Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV

HIV-2 Infection (Last updated July 10, 2019; last reviewed July 10, 2019)

Key Considerations and Recommendations
• The clinical course of HIV-2 infection is generally characterized by a longer asymptomatic stage, lower plasma viral loads, and lower mortality rate than HIV-1 infection. However, progression to AIDS and death will occur in the majority of individuals without treatment.
• No randomized controlled trials have addressed when a person with HIV-2 should start antiretroviral therapy (ART) or which regimens are most effective for initial or second-line ART when treating HIV-2; thus, the optimal treatment strategy is not well defined.
• Existing data on the treatment of HIV-2, and extrapolation from data on the treatment of HIV-1, suggest that ART should be started at or soon after HIV-2 diagnosis to prevent disease progression and transmission of HIV-2 to others **(AIII)**.
• Quantitative plasma HIV-2 RNA viral load testing for clinical care is available and should be performed before initiation of ART **(AIII)**.
• HIV-2 is intrinsically resistant to non-nucleoside reverse transcriptase inhibitors and to enfuvirtide; therefore, these drugs **should not be included** in ART regimens for HIV-2 infection **(AII)**.
• Patients with hepatitis B virus (HBV)/HIV-2 coinfection should be prescribed ART regimens that contain drugs with activity against both HIV-2 and HBV **(AIII)**.
• Initial ART regimens for ART-naive patients who have HIV-2 monoinfection or HIV-1/HIV-2 coinfection should include an integrase strand transfer inhibitor (INSTI) plus two nucleoside reverse transcriptase inhibitors (NRTIs) **(AII)**. An alternative regimen is a boosted protease inhibitor (PI) that is active against HIV-2 (darunavir or lopinavir) plus two NRTIs **(BII)**.
• HIV-2 RNA, CD4 T lymphocyte (CD4) cell counts, and clinical status should be used to assess treatment response **(AIII)**. Unlike persons with HIV-1, persons with HIV-2 should continue to undergo periodic CD4 cell count testing even if their viral loads are persistently suppressed, because disease progression can occur despite an undetectable viral load.
• Resistance-associated viral mutations to INSTIs, PIs, or NRTIs may develop in persons with HIV-2 while they are on ART. However, no validated HIV-2 genotypic or phenotypic antiretroviral resistance assays are approved for clinical use.
• In the event of virologic, immunologic, or clinical failure, a new ART regimen should be constructed in consultation with an expert in HIV-2 management.
Rating of Recommendations: A = Strong; B = Moderate; C = Optional   *Rating of Evidence: I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Overview

HIV-2 infection is endemic in West Africa, with certain countries experiencing a population prevalence of >1%. The possibility of HIV-2 infection should be considered when treating persons of West African origin, persons who have had sexual contact or shared needles with persons of West African origin, and persons who reside 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). Globally, it has been estimated that one million to two million individuals have HIV-2, a number that includes people with HIV-1/HIV-2 dual infection. However, current and accurate prevalence data are scarce, and neither the Joint United Nations Programme on HIV and AIDS nor the World Health Organization have a formal surveillance system for HIV-2.[1]

Clinical Course of HIV-2 Infection

The clinical course of HIV-2 infection is generally characterized by a longer asymptomatic stage, lower plasma viral loads, and a lower mortality rate than HIV-1 infection.[2,3] However, without effective antiretroviral therapy (ART), HIV-2 infection will progress to AIDS and death in the majority of individuals.[4] Concomitant HIV-1 and HIV-2 infection may occur, and the possibility of this coinfection should be considered when treating persons from areas with a high prevalence of HIV-2.

Diagnostic and Monitoring Assays for HIV-2 Infection

In the appropriate epidemiologic setting, HIV-2 infection should be suspected in persons who have clinical

conditions that suggest HIV infection but who have atypical serologic results (e.g., a positive screening assay with an indeterminate HIV-1 Western blot).[5] The possibility of HIV-2 infection should also be considered in the appropriate epidemiologic setting in persons who have serologically confirmed HIV infection but who have low or undetectable HIV-1 RNA levels, or in those who have declining CD4 T lymphocyte (CD4) cell counts despite apparent virologic suppression on ART.

The 2014 Centers for Disease Control and Prevention guidelines for HIV diagnostic testing[6] recommend using an HIV-1/HIV-2 antigen/antibody combination immunoassay for initial testing and using an HIV-1/HIV-2 antibody differentiation immunoassay for subsequent testing. The Geenius HIV 1/2 Supplemental Assay (Bio-Rad Laboratories) is approved by the Food and Drug Administration (FDA) to differentiate HIV-1 infection from HIV-2 infection. The Multispot HIV-1/HIV-2 Rapid Test is no longer available. Commercially available HIV-1 RNA assays do not reliably detect or quantify HIV-2 RNA.[7] Quantitative HIV-2 RNA testing is available at the University of Washington (UW)[8] and the New York State Department of Health (NYSDOH).[9] HIV-2 nucleic acid amplification test-based (total DNA/RNA) diagnostic testing is available for clinical care at UW.[10] However, it is important to note that up to one-third of persons with untreated HIV-2 infection will have HIV-2 RNA levels below the limits of detection (10 copies/mL for UW testing and 7 IU/mL for NYSDOH testing); some of these persons will have clinical progression and CD4 cell count decline. No validated HIV-2 genotypic or phenotypic antiretroviral (ARV) resistance assays are approved by the FDA for clinical use. HIV-2 genotypic ARV resistance assays are available at UW for research use only.

Treatment of HIV-2 Infection

To date, no randomized controlled trials that address when to start ART or the choice of initial or subsequent ART regimens for HIV-2 infection have been completed;[11] thus, the optimal treatment strategy has not been defined. Existing data on the treatment of HIV-2 and extrapolation from data on the treatment of HIV-1 suggest that ART should be started at or soon after HIV-2 diagnosis in order to prevent disease progression and transmission of HIV-2 to others (AIII). However, CD4 cell recovery in persons with HIV-2 who are on ART is generally poorer than that observed in persons with HIV-1.[12,13]

Data from *in vitro* studies suggest that HIV-2 is sensitive to the currently available nucleoside reverse transcriptase inhibitors (NRTIs); however, HIV-2 is more likely to develop resistance to NRTIs than HIV-1.[14] HIV-2 is intrinsically resistant to non-nucleoside reverse transcriptase inhibitors (NNRTIs);[15] thus, NNRTI-based regimens are not recommended for treatment of HIV-2 (AII). Several small studies in individuals with HIV-2 infection have reported poor responses to dual-NRTI regimens[16,17] or regimens that contain an NNRTI plus two NRTIs.[18,19] Clinical data on the effectiveness of triple-NRTI regimens are conflicting.[20,21]

Integrase strand transfer inhibitor (INSTI)-based regimens or protease inhibitor (PI)-based regimens are treatment options for persons with HIV-2. As discussed below, two single-arm clinical trials showed favorable outcomes in patients who received INSTI-based regimens; data regarding the efficacy of PI-based regimens primarily come from observational reports. A randomized controlled trial comparing raltegravir (RAL) plus tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) to lopinavir/ritonavir (LPV/r) plus TDF/FTC is currently underway (FIT-2; NCT02150993).

INSTI-Based Regimens

All FDA-approved INSTIs—RAL, elvitegravir (EVG), dolutegravir (DTG), and bictegravir—have potent activity against HIV-2 *in vitro*.[22-26] INSTI-based regimens have shown favorable treatment responses in observational studies.[27-29] Two single-arm, open-label clinical trials have assessed the effectiveness of INSTI-based regimens in ART-naive individuals with HIV-2. One study evaluated RAL plus TDF/FTC, and the other evaluated EVG/cobicistat/TDF/FTC. Both studies demonstrated favorable clinical and immuno-virologic results at 48 weeks, providing the best evidence to date for HIV-2 treatment recommendations.[30,31]

PI-Based Regimens

In general, regimens that contain boosted PIs that are active against HIV-2 (and that also include two NRTIs) have resulted in more favorable virologic and immunologic responses than regimens that consist of only two or three NRTIs.[12,13,21,32] Darunavir (DRV), LPV, and saquinavir are more active against HIV-2 than other approved PIs.[33-35] Older, unboosted PI-based regimens, including nelfinavir or indinavir plus zidovudine and lamivudine, and atazanavir-based regimens have shown poor clinical success rates.[11,16,17,36,37]

Amongst the entry inhibitors, HIV-2 is intrinsically resistant to enfuvirtide.[38] The CCR5 antagonist maraviroc appears to be active against some HIV-2 isolates;[39] however, there are no FDA-approved assays that can determine HIV-2 co-receptor tropism, and HIV-2 is known to use many other minor co-receptors in addition to CCR5 and CXCR4.[40] There are no data yet on the activity of ibalizumab against HIV-2.

Some national and international guidelines have recommended specific preferred and alternative drug regimens for initial and second-line ART for HIV-2 infection;[41-44] however, there are currently no comparative randomized controlled clinical trial data that support the effectiveness of a specific recommended regimen.

Until there are more definitive data on outcomes, the Panel on Antiretroviral Guidelines for Adults and Adolescents recommends the following regimens for individuals with HIV-2 monoinfection or HIV-1/HIV-2 dual infection:

- A regimen that contains one INSTI plus two NRTIs is the recommended initial ART regimen for most individuals with HIV-2 infection **(AII)**. Recent observational data suggest an increased risk of neural tube defects in infants born to mothers who were receiving DTG at the time of conception. For recommendations on the use of DTG in those of childbearing potential, please refer to Women with HIV.

- An alternative regimen is a boosted PI (DRV or LPV) that is active against HIV-2 plus two NRTIs **(BII)**.

- NNRTI-based regimens **are not recommended** for persons with HIV-2 infection **(AII)**.

- Patients with hepatitis B virus (HBV)/HIV-2 coinfection require ART regimens that contain drugs with activity against both HIV-2 and HBV **(AIII)**. See Hepatitis B Virus/HIV Coinfection for more information.

- HIV-2 plasma RNA levels, CD4 cell counts, and clinical status should be monitored to assess treatment response, as is recommended for HIV-1 **(AII)**.

- Persons who have HIV-2 RNA levels that are below the limits of detection before they initiate ART should still undergo routine HIV-2 plasma RNA monitoring in addition to CD4 cell count and clinical monitoring. Unlike HIV-1, persons with HIV-2 requires continued CD4 cell count monitoring, as disease progression can occur in the setting of undetectable HIV-2 viral load **(AIII)**.

Persons with HIV-2 who are of childbearing potential require similar considerations when choosing a regimen as those with HIV-1 (see What to Start). There are no data on HIV-2 treatment as prevention; however, both data from studies of people with HIV-1 and data on the natural history of HIV-2 transmission suggest that effective ART likely provides a reduced risk of transmission to sexual partners.

Resistance-associated viral mutations to NRTIs, PIs, and/or INSTIs may develop in persons with HIV-2 while on ART.[35,45,46] Currently, transmitted drug resistance appears to be rare among people with HIV-2.[47,48] In several small studies, twice-daily dosing of DTG was found to have some residual activity as a second-line INSTI in some persons with HIV-2 who had extensive ART experience and RAL resistance.[49-52] Genotypic algorithms that are used to predict drug resistance in HIV-1 may not be applicable to HIV-2, because the pathways and mutational patterns that lead to resistance may differ between the HIV types (see the HIV2EU Algorithm and the Stanford University HIV Drug Resistance Database).[53] In the event of virologic, immunologic, or clinical failure, a new ART regimen should be constructed in consultation with an expert in HIV-2 management.

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