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 and Hepatic/Rash Toxicity (Last updated September 14, 2011; last reviewed July 31, 2012)

Panel's Recommendations
• Nevirapine-based regimens should be initiated in women with CD4 T-lymphocyte (CD4-cell) counts >250 cells/mm^3 only if the benefits clearly outweigh the risks because of the drug's potential for causing hepatic toxicity/hypersensitivity reaction **(AII)**.
• Women who become pregnant while receiving nevirapine-containing regimens and who are tolerating the regimen well can continue on the therapy regardless of CD4-cell count **(AII)**.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*
Rating of Evidence: *I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Increases in hepatic transaminase levels (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) associated with rash or systemic symptoms may be observed during the first 18 weeks of treatment with nevirapine. Signs and symptoms of systemic toxicity may be nonspecific and can include fatigue, malaise, anorexia, nausea, jaundice, liver tenderness, or hepatomegaly with or without initially abnormal hepatic transaminases.[1] Development 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.[2, 3] Other studies have found that hepatic adverse events with systemic symptoms (predominantly rash) were 3.2-fold more common in women than in men.[4, 5] The degree of risk of rash and hepatic toxicity also appears to vary 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/mm^3 were 9.8 times more likely than women with lower CD4-cell counts to experience symptomatic, rash-associated, nevirapine-related hepatotoxicity;[4] a single-center study also found higher CD4-cell counts to be associated with increased risk of severe nevirapine-associated skin rash.[2] CD4-cell counts >250 cells/mm^3 predicted rash illness, but not liver enzyme elevation, among pregnant and non-pregnant women initiating nevirapine-based combination antiretroviral (ARV) regimens in three U.S. university clinics.[6] Other international cohorts of non-pregnant women have experienced hepatotoxicity and rash at similar rates as in U.S. studies, but not in association with CD4-cell counts >250 cells/mm^3.[7] In general, in controlled clinical trials, hepatic events, regardless of severity, have occurred in 4.0% (range 0%–11.0%) of patients who received nevirapine; severe or life-threatening rash has occurred in approximately 2% of patients receiving nevirapine.[8]

Several early reports of death due to hepatic failure in HIV-infected pregnant women receiving nevirapine as part of a combination ARV regimen raised concerns that pregnant women might be at increased risk of hepatotoxicity from nevirapine compared with other ARV drugs.[9, 10] Recent data challenge the notion that nevirapine is uniquely associated with increased hepatotoxicity during pregnancy.[11] In an analysis of two multicenter, prospective cohorts, pregnancy itself was a risk factor for liver enzyme elevations (relative risk 4.7; 5% confidence interval, 3.4–6.5), but nevirapine use was not, regardless of pregnancy status.[11] Additional data from the same cohorts did not show any increased risk of hepatotoxicity in HIV-infected pregnant women receiving nevirapine-based combination ARV regimens versus non-nevirapine-based combination ARV regimens.[12] These data suggest that nevirapine is no more toxic in pregnant women than in non-pregnant women. Nevertheless, if nevirapine is used in pregnancy, health care providers should be aware of potential hepatotoxicity with or without rash and should conduct frequent and careful monitoring of clinical symptoms and hepatic transaminases (that is, ALT and AST), particularly during the first 18 weeks of nevirapine use. Some clinicians measure serum transaminases at baseline, every 2 weeks for the first month,

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monthly through Month 4, and every 1 to 3 months thereafter (see the Hepatotoxicity section of the table on Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects in the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*). In patients with pre-existing liver disease, monitoring should be performed more frequently when initiating nevirapine and monthly thereafter.[1] 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 who have asymptomatic but severe transaminase elevations (that is, more than 5 times the upper limit of normal) should stop nevirapine and not receive nevirapine again in the future.

Hepatic toxicity has not been seen in women receiving single-dose nevirapine during labor for prevention of perinatal transmission of HIV.[13] Women who enter pregnancy on nevirapine-containing regimens and are tolerating them well can continue therapy, regardless of CD4-cell count.

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