Glycoprotein and MRP2 on the Pharmacokinetics of Lopnavir." 2010; 160: 1224-1233.
3. Dickinson, L et al. "Sequential Population Pharmacokinetic Modeling of Lopinavir and Ritonavir in Healthy Volunteers and Assessment of Different Dosing Strategies." Antimicrob Agents Chemother 2011; 55(6): 2775-2782.
4. Stek, A et al. "Reduced Lopinavir Exposure During Pregnancy." AIDS 2006; 20: 1931-1939.
5. Mirochnick, M et al. "Lopinavir Exposure With an Increased Dose During Pregnancy." J Acquir Immune Defic Syndr. 2008; 49(5): 485-491.
6. Best, BM el al. "Lopinavir Tablet Pharmacokinetics with an Increased Dose During Pregnancy." J Acquir Immune Defic Syndr. 2010; 54(4): 381-388
7. Cressey, TR et al. "Early Postpartum Pharmacokinetics of Lopinavir Initiated Intrapartum in Thai Women." Antimicrob Agents Chemother 2009; 53(5): 2189-2191.
8. Aweeka, FT et al. "Lopinavir Protein Binding in HIV-1-infected Pregnant Women." HIV Medicine 2010; 11: 232-238.
9. Bouillon-Pichault, M et al. "Population Analysis of the Pregnancy-Related Modifications in Lopinavir Pharmacokinetics and Their Possible Consequences for Dose Adjustment." J Antimicrob Chemother. 2009; 63: 1223-1232.

UCSD-Pfizer Fellowship Acknowledgements

UC San Diego	Pfizer La Jolla
• Edmund Capparelli, Joe Ma, David Adler, Williams Ettouati and Palmer Taylor	• Yazdi Pithavala, Ana Ruiz, Nagdeep Giri, Mike Tortorici, Naveed Shaik, Ying Chen, Diane Wang and Kourosh Parivar