### HIV-2 Infection (Last updated April 8, 2015; last reviewed April 8, 2015)

#### Summary of HIV-2 Infection

- Compared to HIV-1 infection, the clinical course of HIV-2 infection is generally characterized by a longer asymptomatic stage, lower plasma HIV-2 RNA levels, and lower mortality; however, progression to AIDS does occur.
- There have been no randomized trials addressing the question of when to start antiretroviral therapy or the choice of initial or second-line therapy for HIV-2 infection; thus, the optimal treatment strategy has not been defined.
- Although the optimal CD4 T lymphocyte (CD4) cell count threshold for initiating antiretroviral therapy in HIV-2 infection is unknown, therapy should be started before there is clinical progression.
- HIV-2 is intrinsically resistant to non-nucleoside reverse transcriptase inhibitors and to enfuvirtide; thus, these drugs should not be included in an antiretroviral regimen for an HIV-2 infected patient.
- Pending more definitive data on outcomes in an antiretroviral therapy-naïve patient who has HIV-2 mono-infection or HIV-1/HIV-2 dual infection and requires treatment, an initial antiretroviral therapy regimen for these patients should include two nucleoside reverse transcriptase inhibitors plus an HIV-2 active boosted protease inhibitor or integrase strand transfer inhibitors.
- A few laboratories now offer quantitative plasma HIV-2 RNA testing for clinical care (see section text).
- Monitoring of HIV-2 RNA levels, CD4 cell counts, and clinical improvements can be used to assess treatment response, as is recommended for HIV-1 infection.
- Resistance-associated viral mutations to nucleoside reverse transcriptase inhibitors, protease inhibitors, and/or integrase strand transfer inhibitors may develop in HIV-2 infected patients while on therapy. However, no validated HIV-2 genotypic or phenotypic antiretroviral resistance assays are available for clinical use.
- In the event of virologic, immunologic, or clinical failure, second-line treatment should be instituted in consultation with an expert in HIV-2 management.

HIV-2 infection is endemic in West Africa. Although HIV-2 has had only limited spread outside this area, it should be considered in persons of West African origin or in those who have had sexual contact or shared needles with persons of West African origin. The prevalence of HIV-2 infection is also disproportionately high in countries with strong socioeconomic ties to West Africa (e.g., France; Spain; Portugal; and former Portuguese colonies such as Brazil, Angola, Mozambique, and parts of India).

#### Clinical Course of HIV-2 Infection

Compared to HIV-1 infection, the clinical course of HIV-2 infection is generally characterized by a longer asymptomatic stage, lower plasma HIV-2 viral loads, and lower mortality rate.\(^1,2\) However, HIV-2 infection can also progress to AIDS over time. Concomitant HIV-1 and HIV-2 infection may occur and should be considered in patients from areas with a high prevalence of HIV-2.

#### Diagnosis of HIV-2 Infection

In the appropriate epidemiologic setting, HIV-2 infection should be suspected in patients with clinical conditions suggestive of HIV infection but with atypical serologic results (e.g., a positive screening assay with an indeterminate HIV-1 Western blot).\(^3\) The possibility of HIV-2 infection should also be considered in the appropriate epidemiologic setting in patients with serologically confirmed HIV infection but low or undetectable HIV-1 RNA levels or in those with declining CD4 T lymphocyte (CD4) cell counts despite apparent virologic suppression on antiretroviral therapy (ART).

The 2014 Centers for Disease Control and Prevention guidelines for HIV diagnostic testing\(^4\) recommend initial HIV testing using an HIV-1/HIV-2 antigen/antibody combination immunoassay and subsequent testing using an HIV-1/HIV-2 antibody differentiation immunoassay. The Multispot HIV-1/HIV-2 Rapid Test (Bio-Rad Laboratories) is Food and Drug Administration approved for differentiating HIV-1 from HIV-2 infection. Commercially available HIV-1 viral load assays do not reliably detect or quantify HIV-2.\(^5,6\) Quantitative HIV-2 plasma RNA viral load testing has recently become available for clinical care at the University of Washington.
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Treatment of HIV-2 Infection

To date, no randomized trials addressing the question of when to start ART or the choice of initial or second-line therapy for HIV-2 infection have been completed; thus, the optimal treatment strategy has not been defined. Three clinical trials to assess first-line ART for HIV-2 infection are currently underway; 2 are enrolling patients with CD4 counts <500 cells/mm<sup>3</sup> (NCT016058090 and NCT02180438) and 1 is enrolling patients with CD4 count >200 and ≤600 cells/mm<sup>3</sup> (NCT02150993). Although the optimal CD4 cell count threshold for initiating ART in HIV-2 infection is unknown, therapy should be started before there is clinical progression.

HIV-2 is intrinsically resistant to non-nucleoside reverse transcriptase inhibitors (NNRTIs) and to enfuvirtide (T20). Data from in vitro studies suggest that HIV-2 is sensitive to the currently available nucleoside reverse transcriptase inhibitors (NRTIs), although with a lower barrier to resistance than HIV-1. Darunavir (DRV), lopinavir (LPV), and saquinavir (SQV) are more active against HIV-2 than other approved protease inhibitors (PIs); one of these boosted PIs should be used if a PI-based regimen is used. Other PIs should be avoided because of their lack of ARV activity and high failure rates. The integrase strand transfer inhibitors (INSTIs) raltegravir (RAL), elvitegravir (EVG), and dolutegravir (DTG) have potent activity against HIV-2. The CCR5 antagonist maraviroc (MVC) appears active against some HIV-2 isolates; however, no approved assays to determine HIV-2 co-receptor tropism exist and HIV-2 is known to use many other minor co-receptors in addition to CCR5 and CXCR4.

Several small studies suggest poor responses in HIV-2 infected individuals treated with some ARV regimens including dual-NRTI regimens; regimens containing NNRTI plus 2NRTIs; and some unboosted PI-based regimens including nelfinavir (NFV) or indinavir (IDV) plus zidovudine (ZDV) and lamivudine (3TC); and atazanavir (ATV)-based regimens. Clinical data on the effectiveness of triple-NRTI regimens are conflicting. In general, HIV-2 active, boosted PI-containing regimens have resulted in more favorable virologic and immunologic responses than 2 or 3-NRTI-based regimens. However, CD4 cell recovery on therapy are generally poorer than that observed for HIV-1. INSTI-based regimens may also have favorable treatment responses. A recent large systematic review of ART for HIV-2-infected patients (n = 17 studies, 976 HIV-2 infected patients) was unable to conclude which specific regimens are preferred.

Resistance-associated viral mutations to NRTIs, PIs and/or INSTIs commonly develop in HIV-2 infected patients while on therapy. Currently, HIV-2 transmitted drug resistance appears rare. In one small study, DTG was found to have activity as a second-line INSTI in some HIV-2 patients with extensive ARV experience and RAL resistance. Genotypic algorithms used to predict drug resistance in HIV-1 may not be applicable to HIV-2, because pathological and mutational patterns leading to resistance may differ between the HIV types.

Some groups have recommended specific preferred and alternative regimens for initial therapy of HIV-2 infection; however, currently, there are no controlled trial data to support the effectiveness of the recommended regimens. Pending more definitive data on outcomes in an ART-naive patient who has HIV-2 mono-infection or HIV-1/HIV-2 dual infection and requires treatment, a regimen containing two NRTIs plus an HIV-2 active boosted PI or INSTI should be initiated in HIV-2 infected individuals.

HIV-2 plasma RNA levels, CD4 cell counts, and clinical improvements can be monitored to assess treatment response, as is recommended for HIV-1. Patients who have HIV-2 RNA levels below the limits of detection before therapy should still have HIV-2 plasma RNA monitoring, in addition to CD4 cell count and clinical
monitoring. In the event of virologic, immunologic, or clinical failure, second-line treatment should be instituted in consultation with an expert in HIV-2 management.

References


15. Rodes B, Sheldon J, Toro C, Jimenez V, Alvarez MA, Soriano V. Susceptibility to protease inhibitors in HIV-2 primary
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