# Lopinavir Tablet Pharmacokinetics With an Increased Dose During Pregnancy

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**Objective:** Reduced lopinavir concentrations have been demonstrated with use of the capsule formulation during the third trimester of pregnancy. This study determined lopinavir exposure with an increased dose of the new tablet formulation during the third trimester.

**Design:** International Maternal Pediatric Adolescent AIDS Clinical Trials 1026s is a prospective nonblinded pharmacokinetic study in HIV-infected pregnant women, including a cohort receiving 2 lopinavir/ritonavir tablets (400 mg/100 mg) twice daily during the second trimester, 3 tablets (600 mg/150 mg) twice daily during the third trimester, and 2 tablets (400 mg/100 mg) twice daily postdelivery through 2 weeks postpartum.

**Methods:** Steady-state 12-hour pharmacokinetic profiles were performed during pregnancy and at 2 weeks postpartum. Lopinavir and ritonavir were measured by reverse-phase high-performance liquid chromatography (detection limit, 0.09 mcg/mL).

**Results:** Thirty-three women were studied. Median lopinavir AUC for the second trimester (n = 11), third trimester (n = 33), and postpartum (n = 27) were 72, 96, and 133 mcg·hr/mL, respectively. Median minimum lopinavir concentrations were 3.4, 4.9, and 6.9 mcg/mL.

**Conclusions:** The higher lopinavir/ritonavir tablet dose (600 mg/150 mg) provided exposure during the third trimester similar to the average AUC (98 mcg·hr·mL$^{-1}$) in nonpregnant adults taking 400 mg/100 mg twice daily. The higher dose should be used during the second and third trimesters of pregnancy. Postpartum dosing can be reduced to standard dosing before 2 weeks postpartum.

**Key Words:** HIV, lopinavir, mother-to-child transmission, pharmacokinetics, pregnancy

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## INTRODUCTION

Antiretroviral agents are commonly administered to HIV-infected pregnant women to prevent mother-to-child transmission of HIV and to maintain the health of the pregnant woman.[1] Current US Public Health Service guidelines on the management of HIV-infected women during pregnancy recommend use of a combination regimen including 2 nucleoside reverse transcriptase inhibitors and either 1 protease inhibitor or one nonnucleoside reverse transcriptase inhibitor.[2] Among the recommended first-line protease inhibitors is the combination of lopinavir and ritonavir, which is available only as the fixed dose combination formulation Kaletra.

Previous studies of the pharmacokinetics of several protease inhibitors during pregnancy have demonstrated reduced plasma drug exposure in pregnant women.[2,3] We have recently shown that administration of lopinavir/ritonavir during the third trimester of pregnancy using the capsule formulation (lopinavir 133 mg/ritonavir 33 mg) at the standard

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adult dose of 3 capsules (lopinavir 400 mg/ritonavir 100 mg) twice daily resulted in plasma concentrations approximately 50% of those seen in nonpregnant adults.[4] An increased dose of the capsule formulation during the third trimester (lopinavir 533 mg/ritonavir 133 mg; 4 capsules twice daily) provided exposure during pregnancy similar to that observed in nonpregnant adults.[5] However, at 2 weeks postpartum, the increased capsule dose yielded concentrations approximately double those seen with standard dosing in nonpregnant adults, suggesting that after lopinavir dosing is increased in the third trimester, it may be reduced to the standard dose before 2 weeks postpartum. The capsule formulation of lopinavir/ritonavir is no longer available. The new tablet formulation is manufactured with 200 mg lopinavir and 50 mg ritonavir in each tablet, and the standard dose is 2 tablets (lopinavir 400 mg/ritonavir 100 mg) twice daily. The purpose of the current study was to describe lopinavir pharmacokinetics during the third trimester of pregnancy with administration of an increased dose of 3 tablets (lopinavir 600 mg/ritonavir 150 mg) twice daily.

## METHODS

International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network Protocol 1026s is a multicenter prospective study to evaluate the pharmacokinetics of antiretrovirals among pregnant HIV-infected women. This report includes women receiving lopinavir/ritonavir tablets. P1026s is a substudy of P1025, a prospective cohort study of HIV-infected pregnant women receiving care at IMPAACT sites.

Eligibility criteria for this lopinavir arm of P1026s were enrollment in IMPAACT P1025, initiation as part of clinical care either standard dose lopinavir/ritonavir before 26 weeks gestation or the increased dose before the beginning of the 35th week of gestation. Exclusion criteria were: concurrent use of medications known to interfere with the absorption, metabolism or clearance of lopinavir or ritonavir, multiple gestation, and clinical or laboratory toxicity that, in the opinion of the site investigator, would likely require a change in the medication regimen during the study. Local institutional review boards approved the protocol at all participating sites, and signed informed consent was obtained from all subjects before participation. Subjects continued to take their prescribed medications throughout the course of their pregnancies. The choice of additional antiretrovirals was determined by the subject's physician, who prescribed all medications and remained responsible for her clinical management throughout the study. Women continued on study until the completion of postpartum pharmacokinetic sampling.

For women enrolling during the second trimester of pregnancy, lopinavir pharmacokinetics with the standard dose of 2 tablets (lopinavir 400 mg/ritonavir 100 mg) were determined in real time between 20 and 26 weeks gestation. At 30 weeks gestation, the lopinavir dose was increased to 3 tablets (lopinavir 600 mg/ritonavir 150 mg) twice daily, and pharmacokinetic sampling was repeated between 30 and 36 weeks gestation. Women enrolling in the third trimester received the increased dose of 3 tablets (lopinavir 600 mg/ritonavir 150 mg) and had pharmacokinetic sampling performed between 30 and 36 weeks gestation. Subjects continued on the increased dose through the end of their hospital stay for delivery. Upon hospital discharge, doses were reduced to 2 tablets (lopinavir 400 mg/ritonavir 100 mg) twice daily through the postpartum pharmacokinetic sampling at two weeks after delivery. Lopinavir area under the concentration versus time curve ($AUC_{0–12}$) was calculated for each woman and compared with the lopinavir $AUC_{0–12}$ in nonpregnant adult populations taking the standard dose.[5] Each subject's physician was notified of the subject's plasma concentrations and $AUC_{0\text{-}12}$ within 2 weeks of sampling. If the $AUC_{0–12}$ was below the 10th percentile in nonpregnant adult populations (52 mcg·hr·mL$^{-1}$), the physician was offered the option of discussing the results and possible dose modifications with a study team pharmacologist.

### Clinical and Laboratory Monitoring

HIV-related laboratory testing was performed as part of the parent study (P1025) and as part of routine clinical care. Maternal data from P1025 accessed for this analysis were maternal age, ethnicity, weight, concomitant medications, CD4, and plasma viral load assay results. Plasma viral load assays had lower limits of detection ranging from less than 20 copies per milliliter to less than 400 copies per milliliter. Infant data included birth weight, gestational age at birth, and HIV infection status as determined by the P1025 protocol team according to Centers for Disease Control and Prevention criteria.[6] Maternal clinical and laboratory toxicities were assessed through clinical evaluations (history and physical examination) and laboratory assays (alanine aminotransferase, aspartate aminotransferase, creatinine, BUN, albumin, bilirubin, hemoglobin) on each pharmacokinetic sampling day and at delivery. The study team reviewed toxicity reports on monthly conference calls, although the subject's physician was responsible for toxicity management. The Division of AIDS (DAIDS)/NIAID Toxicity Table for Grading Severity of Adult Adverse Experiences was used to report adverse events for study subjects.[7] All toxicities were followed through resolution.

### Sample Collection

Subjects were stable on their antiretroviral regimen for at least 2 weeks before pharmacokinetic sampling. The timing of dosing for the 3 days before and the day of the pharmacokinetic evaluation were the same and were the same for the pharmacokinetic evaluations performed during pregnancy and postpartum. Seven plasma samples were drawn at the second trimester, third trimester, and at the postpartum pharmacokinetic evaluation visits, starting immediately before the morning oral lopinavir dose and at 1, 2, 4, 6, 8, and 12 hours postdose. Lopinavir was given as an observed dose after a standardized meal of approximately 850 kilocalories, with approximately 55% of calories from fat. Other information collected included the time and description of the 2 most recent meals and maternal height and weight. A single maternal plasma sample and an umbilical cord sample after the cord was clamped were collected at delivery.

## Drug Assays

Lopinavir and ritonavir were measured by the University of California, San Diego Pediatric Clinical Pharmacology Laboratory using a validated reversed-phase multiplex high-performance liquid chromatography method. The lower limit of detection was 0.091 mcg/mL for lopinavir and 0.094 mcg/mL for ritonavir. The interassay coefficient of variation was 10.9% at the limit of detection for both drugs and was <10% coefficient of variation for low, middle, and high controls. Overall recovery from plasma was 98% for lopinavir and 117.3% for ritonavir. The University of California, San Diego Pediatric Clinical Pharmacology Laboratory has been enrolled in the AIDS Clinical Trials Group Quality Assurance/Quality Control proficiency testing program since 2001, which tests samples twice a year.[8]

## Pharmacokinetic Analyses

The predose concentration ($C_{predose}$), maximum plasma concentration ($C_{max}$), corresponding time ($T_{max}$), minimum plasma concentration ($C_{min}$), corresponding time ($T_{min}$), and 12-hour postdose concentration ($C_{12h}$) were determined by direct inspection. For concentrations below the assay limit of detection, a value of one-half of the detection limit (0.045 mcg/mL for lopinavir, 0.047 mcg/mL for ritonavir) was used in summary calculations. $AUC_{0-12}$ during the dose interval (from time 0 to 12 hours postdose) for lopinavir and ritonavir were estimated using the trapezoidal rule. Apparent clearance (CL/F) from plasma was calculated as dose divided by $AUC_{0-12}$. Half-life was calculated as dose divided by the terminal slope of the curve ($\lambda_z$), and apparent volume of distribution ($V_d/F$) was determined by CL/F divided by $\lambda_z$.

Both $V_d/F$ and CL/F were also estimated using a 1-compartment model in the software program WinNonlin, version 5.0.1 (Pharsight Corporation, Mountain View, CA). Pharmacokinetic parameters derived from each approach were compared to assess potential limitations of each methodology.

## Statistical Analyses

Target enrollment for the increased dose lopinavir arm of P1026s was at least 25 women with evaluable third trimester pharmacokinetics. Enrollment then continued to obtain at least 10 women with second trimester evaluations. To prevent ongoing enrollment of subjects receiving inadequate dosing, enrollment was to be stopped early if 6 study subjects had third trimester lopinavir $AUC_{0-12}$ below the estimated 10th percentile for the nonpregnant historical controls (52 mcg·hr·mL$^{-1}$). The statistical rationale for this early stopping criterion has been previously described.[4]

Within-subject pair-wise comparisons between second trimester, third trimester, and postpartum lopinavir and ritonavir pharmacokinetic parameters were performed, using 90% confidence limits for the geometric mean ratio of the parameter in pregnant versus nonpregnant conditions. When the true geometric mean of the ratio (the antilog of the true mean of the log ratios) of the pharmacokinetic parameters for pregnant and nonpregnant conditions has a value of 1, this indicates equal geometric mean pharmacokinetic parameters for the pregnant and nonpregnant conditions. If the 90% confidence intervals (CIs) are entirely outside the limits (0.8 and 1.25), the pharmacokinetic parameters for the pregnant and nonpregnant conditions are considered different. If, on the other hand, the 90% confidence limits are entirely within the limits (0.8 to 1.25), the drug exposures are considered equivalent. If the 90% CI overlaps with (0.8 to 1.25), these data alone do not support any conclusions. The differences in pharmacokinetic parameters ante- and postpartum were also assessed with the Wilcoxon signed-rank test. Descriptive statistics were calculated for pharmacokinetic parameters of interest during each study period.

# RESULTS

## Subject Characteristics and Outcomes

Thirty-three women were enrolled between April 2006 and June 2008. Pharmacokinetic sampling was completed during the second trimester in 11, during the third trimester in 33, and at 2 weeks postpartum in 27. The clinical characteristics of the subjects and their pregnancy outcomes are presented in Table 1. Grade 3 or 4 toxicities were noted in 8 subjects, including elevated glucose, elevated aspartate aminotransferase, elevated alanine aminotransferase, elevated lipase, nose bleed, uterine rupture, supraventricular tachycardia, and placental abruption. Only the elevated lipase was considered to be related to lopinavir/ritonavir use. Plasma viral load at delivery was less than 400 copies per milliliter in 23 of 26 subjects. Delivery viral load data were not available for 7 women. Thirty-one infants are uninfected; infection status was indeterminate for 2 infants.

## Lopinavir and Ritonavir Exposure

Lopinavir and ritonavir pharmacokinetic parameters during pregnancy and postpartum are presented in Table 2. Lopinavir concentrations increased with the increase in dose from the second to the third trimester. Despite a decrease back to the standard dose, lopinavir concentrations were highest at the postpartum visit (Fig. 1). Lags in lopinavir absorption were noted in 5 of 11 (45%), 18 of 33 (55%), and 5 of 27 (19%) subjects in the second trimester, third trimester, and postpartum, respectively. An absorption lag was significantly more likely to occur in the third trimester compared with postpartum ($P = 0.006$).

The target lopinavir $AUC_{0-12}$ during pregnancy was at least 52 mcg·hr·mL$^{-1}$, the estimated 10$^{th}$ percentile $AUC_{0-12}$ based on available data from non-pregnant adults.[9] The 50th percentile lopinavir $AUC_{0-12}$ in non-pregnant adults taking capsules is 82.8 mcg·hr·mL$^{-1}$.[9] Nine of the 11 (82%) subjects studied during the second trimester exceeded the 10th percentile $AUC_{0-12}$ target, compared with 30 of 33 (91%) third trimester subjects and all 27 (100%) postpartum subjects (Fig. 2). Lopinavir concentration 12 hours after the witnessed dose (evening trough) exceeded 1.0 mcg/mL in all subjects during pregnancy and postpartum. The predose concentration (morning trough) was below 1.0 mcg/mL in 2 subjects at the second trimester, 2 different subjects at the third trimester, and another 2 different subjects at the postpartum visit.

The geometric mean third trimester/postpartum lopinavir $AUC_{0-12}$ ratio was 0.73 (90% CI, 0.63 to 0.84) (Fig. 2; Table 3). The geometric mean third trimester/postpartum lopinavir and

**TABLE 1.** Subject Characteristics

| Characteristic | n (%) | Median (Range) |
|---|---|---|
| Age (yrs) | 33 | 30.5 (18.4–39.1) |
| Gestational age at second trimester study visit | 11 | 24.4 (20.6–26.4) |
| Gestational age at third trimester study visit | 32 | 34.8 (30.3–37.4) |
| Weight at delivery (kg) | 28 | 77.8 (52.5–123.9) |
| Weeks after delivery at postpartum study visit | 25 | 2.7 (1.9–3.7) |
| Weight 2 weeks postpartum (kg) | 25 | 72.5 (49.7–100.8) |
| $CD4^+$ at delivery (cells/μL) | 31 | 374 (93–1554) |
| Race/ethnicity | | |
| Black Non-Hispanic | 7 (21) | — |
| Hispanic | 20 (61) | — |
| White non-Hispanic | 6 (18) | — |
| Concomitant medications | | |
| Zidovudine + lamivudine | 17 (52) | — |
| Zidovudine + lamivudine + abacavir | 9 (27) | — |
| Other* | 7 (21) | — |
| Third trimester plasma HIV-1 RNA concentration (copies/mL) | 29 | <50 (<20–63,944) |
| Undetectable (<20, 50, 75, or 400)† | 25 (86) | — |
| Detectable (≥400) | 4 (14) | — |
| Delivery plasma HIV-1 RNA concentration (copies/mL) | 26 | <200 (<50–36,739) |
| Undetectable (<50, 75, 200, or 400)‡ | 23 (88) | — |
| Detectable (≥50) | 3 (12) | — |
| Postpartum plasma HIV-1 RNA concentration (copies/mL) | 19 | 52.5 (<20–79,068) |
| Undetectable (<20, 50, 200, or 400)§ | 14 (74) | — |
| Detectable (>400) | 5 (26) | — |
| Pregnancy outcome | | |
| Gestational age at delivery (wks) | 33 | 38.4 (34–41) |
| Birth weight (g) | 33 | 3053 (1935–3755) |

*Other concomitant medications included: stavudine, didanosine, emtricitabine, tenofovir, and nevirapine.

†Two subjects were <20; 15 were <50; 2 were <75; 6 were <400 copies per milliliter.

‡Nine subjects were <50; 2 were <75; 4 were <200; 8 were <400 copies per milliliter.

§One subject was <20; 8 were <50; 2 were <200; 3 were <400 copies per milliliter.

ritonavir oral clearance and apparent volume of distribution ratios fell completely outside of (above) the limits of 0.8 and 1.25, showing that third trimester CL/F and Vd/F were higher than postpartum. Within-subject comparisons of $AUC_{0–12}$, CL/F, Vd/F, $C_{min}$, $C_{max}$, and $C_{12h}$ showed that postpartum lopinavir exposure was higher and CL/F was lower than in the third trimester ($P \leq 0.05$ for all comparisons), even though the postpartum dose was 33% lower than the third trimester dose.

The lopinavir geometric mean $AUC_{0–12}$ ratios of second trimester/third trimester and second trimester/postpartum were 0.77 (90% CI: 0.64 to 0.92) and 0.51 (90% CI: 0.42 to 0.63), respectively. Within-subject comparisons of $AUC_{0–12}$, $V_d$/F, $C_{min}$, $C_{predose}$, $C_{12h}$, and $t_{½}$ were significantly lower in the second trimester compared with the third trimester ($P < 0.05$). Within-subject comparisons of $AUC_{0–12}$, Cl/F, $C_{min}$, $C_{max}$, $C_{predose}$, $C_{12h}$, and $t_{½}$ also showed significantly lower lopinavir exposure in the second trimester compared with postpartum ($P < 0.05$). For ritonavir, similar to lopinavir, the third trimester $AUC_{0–12}$, $C_{min}$, and $C_{max}$ were lower and CL/F and $V_d$/F were higher than at the postpartum visit ($P \leq 0.05$ for all comparisons). The second trimester ritonavir $AUC_{0–12}$, $C_{predose}$, $C_{12h}$, and $t_{½}$ were also lower than the third trimester and postpartum values ($P \leq 0.05$).

The 1-compartment analysis yielded similar lopinavir exposure patterns to the noncompartmental analysis. The 1-compartment median (range) second trimester, third trimester, and postpartum CL/F values were 3.9 L/hr (2.9–6.5 L/hr), 4.3 L/hr (0.02–11.6 L/hr), and 2 L/hr (0.4–4.9 L/hr), respectively. The corresponding $V_d$/F estimated values were 30 L (17–48 L), 35 L (20–128 L), and 21 L (11–33 L).

Maternal plasma and umbilical cord samples were collected at delivery for 26 subjects. One pair was below the assay detection limit in both the maternal and umbilical cord samples.

The median (range) maternal and cord blood lopinavir concentrations were 5.2 mcg/mL (<0.091–12.2 mcg/mL) and 1 mcg/mL (<0.091–4.2 mcg/mL), respectively. The median (range) cord blood/maternal sample concentration ratio was 0.2 (0.04–0.97). A single subject had cord blood concentrations almost equal to the maternal sample concentrations (cord blood lopinavir = 1.8 mcg/mL, maternal plasma lopinavir = 1.9 mcg/mL, ratio = 0.97); all other subjects had less than 60% of the maternal lopinavir concentration detected in the cord blood.

## DISCUSSION

Our first study of lopinavir/ritonavir analyzed complete pharmacokinetic profiles in 17 US women taking standard doses of the soft-gel capsules (3 capsules—400/100 mg twice daily) during the third trimester and postpartum.[4] Standard dosing with the capsule formulation resulted in third trimester lopinavir plasma concentrations and AUCs that were approximately 50% lower than those seen in nonpregnant adults, but 6 week postpartum lopinavir plasma exposure equivalent to that seen in nonpregnant adults.[4] Trough concentrations during the third trimester with standard capsule dosing were below 1000 ng/mL, the usual standard used in therapeutic drug monitoring programs for antiretroviral-naive patients, in 2 of 17 women (12%). Other studies of standard dosing with lopinavir/ritonavir soft-gel capsules in pregnant women have looked only at trough concentrations and have found subtherapeutic values in 6%–25% of third trimester pregnant women receiving standard dosing with lopinavir/ritonavir soft-gel capsules.[10–13]

Our follow-up study described lopinavir/ritonavir complete pharmacokinetic profiles after an increased dose of 4 capsules (533/133 mg twice daily) during the third trimester through 2 weeks postpartum.[5] These subjects had a median third trimester AUC of 87.5 $mcg \cdot hr \cdot mL^{-1}$, nearly equal to the 50th percentile lopinavir AUC in non-pregnant historical controls of 82.8 $mcg \cdot hr \cdot mL^{-1}$.[9,14] None of the third trimester

**TABLE 2.** Median (Range) Lopinavir and Ritonavir Noncompartmental Pharmacokinetic Parameters

| | | Second Trimester, 400 mg/100 mg, n = 11 | Third Trimester, 600 mg/150 mg, n = 33 | Postpartum, 400 mg/100 mg, n = 27 |
|---|---|---|---|---|
| Lopinavir | $AUC_{0-12}$ (mcg·hr·mL$^{-1}$) | 72 (47–93)*† | 96 (43–198)‡ | 133 (66–237) |
| | $C_{predose}$ (mcg/mL) | 5.3 (0.2–7.3)*† | 6.7 (<0.091–14.8) | 8.7 (<0.091–17.6) |
| | $C_{max}$ (mcg/mL) | 8.4 (7.1–10.9)† | 10.7 (5.8–19.1)‡ | 14.6 (9.8–22.8) |
| | $T_{max}$ (hr) | 4 (1–4) | 4 (0–8)‡ | 4 (0–8) |
| | $C_{12h}$ (mcg/mL) | 3.7 (2.2–4.4)*† | 5.1 (1.5–12.2)‡ | 7.2 (2.8–21) |
| | $C_{min}$ (mcg/mL) | 3.4 (0.2–4.4)*† | 4.9 (<0.091–12.2)‡ | 6.9 (<0.091–12.4) |
| | $T_{min}$ (hr) | 12 (0–12) | 12 (0–12) | 12 (0–12) |
| | CL/F (L/hr) | 5.6 (4.3–8.6)† | 6.2 (3–14)‡ | 3.0 (1.7–6) |
| | $V_d$/F (L) | 41 (31–81)* | 59 (32–2163)‡ | 34 (15–122) |
| | $t½$ (hr) | 5.5 (4.1–9.6)*† | 7.9 (3–127) | 7.4 (3.5–33) |
| Ritonavir | $AUC_{0-12}$ (mcg·hr·mL$^{-1}$) | 3.6 (1.2–5.1)† | 4.2 (1.6–19.9)‡ | 5.9 (3.5–18.3) |
| | $C_{pre-dose}$ (mcg/mL) | 0.22 (<0.094–0.35)*† | 0.20 (<0.094–1.25) | 0.30 (<0.094–1.59) |
| | $C_{max}$ (mcg/mL) | 0.49 (0.16–0.81)† | 0.66 (0.19–2.32)‡ | 0.93 (0.41–3.34) |
| | $T_{max}$ (hr) | 4 (1–8) | 4 (0–8) | 4 (0–12) |
| | $C_{12h}$ (mcg/mL) | 0.17 (<0.094–0.21)*† | 0.19 (<0.094–1.12) | 0.23 (<0.094–1.17) |
| | $C_{min}$ (mcg/mL) | 0.13 (<0.094–0.18)† | 0.14 (<0.094–1.12)‡ | 0.21 (<0.094–0.73) |
| | $T_{min}$ (hr) | 12 (0–12) | 6 (0–12) | 12 (0–12) |
| | CL/F (L/hr) | 28 (20–85)† | 48 (10–128)‡ | 17 (6–29) |
| | $V_d$/F (L) | 158 (78–415)* | 309 (124–10967)‡ | 113 (36–3075) |
| | $t½$ (hr) | 3.4 (1.6–8.8)*† | 4.8 (2–59.6) | 5.4 (2.7–116) |

*$P < 0.05$, second trimester compared with third trimester.
†$P < 0.05$, second trimester compared with postpartum.
‡$P < 0.05$, third trimester compared with postpartum.
$AUC_{0-12}$ = area under the plasma concentration–time curve.
$C_{pre-dose}$ = predose concentration.
$C_{max}$ = maximum concentration.
$T_{max}$ = time postdose of maximum concentration.
$C_{12h}$ = 12-hour postdose concentration.
$C_{min}$ = minimum concentration.
$T_{min}$ = time postdose of minimum concentration.
CL/F = oral clearance.
$V_d$/F = apparent volume of distribution.
$t½$ = half-life.

subjects had excessive lopinavir exposure on this higher dose, and only a few had a lopinavir AUC below the target of the 10th percentile AUC in nonpregnant adults. Median second trimester AUC was lower than expected (57.3 mcg·hr·mL$^{-1}$), with 3 of 8 subjects below the nonpregnant 10th percentile. However, median lopinavir AUC at 2 weeks postpartum on the increased capsule dose was nearly double that seen during the third trimester, suggesting that by 2 weeks postpartum, the pregnancy-related changes in lopinavir disposition that result in decreased plasma concentrations have resolved.

Lopinavir/ritonavir soft-gel capsules are no longer available and have been replaced by a tablet formulation. Studies of standard lopinavir/ritonavir doses with the tablet in both nonpregnant and pregnant adults report similar overall exposure compared with the capsule (tablet AUC is ~18% higher than capsule) but with less variability.[15,16] This current study reports lopinavir/ritonavir full pharmacokinetic profiles with standard doses of 2 tablets (lopinavir 400 mg/ritonavir 100 mg) twice daily in the second trimester and at 2 weeks postpartum and with an increase to 150% of the standard dose by using 3 tablets (lopinavir 600 mg/ritonavir 150 mg) twice daily during the third trimester. Overall exposure was lowest in the second trimester. With the increased dose in the third trimester, lopinavir AUC was equivalent to that seen in nonpregnant adults taking standard doses of the tablet [96 mcg·hr·mL$^{-1}$ in this study versus 98 mcg·hr·mL$^{-1}$ (18% higher than 82.8 mcg·hr·mL$^{-1}$)]. A striking finding of our study is that lopinavir exposure with the *increased* dose of 3 tablets during the third trimester of pregnancy is still *lower* than that seen in these same women on the *standard* dose of 2 tablets at 2 weeks postpartum. Second trimester lopinavir exposure on standard doses was significantly lower than that seen postpartum in these women by both within-subject comparisons and bioequivalence standards (geometric mean ratios and CIs). As expected, ritonavir exposure followed similar patterns.

Lopinavir is metabolized primarily by cytochrome P450 3A4. Induction of this pathway during pregnancy likely contributes to the observed decreased lopinavir exposure. Cytochrome 3A4 induction has been documented previously in pregnant women; 1 recent study demonstrated 35% increased cytochrome P450 3A activity throughout pregnancy.[17] Decreased lopinavir exposure during pregnancy could also be explained by pregnancy-related changes in lopinavir absorption or inadequate ritonavir boosting. Alterations in gastrointestinal function with pregnancy may have altered lopinavir or ritonavir absorption. Lopinavir is also a substrate

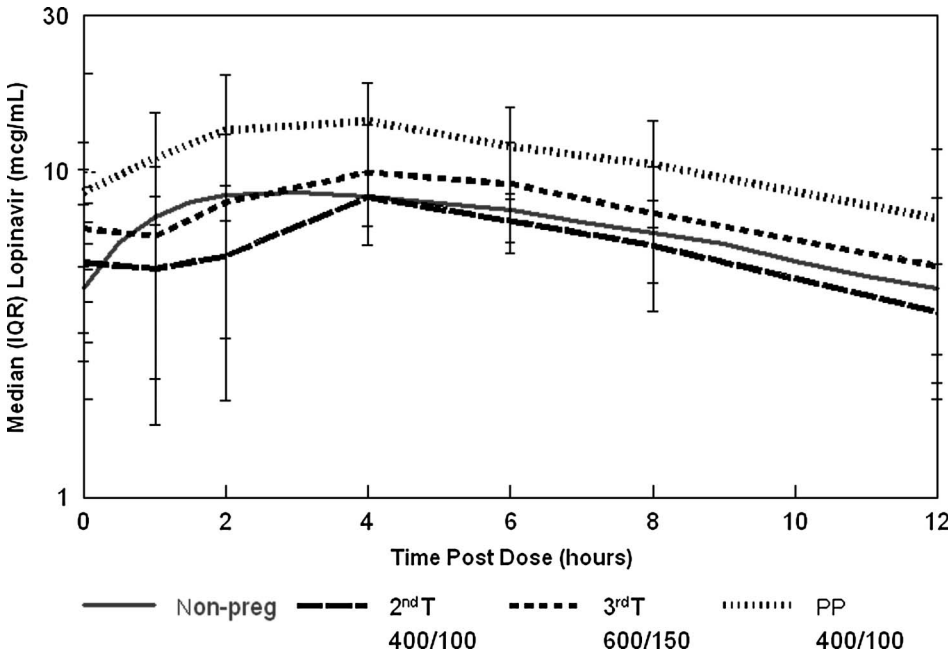


**FIGURE 1.** Median lopinavir concentrations during second trimester, third trimester, and postpartum. Median lopinavir concentration–time curves ± interquartile range during the second trimester (long dashed line, n = 11), third trimester (medium dashed line, n = 33), and postpartum (fine dashed line, n = 27). The solid line represents the expected (50th percentile) concentration–time profile in nonpregnant adults.

for the drug transporter p-glycoprotein, an inducible protein that limits the oral bioavailability of substrates. Thus, decreased oral bioavailability of lopinavir could be a result of increased intestinal p-glycoprotein activity during pregnancy. Without an intravenous lopinavir preparation for comparison, the relative contribution of changes in lopinavir bioavailability versus intrinsic clearance cannot be determined.

Lopinavir is highly bound (98%–99%) to plasma proteins, including albumin and alpha-1 acid glycoprotein (AAG), with its affinity to AAG higher than its affinity to albumin.[14] As with all highly bound drugs, small changes in protein binding may have a large effect on the concentration of free (unbound) drug, which is the pharmacologically active moiety. Protein binding may be reduced during pregnancy due to dilutional decreases in plasma protein concentrations and competitive inhibition from corticosteroid hormones.[18,19] We have recently reported data describing lopinavir protein binding during pregnancy and postpartum using samples from subjects enrolling in our 2 previous studies.[20] Lopinavir protein binding was reduced during pregnancy compared with postpartum, resulting in a 17% increase in the free fraction of lopinavir during the third trimester. The reduction in lopinavir protein binding correlated with lower AAG concentrations observed in the third trimester. A reduction in protein binding of this magnitude will compensate for only a portion of the decrease in lopinavir exposure associated with pregnancy.

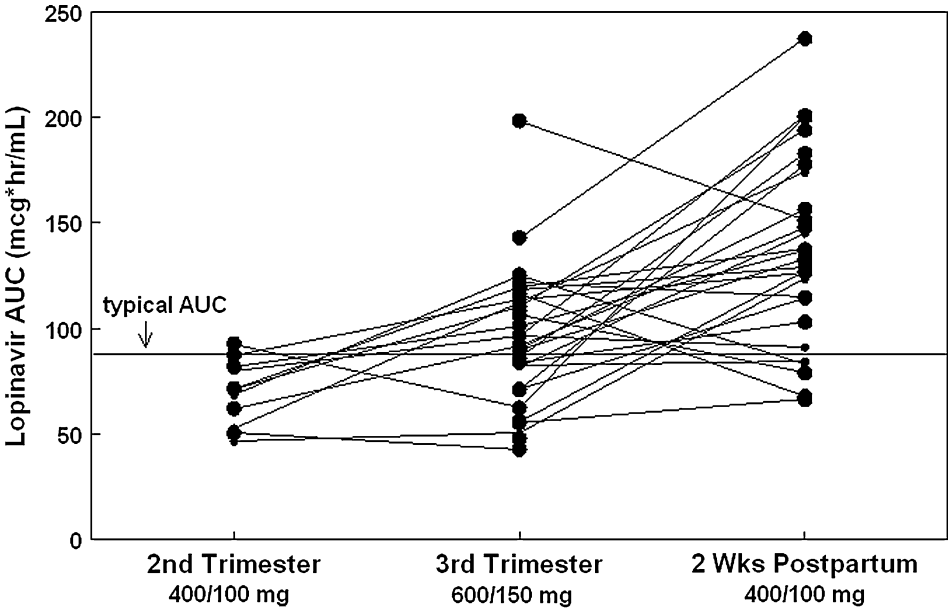


**FIGURE 2.** Lopinavir AUC second trimester, third trimester, and postpartum. Changes in lopinavir area under the concentration–time curves from the second trimester to the third trimester to postpartum (n = 27). The solid line indicates typical value (50th percentile) AUC of tablets in nonpregnant adults of 93 mcg·hr/mL.

**TABLE 3.** Lopinavir and Ritonavir Pharmacokinetic Parameter Geometric Mean (90% CI) Ratios

| | | Second Trimester/Third Trimester, n = 11 | Second Trimester/Postpartum, n = 10 | Third Trimester/Postpartum, n = 27 |
|---|---|---|---|---|
| Lopinavir | $AUC_{0\text{-}12}$ (mcg·hr·mL$^{-1}$) | 0.77 (0.64–0.92) | 0.51 (0.42–0.63)* | 0.73 (0.63–0.84) |
| | $C_{pre\text{-}dose}$ (mcg/mL) | 0.54 (0.3–0.96) | 0.32 (0.16–0.68)* | 0.85 (0.46–1.58) |
| | $C_{max}$ (mcg/mL) | 0.88 (0.71–1.1) | 0.57 (0.48–0.68)* | 0.73 (0.62–0.85) |
| | $T_{max}$ (hr) | 0.72 (0.52–1) | 0.93 (0.66–1.33) | 1.36 (1.05–1.76) |
| | $C_{12h}$ (mcg/mL) | 0.67 (0.53–0.85) | 0.45 (0.32–0.63)* | 0.72 (0.58–0.88) |
| | $C_{min}$ (mcg/mL) | 0.56 (0.34–0.94) | 0.33 (0.17–0.63)* | 0.78 (0.43–1.4) |
| | $T_{min}$ (hr) | 1.00 (0.51–1.96) | 0.78 (0.21–2.87) | 1.04 (0.58–1.87) |
| | CL/F (L/hr) | 0.87 (0.72–1.04) | 1.95 (1.58–2.4)* | 2.07 (1.79–2.38)* |
| | $V_d$/F (L) | 0.50 (0.27–0.94) | 0.98 (0.76–1.26) | 1.95 (1.44–2.64)* |
| | $t½$ (hr) | 0.56 (0.32–0.97) | 0.50 (0.34–0.74)* | 0.96 (0.72–1.28) |
| Ritonavir | $AUC_{0\text{-}12}$ (mcg·hr·mL$^{-1}$) | 0.68 (0.49–0.93) | 0.39 (0.28–0.52)* | 0.62 (0.5–0.77)* |
| | $C_{pre\text{-}dose}$ (mcg/mL) | 0.58 (0.29–1.16) | 0.32 (0.17–0.6)* | 0.69 (0.48–1) |
| | $C_{max}$ (mcg/mL) | 0.69 (0.49–0.97) | 0.34 (0.23–0.51)* | 0.58 (0.45–0.74)* |
| | $T_{max}$ (hr) | 0.87 (0.57–1.33) | 1.08 (0.6–1.97) | 1.18 (0.88–1.59) |
| | $C_{12h}$ (mcg/mL) | 0.58 (0.36–0.94) | 0.35 (0.25–0.5)* | 0.68 (0.51–0.89) |
| | $C_{min}$ (mcg/mL) | 0.68 (0.39–1.18) | 0.35 (0.26–0.47)* | 0.69 (0.5–0.94) |
| | $T_{min}$ (hr) | 0.94 (0.38–2.34) | 0.90 (0.26–3.11) | 0.71 (0.35–1.41) |
| | CL/F (L/hr) | 0.74 (0.54–1.01) | 2.59 (1.91–3.53)* | 3.20 (2.59–3.96)* |
| | $V_d$/F (L) | 0.58 (0.42–0.8) | 1.16 (0.73–1.86) | 2.66 (1.66–4.26)* |
| | $t½$ (hr) | 0.72 (0.56–0.92) | 0.45 (0.32–0.63)* | 0.83 (0.56–1.23) |

*Ninety percent CI fall completely outside of the range, 0.8–1.25, indicating the parameters are different.

The clinical significance of the decreased lopinavir total concentrations with standard dosing during pregnancy is uncertain. However, the risk of virologic breakthrough with low protease inhibitor trough concentrations is a concern, especially for treatment-experienced individuals.[21–24] In our 3 studies of lopinavir during pregnancy, 6%, 12%, and 12% (this study) of subjects had detectable viral loads at delivery.[4,5] Four other cohorts of HIV-infected pregnant women treated with standard lopinavir/ritonavir dosing have reported that 12%–16% were not fully suppressed at delivery.[10–13] The study with the lowest HIV RNA detection rate, 50 copies per milliliter, reported 15.4% of women with detectable viral load at delivery.[10]

Until more is known about the relationship between lopinavir plasma concentrations and virologic response, a reasonable goal of lopinavir therapy during pregnancy is to achieve plasma unbound concentrations in pregnant women equivalent to those seen in nonpregnant adults. Although unbound concentrations increase by approximately 15% in late pregnancy, total lopinavir and ritonavir exposure during pregnancy are reduced by more than 50% likely due to a combination of increased clearance and decreased absorption. These physiologic factors may be addressed by increasing the administered dose of lopinavir/ritonavir. This goal is likely to be especially important in antiretroviral-experienced subjects, where the development of resistance has been associated with lower lopinavir concentrations.[22–24] A recent population pharmacokinetic analysis of soft-gel capsule trough concentrations during pregnancy from a French cohort reported the likelihood of achieving various trough concentration targets with simulated standard versus increased (600/150 mg) tablet doses twice daily.[25] The probability of achieving a trough concentration of >1 mg/L (used for treatment-naive patients) with the standard dose in this cohort was 96%. The probability of achieving a trough concentration of >4 mg/L or >5.7 mg/L (suggested targets for treatment-experienced patients) with standard doses fell to 50 and 21%, respectively. The increased dose of 600/150 mg twice daily had a 99%, 80%, and 53% probability of achieving >1, >4, and >5.7 mg/L, respectively. These authors suggested standard doses for treatment-naive patients and empirically increased doses and/or therapeutic drug monitoring during pregnancy for all others. A recent concentration-controlled study of intensive lopinavir tablet pharmacokinetics in 10 women during the second and third trimesters of pregnancy showed that lopinavir exposure was significantly lower in the second trimester compared with historical nonpregnant controls.[26] Eight of 10 women required dose increases in the second trimester and achieved lopinavir exposure on the increased dose in the third trimester similar to nonpregnant historical controls. These findings are consistent with our findings.

Since this study was performed in US women, extrapolation to other populations may be confounded by differences in size, genetics, diet, and concomitant illnesses and other factors. Another limitation is that the pharmacokinetic evaluations within the first month postpartum may not reflect lopinavir/ritonavir pharmacokinetics in the nonpregnant/nonpostpartum female. Likewise, the changes in lopinavir/ritonavir pharmacokinetics during pregnancy are probably a continuous and dynamic process that cannot be fully characterized by only 2 evaluation time points during pregnancy. Despite these limitations, this study provides important information about lopinavir/ritonavir exposure to guide therapy during pregnancy.

Our current study evaluated complete 12-hour pharmacokinetic profiles with an empiric dose increase during

pregnancy in all subjects, regardless of prior treatment status. A dose of 3 tablets (lopinavir 600 mg/ritonavir 150 mg) twice daily during the third trimester showed comparable exposure and tolerability to the standard dose (lopinavir 400 mg/ritonavir 100 mg twice daily) in nonpregnant adults. These data suggest that the higher lopinavir/ritonavir dose should be used in second and third trimester pregnant women, especially those who are protease inhibitor experienced, and that postpartum lopinavir/ritonavir dosing can be reduced to standard dosing before 2 weeks after delivery.

## ACKNOWLEDGMENT

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## APPENDIX I: MEMBERS OF THE IMPAACT 1026S PROTOCOL TEAM

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