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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Antiretroviral Drug Resistance and Resistance Testing in Pregnancy (Last updated July 31, 2012; last reviewed July 31, 2012)

Panel's Recommendations

- HIV drug-resistance studies should be performed before starting or modifying antiretroviral (ARV) regimens in all pregnant women whose HIV RNA levels are above the threshold for resistance testing (that is >500–1,000 copies/mL) before initiation of ARVs **(AIII)** and for those entering pregnancy with detectable HIV RNA levels while receiving antiretroviral therapy or who have suboptimal viral suppression after starting ARVs during pregnancy **(AII)**.
- In women who present late in pregnancy, an empiric ARV regimen should be initiated promptly without waiting for the results of resistance testing, with adjustment as needed after test results are available, for optimal prevention of perinatal transmission and maternal health **(BIII)**.
- Women who have documented zidovudine resistance and are on regimens that do not include zidovudine for their own health should still receive intravenous zidovudine during labor along with their established ARV regimens if they have HIV RNA levels >400 copies/mL near delivery (see Intrapartum Antiretroviral Prophylaxis/Therapy), unless a history of hypersensitivity is documented **(AII)**.
- The optimal prophylactic regimen for newborns of women with ARV resistance is unknown (see Infant Antiretroviral Prophylaxis). Therefore, ARV prophylaxis for an infant born to a woman with known or suspected drug resistance should be determined in consultation with a pediatric HIV specialist, preferably before delivery (see Infant Antiretroviral Prophylaxis) **(AIII)**.
- HIV-infected pregnant women should be given combination ARV drug regimens to maximally suppress viral replication, which is the most effective strategy for preventing development of resistance and minimizing risk of perinatal transmission **(AII)**.
- All pregnant and postpartum women should be counseled about the importance of adherence to prescribed ARV medications to reduce the potential for development of resistance **(AII)**.
- To minimize development of resistance, pregnant women who receive a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based combination ARV regimen that is discontinued after delivery should receive either dual nucleoside analogue reverse transcriptase agents alone **(AI)** or with a protease inhibitor **(BII)** for 7 to 30 days **(AII)** after stopping the NNRTI drug. The optimal interval between stopping an NNRTI and the other ARV drugs is unknown (see Stopping Antiretroviral Therapy during Pregnancy and Postpartum Follow-Up of HIV-Infected Women).

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*

Indications for Antiretroviral Drug-Resistance Testing in HIV-Infected Pregnant Women

In addition to a comprehensive history of antiretroviral (ARV) drug use, genotypic resistance testing is recommended for all ARV-naive pregnant women with HIV RNA levels above the threshold for resistance testing (e.g., >500–1,000 copies/mL) before initiating antiretroviral treatment (ART) or prophylaxis. For details regarding genotypic and phenotypic resistance testing see *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*.

Resistance testing should also be performed before initiation of ARV drugs in pregnant women with HIV RNA levels above the threshold for resistance testing (meaning >500–1,000 copies/mL) who received prophylaxis in previous pregnancies and are now restarting ARV drugs for prevention of perinatal

transmission. The identification of baseline resistance mutations may allow selection of more effective and durable ARV regimens.

Resistance testing also should be performed following initiation of an ARV regimen during pregnancy or in HIV-infected pregnant women who are receiving ART when they present for obstetrical care if there is suboptimal viral suppression or persistent viral load rebound to detectable levels after prior viral suppression on the ARV regimen.

In most settings, the results of resistance testing guide selection of the initial ARV regimen. In some situations in pregnant women, however, the clinician may choose to initiate an empiric ARV drug regimen before resistance-testing results are available to optimize prevention of perinatal transmission of HIV. Most experts believe that for women in the third trimester, the benefits of immediate initiation of ARV drugs for prevention of mother-to-child transmission (PMTCT), pending results of resistance testing, outweigh the possible risks of short-term use of a regimen that could be suboptimal because of pre-existing resistance. Once resistance-test results are obtained, the ARV drug regimen can be modified as needed.

Incidence and Significance of Antiretroviral Drug Resistance in Pregnancy

The development of ARV drug resistance is one of the major factors leading to therapeutic failure in HIV-infected individuals. Additionally, pre-existing resistance to a drug in an ARV prophylaxis regimen may diminish the regimen's efficacy in preventing perinatal transmission. The development of resistance to drugs used during pregnancy for prophylaxis of perinatal transmission may limit future maternal treatment options or decrease the effectiveness of prophylactic regimens in the current pregnancy or during future pregnancies. Infant treatment options also may be limited if maternal resistance is present or develops and resistant virus is transmitted to the fetus.

Several factors unique to pregnancy may increase the risk of development of resistance. If drugs with significant differences in half-life (such as nevirapine or efavirenz combined with two nucleoside analogue drugs) are included in the ARV regimen, simultaneous postpartum discontinuation of all regimen components may result in persistent subtherapeutic drug levels and increase the risk of development of non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance (see Stopping Antiretroviral Therapy during Pregnancy). Problems such as nausea and vomiting in early pregnancy may compromise adherence and increase the risk of resistance in women receiving ARV drugs. Pharmacokinetic changes during pregnancy, such as increased plasma volume and renal clearance, may lead to subtherapeutic drug levels, increasing the risk that resistance will develop.

ARV drug-resistance mutations have been observed in HIV-infected women receiving combination ARV drug regimens that are stopped postpartum and appear to be most common when drugs with different half-lives or with a low genetic barrier to resistance (such as NNRTI drugs or lamivudine and emtricitabine) are used during pregnancy and subsequently stopped.[1, 2] Thus, as noted above, resistance testing before initiation of ARV drugs is recommended in pregnant women with detectable HIV RNA levels who received prophylaxis in previous pregnancies and are restarting ARV drugs for prevention of perinatal transmission. Issues relating to discontinuation of NNRTI-based combination therapy are discussed in Prevention of Antiretroviral Drug Resistance.

The Impact of Resistance on the Risk of Perinatal Transmission of HIV and Maternal Response to Subsequent Therapy

Perinatal Transmission

Perinatal transmission of resistant virus has been reported, but appears to be unusual. There is little evidence that presence of resistance mutations increases risk of transmission when current recommendations for ARV

management in pregnancy are followed. A substudy of the Women and Infants Transmission Study followed pregnant women receiving zidovudine alone for treatment of HIV infection in the early 1990s. In this study, detection of zidovudine resistance conferred an increased risk of transmission when analysis was adjusted for duration of membrane rupture and total lymphocyte count;[3] however, women in this cohort had characteristics that would indicate a need for ART under the current Department of Health and Human Services recommendations for maternal health and for prevention of perinatal transmission. When transmitting mothers had mixed viral populations of wild-type and virus with low-level zidovudine resistance, only wild-type virus was detected in their infants,[4] and other studies have suggested that drug-resistance mutations may diminish viral fitness,[5] possibly leading to a decrease in transmissibility. In another study, prevalence of ARV drug resistance among HIV-infected newborns in New York State was examined. Eleven (12.1%) of 91 infants born between 1989 and 1999 and 8 (19%) of 42 infants born between 2001 and 2002 had mutations associated with decreased drug susceptibility. However, perinatal exposure to ARVs was not found to be a significant risk factor for the presence of resistance during either time period.[6, 7] Neither resistance to NNRTI drugs that develops as a result of exposure to single-dose nevirapine nor exposure to single-dose nevirapine in a prior pregnancy has been shown to affect perinatal transmission rates.[8, 9]

Maternal Response to Subsequent Treatment Regimens

Few studies have evaluated response to subsequent therapy in women who receive current combination ARV regimens for prophylaxis and discontinue the drugs postpartum. In theory, however, resistance should not occur if the regimen that was discontinued had fully suppressed viral replication. The French Perinatal Cohort evaluated the association between exposure to ARV drugs for PMTCT during a previous pregnancy and presence of a detectable viral load with exposure to ARV drugs during the current pregnancy in women followed between 2005 and 2009.[10] In 1,166 women not receiving ARVs at the time of conception, 869 were ARV naive and 247 had received ARV drugs for PMTCT during a previous pregnancy. Previous ARV prophylaxis was protease inhibitor (PI) based in 48%, non-PI based in 4%, nucleoside reverse transcriptase inhibitor (NRTI) dual ARVs in 19%, and zidovudine as a single ARV in 29%. A PI-based ARV regimen was initiated in 90% of the women during the current pregnancy; in multivariate analysis, previous ARV exposure in a prior pregnancy was not associated with detectable viral load in the current pregnancy. A separate study reported in abstract form—ACTG A5227—evaluated viral suppression in 52 women with prior combination ARV exposure for PMTCT who had stopped ARV at least 24 weeks before study entry and were now initiating ART (efavirenz, tenofovir, and emtricitabine) for treatment.[11] None of the women had prior or recent resistance detected on standard bulk genotyping. Viral suppression was observed in 81% of women after 24 weeks of follow-up, with no difference in response by number of prior ARV exposures for PMTCT or the drug class of prior exposure.

Management of Antiretroviral Drug Resistance during Pregnancy

For women who have documented zidovudine resistance and whose antepartum regimen does not include zidovudine, the drug still should be given intravenously during labor when indicated (meaning HIV RNA >400 copies/mL near delivery; see Intrapartum Antiretroviral Drug Treatment/Prophylaxis). Other ARVs should be continued orally during labor to the extent possible. The rationale for including zidovudine intrapartum when a woman is known to harbor virus with zidovudine resistance is based on several factors. Data thus far have suggested that only wild-type virus appears to be transmitted to infants by mothers who have mixed populations of wild-type virus and virus with low-level zidovudine resistance.[4] Other studies have suggested that drug-resistance mutations may diminish viral fitness and possibly decrease transmissibility.[5] The efficacy of the zidovudine prophylaxis appears to be based not only on a reduction in maternal HIV viral load but also on pre- and post-exposure prophylaxis in the infant.[12-14] Zidovudine crosses the placenta readily and has a high maternal-to-cord blood ratio. In addition, zidovudine is metabolized to the active triphosphate within the placenta,[15, 16] which may provide additional protection against transmission. Metabolism to the active triphosphate, which is required for activity of all nucleoside analogue agents, has

not been observed within the placenta with other nucleoside analogues that have been evaluated (didanosine and zalcitabine). Zidovudine penetrates the central nervous system (CNS) better than do other nucleoside analogues except stavudine, which has similar CNS penetration; this may help to eliminate a potential reservoir for transmitted HIV in the infant.[17, 18] Thus, intrapartum intravenous administration of zidovudine when indicated currently is recommended even in the presence of known resistance because of the drug's unique characteristics and its proven record in reducing perinatal transmission.

The optimal prophylactic regimen for newborns of women with ARV drug-resistant virus is unknown. Therefore, ARV prophylaxis for infants born to women with known or suspected drug-resistant virus should be determined with a pediatric HIV specialist, preferably before delivery (see Infant Antiretroviral Prophylaxis).

Prevention of Antiretroviral Drug Resistance

The most effective way to prevent development of ARV drug resistance in pregnancy is to use and adhere to an effective combination of ARV drugs to achieve maximal viral suppression. More frequent monitoring of viral load in pregnant women than in non-pregnant individuals is recommended because of the potential increased risk of perinatal HIV infection associated with detectable HIV viremia during pregnancy (see Monitoring of the Woman and Fetus During Pregnancy).

Several studies have demonstrated that women's adherence to ART may worsen in the postpartum period.[19-22] Clinicians caring for postpartum women receiving ART should specifically address adherence, including evaluating specific factors that facilitate or impede adherence.

Because of the prolonged half-life of NNRTI drugs, if an NNRTI-based ARV regimen is stopped postpartum there is a risk of development of NNRTI-resistance mutations if all drugs in the regimen are stopped simultaneously. This has been demonstrated for nevirapine and efavirenz but may also be a problem with newer NNRTI drugs with long half-lives, such as etravirine and rilpivirine. Several studies have shown that development of NNRTI resistance is significantly decreased (but not eliminated) when zidovudine/lamivudine is given intrapartum and administered for 3 to 7 days postpartum in women who have received single-dose intrapartum nevirapine.[23-25] A variety of other regimens (such as tenofovir/emtricitabine, zidovudine/didanosine, zidovudine/didanosine/lopinavir/ritonavir) given for 7 to 30 days postpartum following maternal single-dose nevirapine have also been shown to be very effective in reducing the development of NNRTI resistance.[25-28] These data suggest that the NRTI components of an NNRTI-based regimen should be continued for 7 to 30 days after discontinuation of the NNRTI to minimize the risk of resistance. An alternative strategy is to substitute a PI for the NNRTI and to continue the PI with dual NRTIs for a period of time.[29] The optimal duration for continuation of either dual nucleosides or the substituted PI-based regimen after stopping the NNRTI is unknown. NNRTI drugs have long half-lives, and drug levels can persist for up to 1 to 3 weeks after stopping the drugs; efavirenz levels persist longer than nevirapine levels.[30, 31] More research is needed on the optimal duration of time and regimen to "cover" this period of prolonged NNRTI exposure to prevent the emergence of resistance after discontinuation of an NNRTI-based ARV regimen.

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