Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States

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HIV-2 Infection and Pregnancy (Last updated December 7, 2018; last reviewed December 7, 2018)

Panel's Recommendations

- HIV-2 infection should be considered in pregnant women 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 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 women living with HIV-1/HIV-2 coinfection should be treated as per guidelines for HIV-1 monoinfection, but using antiretroviral drugs that are active against HIV-2 (see below).
- 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 and certain boosted protease inhibitors or integrase strand transfer inhibitors is recommended for all pregnant women living with HIV-2 infection **(AIII)**.
- Non-nucleoside reverse transcriptase inhibitors and enfuvirtide are not active against HIV-2 and should not be used **(AIII)**.
- All infants born to mothers living with HIV-2 infection should receive the 4-week zidovudine prophylactic regimen **(BIII)**.
- In the United States, where safe infant formula is readily available, breastfeeding is not recommended for infants of mothers living with HIV-2 infection **(AIII)**.

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, The Gambia, Mali, Senegal, Liberia, Guinea, Burkina Faso, Nigeria, Mauritania, Sierra Leone, Guinea Bissau, Niger, Sao Tome, and Togo. It is also endemic in Angola, Mozambique, and in parts of India.[1-4] It also occurs in countries such as France and Portugal, which have large numbers of immigrants from these regions.[5] 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 the criteria for HIV-2 diagnosis. These 166 cases constituted only 0.01% of the >1.4 million U.S. cases of HIV infection.[6] Of the 50 women aged 15 to 44 years at diagnosis, 24 (48%) were pregnant at HIV-2 diagnosis or became pregnant after diagnosis.[6] HIV-2 infection should be suspected in pregnant women 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 woman may have dual infection with HIV-1 and HIV-2, and both tests will be positive.

In 2014, CDC released a new HIV Testing Algorithm, which may enhance the diagnosis of HIV-2. The first step in that 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, BioRad GS Combo Ag/Ab EIA, Alere Determine).[7] This test does not distinguish between HIV-1 antibodies and HIV-2 antibodies. Specimens which are reactive on this test must be tested with a 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[9] 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 confirmatory testing for HIV-2 by the CDC.[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 (http://www.hiv-grade.de).[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.[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 in women with HIV-2 than in women with HIV-1 infection.[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.[18]

Pregnant women living with HIV-1/HIV-2 coinfection should be treated according to the guidelines for patients with HIV-1 monoinfection, making sure that the antiretroviral therapy (ART) regimen chosen is also appropriate for treatment of HIV-2 (see below). Once treatment is started, ART should be continued postpartum, as is recommended for all patients living with HIV-1 infection. A systematic review analyzed data collected from 1996 to 2012 on treatment outcomes among nonpregnant patients living with HIV-2 infection. The review reported a heterogeneity of treatment outcomes among patients who initiated ART, especially in resource-limited settings.[19] Non-nucleoside reverse transcriptase inhibitors (NNRTIs) and enfuvirtide are not active against HIV-2 and should not be used for treatment or prophylaxis.[20,21] HIV-2 has variable susceptibility to protease inhibitors (PIs), with lopinavir, saquinavir, and darunavir having the most activity.[22] The integrase strand transfer inhibitors (INSTIs) raltegravir, elvitegravir, and dolutegravir also appear to be effective against HIV-2.[3,23-30] Although dolutegravir may be able to rescue a failing raltegravir-based regimen in a person with HIV-2, a study has reported the emergence of dolutegravir resistance mutations in people living with HIV-2.[31] The CCR5 antagonist maraviroc appears to be active against some strains of HIV-2, although there are no approved assays to determine HIV-2 co-receptor tropism.[32,33] HIV-2 drug resistance has been documented with various antiretroviral (ARV) drugs.[34,35] Among 47 ART-naive persons living 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 or INSTIs.[36]

The care of pregnant women living with HIV-2 monoinfection has been based on expert opinion. A regimen with two NRTIs and a ritonavir-boosted PI or an INSTI currently is recommended for all pregnant women living with HIV-2 infection. Based on efficacy and available data on safety in pregnant women with HIV-1 infection, darunavir/ritonavir, lopinavir/ritonavir, raltegravir or dolutegravir (after the first trimester) plus abacavir/lamivudine or tenofovir disoproxil fumarate/emtricitabine or lamivudine is preferred. Dolutegravir **should not be initiated** during the first trimester due to concerns about a possible increased risk of neural tube defects in infants. See Table 6, Table 7, and Interim Panel Recommendations Regarding the Use of Dolutegravir in Pregnancy in Recommendations for Use of Antiretroviral Drugs During Pregnancy. Zidovudine/lamivudine can be used as an alternative dual-NRTI backbone.[37,38] NNRTIs should not be used, because they are not active against HIV-2.

There are no data to address whether treatment should be continued after pregnancy in women living with HIV-2 monoinfection. To date, no randomized trials have addressed the question of an 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.[39] For pregnant women living with HIV-2 infection who have CD4 cell counts >500 cells/mm^3 and no significant clinical disease (and who currently do not require treatment for their own health), some experts would stop ART postpartum; however, many experts would recommend continuing treatment after pregnancy in women living with HIV-2 monoinfection, as is recommended for HIV-1 monoinfection or HIV-1/HIV-2 coinfection.

All infants born to mothers living with HIV-2 should receive a 4 -week zidovudine prophylaxis regimen.[38] The possible risks and benefits of ARV prophylaxis should be discussed with the mothers. The rationale for

zidovudine prophylaxis in this clinical situation is based on the inability to monitor HIV-2 plasma viral load in the mother and the lack of nevirapine activity against HIV-2, which precludes its use as prophylaxis.

There is no evidence that scheduled cesarean delivery in women prevents HIV-2 vertical transmission. 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 countries where safe infant formula is readily available.[15]

Infants born to mothers living with HIV-2 infection should be tested for HIV-2 infection with HIV-2-specific virologic assays at time points similar to those used for HIV-1 testing.[40] 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) can also be performed at age 18 months to confirm clearance of HIV-2 antibodies.[38]

References

1. De Cock KM, Brun-Vezinet F. Epidemiology of HIV-2 infection. *AIDS*. 1989;3 Suppl 1:S89-95. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2514761.
2. De Cock KM, Adjorlolo G, Ekpini E, et al. Epidemiology and transmission of HIV-2. Why there is no HIV-2 pandemic. *JAMA*. 1993;270(17):2083-2086. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8147962.
3. Campbell-Yesufu OT, Gandhi RT. Update on human immunodeficiency virus (HIV)-2 infection. *Clin Infect Dis*. 2011;52(6):780-787. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21367732.
4. Heitzinger K, Sow PS, Dia Badiane NM, et al. Trends of HIV-1, HIV-2, and dual infection in women attending outpatient clinics in Senegal, 1990-2009. *Int J STD AIDS*. 2012;23(10):710-716. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23104745.
5. Cazein F, Lot F, Pillonel J, et al. HIV and AIDS surveillance in France, 2006. *Bull Epidemiol Hebd*. 2007(46-47):386-393. .
6. Centers for Disease Control and Prevention. HIV-2 Infection Surveillance—United States, 1987–2009. *MMWR Morb Mortal Wkly Rep*. 2011;60(29):985-988. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21796096.
7. Centers for Disease Control and Prevention. Laboratory testing for the diagnosis of HIV infection: updated recommendations. 2014. Available at: http://stacks.cdc.gov/view/cdc/23447.
8. Chang M, Gottlieb GS, Dragavon JA, et al. Validation for clinical use of a novel HIV-2 plasma RNA viral load assay using the Abbott m2000 platform. *J Clin Virol*. 2012;55(2):128-133. Available at: http://www.ncbi.nlm.nih.gov/pubmed/228320599.
9. Styer LM, Miller TT, Parker MM. Validation and clinical use of a sensitive HIV-2 viral load assay that uses a whole virus internal control. *J Clin Virol*. 2013;58 Suppl 1:e127-133. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24342472.
10. Branson BM, Pandori M. 2012 HIV diagnostics conference: the molecular diagnostics perspective. *Expert review of molecular diagnostics*. 2013;13(3):243-245. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23570401.
11. Charpentier C, Camacho R, Ruelle J, et al. HIV-2EU: supporting standardized HIV-2 drug resistance interpretation in Europe. *Clin Infect Dis*. 2013;56(11):1654-1658. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23429380.
12. Kanki PJ, Travers KU, S MB, et al. Slower heterosexual spread of HIV-2 than HIV-1. *Lancet*. 1994;343(8903):943-946. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7909009.
13. Matheron S, Courpotin C, Simon F, et al. Vertical transmission of HIV-2. *Lancet*. 1990;335(8697):1103-1104. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1970407.
14. O'Donovan D, Ariyoshi K, Milligan P, et al. Maternal plasma viral RNA levels determine marked differences in mother-to-child transmission rates of HIV-1 and HIV-2 in The Gambia. MRC/Gambia government/university college London medical school working group on mother-child transmission of HIV. *AIDS*. 2000;14(4):441-448. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10770548.
15. Burgard M, Jasseron C, Matheron S, et al. Mother-to-child transmission of HIV-2 infection from 1986 to 2007 in the ANRS French Perinatal Cohort EPF-CO1. *Clin Infect Dis*. 2010;51(7):833-843. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20804413.

16. Adjorlolo-Johnson G, De Cock KM, Ekpini E, et al. Prospective comparison of mother-to-child transmission of HIV-1 and HIV-2 in Abidjan, Ivory Coast. *JAMA*. 1994;272(6):462-466. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8040982.

17. Andreasson PA, Dias F, Naucler A, Andersson S, Biberfeld G. A prospective study of vertical transmission of HIV-2 in Bissau, Guinea-Bissau. *AIDS*. 1993;7(7):989-993. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8357558.

18. Prince PD, Matser A, van Tienen C, Whittle HC, Schim van der Loeff MF. Mortality rates in people dually infected with HIV-1/2 and those infected with either HIV-1 or HIV-2: a systematic review and meta-analysis. *AIDS*. 2014;28(4):549-558. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23921613.

19. Ekouevi DK, Tchounga BK, Coffie PA, et al. Antiretroviral therapy response among HIV-2 infected patients: a systematic review. *BMC Infect Dis*. 2014;14:461. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25154616.

20. Tuaillon E, Gueudin M, Lemee V, et al. Phenotypic susceptibility to nonnucleoside inhibitors of virion-associated reverse transcriptase from different HIV types and groups. *J Acquir Immune Defic Syndr*. 2004;37(5):1543-1549. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15577405.

21. Poveda E, Rodes B, Toro C, Soriano V. Are fusion inhibitors active against all HIV variants? *AIDS Res Hum Retroviruses*. 2004;20(3):347-348. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15117459.

22. Desbois D, Roquebert B, Peytavin G, et al. In vitro phenotypic susceptibility of human immunodeficiency virus type 2 clinical isolates to protease inhibitors. *Antimicrob Agents Chemother*. 2008;52(4):1545-1548. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18227188.

23. Roquebert B, Damond F, Collin G, et al. HIV-2 integrase gene polymorphism and phenotypic susceptibility of HIV-2 clinical isolates to the integrase inhibitors raltegravir and elvitegravir in vitro. *J Antimicrob Chemother*. 2008;62(5):914-920. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18718922.

24. Bercoff DP, Triqueneaux P, Lambert C, et al. Polymorphisms of HIV-2 integrase and selection of resistance to raltegravir. *Retrovirology*. 2010;7:98. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21114823.

25. Andreatta K, Miller MD, White KL. HIV-2 antiviral potency and selection of drug resistance mutations by the integrase strand transfer inhibitor elvitegravir and NRTIs emtricitabine and tenofovir in vitro. *J Acquir Immune Defic Syndr*. 2012. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23187937.

26. Peterson K, Ruelle J, Vekemans M, Siegal FP, Deayton JR, Colebunders R. The role of raltegravir in the treatment of HIV-2 infections: evidence from a case series. *Antivir Ther*. 2012;17(6):1097-1100. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22892365.

27. Descamps D, Peytavin G, Visseaux B, et al. Dolutegravir in HIV-2-infected patients with resistant virus to first-line integrase inhibitors from the French named patient program. *Clin Infect Dis*. 2015;60(10):1521-1527. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25690598.

28. Smith RA, Raugi DN, Pan C, et al. In vitro activity of dolutegravir against wild-type and integrase inhibitor-resistant HIV-2. *Retrovirology*. 2015;12:10. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25808007.

29. Ba S, Raugi DN, Smith RA, et al. A trial of a single tablet regimen of elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate for the initial treatment of HIV-2 infection in a resource-limited setting: 48 week results from Senegal, West Africa. *Clin Infect Dis*. 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29672676.

30. Matheron S, Descamps D, Gallien S, et al. First line raltegravir/emtricitabine/tenofovir combination in HIV-2 infection: phase 2 non-comparative trial (ANRS 159 HIV-2). *Clin Infect Dis*. 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29590335.

31. Requena S, Trevino A, Cabezas T, et al. Drug resistance mutations in HIV-2 patients failing raltegravir and influence on dolutegravir response. *J Antimicrob Chemother*. 2017;72(7):2083-2088. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28369593.

32. Borrego P, Taveira N. HIV-2 susceptibility to entry inhibitors. *AIDS Rev*. 2013;15(1):49-61. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23449229.

33. Visseaux B, Charpentier C, Hurtado-Nedelec M, et al. In vitro phenotypic susceptibility of HIV-2 clinical isolates to CCR5 inhibitors. *Antimicrob Agents Chemother*. 2012;56(1):137-139. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22064539.

34. Charpentier C, Visseaux B, Benard A, et al. Transmitted drug resistance in French HIV-2-infected patients. *AIDS*. 2013;27(10):1671-1674. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23595155.

35. Menendez-Arias L, Alvarez M. Antiretroviral therapy and drug resistance in human immunodeficiency virus type 2 infection. *Antiviral Res*. 2014;102:70-86. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24345729.

36. Storto A, Visseaux B, Bertine M, et al. Minority resistant variants are also present in HIV-2-infected antiretroviral-naive patients. *J Antimicrob Chemother*. 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29415189.

37. Gilleece Y, Chadwick DR, Breuer J, et al. British HIV association guidelines for antiretroviral treatment of HIV-2-positive individuals 2010. *HIV Med*. 2010;11(10):611-619. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20961377.

38. de Ruiter A, Mercey D, Anderson J, et al. British HIV association and children's HIV association guidelines for the management of HIV infection in pregnant women 2008. *HIV Med*. 2008;9(7):452-502. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18840151.

39. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. 2018. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf.

40. Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV. Guidelines for the use of antiretroviral agents in pediatric HIV infection. 2018. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf.