Initial Use of Antiretroviral Therapy During Pregnancy

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Panel's Recommendations
• Antiretroviral therapy (ART) should be initiated as soon as possible during pregnancy, even before results of drug-resistance testing are available, because viral suppression earlier in pregnancy has been associated with lower risk of transmission **(AI).** When ART is initiated before the results of the drug-resistance assays are available, the antiretroviral (ARV) regimen should be modified, if necessary, based on the resistance assay results **(AII).** • During pregnancy, for ART-naive patients who do not have a history of using long-acting cabotegravir (CAB-LA) as pre-exposure prophylaxis (PrEP), *Preferred* regimens consist of the integrase strand transfer inhibitors (INSTIs) dolutegravir (DTG) or bictegravir (BIC) plus a tenofovir-containing dual–nucleoside reverse transcriptase inhibitor combination (see Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy When Antiretroviral Therapy Has Never Been Received and Early [Acute and Recent] HIV Infection) **(AIII).** *Preferred* regimens include: o DTG plus (tenofovir disoproxil fumarate [TDF] or tenofovir alafenamide [TAF]) plus (emtricitabine [FTC] or lamivudine [3TC]) *or* o BIC plus TAF plus FTC (available only as the fixed-dose combination BIC/TAF/FTC) • When CAB-LA has previously been used as PrEP, genotype testing should be performed before the start of ART and should include screening for INSTI-resistance mutations **(AIII).** ART should be started as soon as possible, before the results of genotype testing are available. o *Preferred* regimens for those who have received CAB-LA as PrEP should consist of the ritonavir-boosted protease inhibitor darunavir/ritonavir, rather than an INSTI, with (TAF or TDF) plus (FTC or 3TC) (see Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy When Antiretroviral Therapy Has Never Been Received and Early [Acute and Recent] HIV Infection) **(AIII).** • *Alternative* ARVs for the treatment of HIV during pregnancy when ARV drugs have never been used are shown in Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy When Antiretroviral Therapy Has Never Been Received. • Choice of ART regimen should be based on results of resistance testing, concurrent medical conditions, and current recommendations for ART in pregnancy **(AIII).** For additional information, see Recommendations for Use of Antiretroviral Drugs During Pregnancy: Overview.
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*

Antiretroviral therapy (ART) regimens designated by the Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission (the Panel) as *Preferred* regimens for pregnancy when ART has never been used (i.e., are ART-naive) and long-acting cabotegravir (CAB-LA) has not previously been used as pre-exposure prophylaxis (PrEP) consist of the integrase strand transfer inhibitors (INSTIs) dolutegravir (DTG) or bictegravir (BIC) plus a tenofovir-containing dual–nucleoside reverse transcriptase inhibitor (NRTI) combination. *Preferred*

regimens for the treatment of pregnancy when antiretroviral (ARV) drugs have never been used include:

- DTG plus (tenofovir disoproxil fumarate [TDF] or tenofovir alafenamide [TAF]) plus (emtricitabine [FTC] or lamivudine [3TC])
- BIC plus TAF plus FTC (available only in fixed-dose combination BIC/TAF/FTC)

The NRTI components listed above are *Preferred* because they are recommended for nonpregnant adults and have several advantages, including reassuring pharmacokinetic (PK) data, extensive experience with use in pregnancy, once-daily dosing, less toxicity than zidovudine plus 3TC, and activity against hepatitis B virus (HBV).[1-3]

DTG is a *Preferred* INSTI for use in pregnancy because it has been studied extensively in pregnancy and is associated with high rates of viral suppression, fast rates of viral load decline, high tolerability, and a high genetic barrier to drug resistance.[4-6] For example, two randomized clinical trials that compared DTG-based regimens versus efavirenz (EFV)-based regimens in ART-naive women who initiated therapy during pregnancy found that DTG-based ART produced more rapid viral suppression than EFV-based ART, with a greater proportion of women reaching an undetectable viral load (<50 copies/mL) at the time of birth.[7,8] Higher rates of viral suppression did not translate into statistically significant differences in perinatal transmission rates, which were low with both regimens, and the studies were not powered to detect small differences.[8-10] Safety and efficacy data support the use of DTG-based ART in pregnancy.[10-12] DTG is *Preferred* for use during pregnancy with early (acute or recent) HIV infection without prior use of CAB-LA as PrEP (see Early [Acute and Recent] HIV Infection).

BIC is also classified as a *Preferred* INSTI for use in pregnancy because it is associated with high rates of viral suppression and has high tolerability; has a high genetic barrier to drug resistance; and is coformulated with a *Preferred* dual-NRTI backbone (TAF/FTC) as a single, once-daily pill. In two separate PK studies, BIC exposure was lower in pregnant women who were in the second and third trimester than in nonpregnant or postpartum patients; however, BIC levels remained above the effective concentration to cause 95% HIV inhibition during pregnancy, and most participants demonstrated viral suppression.[13,14] Therefore, BIC is anticipated to suppress viral load without the need for dose adjustment. Across three separate cohorts in the United States and Canada, involving a total of 485 infants exposed to BIC in pregnancy, BIC was not associated with adverse perinatal or birth outcomes and maternal viral suppression was high.[15-17]

Ritonavir-boosted darunavir (DRV/r) is *Preferred* (rather than an INSTI-based regimen) for pregnancy when there is a history of CAB-LA PrEP use, pending results of genotypic resistance testing for INSTI mutations (see Early [Acute and Recent] HIV Infection and Previous Experience With Antiretroviral Medications but Not Currently on Antiretroviral Therapy During Current Pregnancy). For pregnancies when CAB-LA has not previously been used, DRV/r is classified as an *Alternative* ARV drug for use in pregnancy. Its efficacy in pregnancy is well documented; in a large observational study, viral suppression with DRV/r was not statistically significantly different than viral suppression with DTG.[18] Importantly, however, although the use of once-daily dosing for DRV/r is approved for nonpregnant adults, PK data do not support once-daily dosing in pregnancy[19]; therefore, twice-daily dosing is recommended (see Darunavir).

Abacavir (ABC) is also classified as an *Alternative* ARV drug for use in pregnancy. Despite documented efficacy and safety in pregnancy, the use of ABC requires testing for the HLA-B*5701 gene variant before initiating therapy to avoid ABC-associated hypersensitivity reactions. For this reason, providers should choose to use TDF or TAF rather than ABC to avoid delays in ART initiation while awaiting HLA-B*5701 test results. In addition, some data suggest an increased risk of cardiovascular events associated with ABC. Moreover, ABC is not active against HBV; therefore,

ARV drugs that are active against HBV—TDF or TAF with either 3TC or FTC—should be used for chronic HBV coinfection.

Detailed advantages and disadvantages of each of these *Preferred* medications in pregnancy, as well as of those in the *Alternative*, *Insufficient Data*, *Not Recommended*, and *Not Recommended Except in Special Circumstances* categories, are shown in Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy When Antiretroviral Therapy Has Never Been Received.

Recommendations for Regimens Other Than Combination (Three-Drug) Antiretroviral Therapy

The Adult and Adolescent Antiretroviral Guidelines recommend DTG/3TC as the only two-drug ART regimen for nonpregnant ART-naive adults who have no prior history of using CAB-LA as PrEP, have an HIV RNA ≤500,000 copies/mL, have no active HBV coinfection, and for whom HIV resistance and HBV testing results are available before ART initiation. This combination has demonstrated durable efficacy and viral decay rates similar to those of three-drug regimens in nonpregnant adults.[20-23] The component drugs of this regimen have well-described PK that are adequate in pregnancy and without safety concerns. Data for this regimen in pregnancy are limited to a small, single-center study conducted in Brazil in which 20 women who were ART-naive initiated DTG/3TC during pregnancy; all achieved viral suppression before birth with no safety concerns, and no cases of perinatal HIV transmission were detected.[24] DTG/3TC is thus classified as an *Alternative* ART regimen for use in pregnancy when used in individuals without prior CAB-LA PrEP exposure, with HIV RNA ≤500,000 copies/mL, with no active HBV coinfection, and with confirmed 3TC susceptibility on HIV-resistance testing. DTG/3TC **is not recommended** as initial therapy if HBV or resistance testing results are not yet available, as prompt initiation of ART is critical during pregnancy. Other two-drug ART regimens are **not recommended** for initial treatment during pregnancy because of insufficient data.

Recommendations for Presentation in the Third Trimester

INSTIs have an important role when ART is initiated late in pregnancy, particularly when viral loads are high, because of the documented ability of INSTIs to suppress viral load rapidly (a decrease of approximately 2 $\log_{10}$ copies/mL occurs by Week 2 of therapy with these drugs).[25-29]

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 minimum of 28 weeks gestational age (median: 31 weeks). At birth, 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, with a faster time to reach viral loads <50 copies/mL (4.1 vs. 12.1 weeks).[7] 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 weeks to <37 weeks of gestation) to receive raltegravir (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 birth (absolute difference 10%; 95% confidence interval, 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.[30]

RAL and DTG are likely to be similarly effective in rapidly reducing viral load in instances of presentation in the third trimester. DTG is *Preferred* and RAL is *Alternative* when initiating ART when

ARV drugs have never been used because RAL requires twice-daily dosing and has a lower barrier to development of drug resistance than DTG (see Adult and Adolescent Antiretroviral Guidelines). BIC is a *Preferred* INSTI-based regimen when initiating ART during pregnancy, but data are not available specific to initiating BIC during the third trimester. BIC is also likely to be effective in rapidly reducing viral load and may be considered in instances of presentation in the third trimester if a single tablet, once-daily regimen is needed to support adherence. Other INSTIs (i.e., elvitegravir [EVG] and cabotegravir [CAB]) are **not recommended** when initiating ART in pregnancy because of either concern for insufficient levels (EVG) or lack of data during pregnancy as initial treatment for adults or adolescents who are ARV-naive (CAB). DRV/r is *Preferred* for pregnancy when there is a history of CAB-LA PrEP use, including instances of presentation in the third trimester, pending results of genotypic-resistance testing for INSTI mutations. For more information, see Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy When Antiretroviral Therapy Has Never Been Received.

Presentation after early (acute or recent) HIV infection at any time in pregnancy is discussed in Early (Acute and Recent) HIV Infection.

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