

# ACTG A5153s, a substudy for A5150: Pharmacokinetic Exposure and Virological Response in HIV-1-Infected Pregnant Women Treated with Protease Inhibitors

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## Background

### Treatment of HIV Disease in Pregnant Women

Many pregnant women with HIV infection receive combination antiretroviral regimens including a protease inhibitor for maternal control of HIV and to prevent mother-to-child transmission.

The current US Public Health Service Perinatal Guidelines recommend HAART for most pregnant women.<sup>1</sup>

Nelfinavir and lopinavir/ritonavir are the protease inhibitors most commonly used by pregnant women in the United States.

Challenges for treating pregnant women include

1. Pharmacokinetic changes due to pregnancy
2. Ethnic differences in drug metabolism and transport
3. Adherence in context of other challenges, e.g., socioeconomic status, ethanol or drug abuse
4. Drug-drug interactions and fetal safety (i.e., variants in drug detoxification pathways)
5. Availability of antiretroviral (ARV) drugs in resource-poor settings beyond prevention of mother-to-child transmission

### Pharmacology of ARV Drugs

The HIV-1 protease inhibitors are metabolized by cytochrome p450 isozymes. Lopinavir and ritonavir are metabolized primarily by CYP3A4. Nelfinavir is metabolized to an active metabolite (M8) via CYP2C19. M8 is further converted to inactive metabolites via CYP3A4.

The protease inhibitors are substrates for drug transporters including p-glycoprotein and multidrug resistance proteins (MRP). It is common for LPV/r exposure to be altered within the context of interacting drugs or due to physiological changes in drug distribution and metabolism associated with pregnancy.<sup>2</sup>

### Impact of Pregnancy on Drug Disposition

Pregnancy may affect factors of drug disposition including absorption, distribution, elimination, and metabolism. These changes include the following:

**Absorption.** Unclear effects on gut metabolic enzymes or GI motility. Potential ↑ in absorption of acid-labile drugs and ↓ absorption of drugs requiring ↓pH for stability (such as protease inhibitors)

**Distribution.** Plasma volume increases and protein binding decreases (Albumin and AAG: ↓). Therefore, expect diminished protein binding of PIs leading to ↑ free fraction (FU), which impacts interpretation of therapeutic drug monitoring (TDM).

**Elimination.** Increase in glomerular filtration rate (GFR) by 50% in third trimester, potentially impacting drugs eliminated unchanged by the kidney.

**Metabolism.** Hepatic metabolic enzymes:

- ↑ CYP 3A4 and 2D6
- ↓ CYP1A2, xanthine oxidase, and N-acetyl transferase, e.g., caffeine CL ↓ 70%
- Fetal-placental unit has metabolic potential
- One recent study demonstrated 35% increased CYP3A4 throughout pregnancy<sup>3</sup>

### Virological Control During Pregnancy

Controlling viral load during pregnancy and after is important for preventing maternal-infant transmission of HIV and for long-term maternal health.

While pregnancy has not been shown to be associated with HIV disease progression as defined by immunologic or clinical deterioration, several studies have found an increase in viral load postpartum<sup>4,5,6</sup>. ACTG A5150 was designed to examine the extent of this problem and to explore potential mechanisms for viral rebound.

Substudy ACTG A5153s was designed to evaluate whether pharmacokinetic changes during pregnancy contribute to this phenomenon.

## Study Objectives

1. To characterize the pharmacokinetics of nelfinavir and lopinavir/ritonavir in the context of pregnancy and early postpartum period
2. To evaluate in a subgroup of women receiving nelfinavir whether changes in drug exposure between late pregnancy and postpartum as measured by AUC are associated with development of viral rebound at 24 weeks postpartum
3. To evaluate in a subgroup of women receiving lopinavir/ritonavir whether changes in drug exposure between gestation and postpartum as measured by AUC are associated with the development of viral rebound at 24 weeks postpartum

## Study Design

### Enrollment

Pregnant women ≥13 yrs between 22–30 weeks gestation expected to be on stable LPV/r or NFV for ≥8 weeks at delivery. Standard treatment doses were administered for LPV/r (133/33 mg capsules at 400/100 BID, or 533/133 BID for LPV/r Subject 8 only) and NFV (250 mg tablets at 1250 mg BID, or 1500 mg BID for NFV Subjects 4 and 8).

All subjects were on the same NRTI component of their ARV regimen for all of their PK visits. For LPV/r subjects, 4 were taking ZDV/3TC, 2 were taking ABC/ZDV/3TC, 3 subjects were taking a TDF-containing regimen, and 1 subject was taking ZDV/ddI. For NFV subjects, all were taking ZDV/3TC at the time of each of their PK visit.

### Study Procedures

Pharmacokinetic evaluations occurred at 36 weeks gestation and 6 or 24 weeks postpartum (0, 1, 2, 4, and 6 hrs post-dose).

Subjects included in the pharmacokinetic analysis were to have taken their prescribed regimens at the same dosages for at least 2 weeks to assure steady-state conditions.

### Pharmacokinetic Analysis

**Sample analysis.** LPV, RTV, NFV, and M8 were analyzed by LC-tandem MS methodologies within the UCSF Pharmacology Support Laboratory. Methods were approved by the ACTG Pharmacology QA/QC subcommittee. Inter-assay coefficient of variation (CV) for LP, RTV, NFV, and M8 were all less than 11%. Lower limits of quantitation for the 4 analytes were 0.04, 0.025, 0.025, and 0.025 mcg/ml, respectively.

The area under the plasma concentration versus time curve (AUC) from 0 to 6 hours post-dose was calculated using the linear trapezoidal rule. Dose-normalized AUCs were calculated using reference doses of NFV: 1250 mg BID and LPV/r: 400/100 BID.

Cmin was calculated as the concentration obtained at the pre-dose sample time.

Cmax was calculated as the maximum concentration observed over the 0–6 hours of sampling.

### Viral Load Determinations

Plasma HIV-1 RNA levels were measured with the Roche Amplicor HIV-1 Monitor (version 1.5; lower limit of quantification <50 copies).

### Statistical Analysis

Within-subject antepartum (AP) and postpartum (PP) PK parameter estimates were compared using paired difference of the PP to AP on the log(ln)-scale (paired t test).

### Subject Demographics at A5150 Study Entry

	LPV/r (n=10)	NFV (n=9)
Age (yrs)	29 (19,39)*	27 (18,38)*
CD4+ count (cells/mm <sup>3</sup> )	400 (36,658)*	366 (226,1207)*
Weight (kg)	94 (70,148)*	73 (64,125)*
HIV-1 RNA level (log10)	2.2 (1.7,4.6)*	2.0 (1.7,4.2)*
Gestational Age (weeks) at entry**	27 (23,28)*	28 (24,30)*
Weeks on Regimen prior to Delivery	21.3 (12.6,158.7)*	17.3 (7.0,128.9)*
Race/Ethnicity		
White (non-hispanic)	10%	0%
Black (non-hispanic)	50%	11%
Hispanic	30%	89%
Asian/Pacific Islander	0%	0%
Other	10%	0%
On treatment at conception	40%	78%

\* Median (Minimum, Maximum)

\*\*For the LPV/r subjects the third trimester PK visit took place between 35.4 and 37 weeks gestation. For the NFV subjects the third trimester PK visit took place between 35.3 and 36.6 weeks gestation

## Results

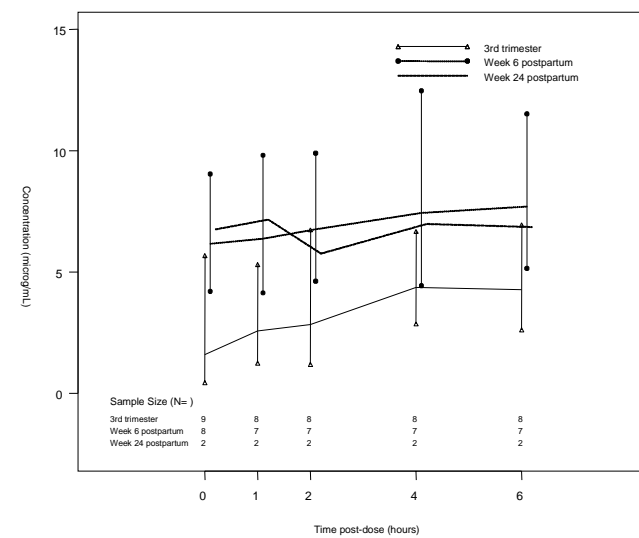
Tables report antepartum (AP) versus postpartum (PP) differences in AUC, Cmax, and Cmin.

Results are reported as the geometric mean ratio, 95% CI. Comparisons were based on paired t-test on the log(ln)-scale.

	AUC 0-6h	Cmax	Cmin
<b>LPV</b>			
vs 6 wk PP (n=6)	0.60 (0.25,1.43) <i>p=0.19</i>	0.57 (0.26,1.26) <i>p=0.099</i>	0.57 (0.28,1.17) <i>p=0.13</i>
<b>RTV</b>			
vs 6 wk PP (n=6)	0.36 (0.14,0.92) <i>p=0.04</i>	0.33 (0.14,0.76) <i>p=0.008</i>	0.34 (0.18,0.66) <i>p=0.019</i>

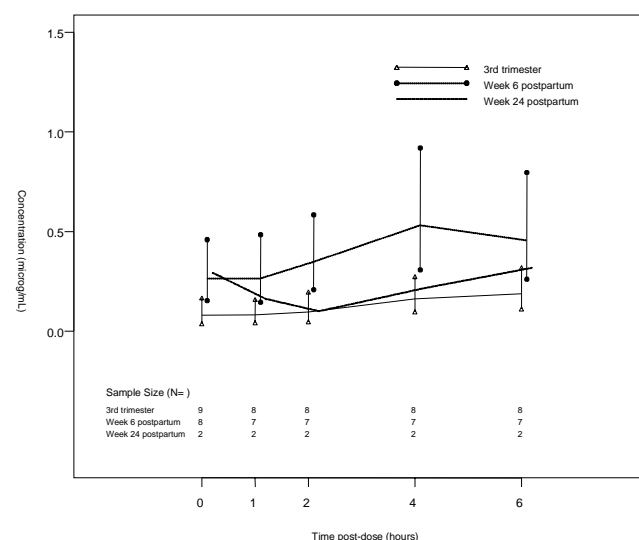
### LPV Exposure, Antepartum and Postpartum

Geometric Mean with 95% CI



### RTV Exposure, Antepartum and Postpartum

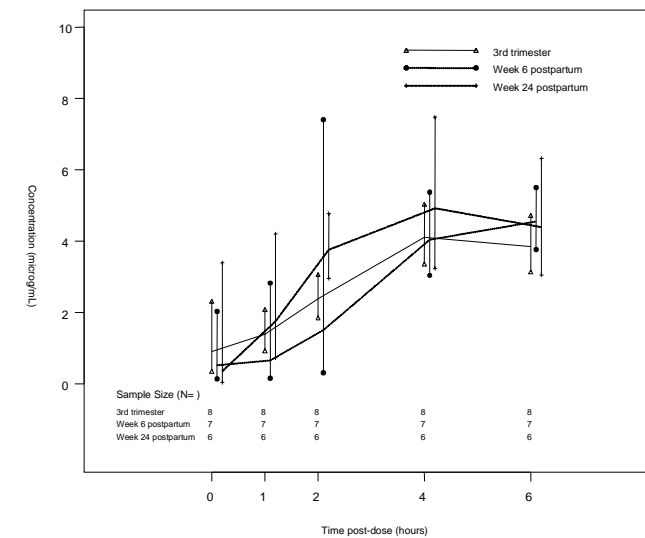
Geometric Mean with 95% CI



	AUC 0-6h	Cmax	Cmin
<b>NFV</b>			
vs 6 wk PP (n=6)	1.01 (0.64,1.62) <i>p=0.95</i>	0.83 (0.71,0.98) <i>p=0.04</i>	3.12 (0.28,35.29) <i>p=0.28</i>
vs 24 wk PP (n=6)	0.77 (0.53,1.12) <i>p=0.13</i>	0.81 (0.49,1.33) <i>p=0.32</i>	3.05 (0.08,121.1) <i>p=0.47</i>
<b>M8</b>			
vs 6 wk PP (n=7)	0.42 (0.11,1.53) <i>p=0.14</i>	0.39 (0.19,0.80) <i>p=0.02</i>	1.04 (0.12,9.05) <i>p=0.21</i>
vs 24 wk PP (n=6)	0.32(0.19,0.56) <i>p=0.003</i>	0.34(0.18,0.64) <i>p=0.007</i>	0.76(0.04,13.83) <i>p=0.17</i>

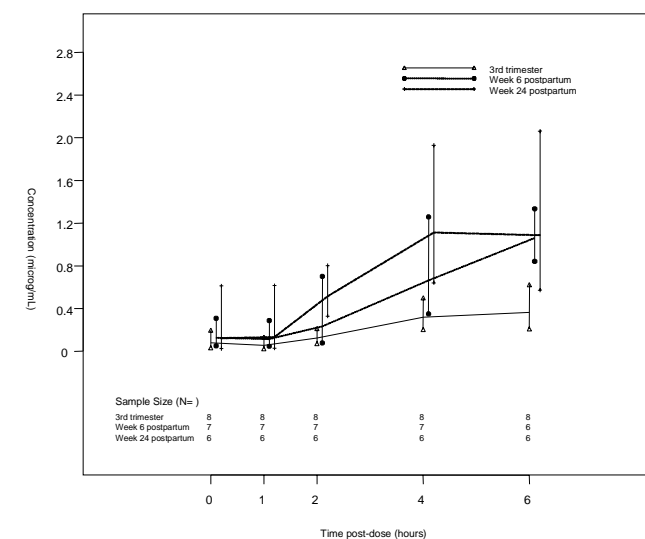
### NFV Exposure, Antepartum and Postpartum

Geometric Mean with 95% CI



### M8 Exposure, Antepartum and Postpartum

Geometric Mean with 95% CI



### Viral Load Results

	Antepartum	6 wk PP	24 wk PP	Comment
<b>LPV</b> (Subject #)				
1	63	*NA	*NA	withdrew wk 39 gestation
2	<50	<50	16,534*	self dc'd meds briefly at 12 wks PP, moved near wk 24 PP
3	<50*	<50	199*	
4	933	50,362	39,449*	off meds for 6 days at wk 4 PP, self dc'd meds 21 wks PP
5	316	<50	25,168*	off meds for 3 days prior to wk 24 PP PK observed dose
6	363	96*	*NA	last dose 34 hrs prior to wk 6 PP PK observed dose
7	1995*	71	*NA	
8	<50	59	*NA	on LPV/r 533/133 bid
9	<50	<50	<50	
10	<50	<50	<50	
<b>NFV</b> (Subject #)				
1	<50	77	8,723*	last dose 62 hrs prior to wk 24 PP PK, "ran out of meds"
2	<50	<50	<50	
3	<50	150	55	
4	<50	154	240	on NFV 1500 mg bid
5	2570	19,894*	8,808	self dc'd meds for 3 wks until 1 day prior to wk 6 PP visit and 7.5–23.5 wks until 4 days prior to her wk 24 PP PK visit
6	<50	<50	<50	
7	<50*	<50	<50*	changed to EFV 17.7 wks PP
8	1000	<50*	145*	on NFV 3125 mg per day, changed to EFV 6 wks PP
9	<50	<50	<50	

\* No PK visit or this PK visit data excluded from analysis.

All infants were HIV-negative except for LPV Subject #1, whose baby's status was unknown as she withdrew consent prior to delivery.

## Conclusions

RTV and M8 AUCs had significantly lower exposure during pregnancy.

Although previous reports have demonstrated a 28% reduction in LPV AUC<sup>2</sup>, this current study only revealed a trend toward diminished exposure for LPV. The lower sample size for this study and the lack of full follow-up on all subjects needs to be taken into consideration.

There was no significant evidence for a change in NFV pharmacokinetics during pregnancy, and previous reports are conflicting.<sup>7,8,9</sup>

Despite variability in ARV exposure, the majority of women achieved and maintained low to undetectable viral load levels in the 3rd trimester through week 6 PP. Those who did not had evidence of non-adherence, which became more of a problem at week 24 PP.

These results suggest dosage adjustment for LPV/r or NFV PIs during pregnancy may not be essential for patients and that adherence issues extend beyond the early PP period.

## Acknowledgements

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