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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Special Situations — Stopping Antiretroviral Drugs During Pregnancy (Last updated July 31, 2012; last reviewed July 31, 2012)

Panel's Recommendations

- HIV-infected women receiving antiretroviral therapy (ART) who present for care during the first trimester should continue treatment during pregnancy **(AII)**. If an antiretroviral (ARV) drug regimen is stopped acutely for severe or life-threatening toxicity, severe pregnancy-induced hyperemesis unresponsive to antiemetics, or other acute illnesses that preclude oral intake, all ARV drugs should be stopped and reinitiated at the same time **(AIII)**.
- If an ARV drug regimen is being stopped electively and the patient is receiving a non-nucleoside reverse transcriptase inhibitor (NNRTI) drug, consideration should be given to either: (1) stopping the NNRTI first and continuing the other ARV drugs for a period of time or (2) switching from an NNRTI to a protease inhibitor (PI) before interruption and continuing the PI with the other ARV drugs for a period of time before electively stopping. The optimal interval between stopping an NNRTI and the other ARV drugs is unknown; at least 7 days is recommended. Given the potential for prolonged detectable efavirenz concentrations for >3 weeks in patients receiving efavirenz-based therapy, some experts recommend continuing the other ARV agents or substituting a PI plus two other agents for up to 30 days **(CIII)**.
- If nevirapine is stopped and more than 2 weeks have passed before restarting therapy, nevirapine should be restarted with the 2-week half-dose escalation period **(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*

Discontinuation of antiretroviral (ARV) drug regimens during pregnancy may be indicated in some situations, including serious drug-related toxicity, pregnancy-induced hyperemesis unresponsive to antiemetics, acute illnesses or planned surgeries that preclude oral intake, lack of available medication, or at patients' request.

HIV-infected women receiving antiretroviral therapy (ART) who present for care during the first trimester should continue treatment during pregnancy. Discontinuation of therapy could lead to an increase in viral load with possible decline in immune status and disease progression as well as adverse consequences for the fetus, including increased risk of *in utero* transmission of HIV. A recent analysis from a prospective cohort of 937 HIV-infected mother-child pairs found that interruption of ART during pregnancy, including interruption in the first and third trimesters, was independently associated with perinatal transmission. In the first trimester, the median time at interruption was 6 weeks' gestation and length of time without therapy was 8 weeks (interquartile range [IQR], 7–11 weeks); in the third trimester, the median time at interruption was 32 weeks and length of time without therapy was 6 weeks (IQR, 2–9 weeks). Although the perinatal transmission rate for the entire cohort was only 1.3%, transmission occurred in 4.9% (95% confidence interval [CI], 1.9%–13.2%; adjusted odds ratio [AOR] 10.33; $P = .005$) with first-trimester interruption and 18.2% (95% CI, 4.5%–72.7%; AOR 46.96; $P = .002$) with third-trimester interruption.[1] Although the use of efavirenz should be avoided during the first trimester when possible, therapy should not be interrupted in women taking the drug who present in the first trimester (see HIV-Infected Pregnant Women Who Are Currently Receiving Antiretroviral Treatment).

Continuation of all drugs during the intrapartum period generally is recommended. Women who are having elective cesarean delivery can take oral medications before the procedure and restart drugs following surgery. Because most drugs are given once or twice daily, it is likely that no doses would be missed or that at most the postpartum dose would be given a few hours late.

When short-term drug interruption is indicated, in most cases, all ARV drugs should be stopped and reintroduced at the same time. This can be problematic with drugs that have a long half-life. However, in conditions such as serious or life-threatening toxicity, severe pregnancy-induced hyperemesis unresponsive to antiemetics, or other acute illnesses precluding oral intake, the clinician has no choice but to stop all therapy at the same time. In the rare case in which a woman has limited oral intake that does not meet food requirements for certain ARV agents, decisions about the ARV regimen administered during the antepartum or intrapartum period should be made on an individual basis and in consultation with an HIV treatment expert.

Non-nucleoside reverse transcriptase inhibitor (NNRTI) drugs such as nevirapine and efavirenz have very long half-lives and can be detected for 21 days or longer after discontinuation; efavirenz has a longer half-life than nevirapine.[2-6] Because other drugs in the ARV regimen have shorter half-lives and are cleared more rapidly, only detectable NNRTI drug levels persist, resulting in subtherapeutic drug levels that can increase the risk of selection of NNRTI-resistant mutations. In addition, certain genetic polymorphisms, which may be more common among ethnic groups such as African Americans and Hispanics, may have the potential to result in a slower rate of clearance.[4, 6] To prevent prolonged exposure to a single drug, some experts recommend stopping the NNRTI first and continuing the other ARV drugs for a period of time.[3] However, the optimal interval between stopping an NNRTI and the other ARV drugs is unknown; detectable levels of NNRTIs may be present from <1 week to >3 weeks after discontinuation, with the longer duration primarily observed with efavirenz.[6] An alternative strategy is to substitute a protease inhibitor (PI) for the NNRTI and to continue the PI with dual nucleoside reverse transcriptase inhibitors (NRTIs) for a period of time. In a post-study analysis of the patients who interrupted therapy in the SMART trial, patients who were switched from an NNRTI- to a PI-based regimen before interruption had a lower rate of NNRTI-resistant mutation after interruption and a greater chance of HIV RNA resuppression after restarting therapy than those who stopped all the drugs simultaneously or stopped the NNRTI before the dual NRTIs.[7]

The optimal duration for continuing either dual nucleosides or the substituted PI-based regimen after stopping the NNRTI is unknown, but a minimum of 7 days is recommended based on studies to reduce resistance following single-dose nevirapine.[8, 9]

A pharmacokinetic study of nevirapine elimination in African adults following cessation of steady-state nevirapine-containing regimens found that nevirapine concentrations were estimated to have fallen below 20 ng/mL in 3 of 19 (16%) and 14 of 19 (74%) subjects by 7 and 14 days, respectively, after the cessation of dosing.[10] Elimination half-life was 39 hours in these subjects, considerably shorter than that observed after peripartum exposure to single doses of nevirapine (average 55–60 hours), likely related to induction of nevirapine metabolism with chronic nevirapine exposure.[2, 11, 12] Because efavirenz concentrations have the potential to be detectable for more than 3 weeks, some experts suggest that if efavirenz-based therapy is stopped, the dual NRTIs or PI may need to be continued for up to 30 days. Further research is needed to assess appropriate strategies for stopping NNRTI-containing combination regimens.

Another consideration is reintroduction of nevirapine if it is temporarily stopped and subsequently restarted. A 2-week, half-dose escalation currently is recommended in patients who are started on nevirapine. Dose escalation is necessary because nevirapine induces its own metabolism by inducing cytochrome P450 3A4 liver metabolic enzymes; thus, initial administration of the full therapeutic dose will result in elevated drug levels until metabolic enzyme induction has occurred. In cases where nevirapine has been discontinued for more than 2 weeks, another 2-week dose escalation is recommended when it is reintroduced.

References

1. Galli L, Puliti D, Chiappini E, et al. Is the interruption of antiretroviral treatment during pregnancy an additional major risk factor for mother-to-child transmission of HIV type 1? *Clin Infect Dis.* May 1 2009;48(9):1310-1317. Available at http://www.ncbi.nlm.nih.gov/pubmed/19309307.

2. Cressey TR, Jourdain G, Lallemant MJ, et al. Persistence of nevirapine exposure during the postpartum period after intrapartum single-dose nevirapine in addition to zidovudine prophylaxis for the prevention of mother-to-child transmission of HIV-1. *J Acquir Immune Defic Syndr*. Mar 1 2005;38(3):283-288. Available at http://www.ncbi.nlm.nih.gov/pubmed/15735445.

3. Mackie NE, Fidler S, Tamm N, et al. Clinical implications of stopping nevirapine-based antiretroviral therapy: relative pharmacokinetics and avoidance of drug resistance. *HIV Med*. May 2004;5(3):180-184. Available at http://www.ncbi.nlm.nih.gov/pubmed/15139985.

4. Nolan M, Fowler MG, Mofenson LM. Antiretroviral prophylaxis of perinatal HIV-1 transmission and the potential impact of antiretroviral resistance. *J Acquir Immune Defic Syndr*. Jun 1 2002;30(2):216-229. Available at http://www.ncbi.nlm.nih.gov/pubmed/12045685.

5. Sadiq ST, Fredericks S, Khoo SH, Rice P, Holt DW. Efavirenz detectable in plasma 8 weeks after stopping therapy and subsequent development of non-nucleoside reverse transcriptase inhibitor-associated resistance. *AIDS*. Oct 14 2005;19(15):1716-1717. Available at http://www.ncbi.nlm.nih.gov/pubmed/16184054.

6. Ribaudo HJ, Haas DW, Tierney C, et al. Pharmacogenetics of plasma efavirenz exposure after treatment discontinuation: an Adult AIDS Clinical Trials Group Study. *Clin Infect Dis*. Feb 1 2006;42(3):401-407. Available at http://www.ncbi.nlm.nih.gov/pubmed/16392089.

7. Fox Z, Phillips A, Cohen C, et al. Viral resuppression and detection of drug resistance following interruption of a suppressive non-nucleoside reverse transcriptase inhibitor-based regimen. *AIDS*. Nov 12 2008;22(17):2279-2289. Available at http://www.ncbi.nlm.nih.gov/pubmed/18981767.

8. McIntyre JA, Hopley M, Moodley D, et al. Efficacy of short-course AZT plus 3TC to reduce nevirapine resistance in the prevention of mother-to-child HIV transmission: a randomized clinical trial. *PLoS Med*. Oct 2009;6(10):e1000172. Available at http://www.ncbi.nlm.nih.gov/pubmed/19859531.

9. Farr SL, Nelson JA, Ng'ombe TJ, et al. Addition of 7 days of zidovudine plus lamivudine to peripartum single-dose nevirapine effectively reduces nevirapine resistance postpartum in HIV-infected mothers in Malawi. *J Acquir Immune Defic Syndr*. Aug 2010;54(5):515-523. Available at http://www.ncbi.nlm.nih.gov/pubmed/20672451.

10. Kikaire B, Khoo S, Walker AS, et al. Nevirapine clearance from plasma in African adults stopping therapy: a pharmacokinetic substudy. *AIDS*. Mar 30 2007;21(6):733-737. Available at http://www.ncbi.nlm.nih.gov/pubmed/17413694.

11. Muro E, Droste JA, Hofstede HT, Bosch M, Dolmans W, Burger DM. Nevirapine plasma concentrations are still detectable after more than 2 weeks in the majority of women receiving single-dose nevirapine: implications for intervention studies. *J Acquir Immune Defic Syndr*. Aug 1 2005;39(4):419-421. Available at http://www.ncbi.nlm.nih.gov/pubmed/16010163.

12. Musoke P, Guay LA, Bagenda D, et al. A phase I/II study of the safety and pharmacokinetics of nevirapine in HIV-1-infected pregnant Ugandan women and their neonates (HIVNET 006). *AIDS*. Mar 11 1999;13(4):479-486. Available at http://www.ncbi.nlm.nih.gov/pubmed/10197376.