

# HIV-2 Infection

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## 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, without treatment, the majority of individuals with HIV-2 will progress to AIDS and death.
- 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 initiating ART **(AIII)**.
- For ART-naïve patients who have HIV-2 mono-infection or HIV-1/HIV-2 coinfection, antiretroviral (ARV) regimens should include an integrase strand transfer inhibitor (INSTI) plus two nucleoside reverse transcriptase inhibitors (NRTIs) **(AII)**. A recommended alternative regimen is a boosted protease inhibitor (PI) that is active against HIV-2 (darunavir or lopinavir) plus two NRTIs **(BII)**.
- HIV-2 is intrinsically resistant to non-nucleoside reverse transcriptase inhibitors (NNRTIs); therefore, NNRTI-based regimens, including long-acting injectable rilpivirine (given with the INSTI cabotegravir), **are not recommended** for treatment of HIV-2 **(AIII)**.
- Patients with hepatitis B virus (HBV)/HIV-2 coinfection should be prescribed ART that contains drugs with activity against both HIV-2 and HBV **(AIII)**.
- HIV-2 RNA, CD4 T lymphocyte (CD4) cell counts, and clinical status should be used to assess treatment response **(AII)**. Unlike people with HIV-1, people with HIV-2 should continue to undergo periodic CD4 testing even if their viral loads are persistently suppressed, because disease progression can occur despite an undetectable viral load **(AIII)**.
- Resistance-associated viral mutations to INSTIs, PIs, or NRTIs may develop in people 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 ARV regimen should be constructed in consultation with an expert in HIV-2 management.
- *In vitro* studies demonstrate that HIV-2 is intrinsically resistant to the fusion inhibitor enfuvirtide, and limited data also show that HIV-2 is intrinsically resistant to fostemsavir; therefore, these drugs **are not recommended** for treatment of people with HIV-2 **(AIII)**.
- For patients with multidrug-resistant virus, ibalizumab and lenacapavir demonstrate *in vitro* potency against HIV-2 and may be considered **(BIII)**.

**Rating of Recommendations:** A = Strong; B = Moderate; C = Weak

**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 people of West African origin, people who have had sexual contact with or shared needles with people of West African origin, and people 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 1 million to 2 million people 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 has formal surveillance systems for HIV-2.<sup>1</sup>

## 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.<sup>2,3</sup> However, without effective antiretroviral therapy (ART), HIV-2 infection will progress to AIDS and death in the majority of individuals.<sup>4</sup> Concomitant infection with HIV-1 and HIV-2 may occur, and the possibility of this coinfection should be considered when treating people 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 people 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).<sup>5</sup> The possibility of HIV-2 infection should also be considered in the appropriate epidemiologic setting in people who have serologically confirmed HIV infection but 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<sup>6</sup> 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 U.S. 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.<sup>7</sup> Quantitative HIV-2 RNA testing is available at the [University of Washington \(UW\)](#)<sup>8</sup> and the [New York State Department of Health \(NYSDOH\)](#).<sup>9</sup> HIV-2 nucleic acid amplification test–based (total DNA/RNA) diagnostic testing is now commercially available for clinical care.<sup>10,11</sup> However, it is important to note that up to one-third of people with untreated HIV-2 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 people will have clinical progression and CD4 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 for HIV-2 have been reported<sup>12</sup>; 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 to prevent disease

progression and transmission of HIV-2 to others (**AIII**). However, CD4 cell recovery in people with HIV-2 who are on ART is generally poorer than that observed in people with HIV-1.<sup>13,14</sup>

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.<sup>15</sup> HIV-2 is intrinsically resistant to non-nucleoside reverse transcriptase inhibitors (NNRTIs)<sup>16</sup>; thus, NNRTI-based regimens, including the long-acting injectable rilpivirine (RPV) (given with the integrase strand transfer inhibitor [INSTI] cabotegravir [CAB]), **are not recommended** for treatment of HIV-2 (**AIII**). Several small studies in individuals with HIV-2 have reported poor responses to dual-NRTI regimens<sup>17,18</sup> or regimens that contain an NNRTI plus two NRTIs.<sup>19,20</sup> Clinical data on the effectiveness of triple-NRTI regimens are conflicting.<sup>21,22</sup>

INSTI-based regimens or protease inhibitor (PI)-based regimens are treatment options for people with HIV-2. As discussed below, three 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 completed, but the results have not been reported (FIT-2; NCT02150993).

## Integrase Strand Transfer Inhibitor–Based Regimens

All FDA-approved INSTIs—RAL, elvitegravir (EVG), dolutegravir (DTG), bictegravir, and CAB—have potent activity against HIV-2 *in vitro*.<sup>23-28</sup> INSTI-based regimens have shown favorable treatment responses in observational studies.<sup>29-31</sup> Three small, single-arm, open-label clinical trials have assessed the effectiveness of INSTI-based regimens in ART-naive individuals with HIV-2. These studies evaluated RAL plus TDF/FTC, EVG/cobicistat/TDF/FTC, and DTG plus either abacavir/lamivudine or TDF/FTC. All the studies demonstrated favorable clinical and immunovirologic results at 48 weeks, providing the best evidence to date for HIV-2 treatment recommendations.<sup>32-34</sup>

## Protease Inhibitor–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.<sup>13,14,22,35</sup> Darunavir (DRV), lopinavir (LPV), and saquinavir are more active against HIV-2 than other approved PIs.<sup>36-38</sup> While LPV/r is more active against HIV-2 than DRV *in vitro*, it is less well tolerated. Some clinicians may use boosted DRV (where available) to enhance adherence. Older unboosted PI-based regimens, including nelfinavir or indinavir plus zidovudine and lamivudine, and atazanavir-based regimens have shown poor clinical success rates.<sup>12,17,18,39,40</sup>

## Other Antiretroviral Drugs

Among the entry inhibitors, HIV-2 is intrinsically resistant to enfuvirtide.<sup>41</sup> The CCR5 antagonist maraviroc appears to be active against some HIV-2 isolates<sup>42</sup>; 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.<sup>43</sup> The post-attachment inhibitor ibalizumab (IBA) has potent *in vitro* activity against HIV-2 isolates.<sup>44</sup> Limited data suggest HIV-2 is intrinsically resistant to the attachment inhibitor fostemsavir (FTR).<sup>45,46</sup>

The capsid inhibitor lenacapavir (LEN) demonstrates nanomolar potency against HIV-2 *in vitro* but is 11- to 25-fold less active against HIV-2 than HIV-1.<sup>47,48</sup>

Some national and international guidelines have recommended specific preferred and alternative drug regimens for initial and second-line ART for HIV-2 infection<sup>49-52</sup>; however, there are currently no comparative randomized controlled clinical trial data that support the effectiveness of a specific recommended regimen.

## The Panel's Recommendations

Until more definitive data on outcomes are available, the Panel on Antiretroviral Guidelines for Adults and Adolescents provides the following recommendations for the management of individuals with HIV-2 mono-infection or HIV-1/HIV-2 dual infection:

- A regimen that contains one INSTI plus two NRTIs is the recommended initial ART for most individuals with HIV-2 **(AII)**.
- An alternative regimen is a boosted PI (DRV or LPV) that is active against HIV-2 plus two NRTIs **(BII)**.
- HIV-2 is intrinsically resistant to NNRTIs; therefore, NNRTI-based regimens, including long-acting injectable RPV (given with the INSTI CAB), **are not recommended** for treatment of HIV-2 **(AIII)**.
- HIV-2 demonstrates intrinsic resistance to the fusion inhibitor enfuvirtide *in vitro*, and limited data show intrinsic resistance to FTR; therefore, these drugs **are not recommended** for treatment of people with HIV-2 **(AIII)**.
- For people with multidrug-resistant HIV-2, IBA and LEN may be considered based on *in vitro* data **(BIII)**.
- Patients with hepatitis B virus (HBV)/HIV-2 coinfection require ART that contains 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 counts, and clinical status should be monitored to assess treatment response, as is recommended for HIV-1 **(AII)**.
- People 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 count and clinical monitoring. Unlike HIV-1, people with HIV-2 require continued CD4 count monitoring, as disease progression can occur in the setting of undetectable HIV-2 viral load **(AIII)**.

Women with HIV-2 who are of childbearing potential require similar considerations when choosing a regimen as women of childbearing potential 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.<sup>53-55</sup>

Viral mutations that are associated with resistance to NRTIs, PIs, and/or INSTIs may develop in people with HIV-2 while they are on ART.<sup>38,56,57</sup> Currently, transmitted drug resistance appears to be rare among people with HIV-2.<sup>58,59</sup> In several small studies, twice-daily dosing of DTG was found to have some residual activity as a second-line INSTI in some people with HIV-2 who had extensive ART experience and RAL resistance.<sup>60-63</sup> 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](#)).<sup>64</sup> 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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