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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**Nevirapine (Viramune, NVP)**

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Available data from the Antiretroviral Pregnancy Registry show no difference in the risk of overall major birth defects for nevirapine compared with the background rate for major birth defects in a U.S. reference population. The Antiretroviral Pregnancy Registry has monitored a sufficient number of first-trimester exposures to nevirapine to be able to detect at least a 1.5-fold increase in risk of overall birth defects and a 2-fold increase in risk of birth defects (in more commonly seen classes of birth defects in the cardiovascular and genitourinary systems); no such increase has been observed.

**Animal Studies**

*Carcinogenicity*

Nevirapine showed no evidence of mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* studies. Hepatocellular adenomas and carcinomas were increased at all doses in male mice and rats and at higher doses in female mice and rats. Systemic exposure at all doses studied was lower than systemic exposure in humans receiving therapeutic nevirapine doses. Given the lack of genotoxic activity of nevirapine, the relevance to humans of hepatocellular neoplasms in nevirapine-treated mice and rats is unknown.

*Reproduction/Fertility*

Evidence of impaired fertility was seen in female rats at nevirapine doses providing systemic exposure comparable to human therapeutic exposure.

*Teratogenicity/Adverse Pregnancy Outcomes*

Teratogenic effects of nevirapine have not been observed in reproductive studies with rats and rabbits at systemic exposures approximately equivalent to or 50% greater than the recommended human dose (based on area under the curve [AUC]). In rats, however, a significant decrease in fetal weight occurred at doses producing systemic concentrations approximately 50% higher than human therapeutic exposure.

**Human Studies in Pregnancy**

*Pharmacokinetics*

The pharmacokinetics (PKs) of nevirapine have been evaluated in pregnant women receiving nevirapine as part of antiretroviral therapy (ART) during pregnancy. A study that determined nevirapine PKs in 26 women during pregnancy (7 second trimester, 19 third trimester) and again in the same women 4 to 12 weeks after delivery found that pregnancy did not alter nevirapine PK parameters. In contrast, nevirapine clearance was 20% greater, AUC was 28% lower, and maximum plasma concentration was 30% lower in 16 pregnant women compared with 13 non-pregnant women, based on nevirapine PK data from a therapeutic drug monitoring program that included 12-hour sampling; they also reported high variability in plasma nevirapine concentrations. A Dutch study reported a nonsignificant trend toward lower nevirapine exposure during pregnancy, with steady-state nevirapine concentrations of 5.2 mcg/mL in 45 pregnant women compared to 5.8 mcg/mL in 152 non-pregnant women (*P* = 0.08). An intensive PK study of 59 women with genotype information found that women who had one or two mutations in CYP 2B6 had higher clearance in pregnancy compared to a different group of postpartum women with mutations. In fast metabolizers (no mutations), no differences in exposure were seen in pregnant women versus postpartum women. No dose adjustment during pregnancy is currently recommended for nevirapine.

*Placental and Breast Milk Passage*

Nevirapine demonstrates rapid and effective placental transfer, achieving near equivalent concentrations in maternal and cord blood (cord-to-maternal-blood ratio ranging from 0.60–1.02). Nevirapine has also been shown to be excreted into human breast milk. In a study of 57 Malawian women receiving postpartum nevirapine-based therapy, breast-milk-to-maternal-serum concentration ratio was approximately 0.6; detectable nevirapine concentrations were found in the breastfeeding infants (inter-quartile range 0.54–1.06 mcg/mL). In data from 15 breastfeeding women receiving nevirapine-based therapy in Botswana, median maternal plasma
concentration at 1 month postpartum was 6.71 mcg/mL and median maternal breast milk concentration was 1.83 mcg/mL, for a median maternal breast-milk-to-plasma ratio of 0.27. Infant exposure was measured at 1 month in 9 infants; all infants had biologically significant detectable nevirapine concentrations in their blood, with a median level of 0.37 mcg/mL (range, 0.24–1.2 mcg/mL), representing approximately 6% of median maternal value. Similar data were reported in a study of 67 mothers receiving nevirapine-based therapy in Kenya; the median concentration of nevirapine in breast milk was 4.55 mcg/mL, with median concentrations at 2, 6, and 14 weeks postpartum in breastfeeding infants of 0.99 mcg/mL, 1.03 mcg/mL, and 0.73 mcg/mL, respectively. An additional study in 122 Nigerian mother/infant pairs found that the median (range) milk-to-plasma nevirapine AUC ratio was 0.95 (0.56–1.5). Infant plasma concentrations from exposure through breast milk were 660 ng/mL (104–3,090).

**Teratogenicity/Adverse Pregnancy Outcomes**

In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to nevirapine in humans have been monitored to be able to detect at least a 1.5-fold increase in risk of overall birth defects and a 2-fold increase in risk of birth defects in more commonly seen classes of birth defects in the cardiovascular and genitourinary systems. No such increase in birth defects has been observed with nevirapine. Among cases of first-trimester nevirapine exposure reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.82% (32 of 1,134 births; 95% CI, 1.93% to 3.97%) compared with a total prevalence of 2.76% in the U.S. population, based on Centers for Disease Control and Prevention surveillance. Similarly, the French Perinatal Cohort reported no association between nevirapine and birth defects with 71% power to detect a 1.5-fold increase.

**Safety**

Severe, life-threatening, and (in some cases) fatal hepatotoxicity—including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure and severe, life-threatening hypersensitivity skin reactions, including Stevens-Johnson syndrome—has been reported in patients with HIV infection receiving nevirapine in combination with other drugs for treatment of HIV disease and in a small number of individuals receiving nevirapine as part of ART for post-exposure prophylaxis of nosocomial or sexual exposure to HIV. In general, in controlled clinical trials, clinical hepatic events, regardless of severity, occurred in 4.0% (range 0% to 11.0%) of patients who received nevirapine; however, the risk of nevirapine-associated liver failure or hepatic mortality has been lower (range 0.04% to 0.40%). The greatest risk of severe rash or hepatic events occurs during the first 6 to 18 weeks of therapy, although the risk of toxicity continues past this period and monitoring should continue at frequent intervals.

Incidence of severe nevirapine-associated skin rash has been reported to be 5.5 to 7.3 times more common in women than men and has been reported in pregnant women. Other studies have found that hepatic adverse events with systemic symptoms (often rash) were 3.2-fold more common in women than men. Several studies suggest that the degree of risk of hepatic toxicity varies with CD4 T lymphocyte (CD4) cell count. In a summary analysis of data from 17 clinical trials of nevirapine therapy, women with CD4 cell counts >250 cells/mm³ were 9.8 times more likely than women with lower CD4 cell counts to experience symptomatic, often rash-associated, nevirapine-related hepatotoxicity. Higher CD4 cell counts have also been associated with increased risk of severe nevirapine-associated skin rash. Rates of hepatotoxicity and rash similar to those in U.S. studies have been seen in international cohorts of non-pregnant women, although not all have reported an association with CD4 cell counts >250 cells/mm³. In a study of 359 non-pregnant women randomized to nevirapine-based therapy in sub-Saharan Africa, higher nevirapine exposure was associated with development of severe skin toxicity, and baseline CD4 cell counts ≥250 cells/mm³ were associated with nevirapine-related liver toxicity and drug discontinuation. Some researchers have suggested that genetic variation in drug metabolism polymorphisms (e.g., CYP2B6 variants), TRAF proteins, and immune human leukocyte antigen loci may be associated with higher risk of nevirapine-associated adverse events and that the relationship between genetic variants and adverse events may vary by race. Published literature indicates that rash and hyperbilirubinemia have been seen in infants exposed to nevirapine through breastmilk.

Although deaths as a result of hepatic failure have been reported in pregnant women with HIV infection...
receiving nevirapine as part of an ART regimen, it is uncertain whether pregnancy increases the risk of hepatotoxicity in women receiving nevirapine or other antiretroviral drugs.\textsuperscript{24} In a systematic review of 20 studies including 3,582 pregnant women from 14 countries, the pooled proportion of women experiencing a severe hepatotoxic event was 3.6\% (95\% CI, 2.4\% to 4.8\%) and severe rash was 3.3\% (95\% CI, 2.1\% to 4.5\%); overall 6.2\% of women stopped nevirapine due to an adverse event (95\% CI, 4.0\% to 8.4\%).\textsuperscript{25} These results were comparable to published frequencies in the general adult population and frequencies comparable to non-pregnant women within the same cohorts. These data suggest that the frequency of adverse events associated with nevirapine during pregnancy is not higher than reported for nevirapine in the general population, consistent with data from two multicenter prospective cohorts in which pregnancy was not associated with an increased risk of nevirapine-associated hepatic toxicity.\textsuperscript{26,27} In contrast, an analysis of data collected in the United Kingdom and Ireland from 2000 to 2011 evaluated 3,426 women, one quarter of whom were pregnant, and found that pregnant women taking efavirenz, maraviroc, or nevirapine were at increased risk of liver enzyme elevation.\textsuperscript{28}

In the systematic review, there was a nonsignificant trend toward an increased likelihood of cutaneous events (OR 1.1, 95\% CI, 0.8–1.6) and severe cutaneous adverse events in pregnant women with CD4 cell counts≥250 cells/mm\textsuperscript{3} (OR 1.4, 95\% CI, 0.8–2.4).\textsuperscript{25} A separate systematic review of 14 studies did report a significant association of increased toxicity risk with initiation of nevirapine-based therapy during pregnancy in women with CD4 cell counts≥250 cells/mm\textsuperscript{3}.\textsuperscript{29} A small case-control study (6 cases, 30 controls) in South Africa reported that pregnancy increased the chance of developing Stevens-Johnson syndrome (OR 14.28, \(P = 0.006\), 95\% CI, 1.54–131.82).\textsuperscript{30} Nevirapine (as a component of a combination regimen) should be initiated in pregnant women with CD4 cell counts≥250 cells/mm\textsuperscript{3} only if the benefit clearly outweighs the risk. Women with CD4 cell counts<250 cells/mm\textsuperscript{3} can receive nevirapine-based regimens, and women who become pregnant while taking nevirapine and who are tolerating their regimens well can continue therapy, regardless of CD4 cell count.

Because pregnancy itself can mimic some of the early symptoms of hepatotoxicity (i.e., pregnancy-related nausea and vomiting), health care providers caring for women receiving nevirapine during pregnancy should be aware of this potential complication. Frequent and careful monitoring of clinical symptoms and hepatic transaminases (i.e., alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) is necessary, particularly during the first 18 weeks of therapy. Some clinicians measure serum transaminases at baseline, every 2 weeks for the first month, and then monthly for the first 18 weeks; in patients with preexisting liver disease, monitoring should be performed more frequently when initiating therapy and monthly thereafter.\textsuperscript{31} Transaminase levels should be checked in all women who develop a rash while receiving nevirapine. Patients who develop suggestive clinical symptoms accompanied by elevation in serum transaminase levels (ALT and/or AST) or have asymptomatic but severe transaminase elevations should stop nevirapine and not receive the drug in the future.
### Excerpt from Table 9

<table>
<thead>
<tr>
<th>Generic Name (Abbreviation)</th>
<th>Trade Name</th>
<th>Formulation</th>
<th>Dosing Recommendations</th>
<th>Use in Pregnancy</th>
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| Nevirapine (NVP)            | Viramune   | Tablets: 200 mg; Oral Suspension: 50 mg/5 mL | Standard Adult Dose: 200 mg once daily Viramune (immediate release) for 14 days (lead-in period); thereafter, 200 mg twice daily or 400 mg (Viramune XR tablet) once daily, without regard to food. | High placental transfer to fetus.\(^b\)
|                             | Viramune XR| Tablets: 100 mg; 400 mg | PK in Pregnancy: PK of immediate release tablets not significantly altered in pregnancy. No data are available on extended release formulations in pregnancy. Dosing in Pregnancy: No change in dose indicated. | 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). Increased risk of symptomatic, often rash-associated, and potentially fatal liver toxicity among women with CD4 cell counts ≥250/mm\(^3\) when first initiating therapy; pregnancy does not appear to increase risk. NVP should be initiated in pregnant women with CD4 cell counts ≥250 cells/mm\(^3\) only if benefit clearly outweighs risk because of potential increased risk of life-threatening hepatotoxicity in women with high CD4 cell counts. Elevated transaminase levels at baseline may increase the risk of NVP toxicity. Women who become pregnant while taking NVP-containing regimens and are tolerating them well can continue therapy, regardless of CD4 cell count. |

\(^a\) Individual ARV 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 Acronyms:** CD4 = CD4 T lymphocyte; NVP = nevirapine; PK = pharmacokinetic

### References


