



Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

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Nelfinavir (Viracept, NFV)

(Last updated June 7, 2016; last reviewed June 7, 2016)

Nelfinavir is classified as Food and Drug Administration Pregnancy Category B.

Animal Studies

Carcinogenicity

Nelfinavir was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. However, incidence of thyroid follicular cell adenomas and carcinomas was increased over baseline in male rats receiving nelfinavir dosages of 300 mg/kg/day or higher (equal to a systemic exposure similar to that in humans at therapeutic doses) and female rats receiving 1000 mg/kg/day (equal to a systemic exposure 3-fold higher than that in humans at therapeutic doses).¹

Reproduction/Fertility

No effect of nelfinavir has been seen on reproductive performance, fertility, or embryo survival in rats at exposures comparable to human therapeutic exposure.¹ Additional studies in rats indicated that exposure to nelfinavir in females from mid-pregnancy through lactation had no effect on the survival, growth, and development of the offspring to weaning. Maternal exposure to nelfinavir also did not affect subsequent reproductive performance of the offspring.

Teratogenicity/Developmental Toxicity

No evidence of teratogenicity has been observed in pregnant rats at exposures comparable to human exposure and in rabbits with exposures significantly less than human exposure.¹

Human Studies in Pregnancy

Pharmacokinetics

A Phase I/II safety and pharmacokinetic (PK) study (PACTG 353) of nelfinavir in combination with zidovudine and lamivudine was conducted in pregnant HIV-infected women and their infants.² In the first 9 pregnant HIV-infected women enrolled in the study, nelfinavir administered at a dose of 750 mg 3 times daily produced drug exposures that were variable and generally lower than those reported in non-pregnant adults with both twice- and three-times-daily dosing. Therefore, the study was modified to evaluate an increased dose of nelfinavir given twice daily (1250 mg twice daily), which resulted in adequate levels of the drug in pregnancy. However, in two other small studies of women given 1250 mg nelfinavir twice daily in the second and third trimesters, drug concentrations in both those trimesters were somewhat lower than in non-pregnant women.^{3,4}

In a PK study of combination therapy including the new nelfinavir 625-mg tablet formulation (given as 1250 mg twice daily) in 25 women at 30 to 36 weeks' gestation (and 12 at 6–12 weeks postpartum), peak levels and area under the curve were lower in the third trimester than postpartum.⁵ Only 16% (4 of 25) of women during the third trimester and 8% (1/12) of women postpartum had trough values greater than the suggested minimum trough of 800 ng/mL; however, viral load was <400 copies/mL in 96% of women in the third trimester and 86% postpartum.

Placental and Breast Milk Passage

In a Phase I study in pregnant women and their infants (PACTG 353), transplacental passage of nelfinavir was minimal.² In addition, in a study of cord blood samples from 38 women treated with nelfinavir during pregnancy, the cord blood nelfinavir concentration was less than the assay limit of detection in 24 (63%), and the cord blood concentration was low (median, 0.35 µg/mL) in the remaining 14 women.⁶ Among 20 mother-infant pairs in the Netherlands, the cord blood-to-maternal-plasma ratio for nelfinavir was 0.14 compared to 0.67 for nevirapine and 0.24 for lopinavir.⁷

Nelfinavir also has low breast milk passage. In a PK study conducted in Kisumu, Kenya, concentrations of nelfinavir and its active metabolite, M8, were measured in maternal plasma and breast milk from 26 mothers receiving nelfinavir as part of antiretroviral therapy and from their 27 infants at birth, 2, 6, 14, and 24 weeks.⁸ Peak nelfinavir concentrations were recorded in maternal plasma and breast milk at Week 2. Median breast milk-to-plasma ratio was 0.12 for nelfinavir and 0.03 for its active metabolite (i.e., M8). Nelfinavir and M8 concentrations were below the limit of detection in 20/28 (71%) of infant plasma dried blood spots tested from nine infants over time points from delivery through Week 24. Overall transfer to breast milk was low and resulted in non-significant exposure to nelfinavir among breastfed infants through age 24 weeks.

Teratogenicity/Developmental Toxicity

In the Antiretroviral Pregnancy Registry (APR), sufficient numbers of first-trimester exposures to nelfinavir have been monitored to be able to detect at least a 1.5-fold increased risk of overall birth defects and a 2-fold increased risk of birth defects in the more common classes of birth defects—the cardiovascular and genitourinary systems. No such increase in birth defects has been observed with nelfinavir. Among cases of first-trimester nelfinavir exposure reported to the APR, prevalence of birth defects was 3.9% (47 of 1,215 births; 95% CI, 2.8% to 5.1%) compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.⁹

Excerpt from Table 8^a

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
Nelfinavir (NFV) <i>Viracept</i>	<p><u>Tablets:</u></p> <ul style="list-style-type: none"> • 250 mg • 625 mg (tablets can be dissolved in small amount of water) <p><u>Powder for Oral Suspension:</u></p> <ul style="list-style-type: none"> • 50 mg/g 	<p><u>Standard Adult Dose:</u></p> <ul style="list-style-type: none"> • 1250 mg twice daily or 750 mg three times daily with food <p><u>PK in Pregnancy:</u></p> <ul style="list-style-type: none"> • Lower NFV exposure in third trimester than postpartum in women receiving NFV 1250 mg twice daily; however, generally adequate drug levels are achieved during pregnancy, although levels are variable in late pregnancy. <p><u>Dosing in Pregnancy:</u></p> <ul style="list-style-type: none"> • Three-times-daily dosing with 750 mg with food not recommended during pregnancy. No change in standard dose (1250 mg twice daily with food) indicated. 	<p>Minimal to low placental transfer to fetus.^b</p> <p>No evidence of human teratogenicity; can rule out 1.5-fold increase in overall birth defects and 2-fold increase in risk of birth defects in more common classes, cardiovascular, and genitourinary.</p> <p>Contains aspartame; should not be used in individuals with phenylketonuria.</p>

^a Individual antiretroviral drug dosages may need to be adjusted in renal or hepatic insufficiency (for details, see [Adult Guidelines, Appendix B, Table 7](#)).

^b Placental transfer categories—Mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6 **Moderate:** 0.3–0.6 **Low:** <0.3

Key to Abbreviations: NFV = nelfinavir; PK = pharmacokinetic

References

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