Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

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HIV-2 Infection and Pregnancy  (Last updated October 26, 2016; last reviewed October 26, 2016)

Panel’s Recommendations

- HIV-2 infection should be considered in pregnant women who are from—or 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 assay. If they are indeed HIV-2 infected it would show negative HIV-1 antibodies and positive HIV-2 antibodies (AII).

- Pregnant women with HIV-1 and HIV-2 coinfection should be treated as per guidelines for HIV-1 monoinfection, but using antiretroviral drugs to which HIV-2 is sensitive (see below).

- No randomized clinical trials have been performed to address when to start treatment or what the optimal treatment is for HIV-2 monoinfection.

- Optimal prophylactic regimens have not been defined for HIV-2-monoinfected pregnant women. A regimen with two nucleoside reverse transcriptase inhibitors and a boosted protease inhibitor or integrase strand transfer inhibitor is recommended for all HIV-2-infected pregnant women (AII).

- Non-nucleoside reverse transcriptase inhibitors and enfuvirtide are not active against HIV-2 and should not be used (AII).

- All infants born to HIV-2-infected mothers should receive the standard 6-week zidovudine prophylactic regimen (BII).

- In the United States, where safe infant formula is readily available, breastfeeding is not recommended for infants of HIV-2-infected mothers (AII).

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 Ivory Coast, Ghana, Cape Verde, Gambia, Mali, Senegal, Liberia, Guinea, Burkina Faso, Nigeria, Mauritania, Sierra Leone, Guinea Bissau, Niger, Sao Tome, and Togo; Angola; Mozambique; and in parts of India. It also occurs in countries such as France and Portugal, which have large numbers of immigrants from these regions. HIV-2 remains rare in the United States. Between 1998 and 2010, 242 HIV-2 cases were reported to the Centers for Disease Control and Prevention (CDC), with 166 cases meeting criteria for HIV-2 diagnosis. These 166 cases constituted only 0.01% of the more than 1.4 million U.S. cases of HIV infection. Of the 50 women aged 15 to 44 years at diagnosis, 24 (48%) were pregnant at or after HIV-2 diagnosis. HIV-2 infection should be suspected in pregnant women who are from—or who have partners from—countries in which the disease is endemic 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 are indeed HIV-2 infected it would show negative HIV-1 antibodies and positive HIV-2 antibodies. In rare instances, a woman may have dual infection with HIV-1 and HIV-2 and both tests will be positive.

In 2014, the CDC released a new HIV Testing Algorithm, which may enhance the diagnosis of HIV-2. The first step in that algorithm is performance on serum or plasma of an HIV-1/HIV-2 antigen/antibody combination assay (e.g., Abbott Architect HIV Ag/Ab combo assay, BioRad GS Combo Ag/Ab EIA, Alere Determine). This test does not distinguish between antibodies to HIV-1 and HIV-2. Specimens which are reactive on this test must be tested with a Food and Drug Administration (FDA)-approved second-generation antibody assay to distinguish HIV-1 from HIV-2 antibodies. There are two HIV-2 antibody supplemental tests now approved by FDA that can be used as part of the CDC recommended HIV laboratory testing algorithm: Multispot HIV-1/HIV-2 Rapid Test (Bio-Rad Laboratories) and GeeniuS (Bio-Rad Laboratories). Viral load assays for HIV-2 are not commercially available, but may be available under research protocols. The University of Washington (http://depts.washington.edu/labweb/AboutLM/Contact.htm) and the New York State Department of Health (http://www.hivguidelines.org/wp-content/uploads/2014/04/human-immunodeficiency-virus-type-2-hiv-2.pdf) offer HIV-2 viral load assays. All HIV-2 cases should be reported to the HIV surveillance program of the state or local health department, which can arrange for additional recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States
confirmatory testing for HIV-2 by the CDC.\textsuperscript{10} No validated HIV-2 genotype or phenotype resistance assays are available in the United States. European experts developed a rule set and an automated tool for HIV-2 drug resistance analyses that is freely available on the Internet (see http://www.hiv-grade.de).\textsuperscript{11}

HIV-2 has a longer asymptomatic phase than HIV-1, with a slower progression to AIDS. The most common mode of HIV-2 transmission is through heterosexual sex. HIV-2 is less infectious than HIV-1, with a 5-fold lower rate of sexual transmission and 20- to 30-fold lower rate of vertical transmission.\textsuperscript{3,12-13} 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 and less cervical viral shedding, compared with that seen in HIV-1-infected women.\textsuperscript{14-17} 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 monoinfection, can occur.\textsuperscript{18}

Pregnant women who have HIV-1/HIV-2 coinfection should be treated according to the guidelines for HIV-1-monoinfected patients, making sure that the antiretroviral therapy (ART) regimen chosen is also appropriate for treatment of HIV-2 (see below). Once treatment is started, the ART regimen should be continued postpartum, as is recommended for all HIV-1-infected patients. In a systematic review of non-pregnant, HIV-2-infected patients from 1996–2012, Ekouevi et al noted a heterogeneity of treatment outcomes among HIV-2-infected patients initiating ART, especially in resource-limited settings.\textsuperscript{19} Non-nucleoside reverse transcriptase inhibitors (NNRTIs) and enfuvirtide are not active against HIV-2 and should not be used for treatment or prophylaxis.\textsuperscript{20,21} HIV-2 has variable sensitivity to protease inhibitors (PIs), with lopinavir, saquinavir, and darunavir having the most activity.\textsuperscript{22} The integrase strand transfer inhibitors (raltegravir, elvitegravir, and dolutegravir) also appear to be effective against HIV-2.\textsuperscript{3,23-28} The CCR5 antagonist maraviroc appears active against some strains of HIV-2, although there are no approved assays to determine HIV-2 co-receptor tropism.\textsuperscript{29,30} HIV-2 drug resistance has been documented with various antiretroviral (ARV) drugs.\textsuperscript{31,32}

The care of HIV-2-monoinfected pregnant women has been based on expert opinion. A regimen with two nucleoside reverse transcriptase inhibitors (NRTIs) and a boosted PI or an integrase strand transfer inhibitor currently is recommended for all HIV-2-infected pregnant women. Based on efficacy and available data on safety in HIV-1-infected pregnant women, darunavir/ritonavir, lopinavir/ritonavir, or raltegravir plus abacavir/lamivudine or tenofovir disoproxil fumarate/emtricitabine or lamivudine is preferred; zidovudine/ lamivudine can be an alternative dual NRTI.\textsuperscript{3,34} NNRTIs should not be used because they are not active against HIV-2. Single-drug prophylaxis with zidovudine alone has also been considered by some experts for prevention of perinatal transmission in women with HIV-2 monoinfection because HIV-2 has a significantly lower risk of perinatal transmission than HIV-1.\textsuperscript{15} However, this may not be an optimal choice as there seems to be a low genetic barrier to resistance in HIV-2, with as few as two mutations conferring full zidovudine resistance.\textsuperscript{33,35}

There are no data to address whether treatment should be continued after pregnancy in HIV-2 monoinfected women. To date, no randomized trials have addressed the question of optimal treatment strategy for HIV-2 infection, although clinical trials are underway. The Adult and Adolescent Guidelines note that although the optimal CD4 T lymphocyte (CD4) cell count threshold to initiate ART in HIV-2 monoinfection is unknown, therapy should be started before there is clinical progression.\textsuperscript{36} For HIV-2 monoinfected pregnant women with CD4 cell counts >500 cells/mm\textsuperscript{3} and no significant clinical disease, who currently do not require treatment for their own health, some experts would stop ART postpartum; however, in analogy to HIV-1 infection, many experts would recommend continuation of treatment after pregnancy in women with HIV-2 monoinfection, as is recommended for HIV-1 monoinfection or HIV-1/HIV-2 coinfection.

All infants born to mothers infected with HIV-2 should receive the standard 6-week zidovudine prophylactic regimen.\textsuperscript{34} The possible risks and benefits of ARV prophylaxis should be discussed with the mothers.

Other than the standard obstetric indications, no data exist regarding the role of elective cesarean delivery in women who are infected with HIV-2. The risk to infants from breastfeeding is lower for HIV-2 than for HIV-1, but breastfeeding should be avoided in the United States and other resource-rich countries where safe infant formula is readily available.\textsuperscript{15}
Infants born to HIV-2-infected mothers should be tested for HIV-2 infection with HIV-2-specific virologic assays at time points similar to those used for HIV-1 testing. Quantitative HIV-2 plasma RNA viral load testing for clinical care is available from the University of Washington and the New York State Department of Health. Testing of infants at age 18 months (e.g., with the Bio-Rad Laboratories Multispot HIV-1/HIV-2 test) also is recommended to confirm clearance of HIV-2 antibodies.

**References**


