HIV-2 Infection and Pregnancy

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Panel's Recommendations
• HIV-2 infection should be considered in pregnant people who are from—or who have partners who are from—countries in which the virus is endemic and who have positive results on an HIV-1/HIV-2 antibody or HIV-1/HIV-2 antigen/antibody immunoassay. They should be tested with a supplemental HIV-1/HIV-2 antibody differentiation assay. If they have only HIV-2 infection, the test will be negative for HIV-1 antibodies and positive for HIV-2 antibodies (AII). • Pregnant people with HIV-2 infection should be treated based on the guidelines for HIV-1 infection but using antiretroviral (ARV) drugs that are active against HIV-2. Non-nucleoside reverse transcriptase inhibitors, enfuvirtide, and fostemsavir are not active against HIV-2 and should not be used (AIII). • No randomized clinical trials have been performed to address when to start treatment or what the optimal treatment is for HIV-2 infection (AIII). A regimen with two nucleoside reverse transcriptase inhibitors (NRTIs) and integrase strand transfer inhibitors or certain boosted protease inhibitors is recommended for all pregnant people with HIV-2 infection (AIII). • Dolutegravir, bictegravir, raltegravir, or darunavir/ritonavir plus a dual-NRTI backbone of abacavir plus lamivudine (3TC), or tenofovir disoproxil fumarate or tenofovir alafenamide plus emtricitabine or 3TC, are recommended for treating HIV-2 -infection alone in pregnant people and in people who are trying to conceive (AIII). Zidovudine (ZDV) plus 3TC can be used as an alternative dual-NRTI backbone. See Recommendations for Use of Antiretroviral Drugs During Pregnancy and Appendix C: Antiretroviral Counseling Guide for Health Care Providers. • If a pregnant individual is already receiving antiretroviral therapy with drugs that are active against HIV-2, treatment should be continued (AIII). • As with HIV-1, the possibility of hepatitis B virus/HIV-2 coinfection should be considered when choosing an ARV regimen to treat HIV-2 (AI) (see Hepatitis B Virus/HIV Coinfection). • All infants born to people with HIV-2 infection (without HIV-1 infection) should receive a 4-week ZDV prophylactic regimen (BIII) (see Table 10. Neonatal Antiretroviral Management According to Risk of HIV Infection in the Newborn and Table 11. Antiretroviral Drug Dosing Recommendations for Newborns). • People with HIV-2 infection should receive patient-centered, evidence-based counseling to support shared decision-making about infant feeding options prior to and during pregnancy; counseling and plans for infant feeding should be reviewed again after delivery (AIII) (see Infant Feeding for Individuals with HIV in the United States).
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*

HIV-2 infection is endemic in West African countries, including Burkina Faso, Cape Verde, The Gambia, Ghana, Guinea, Guinea-Bissau, Ivory Coast, Liberia, Mali, Mauritania, Niger, Nigeria, Sao Tome, Senegal, Sierra Leone, and Togo. It is also endemic in Angola, Mozambique, and parts of India.[1-4] It also occurs in countries that have large numbers of immigrants from these regions, such as France and Portugal.[5]

HIV-2 remains rare in the United States. According to the National HIV Surveillance System, 327,700 diagnoses of HIV were recorded in the United States from 2010 to 2017, of which 198 (0.06%) met the criteria for HIV-2 (HIV-2 infection alone, n = 102; dual HIV-1 and HIV-2, n = 11; probable but unconfirmed HIV-2, n = 85).[6] Among these cases, 99 women had diagnoses of

confirmed or probable HIV-2, and 9 of these women had evidence of pregnancy at or after their diagnosis. No perinatal HIV-2 transmissions were reported. HIV-2 infection should be suspected in pregnant people who are from—or who have partners from—countries in which the disease is endemic and who have positive results on an HIV-1/HIV-2 antibody or HIV-1/HIV-2 antigen/antibody immunoassay. They should be tested with a supplemental HIV-1/HIV-2 antibody differentiation immunoassay. If they have only HIV-2 infection, the test will be negative for HIV-1 antibodies and positive for HIV-2 antibodies. In rare instances, a person may have dual infection with HIV-1 and HIV-2, and both tests will be positive.

In 2014, the Centers for Disease Control and Prevention (CDC) released a new HIV testing algorithm. The first step in this algorithm is performing an HIV-1/HIV-2 antigen/antibody combination assay on serum or plasma (e.g., Abbott Architect HIV Ag/Ab combo assay, Bio-Rad GS Combo Ag/Ab EIA, Alere Determine).[7] This test does not distinguish between HIV-1 antibodies and HIV-2 antibodies. Specimens that are reactive on this test must be tested with a U.S. Food and Drug Administration (FDA)–approved antibody assay to distinguish HIV-1 antibodies from HIV-2 antibodies. The FDA-approved HIV-2 antibody supplemental test Geenius (Bio-Rad Laboratories) is used as part of the CDC-recommended HIV laboratory testing algorithm.

Viral load assays for HIV-2 are not commercially available, but they may be available under research protocols. The University of Washington[8] and the New York State Department of Health, Wadsworth Center[9] also offer HIV-2 viral load assays. The University of Washington accepts specimens forwarded from laboratories, such as Quest Diagnostics. All HIV-2 cases should be reported to the HIV surveillance program of the state or local health department, which can arrange for additional confirmatory testing for HIV-2 by the CDC.[10] No validated HIV-2 genotype or phenotype resistance assays are available in the United States. HIV-2 genotypic resistance assays are available for research use only at the University of Washington. Drug resistance against HIV-2 can be determined using the HIV-2 EU resistance tool, and another French resistance tool.[11,12]

HIV-2 has a longer asymptomatic phase than HIV-1, with a slower progression to AIDS. However, without effective antiretroviral therapy (ART), HIV-2 will progress to AIDS and death in the majority of individuals over time.[13] The most common mode of HIV-2 transmission is through sex. HIV-2 is less infectious than HIV-1, with a fivefold lower rate of sexual transmission and 20-fold to 30-fold lower rate of perinatal transmission.[3,14,15] Several studies confirm that rates of perinatal transmission of HIV-2 are low with and without interventions (0% to 4%), which may be a result of reduced plasma viral loads, higher CD4 T lymphocyte (CD4) cell counts, and less cervical viral shedding in women with HIV-2 infection than in women with HIV-1 infection.[16-19] In a meta-analysis comparing perinatal transmission of HIV-1 and HIV-2, the pooled incidence of HIV-2 perinatal transmission was 0.2% (95% confidence interval [CI], 0.03% to 1.47%) among antiretroviral-naive pregnant women.[20]

HIV-2 also can be transmitted through breastfeeding. HIV-2 infection does not protect against HIV-1, and dual infection—which carries the same prognosis as HIV-1 infection alone—can occur.[21]

Recommended Antiretroviral Therapy for Pregnant People with HIV-2 Infection

Pregnant people with HIV-2 infection should be treated according to the guidelines for patients with HIV-1 infection alone, although clinicians should make sure that the chosen antiretroviral (ARV) regimen is also appropriate for treatment of HIV-2. Once treatment is started, ART should be continued postpartum as is recommended for all patients with HIV-1. A systematic review analyzed

data collected from 1996 to 2012 on treatment outcomes among nonpregnant patients with HIV-2. The review reported a heterogeneity of treatment outcomes among patients who initiated ART, especially in resource-limited settings.[22] Non-nucleoside reverse transcriptase inhibitors (NNRTIs), enfuvirtide, and fostemsavir are not active against HIV-2 and **should not be used** for treatment or prophylaxis.[23,24] The integrase strand transfer inhibitors (INSTIs) raltegravir (RAL), elvitegravir, dolutegravir (DTG), bictegravir (BIC), and cabotegravir (CAB) are effective against HIV-2.[25,26] Although DTG may be able to rescue a failing RAL-based regimen in a person with HIV-2 infection, a study has reported the emergence of DTG-resistance mutations in people with HIV-2 infection.[27] The CCR5 antagonist maraviroc appears to be active against some strains of HIV-2, although no approved assays exist to determine HIV-2 co-receptor tropism.[28,29] HIV-2 drug resistance has been documented with various ARV drugs.[30,31] Among 47 ART-naive people with HIV-2, ultradeep sequencing showed that three people displayed plasma viruses with a resistance-associated mutation (RAM) above the 20% detection threshold, with a prevalence of transmitted drug resistance for nucleoside reverse transcriptase inhibitors (NRTIs) of 7.9% (95% CI, 0.0% to 16.5%). No RAM above the 20% detection threshold was found for protease inhibitors (PIs) or INSTIs.[32] For patients with multidrug-resistant virus, ibalizumab and lenacapavir demonstrate *in vitro* potency against HIV-2 and may be considered; these drugs are not recommended except in special circumstances for use in pregnancy.

HIV-2 has variable susceptibility to PIs, with lopinavir (LPV) and darunavir (DRV) having the most activity.[33]

The care of pregnant people with HIV-2 infection alone has been based on expert opinion. A regimen with two NRTIs and an INSTI or a ritonavir-boosted PI currently is recommended for all pregnant people with HIV-2 infection. The following regimens can be used to treat HIV-2, based on the available efficacy and safety data on these drugs from clinical trials of pregnant people with HIV-1 infection:

- DTG, BIC, RAL, or darunavir/ritonavir plus a dual-NRTI backbone of abacavir plus lamivudine (3TC), or tenofovir disoproxil fumarate or tenofovir alafenamide plus emtricitabine or 3TC are the recommended regimens for treating HIV-2 infection alone in pregnant people and people who are trying to conceive. See Recommendations for the Use of Antiretroviral Drugs During Pregnancy: Overview, Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy for People Who Are Antiretroviral-Naive, Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive, and Appendix C: Antiretroviral Counseling Guide for Health Care Providers.[34]
- Zidovudine (ZDV) plus 3TC can be used as an alternative dual-NRTI backbone.
- NNRTIs **should not be used** because they are not active against HIV-2.

If a pregnant individual is already receiving ART with drugs that are active against HIV-2, treatment should be continued.

When monitoring the plasma viral loads and CD4 counts in pregnant people with HIV-2 infection, clinicians should follow the guidelines outlined for people with HIV-1 infection (see Initial Evaluation and Continued Monitoring of HIV-Related Assessments During Pregnancy). However, disease progression can occur in the setting of undetectable HIV-2 plasma viral load. Patients who have HIV-2 plasma viral loads that are below the limits of detection should still have routine CD4

counts and clinical monitoring (see Plasma HIV-1 RNA [Viral Load] and CD4 Count Monitoring in the Adult and Adolescent Antiretroviral Guidelines).

No data are available to address whether treatment should be continued after pregnancy in people with HIV-2 infection alone. To date, no randomized trials have addressed the question of an optimal treatment strategy for HIV-2 infection. The Adult and Adolescent Antiretroviral Guidelines recommend that all patients with HIV-2 infection should be treated using the guidelines provided for patients with HIV-1 infection, see HIV-2 Infection.

All infants born to people with HIV-2 who do not have HIV-1 should receive a 4-week ZDV prophylaxis regimen (see Table 10. Neonatal Antiretroviral Management According to Risk of HIV Infection in the Newborn and Table 11. Antiretroviral Drug Dosing Recommendations for Newborns). The possible risks and benefits of ARV prophylaxis should be discussed with the birthing parents. As noted above, rates of perinatal transmission of HIV-2 are low with and without interventions, and it is unclear whether infants born to people with undetectable HIV-2 viral loads will benefit from ARV prophylaxis. However, monitoring HIV-2 plasma viral loads in birthing parents and receiving the results in a timely manner can be difficult because plasma samples must be sent to the University of Washington or the New York State Department of Health. Therefore, the Panel on Treatment of HIV During Pregnancy and Interventions to Prevent Perinatal HIV Transmission recommends that all infants born to pregnant people with HIV-2 receive prophylaxis. ZDV prophylaxis is recommended in this clinical situation because nevirapine lacks activity against HIV-2. Guidance on ARV prophylaxis for infants born to individuals with HIV-1 and HIV-2 infection is available in Table 10. Neonatal Antiretroviral Management According to Risk of HIV Infection in the Newborn and Table 11. Antiretroviral Drug Dosing Recommendations for Newborns.

No data exist on the impact of scheduled cesarean delivery on HIV-2 perinatal transmission. The risk to infants from breastfeeding is lower for HIV-2 than for HIV-1, but the risk is not zero.[17] Individuals with HIV-2 infection should receive patient-centered, evidence-based counseling to support shared decision-making about infant feeding. Counseling about infant feeding should begin prior to conception or as early as possible in pregnancy; information about and plans for infant feeding should be reviewed throughout pregnancy and again after delivery (see Infant Feeding for Individuals with HIV in the United States).

Infants born to mothers with HIV-2 should be tested for HIV-2 infection with HIV-2-specific virologic assays at time points similar to those used for HIV-1 testing; see Diagnosis of HIV Infection in Infants and Children.[35] Quantitative HIV-2 plasma RNA viral load testing for clinical care is available from the University of Washington[8] and the New York State Department of Health.[9] Antibody testing of infants (e.g., with the Bio-Rad Laboratories Multispot HIV-1/HIV-2 test) also can be performed at age 18 months to confirm clearance of HIV-2 antibodies.

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