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Pharmacokinetics of Increased Nelfinavir Plasma Concentrations in Women During Pregnancy and Postpartum

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Abstract

This study aims to evaluate the safety, acceptability, and pharmacokinetics (PK) of an increased dose of nelfinavir (NFV) during the third trimester of pregnancy. The study was registered as part of the International Maternal Pediatric Adolescent AIDS Clinical Trials network (IMPAACT-P1026s), an ongoing multicenter prospective cohort study of antiretroviral PK during pregnancy (NCT00042289). NFV intensive PK evaluations were performed at steady state during the third trimester of pregnancy and 2–3 weeks postpartum. Plasma concentrations of NFV and its active metabolite, hydroxyl-*tert*-butylamide (M8) were measured using high-performance liquid chromatography with ultraviolet detection. A total of 18 women are included in the analysis. NFV area under the concentration-time curve (AUC) with the increased dose during the third trimester was nearly identical to the standard dose postpartum, with a geometric mean ratio for third trimester to postpartum AUC of 0.98 (90%CI 0.71–1.35). Despite the increased dose, M8 AUC was lower during the third trimester compared to postpartum (0.53, IQR [0.38–0.75]), as was the M8/NFV AUC ratio (0.51, IQR [0.42–0.63]). NFV AUC_{0-12} was above target in 15 of 18 (83%) of participants during the third trimester compared to 14 of 16 (88%) postpartum. No major safety concerns were noted. Increasing the NFV dose to 1875 mg twice daily during the third trimester achieved similar concentrations postpartum compared to standard dosing (1250 mg twice daily). Increased NFV dose regimens may still have some benefit to human immunodeficiency virus (HIV)-positive pregnant women living in countries where novel protease inhibitors are currently unavailable or in individuals who are intolerant to ritonavir-boosted HIV medications.

Keywords

nelfinavir, pregnancy, hydroxyl-*tert*-butylamide, postpartum

Nelfinavir mesylate (NFV) is a protease inhibitor (PI) with moderately potent activity against human immunodeficiency virus (HIV).[1–3] Although NFV is no longer recommended for use in the United States for prevention of mother-to-child transmission of HIV, it may still be of benefit to HIV-positive individuals living in low-resource countries where novel PIs are currently unavailable or in individuals who are intolerant to ritonavir-boosted HIV medications.[4–8] NFV has also been shown to have in vitro efficacy against a wide range of malignancies by causing apoptosis and nonapoptotic cell death and is under clinical investigation as a cancer therapeutic agent in humans.[9–11]

Pregnant women living with HIV receive antiretrovirals for their own health and to prevent HIV transmission to their infants.[6] Physiologic changes associated with pregnancy may have a large impact on drug disposition, with effects on drug absorption, distribution, metabolism, and elimination of antiretrovirals. NFV is metabolized by cytochrome P450 (CYP)2C19 to hydroxyl-*tert*-butylamide (M8), which has similar potency against HIV as NFV. Both NFV and M8 are both further metabolized by CYP3A4 and CYP 2D6 to less active moieties.[2,3,12] The activity of CYP2C19 has been shown to decrease in pregnancy, whereas activity of CYP3A4 and CYP2D6 increases.[12–18]

In a previous study use of the standard adult NFV dose of 1250 mg twice daily was associated with a 30% reduction in NFV and a 75% reduction in M8 plasma

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concentrations.[19] The goal of the current study was to evaluate NFV and M8 exposures with use of an increased dose during the third trimester.

Methods

The study protocol, the informed consent documents, and all subsequent modifications were reviewed and approved by the local institutional review board/ethics committee responsible for oversight of the study at all 36 institutions/hospitals within the IMPAACT 1026s network (see Supplemental Table S1 for a complete list of hospitals). The study followed all relevant human subject research guidelines. All participants provided signed informed consent before participation, and the study was registered in ClinicalTrials.gov [NCT00042289]. Data were then collected as part of International Maternal Pediatric Adolescent AIDS Clinical Trials Protocol P1026s, an ongoing, multicenter, nonblinded, prospective phase 4 study of the pharmacokinetics and safety of selected antiretroviral drugs in HIV-infected pregnant women that included an arm for pregnant women at sites receiving NFV (the NFV arm of the study recruited only HIV-infected women within the United States).

Pregnant women living with HIV were eligible for enrollment if they were receiving NFV as part of clinical care according to the following dosing schedule: 1250 mg twice daily until 30 weeks of gestation, then 1875 mg twice daily until 2–4 days postpartum, then 1250 mg twice daily until 2–3 weeks postpartum. The samples were collected between May 12, 2009 and December 14, 2014. All antiretroviral medications were prescribed by primary care providers and dispensed by local pharmacies, as per the sites' standard of care. Maternal exclusion criteria were current use of medications known to interfere with NFV metabolism, including lopinavir/ritonavir, atorvastatin, ritonavir, and atazanavir, history of hemophilia, liver disease, diabetes mellitus, hyperlipidemia, phenylketonuria, and other clinical or laboratory toxicity that, per site investigators, would require a change in the antiretroviral regimen. Mothers and their infants continued in the study until 6 months after delivery. Infant HIV status was evaluated at 6 months of life by physical examination and chart abstraction.

Clinical and Laboratory Monitoring

Maternal demographic and clinical information was extracted from the medical record, including maternal HIV-1 RNA, CD4+ lymphocyte count, maternal age, ethnicity, weight, and concomitant medications. Background regimens were similar for all women throughout the evaluation period. Plasma HIV-1 RNA assays were performed locally. Study mothers and infants were followed for clinical and laboratory toxicities through 6 months after delivery. Neonatal gestational age at the time of delivery, birth weight, and HIV infection status data were collected from the infant's medical record. Physical examinations were performed on neonates after delivery, and infant laboratory evaluations were performed only as clinically indicated.

Sample Collection and Drug Assays

Plasma NFV samples for intensive pharmacokinetic (PK) sampling were drawn predose and at 1, 2, 4, 6, 8, and 12 hours postdose. Samples were collected at 20–26 weeks of gestation for second-trimester PK evaluation at 30–36 weeks of gestation for third-trimester PK evaluation, and at 2–3 weeks for postpartum evaluation. Maternal and cord blood samples were collected at delivery, and infant washout PK samples were collected at 2–10, 18–28, 36–72 hours after birth, and at 5–9 days of life.

Plasma NFV and M8 concentrations were determined simultaneously by high-performance liquid chromatography (HPLC) with ultraviolet detection at the University of California, San Diego Pediatric Pharmacology Laboratory. Briefly, plasma proteins were precipitated using acetonitrile and supernatant injected directly onto a LUNA C-18 reversed-phase HPLC column (Phenomenex Inc, Torrance, California). Drugs were separated isocratically using a mobile phase consisting of 10 mmol/L potassium phosphate buffer, pH 4.2: acetonitrile (62:38 v/v). The flow rate was 1.2 mL/min and ultraviolet detection was at 206 nm. The detection limit for both NFV and M8 was 0.039 mg/mL. The mean inter- and intra-assay coefficients of variation were based on validation data (quality control samples were run at multiple different concentrations over the control range of 0.039–8.5 mg/mL). NPV was stable in plasma stored at –20°C. For NFV/M8 HPLC assays, the detection limit was 0.039 μg/mL. Concentrations below the detection limit were treated as half this limit for analysis.

Pharmacokinetic and Statistical Analysis

NFV and M8 plasma concentrations were analyzed using standard descriptive statistics and are presented as medians with interquartile ranges (IQRs). Areas under the concentration-time curve (AUC) for plasma from predose concentration (C_0) to 12 hours postdose ($AUC_{0–12}$) were estimated using the trapezoidal rule, with apparent clearance as dose/$AUC_{0–12}$. Target AUC was 18.5 μg·h/mL, which is the 10th percentile NFV $AUC_{0–12}$ in nonpregnant historical controls. Within-participant comparisons (third trimester versus postpartum) were performed for continuous outcome measures using the Wilcoxon signed-rank test and for dichotomous outcome measures using the McNemar

test. Between-participant comparison was performed for continuous outcome measures using the Wilcoxon rank-sum test and for dichotomous outcome measures using the chi-squared or Fisher exact test. The 90%CIs for the geometric mean ratio of the PK exposure parameters were calculated to describe the range of values that were consistent with the observed data to assess whether there was a clinically significant difference in exposure.

The 90%CI was used to match the usual practice in the PK literature. If the 90%CI is entirely outside the limits of 0.8–1.25, the PK parameter was deemed different for the 2 time points. If the 90%CI is entirely within the limits 0.8–1.25, the parameter is not different between the 2 time points. If the 90%CI overlaps with 0.8–1.25, these data alone do not support any conclusions regarding the pharmacokinetic parameter. Pairwise comparisons of plasma AUC and their ratio within each subject during the third trimester as compared to postpartum were performed using a 2-sided Wilcoxon signed rank test with $P < .01$ considered statistically significant. Data analysis was done using WinNonlin (version 7.0; Pharsight Corporation, Mountain View, California).

Results

Plasma concentration data are available for 18 women in the third trimester and 16 postpartum. Maternal demographic and clinical characteristics of the participants, pregnancy, and fetal outcomes are described in Table 1. The median age of the mothers participating in this study was 28.9 years (IQR 19.8–39.6). Ten of 18 (56.0%) of the mothers were black, 6 of the mothers were Hispanic (33%), and 2 women (11%) were white (non-Hispanic). The mean maternal weights at the time of sampling in the second and third trimesters and postpartum were 86 kg (IQR 79–100.9), 93 kg (IQR 48.5–173.0), and 93.2 kg (IQR 48.2–155.6), respectively. The mean gestational age at the time of sampling in the second trimester was 26 weeks (IQR 24–28), in the third trimester 34 weeks (IQR 30–38), and median postpartum sampling time was 3 weeks after delivery (IQR 2–4).

The median maternal plasma HIV-1 RNA was 58.5 (IQR 48–69) during the second trimester, 48 (42–51) during the third trimester and 48 (IQR 43–52) postpartum. The median CD4 count (cells/mL) was 606 (IQR 521–690) during the second trimester, 506 (IQR 346–690) during the third trimester, and 600 (IQR 346–709) postpartum. The mean gestational age at delivery was 39.1 weeks (IQR 38.0–40.4), with an average birth weight of 3165 g (IQR 2910–3515). One infant was stillborn. Eleven infants (61%) in the cohort were confirmed uninfected, 4 infants (22%) had indeterminate HIV testing results, and 3 infants (17%) were uninfected by the best available data.

Table 1. Demographics of Participants Who Were Recruited Into the NFV Pharmacokinetic Study

Age, y, median (IQR)	28.9 (19.8–39.6)
Weight, kg, median (IQR)	
Second trimester	86.0 (71.0–100.9)
Third trimester	93.0 (48.5–173.0)
Postnatal	93.2 (48.2–155.6)
Race/ethnicity, n (%)	
White, non-Hispanic	2 (11%)
Black, non-Hispanic	10 (56%)
Hispanic	6 (33%)
Gestational age, wk, median (IQR)	
Second trimester	26.1 (24.4–27.9)
Third trimester	34.7 (30.3–38.0)
Postpartum	3.0 (2.0–4.0)
Timing of PK visit, wk, median (IQR)	
Second trimester	26.1 (24.4–27.9)
Third trimester	34.5 (30.3–38.0)
Postpartum	2.7 (1.9–7.3)
HIV-1 RNA, ≤ 50 copies/mL, median (IQR)	
Second trimester	58.5 (48.0–69.0)
Third trimester	48.0 (42.0–51.0)
Postpartum	48.0 (43.0–52.0)
CD4+ cells, cells/mm^3, median (IQR)	
Second trimester	605.5 (521.0–690.0)
Third trimester	505.5 (346.0–690.0)
Postpartum	600.0 (346.0–709.0)
Infant outcomes, median (IQR)	
Gestational age at delivery (wk)	39.1 (38.0–40.4)
Birth weight (g)	3165 (2910–3515)
Length (cm)	49.0 (48.3–51.0)
Infant infection status[a]	
Confirmed uninfected	11/17 (61%)
Indeterminate	4/17 (22%)
Uninfected by best available data	3/17 (17%)

90%CIs were used for analysis.
IQR indicates interquartile range (in parentheses); NFV, nelfinavir; PK, pharmacokinetics.
[a]One infant was stillborn and did not have newborn form entered.

Nelfinavir and M8 pharmacokinetic data are shown in Table 2 and Table 3, respectively. The M8 $AUC_{0–12}$ (geometric mean ratio 0.53 [IQR 0.38–0.75], $P = .03$) was lower in the third trimester compared to postpartum, but this did not reach statistical significance ($P < .01$) (Table 3). M8 C_{max} (geometric mean ratio 0.54 [IQR 0.40–0.73], $P = .005$) and M8/NFV $AUC_{0–12}$ ratio 0.51 (IQR 0.42–0.63) were significantly lower during the third trimester compared to postpartum ($P < .01$) (Table 3). NFV apparent clearance (Cl/F) was higher during the third trimester compared to postpartum (geometric mean ratio 1.54 [IQR 1.12–2.11], $P = .04$) (Table 2). NFV plus M8 drug exposure was similar during the third trimester of pregnancy compared to postpartum, with a geometric mean ratio of 0.93 (IQR 0.68–1.26). Individual concentration-time curves of NFV and M8 plasma concentrations during the

Table 2. NFV PK Comparison of Third Trimester Versus Postpartum

Parameter	Third Trimester: Median (IQR) (n = 18) 1875 mg BID	Postpartum: Median (IQR) (n = 16) 1250 mg BID	Geometric Mean Ratio of Third Trimester/Postpartum (90%CI)	*P* Value[a]
NFV $AUC_{0–12}$, μg·h/mL	34.2 (27.2–46.9)	33.5 (28.6–43.5)	0.98 (0.71–1.35)	.78
[h·μmol/L]	[60.2 (47.9–82.6)]	[58.9 (50.3–76.6)]		
NFV C_{min}, μg/mL	0.47 (0.35–1.33)	0.52 (0.22–0.80)	0.90 (0.71–1.16)	.49
NFV C_{max}, μg/mL	5.1 (4.3–6.5)	5.0 (4.2–5.9)	1.06 (0.85–1.34)	.67
NFV Cl/F, L/h	54.9 (40.4–68.9)	37.4 (28.7–43.7)	1.54 (1.12–2.11)	.04

$AUC_{0–12}$ indicates area under concentration-vs-time curve (0 to 12 hours postdose); BID, twice daily; Cl/F, apparent molar clearance; C_{max}, maximum concentration; C_{min}, minimum concentration; IQR, interquartile range; NFV, nelfinavir; PK, pharmacokinetics.
[a]*P* value from Wilcoxon rank-sum test.

Table 3. M8, M8/NFV, and NFV Plus M8 PK Comparison of Third Trimester Versus Postpartum

Parameter	Third Trimester: Median (IQR) (n = 18) 1875 mg BID	Postpartum: Median (IQR) (n = 16) 1250 mg BID	Geometric Mean Ratio of Third Trimester/Postpartum (90%CI)	*P* Value[a]
M8 $AUC_{0–12}$, μg·h/mL	3.9 (2.7–7.4)	8.6 (6.5–11.6)	0.53 (0.38–0.75)	.03
[h·μmol/L]	[6.7 (4.7–12.6)]	[14.8 (11.2–19.8)]		
M8 C_{min} (μg/mL)	0.11 (0.05–0.15)	0.14 (0.04–0.21)	0.78 (0.40–1.26)	.24
M8 C_{max} (μg/mL)	0.66 (0.48–1.12)	1.20 (1.07–1.71)	0.54 (0.40–0.73)	.005
M8/NFV AUC ratio	0.11 (0.08–0.22)	0.30 (0.17–0.35)	0.51 (0.42–0.63)	.001
NFV+M8 $AUC_{0–12}$	71.6 (54.3–93.1)	73.3 (66.3–91.7)	0.93 (0.68–1.26)	.60

$AUC_{0–12}$ indicates area under concentration-vs-time curve (0 to 12 hours postdose); BID, twice daily; Cl/F, molar clearance; C_{max}, maximum concentration; C_{min}, minimum concentration; IQR, interquartile range; NFV, nelfinavir; PK, pharmacokinetics.
[a]*P* value from Wilcoxon rank-sum test.

third trimester of pregnancy and postpartum are shown in Figure 1. Median NFV $AUC_{0–12}$ was approximately 50% lower in the third trimester compared to postpartum (Figure 1b). However, the median molar sum of NFV plus M8 plasma concentrations was similar during the third trimester and postpartum (Figure 1c). NFV area under the plasma AUCs and Cl/F curves during pregnancy (third trimester) and postpartum are shown in Figure 2. NFV $AUC_{0–12}$ in 15 of the 18 pregnant patients (83%) met AUC target (18.5 μg·h/mL, indicated by a dashed line) in the third trimester, whereas 14/16 (88%) met this target postpartum. For NFV Cl/F, there were 11 out of 18 pregnant patients who had increased Cl/F during the third trimester compared to the postpartum period.

Umbilical cord blood NFV concentrations were measured in 15 patients. NFV was detected in 10 out of 15 cord plasma samples and in 13 out of 15 maternal plasma samples. The median umbilical cord/maternal ratio for nelfinavir in subjects with detectable maternal concentrations was 0.19. M8 was detectable in 10 maternal plasma samples but in only 3 umbilical cord samples.

All the 18 women enrolled in the cohort were on concomitant antiretrovirals in addition to NFV: 16 participants were also on lamivudine/zidovudine, 1 participant was also on lamivudine/zidovudine/nevirapine, and 1 participant was also on abacavir/lamivudine/zidovudine. Of the 18 patients enrolled in the NFV arm of P1026s, 5 (27.7%) experienced 1 or more grade-3 to -4 adverse events. However, none was determined to be treatment-related. No congenital anomalies identified by prenatal ultrasound or physical examination at the time of birth were determined to be treatment related.

Discussion

Pregnancy impacts several drug-metabolizing enzymes and drug exposure.[20] Prior pharmacokinetic data from the IMPAACT P1026s protocol show that there are decreases in exposure with standard doses of CYP3A4-metabolized antiretrovirals.[21–23] These decreases in exposure can often be overcome with increased doses during pregnancy, as has been shown for lopinavir and atazanavir,[23] which may be clinically important in protease inhibitor–experienced pregnant women.[23–25] An exception is darunavir, where darunavir AUC and C_{max} were substantially decreased in pregnancy with standard dosing, but increasing the dose from 600 mg to 800 mg daily had no effect on darunavir plasma concentration.[26] This subsequently led to the practice of not recommending an increased twice-daily darunavir dose during pregnancy for prevention of mother-to-child transmission of HIV. The decrease in darunavir exposure during pregnancy was not associated with an observed increase in mother-to-child transmission of HIV.[27]

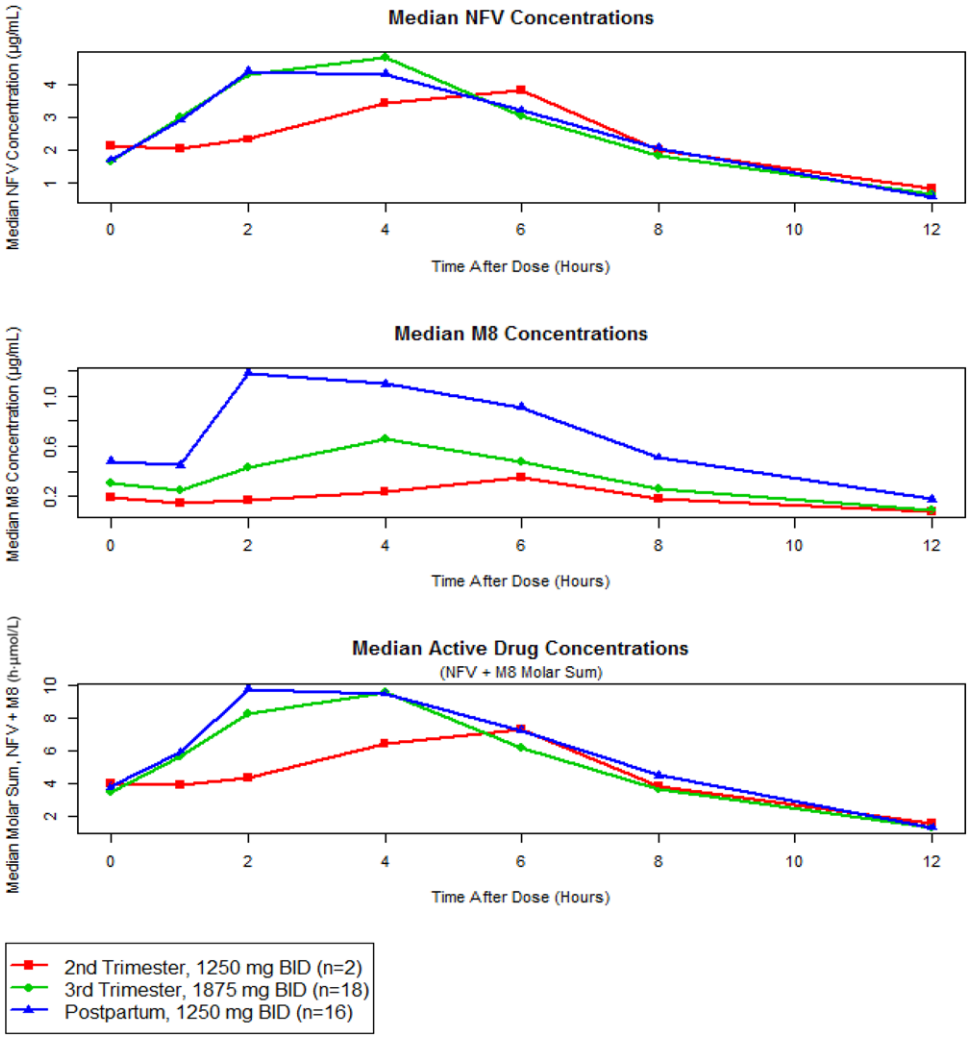

Figure 1. The NFV and M8 curves, including the median AUC plasma concentration, across the second and third trimesters and postpartum. BID indicates twice daily; M8, a metabolite of NFV; NFV, nelfinavir.

If increased CYP3A4 activity was the only effect of pregnancy on NFV metabolism, then NFV exposure would go down. However, NFV is also metabolized by another enzyme, CYP2C19. Activity of CYP2C19 is decreased in pregnancy, and etravirine, a second-generation nonnucleotide reverse transcriptase inhibitor whose predominant route of elimination involves CYP2C19 metabolism, is 1 of the rare drugs whose exposure is increased during pregnancy.[28] If only CYP2C19 were affected by pregnancy, then NFV exposure would go up, whereas M8 exposure and M8/NFV ratio would be decreased. Therefore, examining the effect of NFV and M8 exposures during pregnancy and postpartum provides an opportunity to compare the effect of pregnancy on these 2 enzyme systems. Our data show that during pregnancy, M8 AUC, and the M8/NFV AUC ratio are decreased, likely due to decreased CYP2C19 activity during pregnancy. However, because NFV plasma exposure is also reduced, the effect of pregnancy on CYP3A4 overwhelms its effect on CYP2C19. Hence, reduction in exposure of NFV with standard dosing during pregnancy can be overcome by increasing the dose.

Due to its highly variable drug exposure and rapid metabolism, dose escalation trials of NFV have been done in pregnancy.[19,29,30] The rationale for these studies is that therapeutic drug-monitoring trials of NFV plasma concentrations with appropriate adjustments for low drug exposure resulted in improved outcomes in the nonpregnant population treated with NFV.[31,32] Hence, increasing the dose of NFV during pregnancy was postulated to likely increase bioavailability in the maternal and fetal plasma for prevention of mother-to-child transmission of HIV. IMPAACT 1026[19] previously showed that 1250 mg twice daily dosing decreased NFV exposure by 31% and M8 by 75% during the third trimester of pregnancy versus postpartum, with only 56% of subjects meeting the AUC target

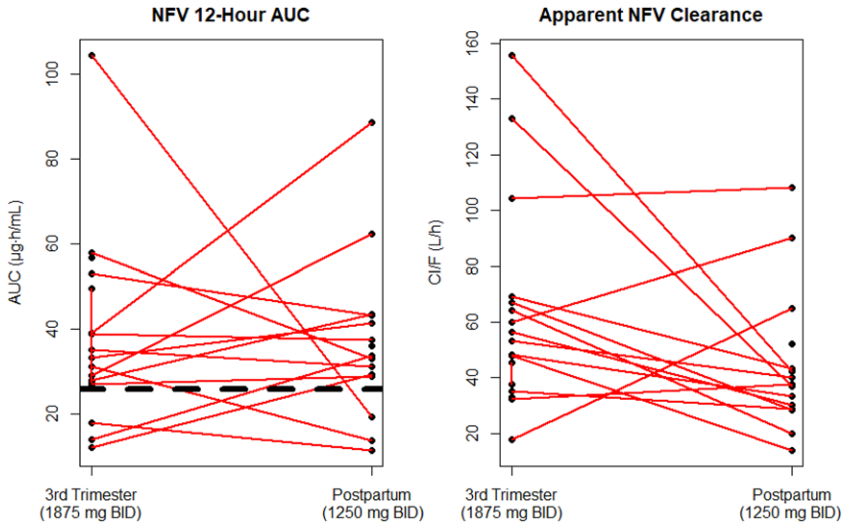

Figure 2. The nelfinavir area under the plasma concentration-time (AUC) and CI/F curves. BID indicates twice daily; CI/F, apparent clearance; NFV, nelfinavir.

during the third trimester.[19] Other studies of increased dosing, such as the PACTG 053 trial,[30] showed that NFV crossed the placenta poorly, and drug exposure was inadequate in most pregnant women receiving 750 mg TID but was much improved with 1250 mg twice daily.

Our study has several strengths. To our knowledge, this is the first study to report the pharmacokinetics of NFV during pregnancy by varying the dosages during the various trimesters, with the highest dose at 1875 mg twice daily between 30 weeks of gestation and the third week postpartum. The participants in our study were followed longitudinally over time, and the collection of clinical findings related to NFV exposure occurred at regular time intervals, so recall error or bias, systematic bias, and confounding by genetic, sociodemographic, and other individual characteristics were minimized. Any random measurement error that arose from the study would tend to diminish apparent effect size, causing estimates to be conservative. There was a high rate of follow-up for mothers and neonates. The collection of samples followed a strict protocol with observed dosing to minimize errors due to sample collection.

This study had its limitations. First, the study cohort included a small number of women, reducing the precision of pharmacokinetic parameters because of greater influence of interindividual variability. Second, the population studied within this network is mainly black or Hispanic, with only a limited number of non-Hispanic white patients included, so that limitations of generalizability may exist. Third, it is not known at what point NFV pharmacokinetics reverted to values observed in the prepregnant state. Ideally, prospective pharmacokinetic studies in women before, during, and after pregnancy will be needed to resolve the exact timing of return to prepregnant levels. Fourth, the association between increased NFV dosing and genetic resistance to HIV virus was not assessed in this study. Genotypic resistance was detected in 50% of women with detectable HIV RNA for whom samples were available for testing in a prior NFV study in pregnant women.[33] Fifth, this study was not designed to identify the precise PK mechanism(s) associated with reduced NFV or M8 during pregnancy. Increased NFV protein binding, volume of distribution, and/or clearance are likely additional reasons for lower exposures of NFV during the third trimester compared to the postpartum period. Sixth, we did not assess the effect of coadministration of NFV with other medications in pregnancy. In prior pharmacokinetic studies, NFV was shown to interact with a myriad of drugs metabolized by the cytochrome P-450 group of enzymes.[34–36] Another limitation is the fact that we did not collect genotyping data; therefore, there is no information on possible protease inhibitor resistance.

In conclusion, our findings confirm that NFV dose should be increased during late pregnancy, and increased NFV dosing may still have some benefit to HIV-positive individuals living in countries where novel protease inhibitors are currently unavailable, or in individuals who are intolerant to ritonavir-boosted HIV medications.

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Financial Disclosures and Conflicts of Interest

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Data Sharing

If interested in our data, please contact David Shapiro (shapiro@sdac.harvard.edu) or Jiajia Wang (jwang@sdac.harvard.edu).

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.