Population Pharmacokinetics (PK) of Lopinavir During Pregnancy and Postpartum

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Oral Abstract Presentation
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Presented by:
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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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{4-9}
IMPAAACT Study 1026s Dataset

• 3 Arms of IMPAAACT 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, 1\textsuperscript{st} order absorption, 1\textsuperscript{st} 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\textsubscript{LPV} was attempted using a median normalized power model and a direct response $I_{\text{max}}$ 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]\text{plasma} on LPV CL/F, and choose best fit model.**

1. Attempt to add observed [Ritonavir]\text{plasma} as a direct continuous covariate on LPV CL/F and F.
2. Add effect of [Ritonavir]\text{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

<table>
<thead>
<tr>
<th>LPV POP-PK Model*</th>
<th>COVARIATES</th>
<th>OBJ FUNC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Compartment Base Model</td>
<td>F_Tab</td>
<td>4240.747</td>
</tr>
<tr>
<td>Pregnancy Covariate Model</td>
<td>F_Tab, 3T_CL, 3T_V, 2T_CL, 2T_V</td>
<td>3559.628</td>
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<tr>
<td>Fixed RTV I(_{\text{max}}) Covariate Model</td>
<td>F_Tab, 3T_CL, 3T_V, 2T_CL, 2T_V, Imax, IC50</td>
<td>3505.401</td>
</tr>
<tr>
<td>RTV I(_{\text{max}}) Covariate Model</td>
<td>F_Tab, 3T_CL, 3T_V, 2T_CL, 2T_V, Imax, IC50</td>
<td>3427.786</td>
</tr>
</tbody>
</table>

*All models contain the following PK parameters: CL/F, V/F, \(k_a\), and BSV \(\eta\)'s on each.

PCAT: 1= POST-PARTUM, 2= 2\(^{\text{ND}}\) TRIMESTER, 3= 3\(^{\text{RD}}\) TRIMESTER
Final Covariate Model

\[
TVV = \theta_v \cdot (\theta_{3T-v})^{PCAT3} \cdot (\theta_{2T-v})^{PCAT2} \\
V/F = TVV \cdot e^{BSV_{vf}} \\
TVCL = \theta_{Cl} \cdot (\theta_{3T-cl})^{PCAT3} \cdot (\theta_{2T-cl})^{PCAT2} \cdot (RTV\_CL) \\
Cl/F = TVCL \cdot e^{BSV_{clf}} \\
RTV\_CL = 1 - \left( \frac{l_{max} \cdot [RTV]_{obs}}{IC_{50} + [RTV]_{obs}} \right) \\
TVK_a = \theta_{K_a} \\
K_a = TVK_a \cdot e^{BSV_{ka}} \\
F1 = 1 \cdot (\theta_{F\_TAB})^{(Form-1)}
\]

Dichotomous Variables

(1 = Yes, 0 = No)
PCAT2 = 2\textsuperscript{nd} trimester
PCAT3 = 3\textsuperscript{rd} trimester
Form = Melt Extrusion Tablet
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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Bootstrap Mean</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OBJ FUNCTION</strong></td>
<td>3427.786</td>
<td>3401.475</td>
<td>(3069.026, 3786.546)</td>
</tr>
<tr>
<td>CL/F (L/hr)</td>
<td>6.91</td>
<td>7.05</td>
<td>(5.14, 8.68)</td>
</tr>
<tr>
<td>BSV CL/F (%)</td>
<td>26.6</td>
<td>26.4</td>
<td>(17.1, 33.4)</td>
</tr>
<tr>
<td>V2/F (L)</td>
<td>85</td>
<td>84.5</td>
<td>(60.4, 109.6)</td>
</tr>
<tr>
<td>BSV V/F (%)</td>
<td>42.7</td>
<td>42.1</td>
<td>(0, 62.1)</td>
</tr>
<tr>
<td>ka (hr⁻¹)</td>
<td>0.656</td>
<td>0.646</td>
<td>(0.440, 0.871)</td>
</tr>
<tr>
<td>BSV ka (%)</td>
<td>39.6</td>
<td>43.4</td>
<td>(0, 67.0)</td>
</tr>
<tr>
<td>F_TAB</td>
<td>1.35</td>
<td>1.35</td>
<td>(1.21, 1.48)</td>
</tr>
<tr>
<td>3T_CL</td>
<td>1.73</td>
<td>1.72</td>
<td>(1.51, 1.95)</td>
</tr>
<tr>
<td>3T_V</td>
<td>1.55</td>
<td>1.62</td>
<td>(0.87, 2.23)</td>
</tr>
<tr>
<td>2T_CL</td>
<td>1.52</td>
<td>1.51</td>
<td>(1.26, 1.78)</td>
</tr>
<tr>
<td>2T_V</td>
<td>1.43</td>
<td>1.49</td>
<td>(0.64, 2.22)</td>
</tr>
<tr>
<td>RTV_CL Imax</td>
<td>1</td>
<td>0.999</td>
<td>(0.998, 1.001)</td>
</tr>
<tr>
<td>RTV_CL IC50</td>
<td>0.419</td>
<td>0.439</td>
<td>(0.155, 0.682)</td>
</tr>
<tr>
<td>Proportional Residual Variability (%)</td>
<td>19.8</td>
<td>19.6</td>
<td>(11.8, 25.4)</td>
</tr>
<tr>
<td>Additive Residual Variability</td>
<td>1.48</td>
<td>1.47</td>
<td>(0.92, 1.88)</td>
</tr>
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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 ($I_{\text{max}}$) 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 $I_{\text{max}}$ 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.
## UCSD-Pfizer Fellowship

### Acknowledgements

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<tr>
<th>UC San Diego</th>
<th>Pfizer La Jolla</th>
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<tr>
<td>• Edmund Capparelli, Joe Ma, David Adler, Williams Ettouati and Palmer Taylor</td>
<td>• Yazdi Pithavala, Ana Ruiz, Nagdeep Giri, Mike Tortorici, Naveed Shaik, Ying Chen, Diane Wang and Kourosh Parivar</td>
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![UC San Diego Fellowship Members](image1)

![Pfizer La Jolla Fellowship Members](image2)