



# High-Dose Lopinavir and Standard Dose Emtricitabine Pharmacokinetics During Pregnancy and Postpartum

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## Original Abstract

**Background:** Emtricitabine (FTC) and the new lopinavir/ritonavir (LPV/r) tablets are widely used in pregnancy but no pharmacokinetic (PK) data during pregnancy are available for either. Standard adult LPV/r doses (400mg/100mg) with exposures during the 3<sup>rd</sup> trimester of pregnancy resulted in reduced LPV/r exposure. Our objectives were to determine 1) LPV/r tablet pharmacokinetics (PK) with a higher dose during the 3<sup>rd</sup> trimester of pregnancy and standard dosing 2 weeks postpartum (PP), and 2) standard dose FTC PK in the 3<sup>rd</sup> trimester and postpartum.

**Methods:** PACTG 1026s is an on-going, prospective, non-blinded study of antiretroviral PK in HIV-infected pregnant women, including an FTC cohort taking 200 mg daily throughout pregnancy and 6–12 weeks PP, and a separate LPV/r cohort taking standard doses in the 2<sup>nd</sup> trimester and PP, and taking 600mg/150mg BID in the 3<sup>rd</sup> trimester. Intensive study-site 12- and 24-hour PK profiles were performed for subjects in the LPV/r and FTC cohorts, respectively. Delivery maternal and umbilical cord blood samples were obtained. Target FTC and LPV/r AUCs were ≥ 7 and 52 mcg\*hr/mL, respectively (approximately the 10<sup>th</sup> percentile AUC in non-pregnant historical controls).

**Results:** As of August 2007, LPV and FTC PK data were available for 21 and 18 women, respectively.

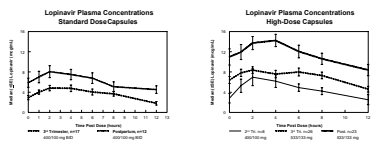
	Optional 2 <sup>nd</sup> Trimester	3 <sup>rd</sup> Trimester	Postpartum
LPV/r tablet dose	400/100 BID	600/150 BID	400/100 BID
LPV AUC (mcg*hr/mL)	72 (51, 86)	92 (43, 198)	131 (66, 237)
Met LPV AUC Target/Total	5/6	19/21	14/14
LPV C <sub>max</sub> (mcg/mL)	3.4 (1.7, 4.4)	4.7 (0.90, 12.2)	6.8 (0.90, 10.6)
FTC AUC (mcg*hr/mL)	New Studied	8.6 (5.2, 15.9)	9.8 (7.4, 30.3)
Met FTC AUC Target/Total	New Studied	12/18	14/14
FTC C <sub>max</sub> (mcg/mL)	New Studied	32 (14, 108)	86 (41, 306)

Mean cord blood LPV and FTC concentrations were 1.5 ± 1 mcg/mL and 300 ± 268 ng/mL. Mean ratios of cord blood/maternal delivery LPV and FTC concentrations were 0.26 ± 0.25 (n=15) and 1.17 ± 0.16 (n=9%).

**Conclusions:** Higher LPV/r dosing provided appropriate exposure during the 3<sup>rd</sup> trimester. With standard dosing, the 2<sup>nd</sup> trimester AUC was 50% lower than PP. The higher LPV/r dose should be used in 3<sup>rd</sup> trimester pregnant women and should be considered in 2<sup>nd</sup> trimester pregnant women, especially those who are protease inhibitor-experienced. LPV/r dose can be reduced to standard in the early PP period. FTC exposure (AUC) was lower during pregnancy than PP, but the magnitude was small (12%) and dose adjustments due to pregnancy may not be necessary.

## Introduction

- The physiologic changes of pregnancy may have a profound effect on drug disposition.
- We have previously shown that the standard lopinavir/ritonavir (LPV/r) capsule dose (400/100 mg twice daily) results in serum concentrations ~50% lower than postpartum<sup>1</sup>, while 533/133 mg provides adequate exposure during the third trimester of pregnancy<sup>2</sup>.



- Optimal antiretroviral exposure during pregnancy is critical for prevention of mother-to-child transmission of HIV and for maintenance of maternal health.
- High-dose tablet LPV and standard-dose FTC pharmacokinetics during pregnancy have not been evaluated previously.

1. Best M, Rossi S, Capparelli E, Smith E, Burchett S, Hu C, Sheeran E, Read J, Mirochnick M, Stek A, et al. IMPAACT P1026s Study Team. Reduced maternal exposure during pregnancy. AIDS 2008;20:1031-1034.  
2. Mirochnick M, Best M, Capparelli E, Smith E, Burchett S, Hu C, Sheeran E, Read J, PACTG 1026s Protocol Team. Adequate exposure achieved with a higher dose during the 3<sup>rd</sup> trimester of pregnancy. CID and Poster Presentation at the 15<sup>th</sup> Conference on Retroviruses and Opportunistic Infections, Denver, CO, 2008.

## Objective

- Our primary objectives were to determine:
- LPV tablet pharmacokinetics with a high dose during the 3<sup>rd</sup> trimester and standard dosing during the 2<sup>nd</sup> trimester and postpartum
  - FTC tablet pharmacokinetics with a standard dose in the 3<sup>rd</sup> trimester and postpartum

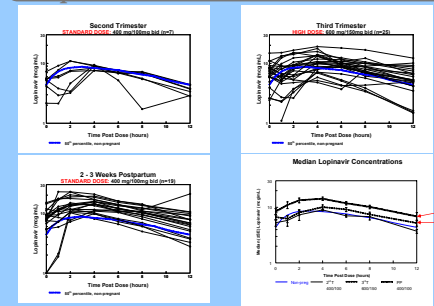
## Study Methods

- All subjects were enrolled in P1025: "PACTG/IMPAACT Perinatal Core Protocol" and its substudy P1026s: "Pharmacokinetic Properties of Antiretroviral Drugs During Pregnancy"
- As of January 1, 2008: PK evaluations were performed after ≥ 2 weeks of stable therapy in 2 separate cohorts of women taking either LPV/r or FTC for routine clinical care.
  - Lopinavir/Ritonavir
    - 2<sup>nd</sup> Trimester: 400/100 mg (2 tablets) twice daily (n=7 subjects)
    - 3<sup>rd</sup> Trimester (≥ 30 weeks): 600/150 mg (3 tablets) twice daily (n=25 subjects)
    - 2 weeks postpartum: 400/100 mg (2 tablets) twice daily (n=19 subjects)
  - Emtricitabine
    - 3<sup>rd</sup> Trimester: 200 mg daily (n=18)
    - 6–12 weeks postpartum: 200 mg bid (n=17)
- Plasma samples collected pre-dose and 1, 2, 4, 6, 8, 12 (and 24 for FTC) hours post-dose
- Cord blood and maternal samples collected at delivery from 17 (LPV/r) and 9 (FTC) mother-infant pairs
- For LPV/r: assayed by validated HPLC (lower limit of quantitation of 0.09 mcg/mL)
- For FTC: assayed by validated MS (lower limit of quantitation of 10 ng/mL)
- Area under the curve (AUC<sub>0-24</sub> or AUC<sub>0-24</sub>) was calculated with the trapezoidal rule

## Clinical Characteristics

Median (Range)	LPV/r	FTC
Age at 3 <sup>rd</sup> Trimester (years)	31 (22 – 39)	30 (19 – 39)
Weight at 3 <sup>rd</sup> Trimester (kg)	81 (58 – 123)	74 (51 – 137)
Race/Ethnicity:		
White Non-Hispanic	4 (16)	4 (22)
Black Non-Hispanic	4 (16)	5 (28)
Hispanic (any race)	17 (68)	7 (39)
Asian, Pacific Islander		1 (5.5)
More than one race		1 (5.5)
CD4+ at Delivery (cells/mL)	376 (52 – 1554)	493 (53 – 1300)
HIV-1 RNA at Delivery (log <sub>10</sub> copies/mL)	<200 (<50 – 606)	<50 (<20 – 400)
Grade ≥ 3 Adverse Effects (1 subject per event unless otherwise noted)	ruptured uterus, SVT, nose bleed, elevated lates: lipase, ALT, AST, glucose (2 subjects)	elevated total bilirubin (2 subjects, also on ATV)
Infant Gestational Age at Birth (weeks)	38.4 (34.1 – 40.7)	37.9 (34.7 – 41.7)
Infant Weight at Birth (kg)	3.09 (1.94 – 3.76)	2.76 (2.23 – 3.77)
Infant Infection Status	9 uninfected 15 pending	15 uninfected 5 pending

## Lopinavir Concentrations Over Time



## Lopinavir Pharmacokinetic Parameters

Median (range)	2 <sup>nd</sup> Trimester	3 <sup>rd</sup> Trimester	Postpartum
n	7	25	19
Dose	400/100 mg BID	600/150 mg BID	400/100 mg BID
AUC <sub>0-24</sub> (mcg*hr/mL)	72 (51 – 93)	97 (43 – 198) <sup>1</sup>	129 (66 – 237)
C <sub>max-dose</sub> (mcg/mL)	5.3 (2.2 – 7.3)	6.7 (<0.09 – 14.8) <sup>1</sup>	8.4 (<0.09 – 15)
C <sub>max</sub> (mcg/mL)	9.1 (7.5 – 10.9)	10.7 (5.8 – 19.1) <sup>1</sup>	14.6 (9.8 – 22.8)
Met LPV AUC Target	6/7 (86%)	23/25 (92%)	19/19 (100%)

<sup>1</sup>p < 0.05 for 3<sup>rd</sup> Trimester versus Postpartum; <sup>2</sup>p < 0.05 for 2<sup>nd</sup> Trimester versus 3<sup>rd</sup> Trimester

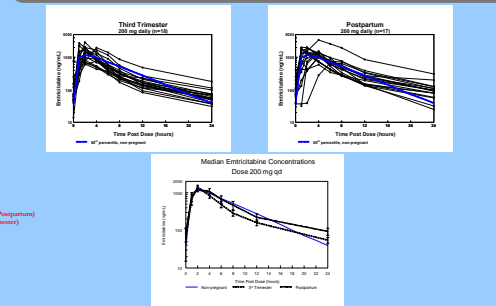
## Cord Blood and Delivery Concentrations

Median (range)	LPV (mcg/mL)	FTC (ng/mL)
	n=17	n=9
Cord blood concentration	1.13 (0.29 – 4.16)	220 (<10 – 814)
Maternal plasma concentration at delivery	5.96 (1.86 – 12.25)	156 (<10 – 1228)
Cord blood/maternal plasma ratio	0.24 (0.04 – 0.97)	1.03 (0.66 – 2.48)

## Acknowledgements

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## Emtricitabine Concentrations Over Time



## Emtricitabine Pharmacokinetic Parameters

Median (range)	3 <sup>rd</sup> Trimester (n=18)	Postpartum (n=17)
AUC <sub>0-24</sub> (mcg*hr/mL)	8.6 (5.2 – 15.9)	9.6 (7.4 – 30.3)
C <sub>max-dose</sub> (ng/mL)	65 (14 – 757)	81 (<10 – 417)
C <sub>max</sub> (ng/mL)	1549 (621 – 2883)	1455 (663 – 3394)
Met FTC AUC Target	12/18 (67%)	17/17 (100%)

## Conclusions

- The higher LPV/r tablet dose (600mg/150mg) was well-tolerated and provided adequate LPV exposure during the 3<sup>rd</sup> trimester.
- Paradoxically, LPV postpartum concentrations on the lower dose (2 tablets) were higher than 3<sup>rd</sup> trimester concentrations on the high dose (3 tablets).
- LPV AUC was 50% lower with standard dosing (400mg/100mg) during the 2<sup>nd</sup> trimester compared to standard dosing postpartum.
- FTC exposure was lower during pregnancy than postpartum, but the magnitude of the difference was small (10%).
- LPV placental transport is poor, while FTC placental transport is excellent, with median cord blood to maternal ratios of 24% and 103%, respectively.
- We suggest that:
  - The higher LPV/r dose should be used in 3<sup>rd</sup> trimester pregnant women and that it should be considered in 2<sup>nd</sup> trimester pregnant women, especially those who are protease inhibitor-experienced.
  - Postpartum LPV/r can be reduced to standard dosing shortly after delivery.
  - Standard dose FTC should be used during pregnancy.