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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Non-Nucleoside Reverse Transcriptase Inhibitors

Glossary of Terms for Supplement
Carcinogenic = producing or tending to produce cancer • Some agents, such as certain chemicals or forms of radiation, are both mutagenic and clastogenic. • Genetic mutations and/or chromosomal damage can contribute to cancer formation.
Clastogenic = causing disruption of or breakages in chromosomes
Genotoxic = damaging to genetic material such as DNA and chromosomes
Mutagenic = inducing or capable of inducing genetic mutation
Teratogenic = interfering with fetal development and resulting in birth defects

Five non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs) currently are approved (delavirdine is no longer available in the United States). Nevirapine and efavirenz have been studied in human pregnancy. No adequate and well-controlled studies of etravirine or rilpivirine use in pregnant women have been conducted.

For information about potential interactions between NNRTIs and methergine, see Postpartum Hemorrhage, Antiretroviral Drugs, and Methergine Use in the perinatal guidelines. For more information regarding nevirapine hepatic/rash toxicity, see Nevirapine and Hepatic/Rash Toxicity in the perinatal guidelines.

Delavirdine (Rescriptor, DLV) is no longer available in the United States.
(Last updated September 14, 2011; last reviewed July 31, 2011)

Efavirenz (Sustiva, EFV) is classified as Food and Drug Administration (FDA) Pregnancy Category D.
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- Animal carcinogenicity studies
  Efavirenz was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Long-term animal carcinogenicity studies with efavirenz have been completed in mice and rats. At systemic drug exposures approximately 1.7-fold higher than in humans receiving standard therapeutic doses, no increase in tumor incidence above background was observed in male mice, but in female mice, an increase above background was seen in hepatocellular adenomas and carcinomas and pulmonary alveolar/bronchiolar adenomas. No increase in tumor incidence above background was observed in male and female rats with systemic drug exposures lower than that in humans receiving therapeutic doses.

- Reproduction/fertility animal studies
  No effect of efavirenz on reproduction or fertility in rodents has been seen.

- Teratogenicity/developmental toxicity
  An increase in fetal resorption was observed in rats at efavirenz doses that produced peak plasma concentrations and area under the curve (AUC) values in female rats equivalent to or lower than those achieved in humans at the recommended human dose (600 mg once daily). Efavirenz produced no reproductive toxicities when given to pregnant rabbits at doses that produced peak plasma concentrations similar to and AUC values approximately half of those achieved in humans administered efavirenz (600

mg once daily). Central nervous system (CNS) malformations and cleft palate were observed in 3 of 20 infants born to pregnant cynomolgus monkeys receiving efavirenz from gestational Days 20 to 150 at a dose of 30 mg/kg twice daily (resulting in plasma concentrations comparable to systemic human therapeutic exposure).[1] The malformations included anencephaly and unilateral anophthalmia in one fetus, microphthalmia in another fetus, and cleft palate in a third fetus.

- Placental and breast milk passage
  Efavirenz crosses the placenta in rats, rabbits, and primates, producing cord blood concentrations similar to concentrations in maternal plasma. In a study of 13 women in Rwanda, efavirenz was given during the last trimester of pregnancy and for 6 months after delivery.[2] Efavirenz concentrations were measured in maternal plasma, breast milk, and infant plasma. Efavirenz passed into breast milk with a ratio of 0.54 (mean breast milk to mean maternal plasma concentration) and 4.08 (mean skim milk to mean newborn plasma concentration). Mean infant plasma efavirenz concentrations were 13.1% of maternal plasma levels. No data currently are available about efavirenz in neonates.

- Human studies in pregnancy
  In pregnancies with prospectively reported exposure to efavirenz-based regimens in the Antiretroviral Pregnancy Registry through January 2012, birth defects were observed in 18 of 679 live births with first-trimester exposure (2.7%, 95% confidence interval [CI], 1.6%–4.2%).[3] Although these data provide sufficient numbers of first-trimester exposures to rule out a 2-fold or greater increase in the risk of overall birth defects, the low incidence of neural tube defects in the general population means that a larger number of exposures are still needed to be able to definitively rule out an increased risk of this specific defect. Prospective reports to the Antiretroviral Pregnancy Registry of defects after first-trimester efavirenz exposure have documented 1 neural tube defect case (sacral aplasia, myelomeningocele, and hydrocephalus with fetal alcohol syndrome) and 1 case of bilateral facial clefts, anophthalmia, and amniotic band.[3] Among retrospective cases, there are 6 reports of CNS defects, including 3 cases of meningomyelocele in infants born to mothers receiving efavirenz during the first trimester.[4] Retrospective reports can be biased toward reporting of more unusual and severe cases and are less likely to be representative of the general population experience.

  In an updated meta-analysis of 19 studies (including the Antiretroviral Pregnancy Registry data) reporting on birth outcomes among women exposed to efavirenz during the first trimester, there were 39 infants with birth defects among live births in 1,437 women receiving first-trimester efavirenz (rate of overall birth defects, 2.0%, 95% CI, 0.8–3.2%).[5] The rate of overall birth defects was similar among women exposed to efavirenz-containing regimens (1,290 live births) and non-efavirenz containing regimens (8,122 births) during the first trimester (pooled relative risk [RR] 0.85, 95% CI, 0.61–1.20). Across all births (1,437 live births with first-trimester efavirenz exposure), 1 neural tube defect (myelomeningocele) was observed, giving a point prevalence of 0.07% (95% CI, 0.002–0.39), within the range reported in the general population. However, the number of reported first-trimester efavirenz exposures still remains insufficient to rule out a significant increase in low-incidence birth defects (incidence of neural tube defects in the general U.S. population is 0.02%–0.2%).

  In contrast to the meta-analysis, the Pediatric AIDS Clinical Trials Protocols (PACTG) 219 and 219C studies reported a higher defect rate among infants with first-trimester exposure to efavirenz compared with those without such exposure (adjusted odds ratio 4.31, 95% CI, 1.56–11.86). However, only 32 infants had efavirenz exposure. The PACTG protocol P1025 is a companion study of PACTG 219 with considerable overlap of the cases enrolled. Whereas the P1025 study reported a significant increased risk of congenital anomalies in infants born between 2002 and 2007 with first-trimester exposure to efavirenz, there is overlap in the defect cases between the two studies and only 42 infants are included in this analysis. Thus, additional data are needed on first-trimester efavirenz exposures to more conclusively

determine if risk of neural tube defects is elevated.

Efavirenz is classified as FDA Pregnancy Category D, which means that there is positive evidence of human fetal risk based on studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Although the limited data on first-trimester efavirenz exposure cannot rule out a 2- or 3-fold increased incidence of a rare outcome, such as neural tube defects, the available data from the meta-analysis on >1,400 births suggest that there is not a large increase (such as a 10-fold increase) in the risk of neural tube defects with first-trimester exposure. Because of the potential for teratogenicity, pregnancy should be avoided in women receiving efavirenz, and treatment with efavirenz should be avoided during the first trimester (the primary period of fetal organogenesis) whenever possible. Women of childbearing potential should undergo pregnancy testing before initiation of efavirenz and should be counseled about the potential risk to the fetus and desirability of avoiding pregnancy. Alternate antiretroviral (ARV) regimens that do not include efavirenz should be strongly considered in women who are planning to become pregnant or who are sexually active and not using effective contraception if such alternative regimens are acceptable to provider and patient and will not compromise the woman's health. However, given that the risk of neural tube defects is restricted to the first 5 to 6 weeks of pregnancy (the neural tube closes at 36–39 days after last menstrual period), pregnancy is rarely recognized before 4 to 6 weeks of pregnancy, and ARV drug changes in pregnancy may be associated with loss of viral control and thus increase risk of transmission to the infant,[6] efavirenz can be continued in pregnant women receiving efavirenz-based antiretroviral therapy (ART) who present for antenatal care in the first trimester, provided that the regimen produces virologic suppression. In such situations, additional fetal monitoring (such as second-trimester ultrasound) should be considered to evaluate fetal anatomy.

Higher rates of failure for hormonal contraceptives containing estrogen and progesterone may be associated with ARV drugs such as efavirenz. Alternate ARV regimens that do not include efavirenz should be strongly considered in women who are planning to become pregnant or who are sexually active and not using effective contraception if such alternative regimens are acceptable to provider and patient and will not compromise the woman's health. Barrier contraception should always be used in combination with other methods of contraception such as hormonal contraceptives and intrauterine devices. A study evaluating the interaction between efavirenz and depot medroxyprogesetrone (DMPA) in 17 women found no change in the pharmacokinetic (PK) profile of either efavirenz or DMPA with concomitant use.[7] DMPA levels remained above the level needed for inhibition of ovulation throughout the dosing interval.

Limited PK data exist for efavirenz in pregnancy. In a study of 25 pregnant women receiving efavirenz during the third trimester as part of clinical care, efavirenz clearance was increased and clearance after 24 hours was decreased compared with postpartum. These differences are not of sufficient magnitude to warrant dose adjustment during pregnancy.[8]

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Etravirine (Intelence, ETV) is classified as FDA Pregnancy Category B.

(Last updated July 31, 2011; last reviewed July 31, 2011)

- Animal carcinogenicity studies
  Etravirine was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Etravirine was evaluated for carcinogenic potential by oral gavage administration to mice and rats for up to approximately 104 weeks. Daily doses of 50, 200, and 400 mg/kg were administered to mice and doses of 70, 200, and 600 mg/kg were administered to rats in the initial period of approximately 41 to 52 weeks. The high and middle doses were subsequently adjusted because of tolerability and reduced by 50% in mice and by 50% to 66% in rats to allow for completion of the studies. In the mouse study, statistically significant increases in the incidences of hepatocellular carcinoma and incidences of hepatocellular adenomas or carcinomas combined were observed in treated females. In the rat study, no statistically significant increases in tumor findings were observed in either sex. The relevance to humans of these liver tumor findings in mice is unknown. Because of tolerability of the formulation in these rodent studies, maximum systemic drug exposures achieved at the doses tested were lower than those in humans at the clinical dose (400 mg/day), with animal versus human AUC ratios being 0.6-fold (mice) and 0.2 to 0.7-fold (rats).

- Reproduction/fertility
  No effect on fertility and early embryonic development was observed when etravirine was tested in rats at maternal doses up to 500 mg/kg/day, resulting in systemic drug exposure equivalent to the recommended human dose (400 mg/day).

- Teratogenicity/developmental toxicity
  Animal reproduction studies in rats and rabbits at systemic exposures equivalent to those at the recommended human dose of 400 mg/day revealed no evidence of fetal toxicity or altered development. Developmental toxicity studies were performed in rabbits (at oral doses up to 375 mg/kg/day) and rats (at oral doses up to 1000 mg/kg/day). In both species, no treatment-related embryo-fetal effects, including malformations, were observed. In addition, no treatment effects were observed in a separate pre- and postnatal study performed in rats at oral doses up to 500 mg/kg/day. The systemic exposures achieved in these animal studies were equivalent to those at the recommended human dose (400 mg/day).

- Placental and breast milk passage
  There are no data on whether etravirine crosses the placenta or is excreted in breast milk in humans.

- Human studies in pregnancy
  No adequate and well-controlled studies of etravirine use in pregnant women have been conducted and very limited case report data are available on etravirine use in pregnancy. One small study described use of etravirine in combination with darunavir/ritonavir and other ARV drugs in four pregnant women; PK sampling was done to determine etravirine plasma concentration during the third trimester.[1] PK data from these women were similar to those in non-pregnant adults. Data on etravirine in postpartum cord blood and concurrent maternal plasma specimens were available for one patient with values of 112 ng/mL and 339 ng/mL (cord/maternal blood ratio 0.33). No maternal, fetal, or neonatal toxicity was reported; one infant was born with a small accessory auricle on the right ear with no other malformations; no birth defects were noted in the other children. Placental passage of etravirine was noted in another report of use of etravirine, darunavir/ritonavir, and enfuvirtide in a pregnant woman who gave birth to twins (cord blood levels 414 ng/mL in Twin 1 and 345 ng/mL in Twin 2).[2] In a separate report on two women receiving etravirine, darunavir/ritonavir, and raltegravir during pregnancy, no perinatal transmission of HIV or congenital abnormalities were observed.[3]

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Nevirapine (Viramune, NVP) is classified as FDA Pregnancy Category B.

(Last updated July 31, 2012; last reviewed July 13, 2012)

- Animal carcinogenicity studies
  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/developmental toxicity
  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 AUC). In rats, however, a significant decrease in fetal weight occurred at doses producing systemic concentrations approximately 50% higher than human therapeutic exposure.

  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 the more common classes, 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 2.7% (28 of 1,020 births; 95% CI, 1.8%–4.0 %) compared with a total prevalence of 2.7% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[1]

- Placental and breast milk passage

  Nevirapine crosses the placenta and achieves neonatal blood concentrations equivalent to that in the mother (cord-to-maternal blood ratio approximately 0.90).[2] Nevirapine is excreted into human breast milk; the median concentration in 4 breast milk samples obtained from 3 women during the first week after delivery was approximately 76% (range 54%–104%) of serum levels.[2] In 19 women receiving combination therapy with nevirapine, lamivudine, and zidovudine, breast milk nevirapine concentration was 6,795 ng/mL, which was 0.67 times that of maternal serum.[3] Median nevirapine breast milk concentration was 4,564 ng/mL in a Kenyan study of 67 HIV-infected nursing mothers receiving a combination of zidovudine, lamivudine, and nevirapine.[3] The median nevirapine concentration was 734 ng/mL in the infants who received the drug only via breast milk.

- Human studies in pregnancy

  Short-Term Peripartum Prophylaxis:

  A Phase I study (PACTG 250) evaluated the safety and PKs of nevirapine administered to infected pregnant women as a single 200-mg dose at the onset of labor and as a single 2-mg/kg dose to infants aged 48 to 72 hours.[2] No adverse effects were seen in the women or the infants.

  The PK parameters of intrapartum nevirapine were similar in pregnant women and in non-pregnant adults, but variability was increased during pregnancy. Nevirapine elimination was prolonged in the infants. The regimen maintained serum concentrations associated with antiviral activity in the infants for the first week of life.

  The safety, toxicity, and PKs of nevirapine were also studied in HIV-infected pregnant women beginning chronic therapy late in the third trimester and their infants.[4] Initial-dose PK profiles in pregnant women were similar to those seen in non-pregnant adults. Serum nevirapine concentrations fell below the 100 ng/mL target concentration by Day 7 of life in four of eight infants, suggesting that nevirapine elimination was accelerated in infants whose mothers received chronic nevirapine administration compared with newborns whose mothers received only a single intrapartum dose.

  The HIVNET 012 study in Uganda compared nevirapine (200 mg orally to the mother at the onset of labor and 2 mg/kg to the neonate within 72 hours of birth) with zidovudine (600 mg orally to the mother at the onset of delivery and 300 mg every 3 hours until delivery, and 4 mg/kg orally twice daily for the first 7 days of life to the neonate). In this study, nevirapine lowered the risk of transmission of HIV by nearly 50% during the first 14 to 16 weeks of life compared with zidovudine.[5] However, the women in this African trial were not receiving any other ARV drugs.

  In the United States, most infected women who know their HIV status during pregnancy receive combination ARV prophylaxis regimens, usually including zidovudine, as well as intravenous zidovudine during delivery, with 6 weeks of zidovudine given to their infant. A Phase III perinatal trial (PACTG 316) conducted in the United States, Europe, the Bahamas, and Brazil evaluated whether the HIVNET 012 single-dose nevirapine regimen in combination with standard combination prophylaxis regimens (at minimum the PACTG 076 zidovudine regimen; 77% of women in the trial received combination ARV

regimens) would provide additional benefits in reducing transmission. Transmission was not significantly different between those who received single-dose nevirapine (1.4%) and those who did not (1.6%).[6] Therefore, use of the single-dose nevirapine regimen is not recommended in women receiving combination regimens in the United States.

Longer-Term Antenatal Combination Therapy (See also Nevirapine and Hepatic/Rash Toxicity):

The PKs of nevirapine have been evaluated in pregnant women receiving nevirapine as part of 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.[7] 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.[8]

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, have been reported in HIV-infected patients receiving nevirapine in combination with other drugs for treatment of HIV disease and in a small number of individuals receiving nevirapine as part of a combination regimen for post-exposure prophylaxis of nosocomial or sexual exposure to HIV.[9] These toxicities have not been reported in women or infants receiving two-dose nevirapine (the HIVNET 012 regimen) for prevention of perinatal transmission. 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.[10-12] Other studies have found that hepatic adverse events with systemic symptoms (often rash) were 3.2-fold more common in women than men.[13] 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 counts >250 cells/mm^3 were 9.8 times more likely than women with lower CD4-cell counts to experience symptomatic, often rash-associated, nevirapine-related hepatotoxicity.[13] Higher CD4-cell counts have also been associated with increased risk of severe nevirapine-associated skin rash.[11] Rates of hepatotoxicity and rash similar to those in U.S. studies have been seen in international cohorts of non-pregnant women but not in association with CD4-cell counts >250 cells/mm^3.[14] In general, in controlled clinical trials, clinical hepatic events, regardless of severity, occurred in 4.0% (range 2.5%–11.0%) of patients who received nevirapine; however, the risk of nevirapine-associated liver failure or hepatic mortality has been lower, in the range of 0.04% to 0.40%.[13, 15] Severe or life-threatening rash occurs in approximately 2% of patients receiving nevirapine.[15]

Although deaths as a result of hepatic failure have been reported in HIV-infected pregnant women receiving nevirapine as part of a combination ARV regimen, it is uncertain if pregnancy increases the risk of hepatotoxicity in women receiving nevirapine or other ARV drugs.[16] In an analysis of two multicenter prospective cohorts, pregnancy itself was a risk factor for liver enzyme elevations (RR 4.7; 95% CI, 3.4–6.5), although nevirapine use was not, regardless of pregnancy status.[17] Additional data from the same cohorts did not show any increased risk of hepatotoxicity in HIV-infected pregnant women receiving nevirapine-based ART versus non-nevirapine-based ART.[18] In a cohort of 612 pregnant and non-pregnant women starting nevirapine-based therapy, CD4-cell count at initiation of therapy but not liver enzyme elevation was a predictor of rash; pregnancy was not an independent risk factor for the development of toxicity.[19] These data suggest that nevirapine is no more toxic in pregnant women than in non-pregnant women.

Women initiating nevirapine with CD4-cell counts >250 cells/mm^3, including pregnant women receiving ARV drugs solely for prevention of transmission, are at increased risk of developing symptomatic, often rash-associated, nevirapine-related hepatotoxicity, which can be severe, life threatening, and in some cases fatal.[20] Therefore, nevirapine should be used as a component of a combination regimen in this setting only if the benefit clearly outweighs the risk. Women with CD4-cell counts <250/mm^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. Hepatic toxicity has not been seen in women receiving single-dose nevirapine during labor for prevention of perinatal transmission of HIV.

Because pregnancy itself can mimic some of the early symptoms of hepatotoxicity, 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 (that is, 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, monthly through 4 months, and every 1 to 3 months thereafter (*Adult Antiretroviral Guidelines*); in patients with pre-existing liver disease, monitoring should be performed more frequently when initiating therapy and monthly thereafter.[21] 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.

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Rilpivirine (Edurant, RPV) is classified as FDA Pregnancy Category B.

(Last updated July 31, 2012; last reviewed July 31, 2012)

- Animal carcinogenicity studies

  Rilpivirine was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Rilpivirine was not carcinogenic in rats when administered at doses 3 times higher than exposure in humans at the recommended dose of 25 mg once daily. Hepatocellular neoplasms were observed in both male and female mice at doses 21 times that of human therapeutic exposure; the observed hepatocellular findings in mice may be rodent specific.[1]

- Reproduction/fertility
  No effect on fertility was observed when rilpivirine was tested in rats at maternal doses up to 400 mg/kg/day, resulting in systemic drug exposure equivalent to 40 times the recommended human dose.

- Teratogenicity/developmental toxicity
  No evidence of embryonic or fetal toxicity or an effect on reproductive function was observed in rat and rabbit dams treated with rilpivirine during pregnancy and lactation at doses 15 and 70 times higher, respectively, than exposure in humans at the recommended dose of 25 mg once daily.

- Placental and breast milk passage
  No data exist on whether rilpivirine crosses the placenta or is excreted in breast milk in humans. Studies in lactating rats and their offspring indicate that rilpivirine is present in rat milk.

- Human studies in pregnancy
  No adequate and well-controlled studies of rilpivirine use in pregnant women have been conducted.

Reference

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