



Introduction

[Medical Care Criteria Committee](#), April 2012

HIV-2 was first described in 1985 [1] and was isolated in 1986 in West Africa [2], where it is currently endemic. The Centers for Disease Control and Prevention (CDC) reported that, from 1988 to June 2010, 166 cases had met the CDC case definition of HIV-2 infection in the United States [3]. The largest number of cases were from the Northeast, including 77 from New York City [3]. The majority of cases had a West African origin or connection [3]. However, a report from New York City suggests that HIV-2 may be underreported because antibody cross-reactivity between HIV-1 and HIV-2 is common and frequently results in misdiagnosis of HIV-2 as HIV-1 or dual infection [4]. Incorporating a type-differentiating immunoassay into the HIV screening protocol can assist in identifying the type [4].

HIV-2 is associated with lower viral load levels and slower rates of CD4 decline and clinical progression compared with HIV-1 [5,6]; 86% to 95% of people infected with HIV-2 are long-term nonprogressors [7,8]. Recent data show that survival of persons with undetectable HIV-2 viral load is similar to that of the general population [8]. However, HIV-2 can cause immunosuppression, as well as AIDS characterized by the same signs, symptoms, and opportunistic infections that are seen in HIV-1. HIV-2-associated AIDS may often be associated with lower viral load levels than HIV-1 (>10,000 copies/mL in HIV-2 versus sometimes millions of copies/mL in HIV-1) [8].

In contrast to the detailed knowledge base for the management of HIV-1, no clinical trials have been conducted to date to guide decision-making in the management of HIV-2-related immunosuppression and progression of disease. Studies of virologic and immunologic responses to antiretroviral therapy (ART) have demonstrated a higher CD4 cell increase in HIV-1-infected patients compared with HIV-2-infected patients after initiation of therapy [9-11]. These factors, combined with the absence of controlled trials of ART for HIV-2, contribute to the challenge of optimal treatment of HIV-2.

⇒ KEY POINTS

- HIV-2-infected individuals with progressive disease are less likely to respond as predictably to ART as patients with HIV-1 infection.
- The choice of ART for HIV-2 differs from that for HIV-1, underscoring the importance of differentiating between HIV-1 and HIV-2 in patients at risk for HIV-2 infection.
- Clinical monitoring of HIV-2 is hampered by the absence of assays with Food and Drug Administration (FDA) approval for quantification of HIV-2 viral load, as well as a lack of consensus on interpretation of HIV-2 resistance testing.

References:

1. Barin F, M'Boup S, Denis F, et al. Serological evidence for virus related to simian T-lymphotropic retrovirus III in residents of West Africa. *Lancet* 1985;2:1387-1389. [[PubMed](#)]
2. Clavel F, Guetard D, Brun-Vezinet F, et al. Isolation of a new human retrovirus from West African patients with AIDS. *Science* 1986;233:343-346. [[PubMed](#)]
3. Centers for Disease Control and Prevention (CDC). HIV-2 Infection Surveillance — United States, 1987-2009. *MMWR Morb Mortal Wkly Rep* 2011;60:985-988. Available at: <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6029a3.htm>
4. Torian LV, Eavey JJ, Punsalang AP, et al. HIV type 2 in New York City, 2000-2008. *Clin Infect Dis* 2010;51:1334-1342. [[PubMed](#)]
5. Andersson S, Norrgren H, DaSilva Z, et al. Plasma viral load in HIV-1 and HIV-2 singly and dually infected individuals in Guinea-Bissau, West Africa: Significantly lower plasma virus set point in HIV-2 infection than in HIV-1 infections. *Arch Intern Med* 2000;160:3286-3293. [[PubMed](#)]
6. Marlink R, Kani P, Thior I, et al. Reduced rate of disease development after HIV-2 infection as compared to HIV-1. *Science* 1994;265:1587-1590. [[PubMed](#)]
7. De Silva TI, Cotten M, Rowland-Jones SL. HIV-2: The forgotten AIDS virus. *Trends Microbiol* 2008;16:588-595. [[PubMed](#)]
8. van der Loeff MF, Larke N, Kaye S, et al. Undetectable plasma viral load predicts normal survival in HIV-2-infected people in a West African village. *Retrovirology* 2010;7:46. [[PubMed](#)]

9. Drylewicz J, Matheron S, Lazaro E, et al. Comparison of viro-immunological marker changes between HIV-1 and HIV-2-infected patients in France. *AIDS* 2008;22:457-468. [[PubMed](#)]
10. Jallow S, Alabi A, Sarge-Njie R, et al. Virological response to highly active antiretroviral therapy in patients infected with human immunodeficiency virus type 2 (HIV-2) and in patients dually infected with HIV-1 and HIV-2 in the Gambia and emergence of drug-resistant variants. *J Clin Microbiol* 2009;47:2200-2208. [[PubMed](#)]
11. Matheron S, Damond F, Benard A, et al. CD4 cell recovery in treated HIV-2-infected adults is lower than expected: Results from the French ANRS CO5 HIV-2 cohort. *AIDS* 2006;20:459-462. [[PubMed](#)]

Natural History and Epidemiology

[Medical Care Criteria Committee](#), April 2012

HIV-2 Mono-Infection

HIV-1 and HIV-2 are closely related retroviruses of the same genus (*Lentiviridae*) and share the same modes of transmission. Both types are considered to have arisen from the introduction of simian immunodeficiency virus into the human population, although they derive from different primate simian immunodeficiency viruses: HIV-2 from SIVsm (sooty mangabey) and HIV-1 from SIVcpz (chimpanzee).

HIV-2 is present throughout West Africa, with the highest prevalence in its area of origin, Guinea-Bissau, where in 1990, 8% of adults and 20% of persons over 40 years of age were infected [1,2]. HIV-2 has been reported in Portugal and France, as well as countries with colonial ties to these nations (Angola, Mozambique, Brazil, and parts of India), due to large West African immigrant populations and/or long histories of commerce and other ties to West Africa.

HIV-1/HIV-2 Co-Infection

HIV-1/HIV-2 co-infection in West Africa is increasing, particularly in border countries between West and East Africa [2]. In the United States, co-infection has also been reported. Among the 166 cases of HIV-2 reported by the CDC, 19 patients (11%) tested positive for possible HIV-1/HIV-2 co-infection. However, the extent of HIV-1/HIV-2 co-infection within the entire patient population could not be assessed due to incomplete HIV-1 testing results for some individuals [3].

The dynamics of interaction between HIV-1 and HIV-2 have been a matter of controversy for decades [4-7], and expertise in the area of HIV-1/HIV-2 co-infection remains limited. One study suggested that mortality rates were higher among HIV-1/HIV-2 co-infected individuals than HIV-1 mono-infected individuals [7], but this may be dependent on which infection occurred first. Over time, HIV-1 seems to out-compete HIV-2 as the primary virus behind disease progression in HIV-1/HIV-2 co-infected persons. Data also suggest that the mortality associated with HIV-1/HIV-2 co-infection is dependent on CD4 count and is higher than in HIV-2 mono-infected individuals matched for disease stage [8].

HIV-1/HIV-2 co-infection is difficult to diagnose due to the cross-reactivity of antibodies, as well as viral antigens, making treatment decisions based on co-infection difficult to determine. Genetic sequence verification of both viral sequences should be encouraged for diagnosis of HIV-1/HIV-2 co-infection. See [HIV-2 > Screening and Diagnosis](#) for guidance on the tests that are best designed to differentiate between HIV-1 and HIV-2.

References:

1. Lemey P, Pybus OG, Wang B, et al. Tracing the origin and history of the HIV-2 epidemic. *Proc Natl Acad Sci USA* 2003;100:6588-6592. [[PubMed](#)]
2. De Silva TI, van Tienen C, Rowland-Jones SL, et al. Dual infection with HIV-1 and HIV-2: Double trouble or destructive interference? *HIV Ther* 2010;4:305-323. [[PubMed](#)]
3. Centers for Disease Control and Prevention (CDC). HIV-2 Infection Surveillance — United States, 1987-2009. *MMWR Morb Mortal Wkly Rep* 2011;60:985-988. Available at: <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6029a3.htm>
4. Greenberg AE, Wiktor SZ, Decock KM, et al. HIV-2 and natural protection against HIV-1 infection. *Science* 1996;272:1959a. [[PubMed](#)]
5. Nkengasong JN, Kestens L, Ghys PD, et al. Dual infection with human immunodeficiency virus type 1 and type 2: Impact on HIV type 1 viral load and immune activation markers in HIV-seropositive female sex workers in Abidjan, Ivory Coast. *AIDS Res Hum Retroviruses* 2000;16:1371-1378. [[PubMed](#)]
6. Koblavi-Dème S, Kestens L, Hanson D, et al. Differences in HIV-2 plasma viral load and immune activation in HIV-1 and HIV-2 dually infected persons and those infected with HIV-2 only in Abidjan, Côte D'Ivoire. *AIDS* 2004;18:413-419. [[PubMed](#)]
7. Holmgren B, da Silva Z, Vastrup P, et al. Mortality associated with HIV-1, HIV-2, and HTLV-I single and dual infections in a middle-aged and older population in Guinea-Bissau. *Retrovirology* 2007;4:85. [[PubMed](#)]
8. Alabi AS, Jaffar S, Ariyoshi K, et al. Plasma viral load, CD4 cell percentage, HLA and survival of HIV-1, HIV-2, and dually infected Gambian patients. *AIDS* 2003;17:1513-1520. [[PubMed](#)]

Screening and Diagnosis

[Medical Care Criteria Committee](#), April 2012

RECOMMENDATIONS

- Specimens submitted for HIV testing should be screened by an enzyme immunoassay (EIA) that detects HIV-1, HIV-1 group O, and HIV-2. All laboratories performing HIV diagnostic testing should incorporate algorithms for differentiation of HIV-1 versus HIV-2 in repeatedly reactive samples. (AIII)
- When HIV-1/HIV-2 combination screening yields a reactive result but is followed by indeterminate or nonreactive HIV-1 Western blot, clinicians should:
 - Obtain a plasma HIV RNA assay to exclude acute HIV-1 infection (AIII)
 - Obtain testing for HIV-2 antibodies with an FDA-approved HIV-1/HIV-2 type-differentiating immunoassay if acute HIV-1 infection has been excluded (AIII)
 - Consider specimens positive for HIV-2 if they are repeatedly reactive on an HIV-1/HIV-2 screening test and reactive for HIV-2 antibodies on the HIV-1/HIV-2 differentiation test (AIII)
- Clinicians should use HIV-1/HIV-2 type-differentiating immunoassays and nucleic acid testing protocols when screening for HIV in patients who meet the criteria outlined below. (AIII)

All New York State public health laboratories and all major commercial laboratories now perform combination screening for antibodies to HIV-1 group M, HIV-1 group O, and HIV-2. Most of the FDA-approved, Clinical Laboratory Improvement Amendment (CLIA)-waived HIV rapid tests also detect HIV-1 and HIV-2 antibodies. For additional information regarding HIV-1/HIV-2 combination rapid tests, see [HIV Testing: Characteristics of FDA-Approved Rapid HIV Tests](#).

When an HIV-1/HIV-2 combination screening test yields a reactive result and an HIV-1 Western blot yields an indeterminate or nonreactive result, additional testing is indicated. Because the current tests used to screen for HIV infection are more sensitive than the Western blot, a negative or indeterminate HIV-1 Western blot could signify early HIV-1 infection or HIV-2 infection; an HIV-1 RNA assay should be performed to diagnose or exclude early HIV-1 infection. If early HIV-1 infection has been excluded,

then HIV-2 antibody testing should be performed with an FDA-approved HIV-1/HIV-2 type-differentiating immunoassay.

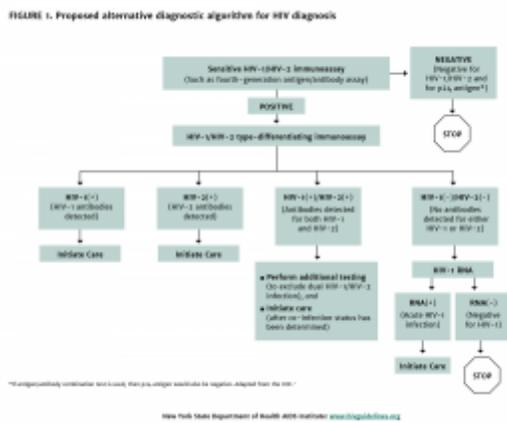


Figure 1: Click to enlarge

HIV-2 Western blot (see Figure 1). According to this algorithm, a sample that is repeatedly reactive on an HIV-1/HIV-2 screening test and reactive for only HIV-2 antibodies on an HIV-1/HIV-2 differentiating immunoassay is considered to be positive for HIV-2 infection. An HIV-2 RNA or DNA detection test may be obtained in addition to serology for further confirmation. In cases where HIV-1 or HIV-2 antibodies are not detected by the HIV-1/HIV-2 type-differentiating immunoassay, the alternative diagnostic algorithm indicates that a plasma HIV-1 RNA assay should be performed to diagnose or exclude early HIV-1 infection.

A limited number of laboratories offer an HIV-2 Western blot test, none of which has FDA approval, and interpretation is complicated due to significant cross-reactivity between HIV-1 and HIV-2 antibodies.

An alternative HIV diagnostic algorithm has been proposed in which an FDA-approved HIV-1/HIV-2 immunoassay that differentiates between HIV-1 and HIV-2 antibodies is used as a supplemental test instead of an HIV-1 or

⇒ KEY POINT

- Diagnostic HIV laboratory tests and interpretation algorithms evolve; individual laboratories have internal protocols for reporting tests with preliminary results. *Indeterminate, inconclusive, non-diagnostic, and pending validation* are among the terms used when preliminary results cannot be classified definitively. The clinician should contact the appropriate laboratory authority to determine the significance of the non-definitive results and the supplemental testing that would be indicated. This is of particular importance in tests from patients with suspected HIV-2 infection. Clinicians should become familiar with the internal test-reporting policies of their institutions.

Populations for whom HIV-1/HIV-2 type-differentiating immunoassays and nucleic acid testing protocols should be included when screening for HIV are listed below.

Clinicians should be alert to the possibility of HIV-2 infection in patients who:

- Originated in or have traveled to an HIV-2-endemic area
- Received medical care, injections, immunizations, phlebotomy, surgery, or blood products or participated in vaccine trials in an HIV-2-endemic area*
- Had sexual or needle-sharing contact with persons who are infected with HIV-2 or are from an HIV-2-endemic area*
- Were born to a mother with HIV-2 infection (see [Testing and Prophylaxis for HIV-2-Exposed Infants](#))
- Had opportunistic infections or other clinical symptoms of HIV/AIDS but tested negative or indeterminate for HIV-1
- Received multiple HIV-1 indeterminate antibody test results
- Have a confirmed diagnosis of HIV-1 but an undetectable viral load that is incompatible with the clinical or immunological status

*Endemic areas include: West African countries (Guinea-Bissau, Cape Verde, Ivory Coast, Gambia, Mali, Mauritania, Nigeria, Sierra Leone, Benin, Burkina Faso, Ghana, Guinea, Liberia, Niger, Sao Tome, Senegal, and Togo), as well as Angola, Mozambique, and India.

For more information regarding HIV-2 testing, contact one of the public health laboratories:

- **Care providers in New York City:** Contact the New York City Department of Health and Mental Hygiene (NYC DOHMH) at 212-447-2864 for assistance with HIV-2 diagnostic testing
- **Care providers in New York State, who are outside of New York City:** Contact the New York State Department of Health (NYSDOH) Wadsworth Center Laboratory at 518-474-2163 for assistance with HIV-2 diagnostic testing

Reference:

1. Centers for Disease Control and Prevention (CDC). DRAFT Recommendations: Diagnostic Laboratory Testing for HIV Infection in the United States. Presented at the

2012 HIV Diagnostics Conference Feedback Session held on December 14, 2012. CDC: Atlanta; 2012. Available at: www.cdc.gov/hiv/testing/lab/guidelines/index.html

Monitoring

April 2012

RECOMMENDATION

- Clinicians should monitor HIV-2-infected patients by clinical evaluation and CD4 cell count. (BIII)

CD4 count is the most readily available means for monitoring disease progression in HIV-2-infected patients. However, CD4 counts often will not increase as dramatically as generally occurs with successful therapy of HIV-1 mono-infection [1]. Commercially available HIV-1 viral load tests do not detect or quantify HIV-2, and currently there is no FDA-approved viral load test for HIV-2. In the U.S, two laboratories have developed and validated HIV-2 viral load tests for clinical use according to Clinical Laboratory Improvement Amendments (CLIA) requirements. Health care providers located in New York State or who provide care for New York State residents should contact the Bloodborne Viruses Laboratory at the Wadsworth Center, New York State Department of Health (NYSDOH) at 518-474-2163.

The Wadsworth Center Laboratory holds a New York State clinical laboratory permit and its HIV-2 viral load test has been approved by the NYSDOH Clinical Laboratory Evaluation Program, as required under New York State Public Health Law. HIV-2 viral load testing is performed free of charge at the Wadsworth Center, but testing is restricted to New York State residents. For HIV-2 viral load testing of patients from states other than New York, health care providers should contact the Clinical Retrovirus Laboratory at the University of Washington at 206-897-5210. The University of Washington's HIV-2 viral load test is conducted in a CLIA-certified and College of American Pathologists (CAP)-accredited laboratory.

Reference:

1. Matheron S, Damond F, Benard A, et al. CD4 cell recovery in treated HIV-2-infected adults is lower than expected: Results from the French ANRS CO5 HIV-2 cohort. *AIDS* 2006;20:459-462. [[PubMed](#)]

Treatment

April 2012

RECOMMENDATIONS

- Clinicians should include two NRTIs and an appropriate boosted PI, such as lopinavir, saquinavir, or darunavir, when prescribing ART for HIV-2 mono-infected or HIV-1/HIV-2 co-infected individuals (see text). (AIII)
- Clinicians should *not* prescribe NNRTIs or the PIs nelfinavir, atazanavir, or fosamprenavir as part of an ART regimen against HIV-2 mono-infection; these agents may be used as part of a regimen for HIV-1/HIV-2 co-infected patients if adequate treatment for HIV-2 is also included [20]. (BIII)
- Clinicians should consult with a provider with experience in the management of HIV-2 before initiating ART in HIV-2-infected patients. (AIII)
- Clinicians should educate patients with confirmed HIV-2 infection about the lack of data regarding treatment of HIV-2 and should review individual benefits and risks of initiating treatment. Patients should make the final decision of whether and when to initiate ART.

No randomized clinical trials have been conducted to determine when to initiate ART in the setting of HIV-2 infection, and the best choices of therapy for HIV-2 infection remain under study. Because the optimal treatment strategy for HIV-2 infection has not been defined, the recommendations provided in this section are based on this committee's expert opinion.

Although HIV-2 is generally less aggressive, and progression to AIDS is less frequent, HIV-2 responds less predictably to ART when progression occurs, and response is more difficult to monitor (see below for available data regarding HIV-2 response to ART). The standard methods and interpretation protocols that are used to monitor ART for HIV-1-infected patients may not apply for HIV-2-infected patients. Some ART regimens that are appropriate for HIV-1 infection may not be as effective for HIV-2. The following factors should be considered when deciding whether or not to initiate ART in HIV-2-infected patients:

- The majority of HIV-2-infected patients are long-term nonprogressors

- HIV-2 may confer more rapid resistance to ART agents due to wild-type genetic sequence that results in a significant increase in resistance to ART agents compared with HIV-1 [2-4]
- Pathways for the development of drug mutations may differ between the two viruses
- Recent data have shown a significant reduction in HIV-1 transmission risk between serodiscordant heterosexual couples when the positive partner was receiving ART [5]; lower viral load level may also reduce HIV-2 transmission risk

⇒ KEY POINT

- Few data exist for the diagnosis and management of HIV-1/HIV-2 co-infection; however, clinical management currently focuses on controlling HIV-1 infection with agents that are active against both HIV-1 and HIV-2.

Efficacy of ART Against HIV-2 Infection

Nucleoside reverse transcriptase inhibitors (NRTIs):

- Although most in vitro studies have shown that similar concentrations of NRTIs are needed to block both HIV-1 and HIV-2 replication, data suggest that some NRTIs may not be as effective against HIV-2 [6]. For example, HIV-1 more readily incorporates zidovudine and is more susceptible to zidovudine than HIV-2, and there is a lower barrier to resistance with HIV-2 than with HIV-1 [2,7].
- Genotypic analysis of HIV-2-infected patients on ART has shown that many of the same amino acid substitutions that are associated with NRTI resistance in HIV-1 may be implicated in HIV-2. Some resistance mutations (K65R, Q151M, and M184V) in combination can confer class-wide NRTI resistance and cause rapid virologic failure [2].

Non-nucleoside reverse transcriptase inhibitors (NNRTIs):

- NNRTIs block HIV-1 reverse transcription through a specific binding site that is not present in HIV-2; this class of drugs will not be effective against HIV-2 [8,9].
- HIV-2 appears to be intrinsically resistant to NNRTIs [8]; the Y188L polymorphism appears naturally in all HIV-2 isolates. Reversion to Y188 restores the reverse transcriptase sensitivity to some NNRTIs, including efavirenz and delavirdine [10].

- In general, NNRTIs inhibit HIV-2 at effective concentrations that are at least 50-fold higher than those that inhibit HIV-1 [11], making the use of these drugs for HIV-2 infection problematic.
- Etravirine appears to have limited activity against HIV-2, but this may not be clinically relevant because the mean 50% effective concentration in MT₄ cells is 2500-fold higher than that observed for HIV-1 [12].

Protease inhibitors (PIs):

- PIs appear to have variable activity and accelerated genotypic resistance [4].
- HIV-2 expresses natural polymorphisms in the protease that may be implicated in emergent drug resistance and accelerate time to development of PI resistance [4].
- One study noted that the pathways for HIV-2 protease drug resistance may differ from those for HIV-1 [6].
- Saquinavir, lopinavir, and darunavir have shown comparable activity against HIV-1 and HIV-2 [13-15].
- Indinavir, nelfinavir, and ritonavir may be less active against HIV-2 than HIV-1.
- Atazanavir has lower and variable activity against HIV-2 in comparison with HIV-1 [14].
- The data regarding tipranavir are conflicting.
- Some natural polymorphisms in HIV-2 may confer baseline resistance to fosamprenavir.

Integrase strand transfer inhibitors (INSTIs):

- Little is known about the use of INSTIs in HIV-2 infection.
- The INSTIs raltegravir and elvitegravir have demonstrated activity *in vitro* [16]. Clinical response to raltegravir was reported in a patient with highly treatment-experienced HIV-2 infection [17], but the emergence of mutations was reported in another patient [18].

CCR5 co-receptor antagonists:

- The activity of maraviroc has been limited to patients with CCR5-tropic viruses.
- Primary HIV-2 isolates can utilize a broad range of co-receptors, including CXCR4, CCR5, CCT-5, GPR15, and CXCR6. This limits the therapeutic utility of maraviroc in

HIV-2 infection.

Fusion inhibitors: HIV-2 is intrinsically resistant to the fusion inhibitor enfuvirtide [11,19].

As with disease monitoring, monitoring of response to treatment for HIV-2 is more challenging than for HIV-1. Viral load and ART resistance assays for HIV-2 are not commercially available. However, such tests may be available under research Investigational New Drug (IND) protocols. Results generated by these assays should be interpreted with caution due to the IND classification and the absence of standardized interpretation protocols [20]. An HIV-2 viral load assay developed by NYSDOH Wadsworth Center is currently undergoing validation for clinical use. Contact the laboratory regarding availability at 518-474-2163.

References:

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. 2011:1-174. Available at: <http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf>
2. Smith RA, Anderson DJ, Pyrak CL, et al. Antiretroviral drug resistance in HIV-2: Three amino acid changes are sufficient for classwide nucleoside analogue resistance. *J Infect Dis* 2009;199:1323-1326. [[PubMed](#)]
3. Rodés B, Sheldon J, Toro C, et al. Susceptibility to protease inhibitors in HIV-2 primary isolates from patients failing antiretroviral therapy. *J Antimicrob Chemother* 2006;57:709-713. [[PubMed](#)]
4. Ntemgwa M, Brenner BG, Oliveira M, et al. Natural polymorphisms in the human immunodeficiency virus type 2 protease can accelerate time to development of resistance to protease inhibitors. *Antimicrob Agents Chemother* 2007;51:604-610. [[PubMed](#)]
5. Cohen MS, Chen YQ, McCauley M, et al.; HPTN 052 Study Team. Prevention of HIV-infection with early antiretroviral therapy. *N Engl J Med* 2011;365:493-505. [[PubMed](#)]
6. Ntemgwa ML, d'Aquin Toni T, Brenner BG, et al. Antiretroviral drug resistance in human immunodeficiency virus type 2. *Antimicrob Agents Chemother* 2009;53:3611-

3619. [[PubMed](#)]
7. Boyer PL, Sarafianos SG, Clark PK, et al. Why do HIV-1 and HIV-2 use different pathways to develop AZT resistance? *PLoS Pathog* 2006;2:e10. [[PubMed](#)]
 8. Tuailon E, Gueudin M, Lemee V, et al. Phenotypic susceptibility to nonnucleoside inhibitors of virion-associated reverse transcriptase from different HIV types and groups. *J Acquired Immune Defic Syndr* 2004;37: 1543-1549. [[PubMed](#)]
 9. Ren J, Bird LE, Chamberlain PP, et al. Structure of HIV-2 reverse transcriptase at 2.35-Å resolution and the mechanism of resistance to non-nucleoside inhibitors. *Proc Natl Acad Sci USA* 2002;99:14410-14415. [[PubMed](#)]
 10. Isaka Y, Miki S, Kawauchi S, et al. A single amino acid change at Leu-188 in the reverse transcriptase of HIV-2 and SIV renders them sensitive to non-nucleoside reverse transcriptase inhibitors. *Arch Virol* 2001;146:743-755. [[PubMed](#)]
 11. Witvrouw M, Pannecouque C, Switzer WM, et al. Susceptibility of HIV-2, SIV and SHIV to various anti-HIV-1 compounds: Implications for treatment and postexposure prophylaxis. *Antivir Ther* 2004;9:57-65. [[PubMed](#)]
 12. Andries K, Azijn H, Thielemans T, et al. TMC125, a novel next-generation nonnucleoside reverse transcriptase inhibitor active against nonnucleoside reverse transcriptase inhibitor-resistant human immunodeficiency virus type 1. *Antimicrob Agents Chemother* 2004;48:4680-4686. [[PubMed](#)]
 13. Benard A, Damond F, Campa P, et al. Good response to lopinavir/ritonavir-containing antiretroviral regimens in antiretroviral-naïve HIV-2-infected patients. *AIDS* 2009;23:1171-1179. [[PubMed](#)]
 14. 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;52:1545-1548. [[PubMed](#)]
 15. Brower ET, Bacha UM, Kawasaki Y, et al. Inhibition of HIV-2 protease by HIV-1 protease inhibitors in clinical use. *Chem Biol Drug Des* 2008;71:298-305. [[PubMed](#)]
 16. 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;62:914-920. [[PubMed](#)]
 17. Garrett N, Xu L, Smit E, et al. Raltegravir treatment response in an HIV-2 infected patient: A case report. *AIDS* 2008;22:1091-1098. [[PubMed](#)]

18. Xu L, Anderson J, Garrett N, et al. Dynamics of raltegravir resistance profile in an HIV type 2–infected patient. *AIDS Res Hum Retroviruses* 2009;25:843–847. [[PubMed](#)]
19. Poveda E, Rodes B, Toro C, et al. Are fusion inhibitors active against all HIV variants? *AIDS Res Hum Retroviruses* 2004;20:347–348. [[PubMed](#)]
20. Matheron S, Damond F, Benard A, et al. CD4 cell recovery in treated HIV–2–infected adults is lower than expected: Results from the French ANRS CO5 HIV–2 cohort. *AIDS* 2006;20:459–462. [[PubMed](#)]

Pregnancy

April 2012

RECOMMENDATION

- Clinicians caring for pregnant patients with suspected or diagnosed HIV-2 should consult with a provider with experience in HIV-2 testing and management, including perinatal ART for HIV-2-infected pregnant women and postnatal ART for HIV-2-exposed infants. (AIII)

HIV-2 Testing for Women during Pregnancy and Delivery

RECOMMENDATION

- Clinicians should use HIV-1/HIV-2 type-differentiating immunoassays and nucleic acid testing protocols when screening for HIV in pregnant women who meet the criteria outlined in the text. (AIII)

HIV testing during pregnancy should be performed using a screening test that detects HIV-1 and HIV-2 antibodies. For pregnant women who meet the criteria outlined previously, HIV-1/HIV-2 type-differentiating immunoassays and nucleic acid testing protocols should be used. In New York State, if a woman presents for delivery without documentation of a negative HIV test during the current pregnancy and is not known to have HIV infection, the mother must receive expedited HIV testing with her consent; if she declines, the newborn must receive testing with or without maternal consent. For more information regarding HIV testing during pregnancy, refer to [HIV Testing During Pregnancy and at Delivery Guideline](#).

HIV-2 Treatment and Prophylaxis during Pregnancy

RECOMMENDATIONS

- Zidovudine plus lamivudine with lopinavir/ritonavir is the currently recommended regimen for HIV-2-infected pregnant women. (AIII)
- For HIV-2-infected women who decline ART or who are unable to adhere to an ART regimen during pregnancy, single-drug prophylaxis with zidovudine during

pregnancy and intrapartum should be used as an alternative for preventing HIV-2 mother-to-child transmission. (BIII)

The risk of mother-to-child transmission (MTCT) of HIV-2 is significantly lower than that of HIV-1 [1,2]. However, high HIV-2 viral load levels may be associated with increased risk for MTCT. In one study, MTCT of HIV-2 occurred more frequently in the setting of high maternal viral load levels (>10,000 copies/mL) [3]. Advanced HIV-2 disease has also been associated with HIV-2 MTCT [4], as has early HIV-2 infection during pregnancy [1]. These findings suggest that ART for HIV-2, regardless of the clinical or immunological status of the patient, may be indicated during pregnancy, similar to the practice for HIV-1.

Based on available data on safety in pregnancy, zidovudine/lamivudine plus lopinavir/ritonavir is the preferred regimen [2]. Tenofovir plus emtricitabine with lopinavir/ritonavir can be considered as an alternative [5,6]. For additional information regarding prescribing ART for pregnant women, refer to [Antiretroviral Therapy](#).

For HIV-2-infected pregnant women who decline ART for their own health, but for whom prevention of MTCT is necessary, two NRTIs plus lopinavir/ritonavir is the recommended regimen [2]. Single-drug prophylaxis with zidovudine alone during pregnancy and intrapartum can be considered as an alternative for preventing HIV-2 MTCT [2]. All ART prescribing considerations, including postnatal ART management, for HIV-2-infected pregnant women should be in consultation with a provider who has experience in the management of ART in these patients.

Testing and Prophylaxis for HIV-2-Exposed Infants

RECOMMENDATIONS

- All infants born to mothers infected with HIV-2 should receive the standard 6-week zidovudine prophylactic regimen [2,6]. (AIII)
- Clinicians should advise HIV-2-infected women about the risk of postpartum MTCT via breast milk. Breastfeeding is contraindicated for both HIV-1- and HIV-2-infected mothers, even when receiving ART [7]. (AI)
- The New York State Department of Health (NYSDOH) strongly recommends that all New York State birth facilities use the pediatric HIV testing services at the

Wadsworth Center (see [Diagnosis of Pediatric HIV Infection in HIV-Exposed Infants](#) for the recommended diagnostic testing schedule).

In New York State, the Newborn Screening Program screens newborns for HIV-1 antibodies using a dried blood spot sample collected from a heel-stick. HIV-2 antibodies, if present in the blood spot, may be detected by the EIA test due to cross-reactivity. This may present as HIV-1 test results that are inconsistent, inconclusive, or negative despite clinical evidence that is consistent with immunodeficiency. All infants who are born to HIV-infected mothers or who test positive for HIV antibodies on the newborn screening test are considered to be exposed to HIV and must have additional testing to definitively diagnose or exclude HIV infection. A blood specimen should be obtained from all exposed infants and should be sent to the Pediatric HIV Testing Service at the NYSDOH Wadsworth Center for diagnostic testing. The Pediatric HIV Testing Service performs an immunoassay that differentiates between HIV-1 and HIV-2 antibodies on all infant samples. If the sample is reactive for HIV-2 antibodies, then a qualitative HIV-2 RNA test is performed to definitively diagnose or exclude HIV-2 infection. See *Diagnosis of Pediatric HIV Infection in HIV-Exposed Infants* for the recommended diagnostic testing schedule.

References:

1. 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;51:833-843. [[PubMed](#)]
2. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. 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. Sep. 14, 2011; pp 85-87. Available at <http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf>
3. 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;14:441-448. [[PubMed](#)]

4. Morgan G, Wilkins HA, Pepin J, et al. AIDS following mother-to-child transmission of HIV-2. *AIDS* 1990;4:879-882. [[PubMed](#)]
5. Gilleece Y, Chadwick DR, Breuer J, et al. British HIV Association guidelines for antiretroviral treatment of HIV-2-positive individuals 2010. *HIV Med* 2010;11:611-619. [[PubMed](#)]
6. 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;9:452-502. [[PubMed](#)]
7. Committee on Pediatric AIDS. Infant feeding and transmission of human immunodeficiency virus in the United States. *Pediatrics* 2013;131;391-396. [[PubMed](#)]

All Recommendations

[Medical Care Criteria Committee](#), April 2012

ALL RECOMMENDATIONS: HIV-2

Screening and Diagnosis

- Specimens submitted for HIV testing should be screened by an enzyme immunoassay (EIA) that detects HIV-1, HIV-1 group O, and HIV-2. All laboratories performing HIV diagnostic testing should incorporate algorithms for differentiation of HIV-1 versus HIV-2 in repeatedly reactive samples. (AIII)
- When HIV-1/HIV-2 combination screening yields a reactive result but is followed by indeterminate or nonreactive HIV-1 Western blot, clinicians should:
 - Obtain a plasma HIV RNA assay to exclude acute HIV-1 infection (AIII)
 - Obtain testing for HIV-2 antibodies with an FDA-approved HIV-1/HIV-2 type-differentiating immunoassay if acute HIV-1 infection has been excluded (AIII)
 - Consider specimens positive for HIV-2 if they are repeatedly reactive on an HIV-1/HIV-2 screening test and reactive for HIV-2 antibodies on the HIV-1/HIV-2 differentiation test (AIII)
- Clinicians should use HIV-1/HIV-2 type-differentiating immunoassays and nucleic acid testing protocols when screening for HIV in patients who meet the criteria outlined in the text. (AIII)

Monitoring

- Clinicians should monitor HIV-2-infected patients by clinical evaluation and CD4 cell count. (BIII)

Treatment

- Clinicians should include two NRTIs and an appropriate boosted PI, such as lopinavir, saquinavir, or darunavir, when prescribing ART for HIV-2 mono-infected or HIV-1/HIV-2 co-infected individuals (see text). (AIII)

- Clinicians should *not* prescribe NNRTIs or the PIs nelfinavir, atazanavir, or fosamprenavir as part of an ART regimen against HIV-2 mono-infection; these agents may be used as part of a regimen for HIV-1/HIV-2 co-infected patients if adequate treatment for HIV-2 is also included. (BIII)
- Clinicians should consult with a provider with experience in the management of HIV-2 before initiating ART in HIV-2-infected patients. (AIII)
- Clinicians should educate patients with confirmed HIV-2 infection about the lack of data regarding treatment of HIV-2 and should review individual benefits and risks of initiating treatment. Patients should make the final decision of whether and when to initiate ART.

Pregnancy

- Clinicians caring for pregnant patients with suspected or diagnosed HIV-2 should consult with a provider with experience in HIV-2 testing and management, including perinatal ART for HIV-2-infected pregnant women and postnatal ART for HIV-2-exposed infants. (AIII)
- Clinicians should use HIV-1/HIV-2 type-differentiating immunoassays and nucleic acid testing protocols when screening for HIV in pregnant women who meet the criteria outlined in the text. (AIII)
- Zidovudine plus lamivudine with lopinavir/ritonavir is the currently recommended regimen for HIV-2-infected pregnant women. (AIII)
- For HIV-2-infected women who decline ART or who are unable to adhere to an ART regimen during pregnancy, single-drug prophylaxis with zidovudine during pregnancy and intrapartum should be used as an alternative for preventing HIV-2 mother-to-child transmission. (BIII)
- All infants born to mothers infected with HIV-2 should receive the standard 6-week zidovudine prophylactic regimen. (AIII)
- Clinicians should advise HIV-2-infected women about the risk of postpartum MTCT via breast milk. Breastfeeding is contraindicated for both HIV-1- and HIV-2-infected mothers, even when receiving ART. (AI)
- The New York State Department of Health (NYSDOH) strongly recommends that all New York State birth facilities use the pediatric HIV testing services at the Wadsworth Center.

