Early Postpartum Pharmacokinetics (PK) of Lopinavir (LPV) when Initiated Intrapartum in Thai Women: a substudy of the International Maternal Pediatric Adolescent AIDS Clinical Trial (IMPAACT) Group P1032 study

Tim R. Cressey¹,³, Russell Van Dyke², Gonzague Jourdain³,¹, Thanyawee Puthanakit⁴, Anuvat Roongpisuthipong⁵, Jullapong Achalapong⁶, Prapap Yuthavisuthi⁷, Sinart Prommas⁸, Nantasak Chotivanich⁹, Robert Maupin¹⁰, Elizabeth Smith¹¹, David E. Shapiro¹, Mark Mirochnick¹² for the IMPAACT P1032 Team

¹Harvard School of Public Health, Boston, MA, USA, ²Tulane University, New Orleans, LA, USA, ³Institut de Recherche pour le Développement (IRD), PHPT-IRD174, Faculty of Associated Medical Sciences, Chiang Mai University, Chiang Mai, Thailand, ⁴Research Institute Health Sciences, Chiang Mai University, Chiang Mai, Thailand, ⁵Sriraj Hospital, Bangkok, Thailand, ⁶Chiang Rai Prachanukoh Hospital, Chiang Rai, Thailand, ⁷Prapokklao Hospital, Chantaburi, Thailand, ⁸Bhumibol Adulyadej Hospital, Bangkok, Thailand, ⁹Chonburi Hospital, Chonburi, Thailand, ¹⁰Louisiana State University, New Orleans, LA, USA, ¹¹Pediatric Medicine Branch, Division of AIDS, National Institute of Allergy and Infectious Diseases, MD, USA, ¹²Boston University Medical School, Boston, MA, USA

*Contact Address: Program for HIV Prevention and Treatment (PHPT-IRD174), 29/7-8 Samlan Road, Soi 1 Prasing, Muang, Chiang Mai, 50205, Thailand

Telephone: +66 5381 4270, Fax: +66 5381 4269, E-mail: tim@phpt.org

Running title: Lopinavir pharmacokinetics in the early postpartum period
Abstract

Lopinavir exposure is reduced during the third trimester of pregnancy. We report the pharmacokinetics of standard lopinavir/ritonavir (LPV/r) dosing (400/100 mg, twice daily) in the immediate and early postpartum period when initiated during labor. In 16 HIV-infected Thai women the median (range) LPV AUC, Cmax and Cmin were 99.7 µg.h/ml (66.1-180.5), 11.2 µg/ml (8.0-17.5) and 4.6 µg/ml (1.7-12.5), respectively, 41 hours (12-74) after delivery. All women attained adequate LPV levels through 30 days postpartum. No serious adverse events were reported.
The addition of a short course intrapartum/postpartum antiretroviral treatment, such as zidovudine/lamivudine for 3 or 7 days (5) or single dose tenofovir/emtricitabine (2) can reduce the incidence of non-nucleoside reverse transcriptase inhibitors (NNRTI) resistance in HIV-infected pregnant women who receive a single intrapartum dose of nevirapine (SD-NVP) for the prevention of mother-to-child transmission of HIV, but the optimal choice and duration of such treatment remains unknown.

The IMPAACT P1032 clinical trial (NCT00109590; www.clinicaltrials.gov) conducted in Thailand is a phase II, 3 arm, randomized, open-label study investigating the efficacy of different short course intrapartum/postpartum antiretroviral regimens to reduce the incidence of nevirapine resistance following SD-NVP. One of the 3 regimens is a triple drug combination of zidovudine (ZDV), didanosine-enteric coated (ddI-EC) and lopinavir coformulated with low dose ritonavir (LPV/r), initiated intrapartum and continued for 30 days postpartum. LPV/r is a potent antiretroviral drug with a short plasma half-life and a high genetic barrier for the selection of viral resistance, making it an ideal choice to include in a short course intrapartum/postpartum antiretroviral regimen. However, studies in US pregnant women have shown a significant reduction in LPV plasma exposure with standard dosing (400/100 mg, twice daily) during the 3rd trimester (7) and it is unknown if these changes continue to affect LPV exposure in the immediate postpartum period. Due to this uncertainty a pharmacokinetic substudy was performed to assess if standard LPV dosing provided adequate exposure during the first 30 days postpartum. At the start of the P1032 trial women randomized to receive ZDV/ddI-EC plus LPV/r during delivery and for 30 days postpartum were scheduled for LPV/r pharmacokinetic assessment postpartum until 12 women had evaluable PK results available.
Study subjects received 300 mg ZDV at the onset of labor, once every 3 hours during labor, and then twice daily for 30 days postpartum; 250 mg ddI-EC (400 mg if body weight ≥60 kg) once daily and 400/100 mg LPV/r (soft-gel capsules) twice daily at the onset of labor, during labor and for 30 days postpartum. Within 72 hours after delivery, a pre-dose blood sample was drawn prior to the scheduled LPV/r dose, after which LPV/r was administered with food, and blood samples were collected at 1, 2, 4, 6, 8, and 12 hours after dosing. At day 30 postpartum, sampling was restricted to pre-dose, 2 and 4 hours post dose. Blood samples were centrifuged, the plasma removed, aliquoted and frozen at -70°C within one hour of collection. LPV/r plasma drug concentrations were performed ‘real-time’ using a high performance liquid chromatography assay (3). Pharmacokinetic parameters including AUC, Cmax, Tmax, and Cmin were calculated with WinNonLin (Version 5.2, Pharsight, USA) using non-compartment methods.

The target LPV area under the concentration-time curve (AUC) was ≥52 µg.h/ml, the 10th percentile for LPV AUC in non-pregnant adults (1, 6). If 3 or more of the first 6 women, or 4 or more of the 12 women, failed to meet the target, we would have 95% confidence that the true rate of pharmacokinetic failure exceeds 10% (i.e., the lower limit of the 90% confidence interval will exceed 10%). If either of these stopping criteria were met pharmacokinetic sampling would be repeated in 12 additional women at an increased dose of LPV/r 533/133 mg.

Adverse events were graded using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (Version 1.0, dated December 2004).

Eighteen women were scheduled for LPV/r PK sampling. No pharmacokinetic sampling was performed in 2 women; one of whom did not receive SD-NVP prior to delivery, and the other who immediately discontinued all study drugs after receiving a drug (methergine) prohibited by the protocol during labor. Sixteen women completed both LPV/r PK sampling...
visits but 2 women did not have evaluable PK results available at Day 30 postpartum due to suspected poor drug adherence. Two additional women were included beyond the target enrollment of 12 women because they had already been scheduled for LPV/r pharmacokinetic assessment when evaluable data on 12 women at both PK time points became available.

At study entry, the 16 women who had LPV/r PK sampling performed had a median (range) age of 27 years (18-38), HIV-1 RNA viral load of 3,369 copies/mL (<400-61,750) and CD4 cell count of 464 cells/mm$^3$ (292-844). Median weight was 58 kg (44-84) within 72 hours after delivery and 53 kg (41-79) at Day 30 postpartum.

Intensive PK sampling was started 47 hours (22-80) after LPV/r initiation (during labor) and 41 hours (12-74) after delivery. Individual LPV plasma concentration versus time curves are shown in Figure 1 and LPV/r pharmacokinetic parameters are presented in Table 1. All women had an LPV AUC above the target within 72 hours postpartum. The median $T_{\text{max}}$ for both LPV and RTV was 3.9 hours. Ritonavir pharmacokinetic parameters in the immediate postpartum were similar to those in HIV-infected adults at steady state. At day 30 postpartum, LPV/r pre-dose levels were significantly higher compared within 72 hours postpartum (Table 1). No serious adverse events were reported.

Given that an approximate 50% reduction in LPV exposure during the 3rd trimester compared to non-pregnant women (7) it is perhaps surprising that standard LPV/r dosing resulted in adequate LPV exposure for all women in this study. However, two factors may account for this difference. Firstly, two retrospective analyses of therapeutic drug monitoring databases have reported an inverse correlation between body weight and lopinavir concentrations (4, 8). Secondly, the timing of LPV initiation is different, i.e. antepartum versus intrapartum, and it is unclear how long the physiological changes affecting LPV exposure during pregnancy persist.
postpartum. Thus, the lower body weight and the timing of LPV/r treatment initiation in the reported study may facilitate higher LPV concentrations.

To maximize the efficacy of short course intrapartum/postpartum antiretroviral treatments to prevent the selection of NNRTI mutations postpartum, it is critical that adequate drug concentrations are rapidly attained and maintained throughout. Standard LPV/r dosing initiated intrapartum and continued for 30 days postpartum provided adequate LPV drug exposure in HIV-infected Thai women.
Acknowledgments

We would like to thank all the women who participated in the IMPAACT P1032 trial and the study staff conducting the protocol at the sites. Overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) was provided by the National Institute of Allergy and Infectious Diseases [U01 AI068632] and by the Eunice Kennedy Shriver National Institute of Child Health and Human Development. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Allergy and Infectious Diseases or the National Institutes of Health. This work was supported by Grant numbers U01AI069399, U01AI069399, U01AI069512 from the National Institute of Allergy and Infectious Diseases. Pharmaceutical support was provided from: Abbott Laboratories, GlaxoSmithKline, and Boehringer Ingelheim. Lopinavir and ritonavir for the antiretroviral drug assay were obtained through the NIH AIDS Research and Reference Program, Division of AIDS, NIAID, NIH.

IMPAACT P1032 Team: Chairs: Russell Van Dyke, Gonzague Jourdain; Vice Chair: Robert Maupin, Jr.; DAIDS Medical Officer: Elizabeth Smith; NICHD Medical Officer: Heather Watts; Clinical Trial Specialist: Jennifer Gardella, Lara Akinsanya; Statisticians: David E. Shapiro, Paula Britto; Field Representative: Maureen Shannon, Pra-ornsuda Sukrakanchana; Data Manager: Bonnie Zimmer; Virologist: Lisa Frenkel, Nicole Ngo-Giang-Huong, Walter A Scott; DAIDS Pharmacist: Paul Tran; Pharmacologists: Mark Mirochnick, Tim R. Cressey; Immunologist: Ann Melvin; Laboratory Technologist: Bill Kabat; Laboratory Data Manager: Travis Behm, Courtney Ashton; Liaison to PICL: Ruth Dickover; Investigators: Kenneth McIntosh, Anuvat Roongpisuthipong; Community Constituency Group Representative: Vinnie
Research Institute for Health Sciences (RIHES), Chiang Mai University, Chiang Mai:

Thanyawee Puthanakit, Virat Srisanshana, Linda Aurpibul, Chintana Khamrong, Nataporn Kosachunhanan, Kittipong Rungruengthanakit.

Sriraj Hospital, Bangkok: Nirun Vanprapar, Kulkanya Chokephaibulkit, Anuvat Roongpisuthipong, Wasana Prasitseubsai, Wimon Anansakunwatt, Pilaipan Puthavathana, Nongluck Seetapun, Nantaka Kongstan, Pirom noisumdaeng

PHPT-IRD174, Chiang Mai: Marc Lallemant, Gonzague Jourdain, Nicole Ngo-Giang-Huong, Tim R. Cressey, Pra-ornsuda Sukrakanchana, Kanchana Than-in-at, Dujrudee Chinwong, Nusara Krapunpongsakul, Wannipa Yenjai, Renoo Wongsrisai, Janjira Thonglo, Tiwacha Timakahan, Yardpiron Taworn, Suriyan Tanasri

Chiang Rai Prachanukoh Hospital, Chiang Rai: Patcharee Kantipong, Jullapong Achalapong, Angkana Sophon, Yupawan Thaweesombat, Chaiporn Kumluang

Chonburi Hospital, Chonburi, Thailand: Chureeratana Bowonwatanuwong, Nantasak Chotivanich, Ladda Argadamnuy, Kessarin Chaisiri, Prakit Yothipitak, Somrat Matchua
Prapokklao Hospital, Chantaburi, Thailand: Prapap Yuthavisuthi, Ubon Chanasit, Pisut Greetanukroh, Suteerat Srisupaluk, Paleerutch Kerdprasert,

Bhumibol Adulyadej Hospital, Bangkok, Thailand: Napawadee Impoolsup, Sinart Promma, Paleerutch Kerdprasert, Marina Thitathan, Titima Taweewattanapan
References


### Table 1:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Within 72 hours Postpartum (n=16)</th>
<th>At Day 30 Postpartum (n=14)</th>
<th>Within Subject Geometric Mean Ratio: 72 hrs/Day 30 (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lopinavir</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC₀-₁₂ (µg.hr/mL)</td>
<td>99.7 (66.3-180.5)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cₘₐₓ (µg /mL)</td>
<td>11.17 (8.01-17.52)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tₘₐₓ (hours)</td>
<td>3.9 (1.9-4.0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cₚₚₑᵈₑₛ (µg /mL)</td>
<td>6.08 (2.34-13.64)</td>
<td>9.17 (5.28-14.97)</td>
<td>0.66 (0.53-0.81)</td>
</tr>
<tr>
<td>C₂ₐₜ (µg /mL)</td>
<td>10.50 (5.87-17.53)</td>
<td>11.72 (7.42-19.88)</td>
<td>0.85 (0.70-1.04)</td>
</tr>
<tr>
<td>C₄ₐₜ (µg /mL)</td>
<td>10.78 (8.01-16.72)</td>
<td>12.96 (8.78-21.37)</td>
<td>0.81 (0.71-0.94)</td>
</tr>
<tr>
<td>C₁₂ₐₜ (µg /mL)</td>
<td>5.18 (1.68-12.54)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Ritonavir</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC₀-₁₂ (µg.hr/mL)</td>
<td>4.27 (1.54-7.89)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cₘₐₓ (µg /mL)</td>
<td>0.60 (0.33-1.33)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tₘₐₓ (hours)</td>
<td>3.9 (1.9-4.0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cₚₚₑᵈₑₛ (µg /mL)</td>
<td>0.16 (&lt;0.05-1.33)</td>
<td>0.29 (0.09-0.66)</td>
<td>0.54 (0.39-0.74)</td>
</tr>
<tr>
<td>C₂ₐₜ (µg /mL)</td>
<td>0.45 (0.14-1.33)</td>
<td>0.61 (0.15-1.45)</td>
<td>0.76 (0.60-0.98)</td>
</tr>
<tr>
<td>C₄ₐₜ (µg /mL)</td>
<td>0.58 0.18-1.33)</td>
<td>0.81 (0.21-3.11)</td>
<td>0.68 (0.50-0.93)</td>
</tr>
<tr>
<td>C₁₂ₐₜ (µg /mL)</td>
<td>0.10 (&lt;0.05-0.26)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Note**: Significantly lower by Wilcoxon signed-rank test: *p=0.009; †p=0.048; ‡p=0.038; §p=0.030; ‖p=0.030
Figure 1:

![Graph showing LPV concentration over time](image-url)
Table Footnotes

Table 1: Lopinavir and ritonavir pharmacokinetic parameters and plasma concentrations within 72 hours and at Day 30 postpartum after initiating 400/100 mg LPV/r intrapartum. Reported values median (range); GM: Geometric Mean
Figure Legends

Figure 1: Individual lopinavir plasma concentration versus time curves within 72 hours postpartum for 16 HIV-infected Thai women who initiated lopinavir/ritonavir (400/100 mg, twice daily) intrapartum.