Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States

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Pregnant Women Living with HIV Who Have Never Received Antiretroviral Drugs (Antiretroviral Naive) (Last updated December 7, 2018; last reviewed December 7, 2018)

Panel's Recommendations

- Antiretroviral therapy (ART) is recommended for all pregnant women living with HIV to reduce the risk of perinatal transmission of HIV and to optimize the health of the mother **(AI)**. Initiation of ART as soon as HIV is diagnosed during pregnancy is recommended, based on data demonstrating that earlier virologic suppression is associated with a lower risk of transmission **(AII)**.
- HIV drug-resistance studies should guide the selection of ART regimens in women whose HIV RNA levels are above the threshold for resistance testing (i.e., >500 to 1000 copies/mL), unless drug-resistance studies have already been performed (see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy) **(AII)**. When ART is initiated before the results of the drug-resistance assays are available, the ARV regimen should be modified, if necessary, based on the resistance assay results **(BIII)**.
- The choice of regimen should be informed by current adult treatment guidelines; what is known about the use of specific drugs in pregnancy; the risk of teratogenicity (see Table 6 and Table 10); and maternal factors such as nausea, vomiting, and comorbid conditions. ART regimens that are preferred for the treatment of pregnant women living with HIV who are ARV-naive include: a dual nucleoside reverse transcriptase inhibitor combination (abacavir/lamivudine or tenofovir disoproxil fumarate/emtricitabine or lamivudine) and either a ritonavir-boosted protease inhibitor (atazanavir/ritonavir or darunavir/ritonavir) or an integrase strand transfer inhibitor (dolutegravir [after the first trimester][a] or raltegravir) (see Table 6 and Interim Panel Recommendations Regarding the Use of Dolutegravir in Pregnancy in Recommendations for the Use of Antiretroviral Drugs During Pregnancy) **(AIII)**.
- Dolutegravir **is not recommended** for use in pregnant women during the first trimester[a,b] and in nonpregnant women who are trying to conceive, due to concerns about a possible increased risk of neural tube defects **(AIII)**.

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*

[a] The first trimester is <14 weeks (up to 13 6/7 weeks) gestational age by last menstrual period. The term "12 weeks post-conception," used in the Adult and Adolescent Antiretroviral Guidelines, is consistent with the first trimester.

[b] Although dolutegravir is not Food and Drug Administration-approved for use in the first trimester, some Panel members would consider using dolutegravir at 12 weeks gestational age by last menstrual period on an individual patient basis.

Pregnant women living with HIV infection should receive standard clinical, immunologic, and virologic evaluation. Clinicians should discuss treatment options with patients and offer antiretroviral therapy (ART) regimens that contain at least three drugs for the woman's health and for the prevention of perinatal transmission of HIV, consistent with the principles of treatment for nonpregnant adults.[1] Use of an ART regimen that successfully reduces plasma HIV RNA to undetectable levels substantially lowers the risk of perinatal transmission of HIV, minimizes the need to consider elective cesarean delivery as an intervention to reduce risk of transmission, and reduces risk of antiretroviral (ARV) drug resistance in the mother.

Decisions about the timing and management of ART in women who have not previously received ART should be guided by several key principles:

A suppressed viral load at the time of delivery markedly reduces transmission risk.

In an analysis of perinatal transmission in a total of 12,486 infants delivered by women living with HIV between 2000 and 2011 in the United Kingdom and Ireland, the overall perinatal transmission rate declined from 2.1% in 2000 and 2001 to 0.46% in 2010 and 2011. The transmission risk was significantly lower in women with viral loads <50 copies/mL (0.09%) than in women with viral loads of 50 to 399 copies/mL (1.0%), regardless of the type of ARV regimen used or the mode of infant delivery.[2] The continued decline in perinatal transmission rates was attributed to the increasing number of women on ART at the time of conception and reductions in the proportion of women who either initiated ART late in pregnancy or who never received ART prior to delivery.

Early initiation of ART increases viral suppression by the time of delivery and further reduces transmission risk.

Although most perinatal transmission events occur late in pregnancy or during delivery, recent analyses suggest that early control of viral replication may be important in preventing transmission. In the prospective multicenter French Perinatal Cohort, both maternal viral load at delivery and timing of ART initiation were independently associated with perinatal transmission rate. For women who achieved viral loads <50 copies/mL at the time of delivery, transmission risks were 0.9% with third-trimester ART initiation, 0.5% with second-trimester initiation, 0.2% with first-trimester initiation, and 0% (of more than 2,500 infants) with preconception ART initiation. Regardless of when ART was initiated, the perinatal transmission rate was higher for women with viral loads of 50 to 400 copies/mL near delivery than for those with <50 copies/mL, and higher still for women with viral loads >400 copies/mL at delivery (4.4% for women initiating ART in the third trimester and with viral loads >400 copies/mL at delivery).[3]

In an earlier publication that reported on the same cohort, lack of early and sustained control of maternal viral load appeared to be strongly associated with residual perinatal transmission of HIV.[4] Similar data from Canada in 1,707 pregnant women with HIV who were followed between 1997 and 2010 showed that the risk of perinatal transmission was 1% in all mothers receiving ART and 0.4% if ART was taken for more than 4 weeks.[5]

These data suggest that ART should be initiated sufficiently early in ARV-naive women to suppress viral replication by the third trimester, as early and sustained control of HIV viral replication is associated with a decreasing risk of transmission. Other studies have demonstrated that baseline viral load is significantly associated with the likelihood of viral suppression by delivery; thus, prompt initiation of ART is particularly important in pregnant women who have high baseline viral loads.[6-8,9]

Early initiation of ART in pregnancy is generally safe.

The susceptibility of fetuses to the potential teratogenic effects of drugs is dependent on multiple factors, including the gestational age of the fetus at exposure (see Teratogenicity). Although fetal effects of ARV drugs are not fully known, in general, data on the incidence of birth defects among fetuses/infants of women enrolled in observational studies who received ARV regimens during pregnancy have been reassuring. For most ARVs, there have been no differences between the rates of birth defects among infants with first-trimester exposures and the rates among infants with later gestational exposures or the rates reported in the general population.[10-13] The decision about when to initiate ART should be discussed by health care providers and their patients. The discussion should include an assessment of a woman's health status and the benefits and risks to her health and the potential risks and benefits to the fetus.

ARV drugs further reduce transmission risk through infant pre- and post-exposure prophylaxis.

Although rates of perinatal transmission are low in women with undetectable or low HIV RNA levels, there is no threshold below which lack of transmission can be ensured.[14-16] ARV drugs reduce the risk of perinatal transmission of HIV through a number of different mechanisms. Although lowering maternal antenatal viral load is an important component of transmission prevention in women with higher viral load, maternal ART use reduces transmission even in women with low viral loads.[17-21] Additional mechanisms of protection include pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis of the infant. With PrEP, passage of an ARV drug across the placenta produces drug levels that inhibit viral replication in the fetus, particularly during the birth process when there is intensive viral exposure. Therefore, whenever possible, ART regimens initiated during pregnancy should include a nucleoside reverse transcriptase inhibitor (NRTI) with high transplacental passage, such as lamivudine, emtricitabine, tenofovir disoproxil fumarate, or abacavir (see Table 10).[22-25] With post-exposure prophylaxis, ARV drugs are administered to the infant after birth (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV).

Specific ART regimens are preferred in pregnancy.

Table 6 outlines the ARV regimens that are preferred for treatment of pregnant women living with HIV who have never received ARV drugs. These regimens are recommended because they contain effective and durable

ARV drugs that have acceptable toxicity profiles and are easy to use. Pharmacokinetic data in pregnant people is also available for these drugs, and they lack any evidence of teratogenic effects or established adverse outcomes for the mother, fetus, or newborn. Preferred regimens include a dual-NRTI combination (abacavir plus lamivudine or tenofovir disoproxil fumarate with emtricitabine or lamivudine) used in combination with either a ritonavir-boosted protease inhibitor (PI) (atazanavir/ritonavir or darunavir/ritonavir) or an integrase strand transfer inhibitor (INSTI) (dolutegravir or raltegravir).

Dolutegravir is a preferred INSTI for ART-naive women **after the first trimester**. It is a recommended option for an initial ART regimen in adults, and there are sufficient data about the efficacy and safety of dolutegravir when this drug is initiated during pregnancy.[26,27] However, dolutegravir **is not recommended** for use in women during the first trimester or women trying to conceive, due to concerns about possible neural tube defects observed in infants born to women who conceived while receiving dolutegravir (see Interim Panel Recommendations Regarding the Use of Dolutegravir in Pregnancy in Recommendations for the Use of Antiretroviral Drugs During Pregnancy).

Raltegravir is also a preferred INSTI for women who are ARV-naive, and experience with its efficacy and safety in pregnant women is increasing. The selection of drugs for an ART regimen should be based on individual patient characteristics and needs (see Table 6). Table 7 summarizes recommendations for women who are ART naive and pregnant, continuing or restarting ART in pregnancy, or trying to conceive.

Raltegravir or dolutegravir have been suggested for use when ART is initiated late in pregnancy, particularly for women who have high viral loads, because of their ability to rapidly suppress viral load (approximately 2 log copies/mL decrease by Week 2 of therapy).[28-32] Dolutegravir should be considered for treatment of acute infection during pregnancy after the first trimester, because it has a higher barrier to resistance than raltegravir and can be administered with once-daily dosing. Raltegravir has a lower barrier to resistance than dolutegravir; thus, it **is not recommended** for use during acute infection, when viral loads are expected to be high (see Acute HIV Infection). For a discussion regarding the addition of dolutegravir or raltegravir to current ART regimens, see Lack of Viral Suppression.

Resistance tests should be performed, but ART initiation should not be delayed while waiting for results.

Standard ARV drug-resistance testing should be performed before starting an ARV regimen when plasma HIV RNA levels are above the threshold for resistance testing (i.e., >500 to 1,000 copies/mL). Integrase inhibitor resistance testing is not routinely recommended, but it should be performed for women who are at risk for INSTI resistance (e.g., women with partners who were treated with INSTIs or women who had prior treatment that included INSTIs; (see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy). For details regarding genotypic and phenotypic resistance testing, see the Adult and Adolescent Antiretroviral Guidelines. Given the association between earlier viral suppression and a lower risk of transmission discussed above, during pregnancy, ART should be initiated as soon as HIV is diagnosed without waiting for the results of resistance testing. The regimen can be modified, if required, when test results return. Either a PI-based or an INSTI-based ART regimen can be considered when the results of resistance testing are not available to inform the selection of ARV drugs, because clinically significant resistance to PIs and INSTIs is uncommon in ARV-naive individuals.

Regimens other than combination (three-drug) ART are not recommended.

The use of zidovudine monotherapy during pregnancy **is no longer recommended**, because ART provides clear health benefits to the mother and helps prevent the perinatal transmission of HIV. In the past, use of zidovudine alone during pregnancy for prophylaxis of perinatal transmission was an option for women who had low viral loads (i.e., <1,000 copies/mL) on no ARV drugs. Although the Adult and Adolescent Antiretroviral Guidelines recommend some two-drug ART regimens in certain clinical circumstances, two-drug ART regimens **are not recommended** for use in pregnant women.

All pregnant women living with HIV infection should be counseled that ART is recommended, regardless of viral load, to optimally reduce the risk of perinatal transmission. If, after counseling, a woman chooses to forgo the use of ARV drugs during pregnancy, this decision should be re-addressed during subsequent medical

appointments. The Perinatal HIV Hotline (1-800-439-4079) is a resource that can be accessed to assist with the discussion.

ART regimens can be modified postpartum.

ART regimens that were initiated during pregnancy can be modified after delivery. Women may be able to use some simplified regimens that could not be used during pregnancy because the pregnancy, safety, and/or pharmacokinetic data for those regimens were insufficient. Decisions regarding the continuation of an ART regimen or which specific ARV agents to use postpartum should be made by women in consultation with their HIV care providers, considering current adult ART recommendations, plans for contraceptive use and future pregnancies, and individual adherence considerations and medication preferences (see General Principles Regarding Use of Antiretroviral Drugs during Pregnancy).

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