Preventing Perinatal HIV Transmission

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Section 1: Prevention of HIV
Topic 1: Preventing Perinatal HIV Transmission

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Overview
Risk of Perinatal HIV Transmission

The World Health Organization estimates that nearly 10 million cases of perinatal HIV transmission have occurred globally since the beginning of the HIV epidemic, with most of these in resource-poor settings.[1] In the United States, the annual number of perinatal HIV infections peaked at 1650 cases in 1991;[2, 3] since 2013, the number of perinatal HIV infections in the United States has consistently been less than 150 cases per year (Figure 1).[4] In the United States, on an annual basis, approximately 5,000 women living with HIV give birth.[5] For pregnant women with HIV, the estimated rate of perinatal transmission of HIV in the absence of intervention is approximately 25%; among children who acquire HIV perinatally, about 20% of the transmission events occur before 36 weeks of gestation, 50% between 36 weeks and delivery, and 30% during active labor and delivery.[6, 7] With the use of suppressive combination antiretroviral therapy during pregnancy, followed by postnatal infant antiretroviral prophylaxis (and with the judicious use of elective cesarean section and the avoidance of breastfeeding), the current rate of perinatal HIV transmission rate in the United States is less than 1%.[8, 9, 10]

Impact of Antiretroviral Therapy on Perinatal HIV Transmission

In 1994, the landmark Pediatric AIDS Clinical Trials Group (PACTG) 076 trial established that a three-part zidovudine regimen reduced perinatal HIV transmission by 67.5% when compared with placebo (Figure 2).[6] In this trial, the three-part regimen consisted of (1) oral zidovudine initiated at 14 to 34 weeks of gestation and continued throughout pregnancy for mothers with HIV, (2) intravenous zidovudine given during labor and delivery, and (3) oral zidovudine given to the newborn for 6 weeks. The HIV transmission rate (determined at 18 months after birth) was 8.3% in the three-part zidovudine group compared to 25.5% in the placebo group.[6] Later that year, the U.S. Public Health Service (USPHS) issued guidelines recommending the use of zidovudine to reduce perinatal HIV transmission. The PACTG study and the subsequent USPHS recommendations spurred a dramatic decline in the number of cases of HIV perinatal transmission during the 1990s in the United States (Figure 3).[11] Clinical trials and observational studies in the United States, as well as clinical trials of shorter course regimens in lower resource settings, have demonstrated that a variety of antiretroviral regimens markedly reduce the risk of perinatal HIV transmission, with the greatest risk reductions seen with longer duration of antiretroviral therapy during pregnancy (Figure 4) and with use of combination antiretroviral therapy (Figure 5).[1, 11, 12, 13, 14]

Information and Consultation Resources

This topic review will highlight key points from the Perinatal Guidelines.[15] The full text of the Perinatal Guidelines should be consulted for all management decisions and for further reading. In addition, expert consultation can be obtained by calling the National Clinician Consultation Center’s
Perinatal HIV/AIDS Line at (888) 448-8765 that provides information and clinical consultation to medical providers caring for pregnant women with HIV infection and their infants. The Perinatal HIV/AIDS phone consultation service is available 24 hours a day, 7 days a week.
Screening for HIV Infection During Pregnancy

Multiple organizations strongly recommend screening all pregnant women for HIV infection.[16, 17, 18] This recommendation is grounded in data that knowledge of HIV status during pregnancy provides an opportunity to administer antiretroviral therapy to the mother during pregnancy, optimize strategies during delivery to minimize transmission risk, give post-delivery antiretroviral therapy to the newborn, and counsel women to avoid breastfeeding—all of which markedly reduce the risk of perinatal HIV transmission. The recommendation to test women for HIV applies to women presenting at any stage of pregnancy, including during labor. It is also important to remember that women who are at increased risk for HIV acquisition and who test negative for HIV in the first trimester should undergo repeat HIV testing in the third trimester.[16, 19] Further, additional HIV testing should be performed during pregnancy if a woman has a suspected or confirmed diagnosis of sexually transmitted infection.[19] Any pregnant or breastfeeding woman who presents with symptoms suggestive of acute HIV infection should have prompt diagnostic evaluation for acute HIV infection.[19, 20]
Antepartum Management

Indications for Antiretroviral Therapy in Pregnancy

The Perinatal Guidelines recommend using combination antiretroviral therapy for all pregnant women with HIV, regardless of CD4 count or HIV RNA level, to decrease the risk of perinatal HIV transmission and to benefit the mother's health.[21,22] The risk of perinatal HIV transmission increases with higher maternal plasma HIV RNA levels, but transmission can occur in women who have low plasma HIV RNA levels.[23] Therefore, even pregnant women with a low plasma HIV RNA level should receive antiretroviral therapy.

Timing of Initiating Antiretroviral Therapy in Pregnancy

Due to the overwhelming benefits of antiretroviral therapy in preventing perinatal HIV transmission, the Perinatal Guidelines recommend all women with HIV who become pregnant and are not receiving antiretroviral therapy should start antiretroviral therapy without delay.[21] Prior to starting antiretroviral therapy, HIV genotypic drug-resistance testing should be ordered and the blood sample obtained, but treatment should not be delayed while waiting for the drug resistance test results; the antiretroviral regimen can subsequently be modified, if needed, based on the HIV drug resistance test results.[21] A French prospective cohort study reported that perinatal transmission was inversely related to duration of antenatal antiretroviral therapy, with higher rates of transmissions occurring in patients with a short duration of antenatal antiretroviral therapy, as well as in those with preterm delivery at less than 33 weeks (Figure 6).[10] A subsequent nested case control study of the initial French cohort showed that high HIV RNA levels in the early part of pregnancy were responsible for cases of HIV transmission from women who received antiretroviral therapy and had low or undetectable HIV RNA levels near delivery.[24] Given that approximately 80% of perinatal transmissions occur between 36 weeks and the time of birth, intense efforts are warranted to lower HIV RNA levels as much as possible prior to the delivery, even in women who are diagnosed with HIV late in pregnancy.[1,7]

Use of Dolutegravir in Pregnant Women and Women Trying to Conceive

In May of 2018, the U.S. Food and Drug Administration issued a safety alert that warned of potential serious neural tube birth defects in infants born to mothers who received dolutegravir at the time of becoming pregnant or early in the first trimester. This announcement was preceded by preliminary data from an observational surveillance study of birth outcomes in a cohort of pregnant women with HIV in Botswana who received dolutegravir.[25] The slightly higher rate of neural tube defects in infants born to pregnant women receiving dolutegravir led to much alarm and dolutegravir being removed from the list of recommended antiretroviral regimens for pregnant individuals in their first trimester. More recently, these data from Botswana were updated and investigators reported a lower rate of neural tube defects than initially thought, albeit slightly higher than baseline rate of neural tube defects in the population and slightly higher than in pregnant women who received efavirenz.[26] Weighing this evidence against the known benefits of dolutegravir as a potent, well tolerated antiretroviral agent providing rapid and sustained viral suppression, the Perinatal Guidelines now recommend dolutegravir as a preferred drug for pregnant women, regardless of trimester and consider it an alternative regimen for women trying to conceive.[22,27] The Perinatal Guidelines also recommend the clinician and patient have a thorough discussion regarding the risks and benefits of dolutegravir in order to make an informed decision.[28]

Women Already on Antiretroviral Therapy Who Become Pregnant

In most circumstances, if a woman with HIV infection is taking a fully suppressive combination antiretroviral regimen and becomes pregnant, she should continue the current antiretroviral regimen; discontinuing therapy could cause a viral rebound that could increase the risk of HIV
transmission to the fetus. There are, however, several medications or drugs that, according to the Perinatal Guidelines, may require discontinuation, or at least special consideration.

- **Cobicistat**: Recent preliminary data from the IMPAACT protocol P1026s suggest that women taking a regimen that includes elvitegravir-cobicistat have significantly reduced drug levels of elvitegravir and cobicistat during the third trimester of pregnancy, which would presumably lead to an increased risk of virologic failure late in pregnancy. Similar concern has been raised with regimens containing atazanavir-cobicistat or darunavir-cobicistat. Accordingly, for pregnant women taking either elvitegravir-cobicistat, atazanavir-cobicistat, or darunavir-cobicistat, the medical provider should consider switching to a recommended regimen that does not include cobicistat. If a regimen that includes cobicistat is continued, frequent HIV RNA monitoring (e.g. every 1 to 2 months) should be performed during the pregnancy.

- **Didanosine or Stavudine**: Women taking a regimen that contains didanosine, stavudine, or both should not continue on any of these medications during pregnancy due to toxicity risks.

- **Dolutegravir**: Pregnant women receiving dolutegravir who present in the first trimester should be informed that use of dolutegravir is associated with a small but statistically significant increased risk of neural tube defects. The first trimester is considered less than 14 weeks of gestation by last menstrual period, which is consistent with the definition of first trimester as 12 weeks post conception.

- **Efavirenz**: Women taking an efavirenz-based regimen who present for care during pregnancy, including during the first trimester, can continue to take efavirenz, if the regimen is adequately suppressing HIV RNA levels. The first trimester is considered less than 14 weeks of gestation by last menstrual period, which is consistent with the definition of first trimester as 12 weeks post conception. The rationale for the recommendation to permit efavirenz use in the first trimester is threefold: (1) the risk of neural tube defects is limited to the first 5 to 6 weeks of pregnancy and confirmation of pregnancy typically occurs after week 6, (2) a meta-analysis that did not show an increased risk of birth defects among infants born to women with exposure to efavirenz during the first trimester of pregnancy, and (3) unnecessary changes in antiretroviral therapy could lead to loss of suppression of HIV RNA levels. In recent years, the issue of efavirenz use in pregnancy has become less important since efavirenz is no longer included as a preferred antiretroviral regimen for adults.

- **Rilpivirine**: Although rilpivirine plasma levels are expected to decrease during the second and third trimester of pregnancy, the level of reduction is considered unlikely to result in virologic failure. Rilpivirine can be continued at standard doses during pregnancy, but maternal plasma HIV RNA levels should be monitored every 1-2 months during the second and third trimester of pregnancy.

- **Tenofovir alafenamide**: There are sparse data on the safety and pharmacokinetics for tenofovir alafenamide in pregnancy. Accordingly, tenofovir alafenamide is not recommended for routine use in pregnancy. For women who become pregnant while taking tenofovir alafenamide and have a suppressed HIV RNA level, the available data support continuing tenofovir alafenamide, as long as it is not in a fixed-dose combination with elvitegravir-cobicistat-tenofovir alafenamide-emtricitabine.

### Women with Prior Antiretroviral Treatment but Not on Therapy

Some women with HIV who become pregnant may have previously received antiretroviral therapy or antiretroviral prophylaxis, but are not currently taking any antiretroviral medications at the time they are first evaluated during their pregnancy. In this situation, it is very important to review the history and medical records to obtain detailed information regarding past regimens, tolerance of prior medications, adherence with past regimens, evidence of prior virologic failure, and resistance testing data, if available. If the woman's current HIV RNA level is above the threshold for resistance testing (e.g. greater than 500 to 1,000 copies/mL depending on the laboratory performing
the testing), then resistance testing should be ordered prior to starting the antiretroviral regimen during pregnancy. After the drug resistance test blood sample has been obtained, antiretroviral therapy should be started, with modification of the regimen as needed when results from the drug resistance test become available.[32] For women who previously took antiretroviral therapy and have no history of virologic failure or HIV drug resistance, then reinitiating antiretroviral therapy is relatively straightforward. For those women with prior virologic failure and HIV drug resistance, choosing an antiretroviral regimen is more complicated and should ideally be done in conjunction with an HIV treatment specialist.[32]

### Recommended Antiretroviral Regimens in Treatment-Naïve Pregnant Women

The Perinatal Guidelines provide recommendations for initial combination regimens for antiretroviral-naïve pregnant women that include four categories:[27]

- Preferred initial regimens in pregnancy (Table 1),
- Alternative initial regimens in pregnancy (Table 2),
- Insufficient data in pregnancy to recommend routine use in initial regimen (Table 3),
- Not recommended for initial antiretroviral therapy in pregnancy (Table 4).[27]

The preferred antiretroviral regimens for use in pregnancy consist of a dual nucleoside reverse transcriptase inhibitor (NRTI) backbone combined with either a protease inhibitor (PI) boosted with low-dose ritonavir or an integrase strand transfer inhibitor (INSTI).[27]

### Dosing of Darunavir and Atazanavir in Pregnancy

Available data suggest that levels of darunavir significantly decline during pregnancy, even when given with a booster.[33,34] Accordingly, the recommended dosing during pregnancy is darunavir 600 mg twice daily given with ritonavir 100 mg twice daily, taken with food; once-daily darunavir plus ritonavir is not recommended during pregnancy.[33,34] In addition, darunavir-cobicistat should be avoided during pregnancy.[34] When atazanavir is used in pregnancy, it should always be combined with low-dose ritonavir boosting and it should be administered with food.[34] In addition, some experts recommend increasing the dose of atazanavir (from 300 mg once daily to 400 mg once daily) during the second and third trimester to generate levels similar to those in nonpregnant persons.[34,35] Atazanavir-cobicistat is not recommended during pregnancy, due to the concern of lowered drug levels in the second and third trimester.[34]

### Use of Raltegravir or Dolutegravir Late in Pregnancy

Some experts recommend utilizing the INSTI raltegravir or dolutegravir as a component of the antiretroviral regimen for women with high baseline HIV RNA levels who start antiretroviral therapy late in pregnancy, since INSTIs generate a very rapid decline in HIV RNA levels (estimated 2 log decline in 2 weeks).[36,37] In addition, some experts have added raltegravir (to an existing regimen) in the setting of incomplete virologic suppression late in pregnancy;[37,38,39] the benefit of this approach remains unproven and concerns exist that resistance could develop to raltegravir when used in this setting. The Perinatal Guidelines now suggest that a clinician may opt to intensify an inadequate antiretroviral therapy regimen by adding an INSTI for women without virologic suppression late in pregnancy, as long as the woman’s treatment history, including any information on antiretroviral drug resistance testing, has been thoroughly reviewed and the woman’s failing regimen does not already contain an INSTI.[40]
Intrapartum Management

For pregnant women with HIV, the major management decisions at the time of labor are whether to administer intravenous zidovudine and whether to perform cesarean section. These decisions are primarily based on the mother's antiretroviral history during the pregnancy and recent HIV RNA levels.

In Labor without Antepartum Antiretroviral Therapy

For women who present in labor and have unknown HIV antibody status, expedited HIV-1/2 antigen-antibody testing is recommended.[41] Women who have a reactive test (preliminary positive) should be assumed to have HIV infection and all available prevention measures (for the mother and the infant) should be initiated immediately to reduce the risk of perinatal transmission. If the initial HIV screening test is positive, additional confirmatory testing should be performed with an HIV-1/2 differentiation assay and an HIV RNA level. Continuation of antiretroviral therapy for the mother and infant will depend on results of these subsequent HIV confirmatory tests. Since most perinatal HIV transmission occurs at or near the time of delivery, intrapartum intravenous zidovudine should be provided to all women with HIV who are newly diagnosed at the time of labor and to women with known HIV infection who are not taking antiretroviral therapy late in pregnancy.[41] In these settings, the use of intrapartum and postpartum zidovudine reduces the risk of perinatal HIV transmission from 27% to 10%. [14] Most experts recommend cesarean delivery for women newly diagnosed with HIV at the time of labor and for those with known HIV who are not on antiretroviral therapy, since these women are likely to have an HIV RNA level above 1,000 copies/mL—the threshold for elective cesarean section.[42] The benefit of cesarean section after rupture of membranes or onset of labor is unknown.

Continuation of Antiretroviral Therapy During Labor

Pregnant women who have been taking combination antiretroviral therapy prior to onset of labor should continue taking their antiretroviral regimen on schedule (as best as possible) during and after labor.[41] If, however, the combination oral antiretroviral regimen includes zidovudine and the woman receives intravenous zidovudine during labor, the oral zidovudine can be held while she receives intravenous zidovudine.

Indications for Intravenous Zidovudine in Labor

Intravenous zidovudine, when given early in labor, rapidly crosses the placenta and thus can efficiently provide high systemic levels of zidovudine for the infant. Available data show the use of intravenous zidovudine in labor clearly reduces perinatal HIV transmission when the mothers has an HIV RNA level greater than 1,000 copies/mL near the time of delivery.[43] Accordingly, the Perinatal Guidelines recommendation for the use of intravenous zidovudine during delivery for women depends on the maternal HIV RNA level near the time of delivery and whether there are any concerns for maternal antiretroviral medication adherence near delivery.[41]

- **HIV RNA Level Greater than 1,000 copies/mL**: Intravenous zidovudine during delivery is recommended if the maternal HIV RNA level is either known (or suspected) to be greater than 1,000 copies/mL or unknown near delivery.
- **HIV RNA Level between 50 and 1,000 copies/mL**: For women who have an HIV RNA level between 50 and 1,000 copies/mL, inadequate data exist to guide a clear recommendation, but some experts would use intravenous zidovudine in this setting; these situations should be addressed on a case by case basis.[41]
- **Maternal HIV RNA Level Less than 50 copies/mL**: The use of intrapartum zidovudine is not required in women who have an HIV RNA level equal to or less than 50 copies/mL near the time of delivery, as long as no concerns exist regarding antiretroviral adherence.[41]
Dosing of Zidovudine in Labor

The recommended intravenous dose of zidovudine during labor is a 2 mg/kg loading dose over the first hour, followed by a continuous infusion of 1 mg/kg/hour until delivery.\[34\] The intravenous zidovudine should ideally be started at the onset of active labor. For women scheduled to have a cesarean delivery, the intravenous infusion should be started 3 hours prior to the scheduled delivery.\[41\]

Single-dose Nevirapine in Labor is Not Recommended

The Perinatal Guidelines do not recommend giving single-dose nevirapine during labor for any women with HIV in the United States, regardless of whether they have received antepartum combination antiretroviral therapy.\[41\]

Indications for Cesarean Section Delivery

The Perinatal Guidelines recommend performing a scheduled cesarean section at 38 weeks for all women with HIV who have an HIV RNA level greater than 1,000 copies/mL near the time of delivery or with unknown HIV RNA levels near the time of delivery, regardless of whether they are receiving antiretroviral therapy.\[42\] The woman’s CD4 cell count has no bearing on recommendations regarding cesarean delivery. Insufficient data exist to indicate cesarean section would reduce the risk of HIV transmission for women receiving antiretroviral therapy who have detectable viremia that is less than 1,000 copies/mL near the time of delivery. Accordingly, the Perinatal Guidelines do not recommend cesarean section specifically for the purpose of preventing HIV transmission for women who have an HIV RNA level less than 1,000 copies/mL near the time of delivery.\[42\] For women who have an HIV RNA level above 1,000 copies/mL, but who present with rupture of membranes (or present after the onset of labor), the benefit of cesarean is unknown; a meta-analysis has found that the risk of HIV transmission increases by 2% every hour following rupture of membranes.\[42\] For women receiving antiretroviral therapy with an HIV RNA level less than 1,000 copies/mL, the duration of membrane rupture has not been shown to correlate with risk of perinatal HIV transmission and vaginal delivery is recommended in this setting.\[42,44,45,46\] Complex cases should be managed in consultation with an expert in HIV perinatal transmission.

Timing for Cesarean Section Delivery

Despite the potential risk of iatrogenic prematurity, the American Congress of Obstetricians and Gynecologists (ACOG) and the Perinatal Guidelines recommend performing the elective cesarean for women with HIV RNA levels greater than 1,000 copies/mL (or unknown HIV RNA levels) at 38 weeks to avoid onset of labor.\[42\] If the patient has an HIV RNA level less than 1,000 copies/mL and the decision is made to perform a cesarean section for obstetric reasons, the elective cesarean should be performed at the standard time for the specific obstetrical indication.\[42\]

Obstetric Procedures and Risk of HIV Transmission

Although limited data exist regarding the impact of obstetrical procedures on HIV transmission risk, the Perinatal Guidelines recommend against the routine use of any of the following procedures: artificial rupture of membranes, invasive fetal scalp monitoring with scalp electrodes, and operative delivery with forceps or vacuum extractor.\[13,47\] If, however, any of these procedures are deemed to have a clear obstetrical indication, they should be performed. The possible risk of HIV transmission from these procedures is likely lower in women who have an undetectable HIV RNA level at the time of delivery. Epidural anesthesia is considered safe for women with HIV infection in labor, regardless of the antiretroviral regimen the woman is receiving.\[42,47\] In addition, the indications for episiotomy should be the same for women with or without HIV.
Methylergonovine for Postpartum Hemorrhage

Methylergonovine and other ergot alkaloids, which are generally the first-line treatment for postpartum hemorrhage due to uterine atony, are metabolized primarily by the P450 CYP3A4 enzyme system. Potent CYP3A4 inhibitors, such as ritonavir or cobicistat, significantly increase systemic levels of methylergonovine whereas CYP34A inducers, such as efavirenz or nevirapine, lower systemic levels of methylergonovine. Coadministering methylergonovine with medications that may cause a drug interaction can lead to overtreatment (with resulting excessive vasoconstriction) or undertreatment of uterine atony, respectively. Accordingly, other treatment options for uterine atony and bleeding should be considered if the mother is taking a cytochrome P450 CYP3A4 enzyme inhibitor or inducer.[47]
Management of the Infant Exposed to HIV

Antiretroviral Medications for the Newborn

Appropriate management of infants born to mothers with HIV plays a significant role in preventing perinatal HIV transmission. All newborns with perinatal HIV exposure should receive antiretroviral medications in the neonatal period, with the first doses initiated as soon as possible after birth, ideally within 6 to 12 hours following delivery.\(^4\) Antiretroviral management of the newborn with perinatal HIV exposure consists of the administration of one or more antiretroviral drugs as antiretroviral prophylaxis or empiric HIV therapy depending on the estimated risk of perinatal HIV transmission (Table 5).\(^4\) The risk of perinatal HIV transmission is estimated primarily by whether the mother received antiretroviral therapy during pregnancy and what her HIV RNA levels were near delivery; this information, as well as some other factors, are used to make decisions about the neonatal antiretroviral intervention (Table 6).\(^4\) The dosing for all antiretroviral medications in neonates should be based on weight and gestational age.\(^4\)

Initial Care of the Neonate Exposed to HIV Infection

In addition to providing antiretroviral management for all neonates born to mothers with HIV, other aspects of care need to be addressed. Breastfeeding is not recommended for infants born to mothers with confirmed or presumed HIV infection.\(^4\) Following delivery, infants born to mothers with HIV infection require hematological monitoring in addition to routine infant care; there is no evidence that changes in routine bathing practices or timing of circumcision are required.\(^4\) A complete blood count (CBC) and differential should be performed at birth prior to the initiation of infant antiretroviral drug prophylaxis and again at 4 weeks of age since anemia is the primary complication of zidovudine.\(^4\) In addition, some experts advise checking serum chemistry and liver function tests depending on which antiretroviral therapies the infant was exposed to in utero.

Evaluating the Infant for HIV Infection

Initial HIV testing in infants should be performed using an HIV nucleic acid amplification test (NAAT), and either an HIV DNA or HIV RNA assay.\(^5\) Routine HIV antibody testing should not be used in newborns since maternal HIV antibody crosses the placenta and can persist through 18 months of age in infants exposed to HIV.\(^4\) For the criteria listed below for presumptive and definitive exclusion of infant HIV infection, the child should not have any laboratory or clinical indicator that may suggest HIV infection (e.g. a low CD4 cell count or any clinical findings).

- **Recommended Testing**: Virologic testing with either an HIV DNA or HIV RNA test should be performed at 14 to 21 days of life, 1 to 2 months of age, and 4 to 6 months of age. If the risk for infection is higher than usual, such as when the mother does not have virologic suppression near the time of delivery, some experts recommend obtaining an HIV NAAT on the infant at birth (Figure 7).\(^4\)

- **Testing for Non-B Virus Subtypes**: Due to the increasing proportion of foreign-born children with HIV in the United States, testing for non-B viral subtypes is now recommended and the HIV nucleic acid testing should be performed in a laboratory that will detect non-B HIV subtypes if the mother is known to have or suspected to have non-B subtype HIV.\(^4\)

- **Antibody Testing After 12 Months of Age**: A negative HIV antibody test at 12 to 18 months of age provides further confirmation of the child’s HIV negative status and some experts perform antibody testing at this age in infants with prior negative HIV NAAT.\(^4\)

- **Presumptive Exclusion of HIV**: In non-breastfed infants, HIV can be presumptively excluded when any of the following criteria are met: (1) two or more negative HIV NAATs (one at age 14 days or older and the other at age 1 month or older), (2) one negative HIV NAAT at age 8 weeks or older, or (3) one negative HIV antibody test at age 6 months or older.\(^5\)

- **Definitive Exclusion of HIV**: Definitive exclusion of HIV in non-breastfed infants can be
based on either (1) two or more negative HIV NAATs, with one test performed at age 1 month or older and the other test at age 4 months or older, or (2) two negative HIV antibody tests obtained at 6 months of age or older.[50]

- **Indeterminate HIV Infection Status**: This refers to an HIV-exposed child aged younger than 18 months of age who was born to a woman living with HIV and the child does not meet the criteria for having HIV infection or for not having contracted HIV.[50]

**Pneumocystis Pneumonia Prophylaxis for the Infant**

At 4 to 6 weeks of age, all infants born to women with HIV infection should begin prophylaxis for *Pneumocystis* pneumonia, unless HIV infection has been presumptively excluded with virologic testing.[49] The preferred agent for *Pneumocystis* pneumonia prophylaxis in neonates is trimethoprim-sulfamethoxazole.[51] The prophylaxis for *Pneumocystis* pneumonia can be discontinued if the HIV diagnosis in the child is presumptively or definitively excluded.

**Long-term Follow-up of Infants Born to Mothers with HIV Infection**

Although the long-term effects of *in utero* exposure to antiretroviral therapy and to HIV itself (even if the infant was not infected) are not fully known, available data suggest that antiretroviral therapy taken during pregnancy does not cause subsequent long-term risk of neoplasia or organ toxicities to the children of these mothers.[52,53,54,55,56] Nevertheless, further study is needed since newer antiretroviral agents continue to be used in pregnant women with HIV. Multiple studies and surveillance projects, at both the state and national levels, are ongoing. The Perinatal Guidelines recommend that any children with *in utero/perinatal* exposure to antiretroviral therapy who develop organ system abnormalities, particularly neurological or cardiac, should be evaluated for mitochondrial dysfunction, and follow-up of children exposed to antiretroviral medications should continue lifelong due to concern for potential carcinogenicity of nucleoside reverse transcriptase inhibitor drugs.[55] In the long-term medical record of the child, the medical provider should document specific information related to the child's exposure to antiretroviral medications *in utero* and in the postpartum period.
Acute HIV in Pregnancy

Diagnosis of Acute HIV in Pregnancy or in Breastfeeding Mothers

Women have an increased risk of acquiring HIV throughout pregnancy and during the postpartum period.\[57,58\] Acute HIV infection of a woman during pregnancy or while breastfeeding confers a very high risk of HIV transmission to the child because of high HIV RNA levels in the mother’s plasma, genital tract, and breastmilk that occur with acute infection. In one cohort study in New York state, investigators reported the rate of perinatal transmission was 22% among neonates born to mothers who acquired HIV during pregnancy compared to 1.8% of newborns whose mothers did not acquire HIV during pregnancy.\[59\] Therefore, pregnant or breastfeeding women with symptoms of acute retroviral syndrome should undergo prompt evaluation for acute HIV infection.\[20\] When acute HIV is suspected during pregnancy or while breastfeeding, the evaluation should include an HIV RNA assay in combination with antibody testing (preferably a fourth-generation antigen-antibody test).\[20\] If acute HIV is diagnosed, an HIV drug resistance genotype should be ordered, the mother immediately started on antiretroviral therapy, and contact initiated with a pediatric HIV expert.

Antiretroviral Therapy for Acute HIV in Pregnancy

Given the high risk of HIV transmission to the fetus in the setting of acute maternal HIV infection, the Perinatal Guidelines recommend pregnant or breastfeeding women with acute HIV infection should immediately begin triple antiretroviral therapy while the HIV drug resistance genotype is pending, preferably with the regimen of dolutegravir plus tenofovir DF-emtricitabine (regardless of the trimester).\[20\] Alternatively, the woman can start on raltegravir plus tenofovir DF-emtricitabine or a ritonavir-boosted protease inhibitor plus tenofovir DF-emtricitabine.\[20\] If needed, adjustments to the regimen can be made once the genotype results are known.\[20\] If acute HIV infection is diagnosed during pregnancy and the mother continues to receive a dolutegravir-based regimen after birth, the desire for further children should be addressed along with the risks and benefits of conceiving while taking dolutegravir and options for postpartum contraception.\[20\]

Acute HIV in the Postpartum Period

If acute HIV infection is suspected in the postpartum period, the newly diagnosed mother should be counseled to stop breastfeeding until acute HIV infection is ruled out (if HIV infection is confirmed, breastfeeding should be permanently discontinued).\[20\] In this situation, expert consultation should be obtained regarding the evaluation and management of the breastfeeding infant who may have been exposed to HIV. If acute HIV is confirmed in the mother, drug resistance genotype should be ordered and the mother should be promptly started on antiretroviral therapy.\[60\]
Postpartum Follow-Up for Women with HIV

Breastfeeding and Premastication Recommendations

In the United States, breastfeeding is not recommended for mothers living with HIV. Colostrum and breastmilk can efficiently transmit HIV from mother to infant and mothers with HIV who are not on antiretroviral therapy have a 15 to 20% risk of transmitting HIV to their child over a 2-year period of breastfeeding.[49,61] This risk is even higher (25 to 30%) if the mother is infected with HIV during the postpartum period while breastfeeding. [62] It is also important to note that transmission of HIV has occurred via breastfeeding in mothers on antiretroviral therapy who had an undetectable HIV RNA level.[63] Studies have shown that infants who become infected with HIV through breastfeeding when the mother is taking antiretroviral therapy have an increased risk of acquiring drug-resistant HIV.[61,64] Mothers with HIV should also receive instruction to avoid premastication (prechewing or prewarming) of food for their infant.[65] Mothers who elect to breastfeed despite intensive counseling, should receive counseling on using harm reduction methods to minimize the risk of HIV transmission to their child.

Postpartum Antiretroviral Therapy for the Mother

Pregnant women with HIV infection who receive antiretroviral therapy during pregnancy should continue to receive antiretroviral therapy after delivery, both for their own health and to prevent forward sexual transmission of HIV.[65] The HPTN 052 study, among others, has shown that antiretroviral therapy markedly reduces the risk of sexual HIV transmission to uninfected partners in HIV-serodifferent couples.[66] Taking antiretroviral therapy in the postpartum period may be very challenging due to the mother’s fatigue, psychosocial stress, and demands and responsibilities of taking care of a newborn. Indeed, multiple studies have shown that antiretroviral adherence and viral suppression decline after women give birth.[67,68,69] All women should undergo screening for postpartum depression since depression in the postpartum period is more common in women with HIV than in women without HIV and may negatively impact antiretroviral adherence.[68] The Perinatal Guidelines emphasize that maternal services should be coordinated with the woman’s HIV medical provider and decisions about any postpartum changes to the antiretroviral regimen should ideally be made prior to delivery.[65] Medical providers should make sure that women receive antiretroviral medications for themselves and their infants prior to hospital discharge.[65]
Summary Points

- All pregnant women should undergo screening for HIV infection, including women who present in labor without prior testing during the pregnancy.
- For pregnant women with HIV infection, perinatal HIV transmission rates less than 1% can be achieved with a comprehensive, multipronged approach that includes suppressive combination antiretroviral therapy during pregnancy, use of elective cesarean section (when indicated), intravenous zidovudine during labor (when indicated), postnatal infant antiretroviral prophylaxis, and avoidance of breastfeeding.
- The risk of perinatal HIV transmission correlates with maternal HIV RNA levels, but there is no HIV RNA level cutoff at which transmission cannot occur.
- All women diagnosed with HIV infection during pregnancy should start combination antiretroviral therapy and continue it throughout the pregnancy.
- Women with known HIV infection who become pregnant and are not receiving antiretroviral therapy should start antiretroviral therapy and continue therapy throughout the pregnancy.
- In most circumstances, women with established HIV infection who become pregnant and are already taking fully suppressive antiretroviral therapy should continue the same regimen. Consideration should be given to switching any regimen that contains cobicistat.
- Laboratory monitoring of HIV RNA levels should occur every 3 months during pregnancy to evaluate for viral suppression; obtaining an HIV RNA level at 34 to 36 weeks is important in making decisions about delivery and newborn management.
- Since approximately 80% of perinatal transmission takes place between week 36 and birth, women who present late to prenatal care should start on antiretroviral therapy immediately, and additional interventions, including intravenous zidovudine and elective cesarean section, may be recommended to help decrease the risk of perinatal transmission.
- For pregnant women with HIV infection, cesarean section and intravenous zidovudine during labor are indicated if the HIV RNA level is greater than 1000 copies/mL near the time of delivery (or if they have an unknown HIV RNA level near the time of delivery).
- Evaluation for HIV infection of infants younger than 18 months of age who are born to mothers with HIV requires use of HIV nucleic acid amplification tests; a positive HIV antibody test is not reliable since maternal HIV antibody crosses the placenta and often persists in the infant for at least 18 months.
- Infants born to mothers with HIV should receive antiretroviral management based on the infant’s risk of having acquired HIV, which is determined by the mother’s antiretroviral history, her HIV RNA levels near delivery, and the neonate’s HIV diagnostic test results.
- Women with HIV infection in the United States are advised to avoid breastfeeding due to the possibility of transmitting HIV through colostrum and breastmilk and the availability of affordable, safe, and acceptable feeding alternatives.
Citations


with HIV who have never received antiretroviral drugs (antiretroviral naive). December 12, 2019. [AIDSinfo] -


30. Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission. Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States. Recommendations for use of antiretroviral drugs during pregnancy: pregnant women living with HIV who have previously received antiretroviral treatment or prophylaxis but are not currently receiving any antiretroviral medications. December 24, 2019. [AIDSinfo] -


43. Eppes C. Is it time to leave the avoidance of rupture of membranes for women infected with HIV and receiving cART in the past? BJOG. 2016 May;123:982. [PubMed Abstract] -


63. Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission. Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with


References


Figures

Figure 1 Perinatal HIV Infections in the United States, 2013-2018

In the Pediatric AIDS Clinical Trials Group Protocol (PACTG) 076, pregnant women with HIV infection were randomized to receive either zidovudine or placebo. The zidovudine regimen consisted of antepartum oral zidovudine, intravenous zidovudine during labor and delivery, and postpartum oral zidovudine for the infant. The proportion of babies who were determined to have HIV infection at 18 months postpartum was 67.5% lower in the zidovudine arm.

Figure 3 Perinatal HIV Transmission Rates in United States, 1990-1999

This graphic shows trends in maternal-to-infant HIV transmission rates during the years 1990-1999. A major decline occurred in 1994 concurrent with clinician implementation of findings from PATG 076 and then again in 1996 with the more widespread use of antenatal combination antiretroviral therapy.

Figure 4 Timing of Abbreviated Regimens of Zidovudine and Risk of Maternal-Child Transmission of HIV

**Figure 5 Antenatal Antiretroviral Therapy and Impact on Perinatal HIV Transmission**

Figure 6 Mother-to-Child HIV-1 Transmission Rates According to HIV RNA level at Delivery: The ANRS French Perinatal Cohort (1997-2004)

In the ANRA French Perinatal Cohort study, investigators evaluated the risk of mother-to-child HIV-transmission in 5,271 mothers who received antiretroviral therapy during pregnancy. This graph shows the HIV transmission rate based on the HIV RNA level of the mother at delivery and the time of gestation when the baby was born.

Figure 7 Recommended Virologic Testing Schedules for Infants Exposed to HIV by Perinatal HIV Transmission Risk

Abbreviations: NAT = nucleic acid test

For lower-risk infants the last test may be timed to occur at least 2 weeks after stopping antiretroviral therapy.* For higher-risk infants, additional virologic diagnostic testing should be considered at birth and 2 to 6 weeks after cessation of antiretroviral prophylaxis (i.e., at 8 to 12 weeks of life). "Low Risk" refers to infants born to mothers with HIV who received standard antiretroviral therapy during pregnancy and achieved sustained suppression of HIV RNA levels and no concerns exist regarding maternal adherence. "Higher risk infants are those born to mothers with HIV who either did not receive prenatal care, did not receive antepartum or intrapartum antiretroviral therapy, received only intrapartum antiretroviral medications, initiated antiretroviral therapy late in pregnancy (late second or third trimester), diagnosed with acute HIV infection during pregnancy, or had detectable HIV viral loads close to the time of delivery.


<table>
<thead>
<tr>
<th></th>
<th>Birth</th>
<th>2 weeks</th>
<th>3 weeks</th>
<th>4 weeks</th>
<th>8 weeks</th>
<th>10 weeks</th>
<th>4 months</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td></td>
<td></td>
<td></td>
<td><strong>NAT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher Risk</td>
<td><strong>NAT</strong></td>
<td><strong>NAT</strong></td>
<td><strong>NAT</strong></td>
<td><strong>NAT</strong></td>
<td><strong>NAT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 1. *Perinatal Guidelines: Recommendations for Use of Antiretroviral Drugs During Pregnancy*

**Preferred Initial Combination Regimens for Antiretroviral-Naïve Pregnant Women**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preferred Initial Regimens in Pregnancy:</strong></td>
<td></td>
</tr>
<tr>
<td>Drugs or drug combinations are designated as <em>Preferred</em> for therapy in pregnant women when clinical trial data in adults have demonstrated efficacy and durability with acceptable toxicity and ease of use, and pregnancy-specific pharmacokinetic 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 antiretroviral drug options; the assessment of risks and benefits should incorporate outcomes for women, fetuses, and infants. Some <em>Preferred</em> drugs or regimens may have minimal toxicity or teratogenicity risks that are offset by other advantages for women with HIV who are pregnant or who are trying to conceive. Therefore, it is important to read all the information on each drug in the Perinatal Guidelines before administering any of these medications to patients.</td>
<td></td>
</tr>
<tr>
<td><strong>Preferred Dual-NRTI Backbones</strong></td>
<td></td>
</tr>
</tbody>
</table>
| Abacavir-lamivudine | • Available as fixed-dose combination. Can be administered once daily.  
• Abacavir **should not be used** in patients who test positive for HLA-B*5701 because of risk of hypersensitivity reaction.  
• Abacavir-lamivudine with either ritonavir-boosted atazanavir or efavirenz is not recommended if pretreatment HIV RNA is >100,000 copies/mL. |
| Tenofovir DF-emtricitabine  
*or*  
Tenofovir DF plus lamivudine | • Tenofovir DF-emtricitabine is available as a fixed-dose combination.  
• Either coformulated tenofovir DF-emtricitabine or separate doses of tenofovir DF and lamivudine can be administered once daily.  
• Tenofovir DF has potential renal toxicity, thus tenofovir DF-based dual NRTI combinations should be used with caution in patients with renal insufficiency. |
| **Preferred Integrase Stand Transfer Inhibitor (INSTI) Regimens** | |  
| Dolutegravir-Abacavir-Lamivudine  
*or*  
Dolutegravir plus a Preferred Dual-NRTI Backbone | • Administered once daily.  
• The use of dolutegravir-abacavir-lamivudine requires HLA-B*5701 testing, because this fixed-dose combination contains abacavir.  
• INSTI-based regimens may be useful when drug interactions or the potential for preterm delivery with a PI-based regimen are a concern.  
• In nonpregnant adults, dolutegravir is associated with lower rates of INSTI resistance than raltegravir; like raltegravir, dolutegravir has been shown to rapidly decrease viral load in antiretroviral-naïve pregnant women who present to care later in pregnancy.  
• Dolutegravir is *Preferred* for the treatment of pregnant women with acute HIV infection and for women who present to care late in pregnancy.  
• There are specific timing and/or fasting recommendations if dolutegravir is taken with calcium or iron (e.g., in prenatal vitamins).  
• The use of dolutegravir at conception and in very early pregnancy has been associated with a small but statistically
<table>
<thead>
<tr>
<th>Drug</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>significant increase in the risk of neural tube defects; this information should be discussed with patients to ensure informed decision-making. For more information, see Updated Guidance About the Use of Dolutegravir in Pregnancy in the Perinatal Guidelines.</td>
</tr>
</tbody>
</table>
| Raltegravir plus a Preferred Dual-NRTI Backbone | - Pharmacokinetic data are available for raltegravir use in pregnancy, and experience with use in pregnancy is increasing.  
- Raltegravir has been shown to produce rapid viral load decline to undetectable levels in women who present for initial therapy late in pregnancy.  
- INSTI-based regimens may be useful when drug interactions or the potential for preterm delivery with PI-based regimens are a concern.  
- Twice-daily dosing required.  
- There are specific timing and/or fasting recommendations if raltegravir is taken with calcium or iron (e.g. in prenatal vitamins). |

### Preferred Protease Inhibitor (PI) Regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Atazanavir boosted with ritonavir plus a Preferred Dual-NRTI Backbone | - Once-daily administration.  
- Extensive experience in pregnancy.  
- Maternal hyperbilirubinemia; no clinically significant neonatal hyperbilirubinemia or kernicterus reported, but neonatal bilirubin monitoring recommended.  
- Cannot be administered with proton-pump inhibitors; specific timing recommended for dosing with H2 blockers. |
| Darunavir boosted with ritonavir plus a Preferred Dual-NRTI Backbone | - Better tolerated than lopinavir-ritonavir.  
- Experience with use in pregnancy is increasing. Must be used twice daily in pregnancy. |

**Abbreviations**: INSTI = integrase strand transfer inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor

**Source:**
Table 2. **Perinatal Guidelines: Recommendations for Use of Antiretroviral Drugs During Pregnancy**

**Alternative Initial Combination Regimens for Antiretroviral-Naïve Pregnant Women**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alternative Initial Regimens in Pregnancy:</strong></td>
<td></td>
</tr>
<tr>
<td>- Drugs or drug combinations are designated as <em>Alternative</em> options for therapy in pregnant women when clinical trial data in adults show efficacy and the data in pregnant individuals are generally favorable but limited. Most <em>Alternative</em> drugs or regimens are associated with more pharmacokinetic, dosing, tolerability, formulation, administration, or interaction concerns than those in the <em>Preferred</em> category, but they are acceptable for use in pregnancy. Some <em>Alternative</em> drugs or regimens may have known toxicity or teratogenicity risks that are offset by other advantages for women with HIV who are pregnant or who are trying to conceive. Therefore, it is important to read all the information on each drug in the Perinatal Guidelines before administering any of these medications to patients.</td>
<td></td>
</tr>
<tr>
<td><strong>Alternative Dual-NRTI Backbones</strong></td>
<td></td>
</tr>
</tbody>
</table>
| Zidovudine-lamivudine             | - Available as a fixed-dose combination.  
- Although not recommended for initial therapy in nonpregnant adults, zidovudine-lamivudine is the NRTI combination with most experience for use in pregnancy.  
- It has the disadvantages of requiring twice-daily administration. |       |

Page 34/46
Drug | Comment
--- | ---

and having an increased potential for hematologic toxicities and other toxicities.

**Alternative PI Regimens**

| Lopinavir-ritonavir plus a Preferred Dual-NRTI Backbone | • Abundant experience and established pharmacokinetics in pregnancy.  
• More nausea than with preferred agents.  
• Twice-daily administration. A dose increase is recommended during the third trimester.  
• Once-daily lopinavir-ritonavir is **not recommended** for use in pregnant women. |

**Alternative NNRTI Regimens**

| Efavirenz-Tenofovir DF-Emtricitabine  
| or  
| Efavirenz-Tenofovir DF-Lamivudine  
| or  
| Efavirenz plus a Preferred Dual-NRTI Backbone | • Birth defects have been seen in primate studies of efavirenz, but there has been no evidence of an increased risk of birth defects in human studies and extensive experience in pregnancy; cautionary text remains in package insert.  
• These regimens are useful for women who require treatment with |
<table>
<thead>
<tr>
<th>Drug</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>drugs that have significant interactions with Preferred agents, or who need the convenience of a coformulated, single-tablet, once-daily regimen and are not eligible for dolutegravir or rilpivirine.</td>
<td></td>
</tr>
<tr>
<td>• Screening for antenatal and postpartum depression is recommended. Higher rate of adverse events than some Preferred drugs.</td>
<td></td>
</tr>
<tr>
<td>Rilpivirine-tenofovir DF-emtrictabine or Rilpivirine plus a Preferred Dual-NRTI Backbone</td>
<td>• Rilpivirine <strong>is not recommended</strong> with pretreatment HIV RNA &gt;100,000 copies/mL or CD4 cell count &lt;200 cells/mm³.</td>
</tr>
<tr>
<td></td>
<td>• Do not use with proton pump inhibitors (PPIs).</td>
</tr>
<tr>
<td></td>
<td>• PK data are available for pregnant individuals, but there is relatively little experience with use in pregnancy.</td>
</tr>
<tr>
<td></td>
<td>• PK data suggest lower drug levels and risk of viral rebound in second and third trimesters.</td>
</tr>
<tr>
<td>Drug</td>
<td>Comment</td>
</tr>
<tr>
<td>------</td>
<td>---------</td>
</tr>
<tr>
<td></td>
<td>third trimesters; if used, consider monitoring viral load more frequently.</td>
</tr>
<tr>
<td></td>
<td>• Should be taken with food. Available in a coformulated, single-tablet, once-daily regimen.</td>
</tr>
</tbody>
</table>

**Abbreviations:** NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor

**Source:**
  [AIDSinfo]
### Table 3. Perinatal Guidelines: Recommendations for Use of Antiretroviral Drugs During Pregnancy

**Insufficient Data in Pregnancy to Recommend Routine Use in Initial Regimens for Antiretroviral-Naïve Women**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Insufficient Data in Pregnancy to Recommend Routine Use in Initial Regimens for Antiretroviral-Naïve Women:</em></td>
<td></td>
</tr>
<tr>
<td>- These drugs are approved for use in adults but lack adequate pregnancy-specific pharmacokinetic or safety data.</td>
<td></td>
</tr>
</tbody>
</table>
| Bictegravir-tenofovir alafenamide-emtricitabine (Fixed-dose combination) | - No data of the use of bictegravir in pregnancy.  
- Limited data on use of tenofovir alafenamide in pregnancy. |
| Doravirine | - No data of the use of doravirine in pregnancy. |
| Ibalizumab | - No data of the use of ibalizumab in pregnancy. |
| Tenofovir alafenamide-emtricitabine and Rilpivirine-tenofovir alafenamide-emtricitabine (Fixed-dose combination) | - Plasma tenofovir alafenamide exposures in pregnant adults are similar to those seen in nonpregnant adults, whether tenofovir alafenamide is administered with a boosting agent or not.  
- Tenofovir alafenamide has been studied in pregnant women, but data are not yet sufficient to... |
<table>
<thead>
<tr>
<th>Drug</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>recommend initiating tenofovir alafenamide in pregnancy.</td>
</tr>
</tbody>
</table>

Table 4. Perinatal Guidelines: Recommendations for Use of Antiretroviral Drugs During Pregnancy

### Not Recommended for Initial ART or Use in Pregnancy:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Not Recommend for Initial Antiretroviral Therapy or Use in Pregnancy:</strong></td>
<td></td>
</tr>
<tr>
<td>• These drugs and drug combinations are recommended for use in adults but are <strong>not recommended</strong> for use during pregnancy because of concerns about maternal or fetal safety or inferior efficacy, including viral breakthroughs in the second and third trimester</td>
<td></td>
</tr>
<tr>
<td><strong>Note:</strong> When a pregnant woman presents to care while virally suppressed on one of these drugs or drug combinations, providers should consider whether to continue her current regimen or switch to a recommended antiretroviral regimen.</td>
<td></td>
</tr>
<tr>
<td>Atazanavir-cobicistat</td>
<td>• Limited data on the use of atazanavir with cobicistat in pregnancy.</td>
</tr>
<tr>
<td></td>
<td>• Substantial reductions in trough levels of atazanavir in the second and third trimesters have been reported when taken with cobicistat.</td>
</tr>
<tr>
<td>Darunavir-cobicistat (fixed-dose combination) or Darunavir-cobicistat-tenofovir alafenamide-emtricitabine (fixed-dose combination)</td>
<td>• Limited data on use of darunavir with cobicistat in pregnancy.</td>
</tr>
<tr>
<td></td>
<td>• Inadequate levels of both darunavir and cobicistat in the second and third trimesters, as well as viral breakthroughs, have been reported.</td>
</tr>
<tr>
<td>Elvitegravir-cobicistat-tenofovir alafenamide-emtricitabine** (fixed-dose combination)</td>
<td>• Limited data on use of elvitegravir with cobicistat in pregnancy and insufficient data on the use of tenofovir alafenamide in pregnancy.</td>
</tr>
<tr>
<td></td>
<td>• Inadequate levels of both elvitegravir and cobicistat in the second and third trimesters, as well as viral breakthroughs, have been reported.</td>
</tr>
<tr>
<td></td>
<td>• Specific timing and/or fasting recommendations, especially if taken with calcium or iron (e.g., in prenatal vitamins).</td>
</tr>
<tr>
<td>Elvitegravir-cobicistat-tenofovir DF-emtricitabine** (fixed-dose combination)</td>
<td>• Limited data on use of elvitegravir with cobicistat in pregnancy.</td>
</tr>
<tr>
<td></td>
<td>• Inadequate levels of both elvitegravir and cobicistat in the second and third trimesters, as well as viral breakthroughs, have been reported.</td>
</tr>
<tr>
<td></td>
<td>• Specific timing and/or fasting recommendations, especially if taken with calcium or iron (e.g., in prenatal vitamins).</td>
</tr>
</tbody>
</table>

### Not Recommend for Initial Antiretroviral Therapy in Pregnancy:

<p>| <strong>Not Recommend for Initial Antiretroviral Therapy in Pregnancy:</strong> | |
| • These drugs are <strong>not recommended</strong> for use in pregnant women who have never received antiretroviral therapy. |</p>
<table>
<thead>
<tr>
<th>Drug</th>
<th>Comment</th>
</tr>
</thead>
</table>
| With the exception of nevirapine, data about the PKs, safety, and efficacy of these drugs during pregnancy are limited.  
• Some of these drugs are also categorized as not recommended except in special circumstances during pregnancy, because the Panel recognizes that may be circumstances where pregnant women who are antiretroviral-experienced may need to initiate or continue these drugs to reach or maintain viral suppression. |                                                                                                  |
| Etravirine       | • Not recommended for use in antiretroviral-naïve populations.                                    |
| Maraviroc        | • Not recommended for use in antiretroviral-naïve populations.                                    |
|                  | • Maraviroc requires tropism testing before use.                                                   |
|                  | • Available PK data suggest that using the standard adult dose is appropriate for pregnant patients, although data about use during pregnancy are limited. |
| Nevirapine       | • Not recommended because of greater potential for adverse events, complex lead-in dosing, and low barrier to resistance. |
|                  | • Nevirapine should be used with caution when initiating antiretroviral therapy in women with CD4 cell count >25 cells/mm³. |
|                  | • Use nevirapine and abacavir together with caution; both can cause hypersensitivity reactions within the first few weeks after initiation. |
| Enfuvirtide (T-20) | • Not recommended in antiretroviral-naïve populations.                                              |

Source:
Table 5. **Perinatal Guidelines: Management of Infants Born to Women with HIV Infection**

### Types of Antiretroviral Management of Newborns with Perinatal HIV Exposure

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARV Prophylaxis</td>
<td>The administration of one or more antiretroviral drugs to a newborn without documented HIV infection to reduce the risk of perinatal acquisition of HIV.</td>
</tr>
<tr>
<td>Empiric Therapy</td>
<td>The administration of a three-drug combination antiretroviral regimen to newborns at highest risk of perinatal acquisition of HIV. Empiric HIV therapy is intended to be preliminary treatment for a newborn who is later documented to have HIV, but also serves as antiretroviral prophylaxis against HIV acquisition for those newborns who are exposed to HIV in utero, during the birthing process, or during breastfeeding and who do not acquire HIV.</td>
</tr>
<tr>
<td>HIV Therapy</td>
<td>The administration of a three-drug antiretroviral regimen at treatment dosages (antiretroviral therapy) to newborns with documented HIV infection.</td>
</tr>
</tbody>
</table>

Source:

Table 6. **Perinatal Guidelines: Management of Infants Born to Women with HIV Infection**

**Newborn Antiretroviral Management According to Risk of HIV Infection in the Newborn**

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Neonatal Antiretroviral Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low Risk of Perinatal HIV Transmission</strong></td>
<td>Mothers who received ART during pregnancy with sustained viral suppression (defined as a confirmed HIV RNA level less than 50 copies/mL) near delivery and no concerns related to adherence</td>
<td>Zidovudine for 4 weeks</td>
</tr>
<tr>
<td><strong>Higher Risk of Perinatal HIV Transmission</strong></td>
<td>Mothers who received neither antepartum nor intrapartum ARV drugs</td>
<td>Empiric HIV therapy using either zidovudine, lamivudine, and nevirapine (treatment dose) or zidovudine, lamivudine, and raltegravir administered from birth to age 6 weeks$^d$</td>
</tr>
<tr>
<td></td>
<td>Mothers who received only intrapartum ARV drugs</td>
<td>or</td>
</tr>
<tr>
<td></td>
<td>Mothers who received antepartum and intrapartum ARV drugs but who have detectable viral loads near delivery, particularly if delivery was vaginal</td>
<td>Two-drug ARV prophylaxis with 6 weeks zidovudine and 3 doses of nevirapine (prophylactic dosage). The timing of the nevirapine doses is:</td>
</tr>
<tr>
<td></td>
<td>Mothers with acute or primary HIV infection during pregnancy or breastfeeding (in which case, the mother should discontinue breastfeeding)$^c$</td>
<td>• 1st dose at birth to 48 hours&lt;br&gt;• 2nd dose 48 hours after first dose&lt;br&gt;• 3rd dose 96 hours after second dose</td>
</tr>
<tr>
<td><strong>Presumed Newborn HIV Exposure</strong></td>
<td>Mothers with unconfirmed HIV status who have at least one positive HIV test at delivery or postpartum or whose newborns have a positive HIV antibody test</td>
<td>ARV management as above (for higher risk of perinatal HIV transmission).&lt;br&gt;Infant ARV management should be discontinued immediately if supplemental testing confirms that mother does not have HIV.</td>
</tr>
<tr>
<td><strong>Newborn with Confirmed HIV$^e$</strong></td>
<td>Positive newborn HIV virologic test/nucleic acid test</td>
<td>Three-drug combination ARV regimen at treatment dosages</td>
</tr>
</tbody>
</table>

$^a$ See text for evidence supporting combination ARV prophylaxis and empiric HIV therapy.<br>$^b$ See the Intrapartum Care section for guidance on indications for scheduled cesarean delivery and intrapartum intravenous zidovudine to reduce the risk of perinatal HIV transmission for mothers with elevated viral load at delivery.<br>$^c$ Most experts would opt to administer empiric HIV therapy to infants whose mothers had acute HIV during pregnancy because of the high risk for in utero infection. If acute HIV is diagnosed during breastfeeding, mother should stop breastfeeding.<br>$^d$ The optimal duration of empiric HIV therapy in newborns at higher risk of perinatal HIV transmission is unknown. Some Panel members opt to discontinue nevirapine, raltegravir, and/or
lamivudine when a birth nucleic acid test returns negative, while others would continue empiric HIV therapy for infants at highest risk of HIV acquisition for 6 weeks. In all cases, zidovudine should be continued for 6 weeks. It is recommended that providers consult with an expert in pediatric HIV infection to determine therapy duration based on case-specific risk factors and interim HIV nucleic acid test results.

Most panel members do not recommend delaying the initiation of ART while waiting for the results of the confirmatory HIV nucleic acid test, given low likelihood of false-positive HIV NAT testing.

Note: ARV drugs should be initiated as close to the time of birth as possible, preferably within 6 to 12 hours of delivery. See Table 8 in Perinatal Guidelines for dosing specifics.

Key to Acronyms: ART = antiretroviral therapy; ARV = antiretroviral; NAT = nucleic acid test;

Source:
