Pregnant People with HIV Who Have Never Received Antiretroviral Drugs (Antiretroviral Naive)

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Panel's Recommendations
• Antiretroviral therapy (ART) is recommended for all pregnant people with HIV to reduce the risk of perinatal HIV transmission and to optimize the health of the pregnant person **(AI)**. Initiating ART as soon as possible in pregnant people who have never received antiretroviral (ARV) drugs is recommended, based on data demonstrating that earlier virologic suppression is associated with a lower risk of transmission **(AII)**. • The results of HIV drug-resistance studies should guide the selection of ARV regimens in people whose HIV RNA levels are above the threshold for resistance testing (i.e., >500 copies/mL to 1,000 copies/mL), unless drug-resistance studies have 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)**. • ARV regimens that are *Preferred* for the treatment of pregnant people with HIV who are ARV-naive include a dual-nucleoside reverse transcriptase inhibitor combination (abacavir plus lamivudine or tenofovir disoproxil fumarate plus either emtricitabine or lamivudine) and either a ritonavir-boosted protease inhibitor (atazanavir/ritonavir or darunavir/ritonavir) or an integrase strand transfer inhibitor (dolutegravir [irrespective of trimester] or raltegravir; see Table 4 and Recommendations for Use of Antiretroviral Drugs During Pregnancy) **(AIII)**. • The Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission emphasizes the **importance of counseling and informed decision making**, with regard to all ARV regimens for people with HIV **(AIII)**. See Appendix C: Antiretroviral Counseling Guide for Health Care Providers for more information.
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

Pregnant people with HIV should receive standard clinical, immunologic, and virologic evaluations. Consistent with the principles of HIV treatment for nonpregnant adults, clinicians should discuss treatment options with pregnant people and offer antiretroviral (ARV) regimens that contain at least three drugs. These regimens reduce the risk of perinatal HIV transmission and optimize the person's health. Use of an ARV 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 the risk of transmission, and reduces the risk of ARV drug resistance in the mother.

Decisions about the timing and management of antiretroviral therapy (ART) in people who have not previously received ART should be guided by several key principles:

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

In an analysis of 12,486 infants delivered by people 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 people with viral loads <50 copies/mL (0.09%) than in people with viral loads of 50 copies/mL to 399 copies/mL (1.0%), regardless of the type of ARV regimen used or the mode of infant delivery.[1] The decline in perinatal transmission rates was attributed to the increasing number of people on ART at the time of conception and reductions in the proportion of people who either initiated ART late in pregnancy or who never received ART prior to delivery.

Initiating ART early increases the likelihood that a person will achieve viral suppression by the time of delivery, further reducing 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 the timing of ART initiation were independently associated with perinatal transmission rate. For people who had achieved viral loads <50 copies/mL at the time of delivery, transmission risk was 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, perinatal transmission rate was higher for people with viral loads of 50 copies/mL to 400 copies/mL near delivery than for those with <50 copies/mL, and it was higher for people with viral loads >400 copies/mL at delivery (4.4% for people who initiated ART in the third trimester and who had viral loads >400 copies/mL at delivery).[2]

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.[3] Similar data from Canada in 1,707 pregnant people with HIV, who were followed between 1997 and 2010, showed that the risk of perinatal transmission was 1% in all mothers who received ART and 0.4% if ART was taken for more than 4 weeks.[4]

These data suggest that ART should be initiated as early as possible in ARV-naive people, because early and sustained control of HIV viral replication is associated with a decreased risk of transmission. Other studies have demonstrated that baseline viral load is significantly associated with the likelihood of viral suppression by the time of delivery; thus, prompt initiation of ART is particularly important in pregnant people who have high baseline viral loads.[5–8]

The benefits of initiating ART early in pregnancy generally outweigh the risks.

The susceptibility of fetuses to the potential adverse effects of drugs is dependent on multiple factors, including the gestational age of the fetus at the time of medication exposure (see Teratogenicity and Antiretroviral Drug Regimens and Maternal and Neonatal Outcomes). The effects of taking ARV drugs during pregnancy are not fully known; however, in general, the data from observational studies on the incidence of birth defects among fetuses/infants of people who received ARV regimens during pregnancy have been reassuring. No differences have been found between the rates of birth defects among infants with first-trimester exposures to most ARV drugs and the rates among infants with later gestational exposures or the rates reported in the general population[9–12] (see Teratogenicity for a more detailed discussion of the adverse events that are associated with the use of specific ARV drugs). 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 person's health status, the risks and benefits to the individual's health, and the potential risks and benefits to the fetus.

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

Although rates of perinatal transmission are low in people with undetectable or low HIV RNA levels, no threshold exists below which lack of transmission can be ensured.[13–15] ARV drugs reduce the risk of perinatal HIV transmission through a number of different mechanisms. Although lowering maternal antenatal viral load is an important component of preventing transmission in people with higher viral loads, maternal ART use reduces transmission even in people with low viral loads.[16–20] Additional mechanisms that reduce the risk of perinatal HIV transmission include pre-exposure prophylaxis and postexposure prophylaxis for the infant.

With pre-exposure prophylaxis, the passage of an ARV drug across the placenta produces drug levels that inhibit viral replication in the fetus, particularly during the birth process when intensive viral exposure occurs.

Therefore, whenever possible, ARV regimens initiated during pregnancy should include a nucleoside reverse transcriptase inhibitor (NRTI) with high transplacental passage, such as lamivudine (3TC), emtricitabine (FTC), tenofovir disoproxil fumarate (TDF), or abacavir (ABC) (see Table 10).[21–24] With postexposure prophylaxis, ARV drugs are administered to the infant after birth (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection).

Specific ARV regimens are *Preferred* for use in pregnancy.

The decision about which ARV drugs to use during pregnancy should be made by a person after discussing the known and potential benefits and risks to the individual and the fetus (infant).

Table 4 and Table 5 outline the ARV regimens that are designated by the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission as *Preferred* for treatment of pregnant people with HIV who have never received ARV drugs, people who are continuing or restarting ART in pregnancy, or people who are trying to conceive (see Pregnant Women with HIV Who Have Previously Received Antiretroviral Treatment and Preconception Counseling and Care for Women of Childbearing Age with HIV. Drugs or drug combinations are designated as *Preferred* for therapy in pregnant people when clinical trial data in adults have demonstrated efficacy and durability with acceptable toxicity and ease of use, and when pregnancy-specific pharmacokinetic (PK) data are available to guide dosing. In addition, the available data must suggest a favorable risk-benefit balance for the drug or drug combination compared to other ARV drug options; the assessment of risks and benefits should incorporate outcomes for people, fetuses, and infants. Some *Preferred* drugs or regimens may have minimal toxicity or teratogenicity risks that are offset by other advantages for people with HIV who are pregnant or who are trying to conceive. Therefore, it is important for health care providers to read all the information on each drug in the Perinatal Guidelines before administering any of these medications to patients (see Appendix B: Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy), and provide appropriate patient counseling to support informed decision-making (see Appendix C: Antiretroviral Counseling Guide for Health Care Providers). *Preferred* regimens include a dual-NRTI combination (ABC plus 3TC or TDF plus FTC or 3TC) used with either a ritonavir-boosted protease inhibitor (PI; atazanavir/ritonavir or darunavir/ritonavir) or an integrase strand transfer inhibitor (INSTI; DTG or raltegravir [RAL]).

DTG is considered a *Preferred* INSTI for ART-naive pregnant people, irrespective of trimester. It is a recommended option for an initial ARV regimen in nonpregnant adults. Sufficient data exist about the efficacy and safety of DTG in pregnancy.[25–28] Maternal use of DTG at the time of conception or in early pregnancy has been associated with an increased risk of neural tube defects (NTDs) in infants. However, given the benefits of DTG in terms of rapid viral suppression and low incidence of side effects, as well as updated evidence that indicates a very low potential risk of NTDs with preconception use, DTG is a *Preferred* ARV during pregnancy, irrespective of trimester, and it is now also a *Preferred* ARV for people trying to conceive (see Recommendations for Use of Antiretroviral Drugs During Pregnancy).

RAL is also a *Preferred* INSTI for ARV-naive people, and the amount of efficacy and safety data for RAL in pregnant people is increasing. The selection of drugs for an ARV regimen should be based on individual patient characteristics and needs (see Table 4 and Table 5).

RAL or DTG have been suggested for use when ART is initiated late in pregnancy, particularly for people who have high viral loads, because of the ability of RAL and DTG to rapidly suppress viral load (a decrease of approximately 2 $\log^{10}$ copies/mL occurs by week 2 of therapy with these drugs).[29–33] In the Dolutegravir in Pregnant HIV Women and Their Neonates (DolPHIN 2) study, 268 ART-naive women in Uganda and South Africa were randomized to receive DTG plus two NRTIs or EFV plus two NRTIs at a median gestational age of 31 weeks. At delivery, women in the DTG arm were significantly more likely to achieve viral loads of

<50 copies/mL (74.1% vs. 42.7%; adjusted risk ratio 1.64 [1.31–2.06], $P < 0.0001$) than women in the EFV arm.[28] Similarly, the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) 1081 trial randomized 408 ART-naive women in South America, Africa, Thailand, and the United States who presented late in pregnancy (20 to <37 weeks gestation) to receive RAL plus two NRTIs or EFV plus two NRTIs. Among 307 women in the primary efficacy analysis, 84% in the EFV group and 94% in the RAL group achieved a viral load of <200 copies/mL at or near delivery (absolute difference 10% [95% CI, 3% to 18%], $P = 0.0015$); the difference primarily occurred among women enrolling later in pregnancy (interaction $P = 0.040$). The median time to achieve a viral load of <200 copies/mL was 8 days for women who received RAL-based ART and 15 days for women who received EFV-based ART. The decline in viral load was greater in the women who received RAL than in those who received EFV at 2, 4, and 6 weeks after initiation.[34]

DTG is *Preferred* for treatment of acute HIV infection during pregnancy, irrespective of trimester, because it has a higher barrier to resistance than RAL and can be administered once daily. Because RAL has a lower barrier to resistance than DTG, it is an *Alternative* ARV for the treatment of acute HIV infection during pregnancy (see Acute HIV Infection). For a discussion regarding the addition of DTG or RAL to current ARV regimens, see Women Who Have Not Achieved Viral Suppression on Antiretroviral Therapy.

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 copies/mL to 1,000 copies/mL). INSTI-resistance testing is not routinely recommended, but it should be performed for people who are at risk for INSTI resistance (e.g., people with partners who were treated with INSTIs, people 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 lower risk of perinatal transmission, ART should be initiated as soon as possible in pregnant people who have never received ARV drugs 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 ARV 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 (ZDV) monotherapy during pregnancy **is no longer recommended**, because ART provides clear health benefits to the mother and helps prevent perinatal HIV transmission. In the past, the use of ZDV monotherapy during pregnancy for prophylaxis of perinatal transmission was an option for people 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 ARV regimens in certain clinical circumstances, two-drug ARV regimens **are not recommended** for use in pregnant people.

All pregnant people with HIV should be counseled that the use of ART is recommended, regardless of viral load, to optimally reduce the risk of perinatal transmission. If, after counseling, a person 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) can provide information to assist with the discussion.

ARV regimens can be modified postpartum.

ARV regimens that were initiated during pregnancy can be modified after delivery. People may be able to use some simplified regimens that could not be used during pregnancy because the pregnancy, safety, and/or PK

data for those regimens were insufficient. Decisions regarding which specific ARV agents to use postpartum should be made by people after they have discussed their options with their HIV care providers. These decisions should take several factors into consideration, including the current adult ART recommendations, a person's 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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