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Diagnosis and Management of HIV-2 in Adults

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Contents

Guideline Information

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Updates

- **October 2021: (1)** Recommended initial ART regimens were updated to reflect corresponding updates to the NYSDOH AI guideline *Selecting an Initial ART Regimen*. **(2)** Dolutegravir prior to 8 weeks of pregnancy was removed from the list of ART regimens to avoid for a pregnant individual with HIV-2.
- **September 2020:** The red text below was added to the *Treatment of HIV-2* section: "Bictegravir is highly potent against HIV-2 in vitro [Tsiang, et al. 2016; Le Hingrat, et al. 2018; Smith, et al. 2019]; however, there are no published data on the use of TAF/FTC/BIC in patients with HIV-2. If no drug resistance testing is available, DTG and BIC should be used with caution in ART-experienced patients with HIV-2 who have virologic failure on a RAL- or EVG- based ART regimen. The chemokine receptor antagonist maraviroc (MVC) is active against HIV-2 strains that exclusively use CCR5 for viral entry [Borrego, et al. 2012]. However, its use in the treatment of HIV-2 is limited because there is no commercially available tropism assay for HIV-2 to predict susceptibility to MVC. The fusion inhibitor enfuvirtide has no in vitro activity against HIV-2 [Menendez-Arias and Alvarez 2014; FDA 2018]. The recently approved attachment inhibitor fostemsavir has no activity against HIV-2 [FDA 2020]. Ibalizumab, a humanized monoclonal IgG-4 antibody that prevents HIV cell entry by binding to the host CD4 receptor, has in vitro evidence of activity against HIV-2 with IC50 levels comparable to those found in HIV-1 group M strains [Hingrat 2020]. However, the in vivo efficacy of an ibalizumab-based regimen in individuals with antiretroviral-resistant HIV-2 infection has not been established."

Diagnosis and Management of HIV-2 in Adults

Purpose of This Guideline

- Inform clinicians about when to suspect and how to diagnose and manage the care of adults with HIV-2.
- Identify the similarities and differences in treatment for individuals with HIV-1 and HIV-2.
- Recommend preferred antiretroviral (ARV) regimens for treatment and identify ARVs to avoid.
- Encourage clinicians to use the services of the NYSDOH Wadsworth Center, the NYS public health laboratory, for testing used in monitoring HIV-2.
- Integrate current evidence-based clinical recommendations into the healthcare-related implementation strategies of the *Ending the Epidemic (ETE) initiative*, which seeks to end the AIDS epidemic in NYS by the end of 2020.

HIV-2 Overview

The HIV-2 virus was first isolated in West Africa in the mid-1980s among individuals living with AIDS [Clavel, et al. 1986]. HIV-2 infection is endemic in West Africa, with the highest prevalence in Cape Verde, the Ivory Coast, Gambia, Guinea-Bissau, Mali, Mauritania, Nigeria, and Sierra Leone [Gottlieb, et al. 2018]. Although rare, HIV-2 infection has also been reported in several countries in Europe, South America, and Asia, and in the United States [Gottlieb 2018]. As of June 2010, 166 cases of HIV-2 had been reported in the United States and 46% of those were from New York City [CDC 2011]. The majority of individuals with HIV-2 are from West Africa or have had sexual contact or shared injection drug equipment with someone from this region [Torian, et al. 2010].

HIV-2 infection is associated with slower disease progression than HIV-1 infection because of lower plasma viral load levels of HIV-2 [van der Loeff, et al. 2010; MacNeil, et al. 2007; Gottlieb, et al. 2002; Popper, et al. 1999; Simon, et al. 1993]. With lower levels of virus, HIV-2 is transmitted less efficiently than HIV-1 through sexual behavior and from mother to child [Burgard, et al. 2010; O'Donovan, et al. 2000; Adjorlolo-Johnson, et al. 1994]. Similar to HIV-1, HIV-2 disease progression correlates with increasing plasma HIV-2 viral load [Gottlieb, et al. 2002]. Although HIV-2 is less virulent than HIV-1, individuals with HIV-2 manifest clinical signs, symptoms, and opportunistic infections (OIs) similar to those seen with HIV-1. In addition, the majority of individuals with HIV-2, if untreated, will eventually progress to AIDS and death [Esbjornsson, et al. 2018].

There are many similarities in the management of patients with HIV-1 and those with HIV-2, including prophylaxis for and treatment of OIs and timing of antiretroviral therapy (ART) initiation. As noted in the section on treatment, below, ART should be recommended for all patients diagnosed with HIV-2 [Ba, et al. 2018]. As with HIV-1, the patient should make the final decision of whether and when to initiate ART.

A key difference in the clinical management of HIV-2 compared with HIV-1 is that resistance testing is not commercially available in the United States and guidance in interpreting mutations is not readily available for HIV-2. Another important difference in management is that the non-nucleoside reverse transcriptase inhibitor (NNRTI) class of ARV medications is not effective against HIV-2. Furthermore, unlike in HIV-1, there are no randomized clinical trials of ARV treatment for HIV-2 that indicate the optimal time to initiate treatment or the preferred initial regimen. Therefore, treatment recommendations for HIV-2 are in large part derived from clinical studies conducted in HIV-1. Because HIV-1 and HIV-2 share the same pathogenic process, extrapolating to HIV-2 from HIV-1 is a clinically valid approach.

Diagnosis of HIV-2

☑ RECOMMENDATIONS

Diagnosis

- To diagnose HIV-2 infection, clinicians should follow the steps in the Centers for Disease Control and Prevention/Association of Public Health Laboratories (CDC/APHL) *HIV Diagnostic Testing Algorithm* and the recommendations in the NYSDOH AI guideline *HIV Testing.* (A1)
  - See the NYSDOH guideline *HIV Testing > Steps in the HIV Diagnostic Testing Algorithm and HIV-2 RNA Tests for Diagnostic Use*
- In individuals who are confirmed to have HIV-2 antibodies, clinicians should perform a clinical evaluation for HIV-2 infection that is similar in scope to the evaluation of patients with HIV-1. (A1) HIV-2 antibodies are confirmed by a reactive result to an HIV-1/2 or HIV-1/2 antigen/antibody (Ag/Ab) immunoassay and a positive result for HIV-2 Abs on a Food and Drug Administration (FDA)-approved supplemental HIV-1/2 Ab differentiation assay.
  - See the NYSDOH guideline *HIV Testing > HIV-2 RNA Tests for Diagnostic Use*

Before the 4th-generation HIV-1/2 Ag/Ab and HIV-1/2 Ab differentiation immunoassays for HIV testing became widely available, clinicians suspected chronic HIV-2 infection in certain clinical scenarios, such as a declining CD4 cell count in an HIV-1–seropositive, untreated individual with an undetectable HIV-1 plasma viral load, or an opportunistic infection in an individual from West Africa who is not HIV-1 seropositive.

Currently, all HIV testing performed according to the CDC/APHL algorithm begins with a FDA-approved 4th-generation HIV-1/2 Ag/Ab combination immunoassay [CDC 2018], which detects HIV-1 p24 antigen and HIV-1 and HIV-2 antibodies but not HIV-2 antigen. If the combination immunoassay is reactive, a supplemental HIV-1/2 Ab differentiation assay is performed. There are 4 scenarios, described below, in which clinicians should consider HIV-2 infection.

- **HIV-1/HIV-2 differentiation assay is reactive for HIV-2 antibody:** The individual is considered HIV-2 antibody positive, and a clinical evaluation for HIV-2 infection should be performed (see *Monitoring ART in Individuals With HIV-2* in this guideline).
- **HIV-1/HIV-2 differentiation assay is reactive for HIV-1 and HIV-2 antibody:** The individual is considered HIV positive, undifferentiated, and HIV-1 RNA and HIV-2 RNA or DNA testing should be performed to confirm or exclude HIV-1/HIV-2 coinfection. A minority of individuals with HIV-2 are coinfected with HIV-1. Qualitative and quantitative HIV-2 viral load testing is available by contacting the Bloodborne Viruses Laboratory at the Wadsworth Center (see *Box 1: Wadsworth Center Bloodborne Viruses Laboratory Services*, below).
- **HIV-1/HIV-2 differentiation assay is nonreactive or indeterminate for HIV-1 and/or HIV-2 antibody:** Plasma HIV-1 RNA testing should be performed to confirm or exclude acute HIV-1 infection [CDC 2018].
  - If the Ab differentiation assay is nonreactive or HIV-1 indeterminate and HIV-1 RNA is not detected, the individual is considered negative for HIV-1 and HIV-2.
  - If the antibody differentiation assay is either HIV-2 indeterminate or HIV indeterminate and HIV-1 RNA is not detected, then HIV-2 RNA testing may be used to confirm HIV-2 infection. However, because HIV-2 RNA levels can be low or undetectable in a person with HIV-2 infection, the absence of HIV-2 RNA does not exclude HIV-2 infection. Therefore, in a person at high risk for HIV-2 infection who has undetectable HIV-2 RNA, clinicians should consider testing for HIV-2 DNA or repeating the HIV testing algorithm in 2 to 4 weeks, starting with the HIV-1/2 Ag/Ab combination immunoassay. If results remain unclear, clinicians may consider obtaining other HIV-2–specific tests through public health or commercial laboratories or the CDC.
- **Nonreactive 4th-generation HIV-1/2 Ag/Ab immunoassay and suspected recent exposure to HIV-2** (e.g., exposure from a sex partner from an HIV-2 endemic area)**:** HIV-2 RNA testing may be required or the HIV testing algorithm may be repeated, beginning with the 4th-generation HIV-1/2 Ag/Ab immunoassay, 4 weeks (and not later than 12 weeks) after the first test.

Box 1: Wadsworth Center Bloodborne Viruses Laboratory Services

- The Wadsworth Center offers HIV-2 viral load testing, free of charge, for patients and healthcare providers in New York State. To submit a specimen for HIV-2 viral load testing, please contact the Bloodborne Viruses Laboratory at (518) 474-2163. Specific services include:
  - Quantitative detection of HIV-2 RNA in plasma samples for baseline and subsequent monitoring of response to ART in patients with confirmed HIV-2 infection.
  - HIV-2 RNA viral load testing during pregnancy. Contact the lab at (518) 474-2163 early in the patient's pregnancy to discuss the protocol and timing for testing.
  - HIV testing for all newborns exposed to HIV (HIV-1 and HIV-2) in New York State, free of charge.
  - If a sample is reactive for HIV-2 antibodies, the Pediatric HIV Testing Service will perform a reverse transcription polymerase chain reaction (RT-PCR) test for qualitative detection of HIV-2 RNA.

Note: HIV-2 phenotypic and genotypic resistance testing is not offered at Wadsworth or commercially available in the United States.

Treatment of HIV-2

☑ RECOMMENDATIONS

Treatment

- Clinicians should recommend ART for all individuals diagnosed with HIV-2. (A2†)
- Clinicians should not prescribe any NNRTI for treatment of HIV-2 infection. (A*)
- Clinicians should recommend a single-tablet regimen (STR) that includes 2 nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) plus an integrase strand transfer inhibitor (INSTI) as the initial treatment for adults with HIV-2 who are not pregnant and not planning to become pregnant, including those with acute HIV-2 infection (see *Tables 1 and 2: Preferred and Alternative ART Regimens for Initial Treatment of Nonpregnant Adults with HIV-2*). (A2)
- For individuals with HIV-1/HIV-2 coinfection, clinicians should:
  - Perform HIV-1 drug resistance testing to guide the choice of an initial regimen or to modify a regimen if virologic failure develops. (A2)
  - Recommend an ART regimen that will suppress both viruses effectively. (A*)

Table 1: Preferred ART Regimens for Initial Treatment of Nonpregnant Adults With HIV-2 [a]
(listed alphabetically; for specific details, see drug package inserts; for full recommendations on initiating ART in patients with HIV, see the NYSDOH AI guideline *Selecting an Initial ART Regimen*)

Regimen	Comments	Rating
Available as a Single-Tablet Formulation		
Abacavir/lamivudine/dolutegravir [b,c] (ABC/3TC/DTG; Triumeq)	• Initiate ***only*** in patients confirmed to be negative for HLA-B*5701, including when a "rapid-start" or "test-and-treat" initiation of ART occurs before baseline laboratory test results are available. • Initiate ***only*** in patients with CrCl ≥30 mL/min [d]. • Consider underlying risk of coronary heart disease. • Documented DTG resistance after initiation in treatment-naive patients is rare. • Magnesium- or aluminum-containing antacids may be taken 2 hours before or 6 hours after DTG; calcium-containing antacids -or iron supplements may be taken simultaneously if taken with food.	A1

Table 1: Preferred ART Regimens for Initial Treatment of Nonpregnant Adults With HIV-2 [a]
(listed alphabetically; for specific details, see drug package inserts; for full recommendations on initiating ART in patients with HIV, see the NYSDOH AI guideline *Selecting an Initial ART Regimen*)

Regimen	Comments	Rating
Lamivudine/dolutegravir [b,c] (DTG/3TC; Dovato)	• Initiate ***only*** in patients with CrCl ≥30 mL/min [d]. • Do not use in patients with hepatitis B virus coinfection. • Do not initiate before HIV resistance tests results are available. • Do not initiate in patients with NRTI resistance, including the M184V/I mutation. • Do not initiate in patients with baseline HIV RNA levels >500,000 copies/mL until additional study data are available. • Documented DTG resistance after initiation in treatment-naive patients is rare. • Magnesium- or aluminum-containing antacids may be taken 2 hours before or 6 hours after DTG; calcium-containing antacids or iron supplements may be taken simultaneously if taken with food.	A1
Tenofovir alafenamide/emtricitabine/ bictegravir [c] (TAF 25 mg/FTC/BIC; Biktarvy)	• Initiate ***only*** in patients with CrCl ≥30 mL/min [d]. • Contains 25 mg of TAF, unboosted [c]. • Magnesium- or aluminum-containing antacids may be taken 2 hours before or 6 hours after BIC; calcium-containing antacids or iron supplements may be taken simultaneously if taken with food. • Documented DTG resistance after initiation in treatment-naive patients is rare.	A1
Available as a Multi-Tablet Regimen With Once-Daily Dosing		
Tenofovir alafenamide/emtricitabine or tenofovir disoproxil fumarate/emtricitabine *and* dolutegravir [b,c] (TAF 25 mg/FTC or TDF 300 mg/FTC *and* DTG; Descovy or Truvada *and* Tivicay)	• For TAF/FTC, initiate ***only*** in patients with CrCl ≥30 mL/min [d]. • Contains 25 mg of TAF, unboosted [c]. • For TDF/FTC, initiate ***only*** in patients with CrCl ≥50 mL/min [d]. • For TDF/FTC, consider bone mineral density. • Magnesium- or aluminum-containing antacids may be taken 2 hours before or 6 hours after DTG; calcium-containing antacids or iron supplements may be taken simultaneously if taken with food. • Documented DTG resistance after initiation in treatment-naive patients is rare.	A1
Tenofovir alafenamide/emtricitabine or tenofovir disoproxil fumarate/emtricitabine *and* raltegravir HD [c] (TAF 25 mg/FTC or TDF 300 mg/FTC *and* RAL HD; Descovy or Truvada *and* Isentress HD)	• For TAF/FTC, initiate ***only*** in patients with CrCl ≥30 mL/min [d]. • Contains 25 mg of TAF, unboosted [c]. • For TDF/FTC, initiate ***only*** in patients with CrCl ≥50 mL/min [d]. • For TDF/FTC, consider bone mineral density. • Administer as TAF/FTC or TDF/FTC once daily and RAL HD 1200 mg once daily, dosed as two 600 mg HD tablets. • To date, no clinical trials have been conducted with TAF and RAL; data are based on bioequivalence pharmacokinetic studies. • Magnesium- or aluminum-containing antacids are contraindicated; coadministration of calcium-containing antacids is not recommended with RAL HD.	A2

Table 1: Preferred ART Regimens for Initial Treatment of Nonpregnant Adults With HIV-2 [a]
(listed alphabetically; for specific details, see drug package inserts; for full recommendations on initiating ART in patients with HIV, see the NYSDOH AI guideline *Selecting an Initial ART Regimen*)

Regimen	Comments	Rating

Abbreviations: ART, antiretroviral therapy; CrCl, creatinine clearance; DHHS, U.S. Department of Health and Human Services; NRTI, nucleoside/nucleotide reverse transcriptase inhibitors.

Notes:

a. Refer to DHHS for ART regimens for individuals of childbearing potential: *Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States.*
b. See *Use of Dolutegravir in Individuals of Childbearing Capacity.*
c. Substitutions:
   - In all cases, FTC and 3TC are interchangeable.
   - TAF 10 mg and TAF 25 mg are not interchangeable.
d. For dose adjustments, refer to the NYSDOH AI guideline *Selecting an Initial ART Regimen > Table 9: Recommended Dose Adjustments for Use of Selected Fixed-Dose Combination Antiretroviral Medications in Patients With Hepatic or Renal Impairment.*

Table 2: Alternative ART Regimens for Initial Treatment of Nonpregnant Adults With HIV-2 [a]
(listed alphabetically; for specific details, see drug package inserts; for full recommendations on initiating ART in patients with HIV, see the NYSDOH AI guideline *Selecting an Initial ART Regimen*)

Regimen	Comments	Rating
Available as a Single-Tablet Formulation		
Tenofovir alafenamide/emtricitabine/ darunavir/cobicistat [b] (TAF 10 mg/FTC/DRV/COBI; Symtuza)	• Initiate ***only*** in patients with CrCl ≥30 mL/min [c]. • Carefully consider drug-drug interactions with COBI [Eron, et al. 2018]. • Contains 10 mg TAF, boosted [b].	B2
Tenofovir alafenamide/emtricitabine/ elvitegravir/cobicistat [b] (TAF 10 mg/FTC/EVG/COBI; Genvoya)	• Initiate ***only*** in patients with CrCl ≥30 mL/min [c]. • Carefully consider drug-drug interactions with COBI. • Contains 10 mg of TAF, boosted with COBI [b]. • Separate dosing of cation-containing (Ca++, AL, Mg) antacids by 2 hours, either before or after dose of EVG.	B1
Available as a Multi-Tablet Regimen With Twice-Daily Dosing		
Tenofovir alafenamide/emtricitabine or tenofovir disoproxil fumarate/emtricitabine *and* raltegravir [b] (TAF 25 mg/FTC or TDF 300 mg/FTC *and* RAL; Descovy or Truvada *and* Isentress)	• For TAF/FTC, initiate ***only*** in patients with CrCl ≥30 mL/min [c]. • For TDF/FTC, initiate ***only*** in patients with CrCl ≥50 mL/min [c]. • For TDF/FTC, consider bone mineral density. • Administer as TAF/FTC or TDF/FTC once daily and RAL 400 mg twice daily. • Magnesium- or aluminum-containing antacids are contraindicated; calcium-containing antacids are acceptable with RAL.	B3

Abbreviations: ART, antiretroviral therapy; CrCl, creatinine clearance; CYP, cytochrome P450; DHHS, U.S. Department of Health and Human Services.

Notes:

a. Refer to DHHS for ART regimens for individuals of childbearing potential: *Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States.*
b. Substitutions:
   - In all cases, FTC and 3TC are interchangeable.
   - TAF 10 mg and TAF 25 mg are not interchangeable.
   - COBI and RTV should not be considered interchangeable because of their drug-interaction profiles.
c. For dose adjustments, refer to the NYSDOH AI guideline *Selecting an Initial ART Regimen > Table 9: Recommended Dose Adjustments for Use of Selected Fixed-Dose Combination Antiretroviral Medications in Patients With Hepatic or Renal Impairment.*

All FDA-approved NRTIs effectively inhibit HIV-2 reverse transcriptase [Menendez-Arias and Alvarez 2014]. Three HIV protease inhibitors effectively inhibit HIV-2, but given the availability of darunavir, use of lopinavir and saquinavir should be limited. Atazanavir, fosamprenavir, tipranavir, and nelfinavir have no or greatly reduced in vitro inhibitory activity against HIV-2. As a class, NNRTIs are not active against HIV-2 [Menendez-Arias and Alvarez 2014].

→ KEY POINTS

- If a protease inhibitor is being considered as part of an ART regimen for treatment of HIV-2, boosted darunavir is preferred.
- Atazanavir **should not be used** because of its lack of potency in vitro against HIV-2 [Menendez-Arias and Alvarez 2014; Cavaco-Silva, et al. 2013].

Based on limited clinical trial data using the INSTIs elvitegravir and raltegravir, and in vitro data, it is expected that a DTG- or BIC-based regimen with 2 NRTIs can be used to treat treatment-naive patients with HIV-2. In one study of a single-tablet regimen (EVG/COBI/TDF/FTC), 93.3% of subjects had viral suppression at 48 weeks [Ba, et al. 2018]. A study of a multi-tablet regimen (TDF/FTC *and* RAL) demonstrated that 96% of participants with HIV-2 completing the 48-week follow-up had an HIV-2 viral load <40 copies/mL [Matheron, et al. 2018]. It is important to involve patients in the decision-making process regarding initiation of ART, and clinicians should work to remove barriers to treatment initiation, such as lack of access to combination therapy.

In treatment-experienced patients with HIV-2, the ARVs listed in Tables 1 and 2 can be considered if their potency has not been compromised by prior treatment failure and the likely emergence of drug resistance/cross-resistance. There are no commercially available genotypic or phenotypic drug resistance assays for HIV-2 available in the United States that can be used to guide the selection of an alternative ART regimen in the setting of virologic failure.

Bictegravir is highly potent against HIV-2 in vitro [Smith, et al. 2019; Le Hingrat, et al. 2018; Tsiang, et al. 2016]; however, there are no published data on the use of TAF/FTC/BIC in patients with HIV-2. If no drug resistance testing is available, DTG and BIC should be used with caution in ART-experienced patients with HIV-2 who have virologic failure on a RAL- or EVG- based ART regimen. The chemokine receptor antagonist maraviroc (MVC) is active against HIV-2 strains that exclusively use CCR5 for viral entry [Borrego, et al. 2012]. However, its use in the treatment of HIV-2 is limited because there is no commercially available tropism assay for HIV-2 to predict susceptibility to MVC. The fusion inhibitor enfuvirtide has no in vitro activity against HIV-2 [FDA 2018; Menendez-Arias and Alvarez 2014]. The recently approved attachment inhibitor fostemsavir has no activity against HIV-2 [FDA 2020]. Ibalizumab, a humanized monoclonal IgG-4 antibody that prevents HIV cell entry by binding to the host CD4 receptor, has in vitro evidence of activity against HIV-2 with IC50 levels comparable to those found in HIV-1 group M strains [Hingrat, et al. 2020]. However, the in vivo efficacy of an ibalizumab-based regimen in individuals with antiretroviral-resistant HIV-2 infection has not been established.

In the setting of HIV-1/HIV-2 coinfection, HIV-1 drug resistance testing should be performed to guide the choice of an initial regimen or to modify a regimen if virologic failure develops. If HIV-1 drug-resistant virus has been identified, ARV agents that are active only against HIV-1 (such as an NNRTI) can be used to treat individuals with HIV-1/HIV-2 coinfection, as long as a combination of anti–HIV-2 active agents is also used to fully suppress both viruses.

Monitoring ART in Individuals with HIV-2

☑ RECOMMENDATIONS

Monitoring

- For individuals who are newly diagnosed with HIV-2, clinicians should perform the same laboratory and diagnostic testing currently recommended for individuals with HIV-1, with the exception of drug resistance testing, which is not available. (A3)
  - Testing includes CD4 cell count, HIV-2 viral load, creatinine clearance, and status of coinfections such as hepatitis B and C viruses and tuberculosis (see NYSDOH AI guideline *Selecting an Initial ART Regimen > ART-Initiation Laboratory Testing*).

☑ RECOMMENDATIONS

- Clinicians should use HIV-2 viral load testing and CD4 cell count to determine the effectiveness of an ART regimen in patients with HIV-2. (A2)
- If HIV-2 viral load testing is not available, clinicians should suspect treatment failure if individuals experience a sustained decrease in CD4 cell count or have clinical disease progression. (A2)
- If a clinical practice in New York State cannot obtain HIV-2 viral load testing from the Wadsworth Laboratory, clinicians should refer individuals with HIV-2 to a practice that has the ability to access HIV-2 viral load testing from the Wadsworth Laboratory. (A3)

There is no FDA-approved, HIV-2 quantitative viral load assay commercially available. However, an HIV-2 quantitative viral load test is available by contacting the Bloodborne Viruses Laboratory at the Wadsworth Center (see *Diagnosis of HIV-2 > Box 1: Wadsworth Center Bloodborne Viruses Laboratory Services* in this guideline). In New York State, HIV-2 viral load testing should be used to determine the effectiveness of an ART regimen in patients with HIV-2 [Ba, et al. 2018; Matheron, et al. 2018]. If clinicians outside of New York State do not have access to HIV-2 viral load testing, they should suspect treatment failure if an individual with HIV-2 has a sustained or progressive decline in CD4 cell count or experiences clinical disease progression on therapy. Data from a multi-cohort study indicate that patients with HIV-2 who were initiated on a first-line combination ART regimen had less robust CD4 cell count increases than individuals with HIV-1, even after adjustment for plasma viral load levels [Wittkop, et al. 2017]. In HIV-2, a muted CD4 cell count increase from baseline after treatment initiation may not necessarily imply that the regimen is ineffective. If patients with HIV-2 have either immunologic or virologic treatment failure, clinicians are strongly urged to refer them to or consult with experienced HIV-2 clinical management specialists.

In addition to monitoring ART, patients with HIV-2 require the same laboratory and diagnostic testing, use and appropriate discontinuation of prophylaxis for OIs, and use of immunizations as patients with HIV-1 (see the NYSDOH AI guideline *Comprehensive Primary Care for Adults With HIV > Prevention of Opportunistic Infections and Immunizations for Adults With HIV*).

→ KEY POINT

- In New York State, the standard of care for individuals with HIV-2 is to initiate and maintain ART in order to achieve an undetectable HIV-2 viral load.

Management of HIV-2 in Pregnancy

☑ RECOMMENDATIONS

Management in Pregnancy

- Clinicians should recommend ART for all pregnant individuals with HIV-2. (A2†)
  - Clinicians should recommend one of the ART regimens in Table 3. (A3)
  - Clinicians should not delay initiation of ART in pregnant individuals even if there is no or limited access to HIV-2 viral load testing. (A2†)
- In selecting an ART regimen for a pregnant individual with HIV-2, clinicians should **not** include:
  - Boosted atazanavir, because of its lack of efficacy against HIV-2. (A*)
  - Efavirenz and rilpivirine, the non-nucleoside reverse transcriptase inhibitors recommended for treatment of HIV-1 during pregnancy, because of a lack of efficacy against HIV-2. (A*)

Note: For recommendations regarding administration of zidovudine for prophylaxis during labor and delivery, please see the NYSDOH AI guidance *Good Practices to Prevent Perinatal HIV Transmission* or the U.S. Department of Health and Human Services (DHHS) *Special Populations: HIV-2 Infection and Pregnancy* in the guideline *Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States*.

A combination of either TDF/FTC or ABC/3TC (if HLA-B*5701 is negative) plus either twice-daily RAL or twice-daily DRV/r is recommended during pregnancy. For individuals with HIV-2, viral load monitoring during pregnancy and prophylactic ART for the HIV-2–exposed infant should follow the recommendations for pregnancy and infant exposure in the setting of HIV-1 (see the NYSDOH AI guidance *Good Practices to Prevent Perinatal HIV Transmission* or the DHHS *Special Populations: HIV-2 Infection and Pregnancy* in the guideline *Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States*). During the early part of pregnancy, it is important that healthcare providers follow the Wadsworth Center protocol for accurate and timely submission of specimens and know the amount of time needed to return the results of HIV-2 viral load testing. For example, the Wadsworth Center Bloodborne Viruses Laboratory is not open on weekends, so if a patient's blood is drawn on a Thursday or Friday, the separated plasma should be stored at the drawing facility in a freezer and shipped on Monday, Tuesday, or Wednesday of the following week to ensure weekday delivery to the laboratory.

Serial HIV-2 diagnostic testing in HIV-2–exposed infants to confirm or exclude HIV-2 infection is available free of charge from the Wadsworth Center (see *Diagnosis of HIV-2 > Box 1: Wadsworth Center Bloodborne Viruses Laboratory Services* in this guideline*)*. For diagnostic testing of infants exposed to HIV-2, whole blood collected in an EDTA tube (purple top, prevents blood clotting) must be received in the laboratory within 3 days of collection. Collection kits for pediatric HIV diagnostic testing may be requested from the Wadsworth Center Order Desk at (518) 474-4175.

Table 3: ART Regimens for Initial Treatment of Pregnant Adults With HIV-2*

Abacavir/lamivudine (ABC/3TC; Epzicom) if HLA-B*5701 is negative and HBsAg is negative **OR** Tenofovir disoproxil fumarate/emtricitabine (TDF/FTC; Truvada)	**AND**	Raltegravir twice daily (RAL; Isentress) **OR** Ritonavir-boosted darunavir twice daily (DRV/r; Prezista *and* Norvir)

*Listed alphabetically; for specific details, see NYSDOH AI guideline *Selecting an Initial ART Regimen > Specific Factors to Consider and Discuss With Patients* and drug package inserts.

Pre- and Post-Exposure Prophylaxis for HIV-2

☑ RECOMMENDATION

PrEP and PEP for HIV-2

- Clinicians should recommend TDF/FTC *and* RAL as post-exposure prophylaxis (PEP) after HIV-2 exposure (3TC may be substituted for FTC). (A2†)
  - DTG can be used instead of RAL in a PEP regimen if the exposed individual is not pregnant; if the individual is of childbearing potential, effective birth control should be in use (see *Use of Dolutegravir in Individuals of Childbearing Capacity*).
  - See the NYSDOH AI guideline on *PEP to Prevent HIV Infection*

As with HIV-1, TDF/FTC is active against HIV-2 [Menendez-Arias and Alvarez 2014] and could be used as a pre-exposure prophylaxis (PrEP) regimen to prevent infection with HIV-2. For more information on evaluating patients for PrEP see NYSDOH AI guideline *PrEP to Prevent HIV and Promote Sexual Health*.

All Recommendations

☑ All RECOMMENDATIONS

Diagnosis

- To diagnose HIV-2 infection, clinicians should follow the steps in the Centers for Disease Control and Prevention/Association of Public Health Laboratories (CDC/APHL) *HIV Diagnostic Testing Algorithm* and the recommendations in the NYSDOH AI guideline *HIV Testing.* (A1)
  - See the NYSDOH guideline *HIV Testing > Steps in the HIV Diagnostic Testing Algorithm and HIV-2 RNA Tests for Diagnostic Use*
- In individuals who are confirmed to have HIV-2 antibodies, clinicians should perform a clinical evaluation for HIV-2 infection that is similar in scope to the evaluation of patients with HIV-1. (A1) HIV-2 antibodies are confirmed by a reactive result to an HIV-1/2 or HIV-1/2 antigen/antibody (Ag/Ab) immunoassay and a positive result for HIV-2 Abs on a Food and Drug Administration (FDA)-approved supplemental HIV-1/2 Ab differentiation assay.
  - See the NYSDOH guideline *HIV Testing > HIV-2 RNA Tests for Diagnostic Use*

Treatment

- Clinicians should recommend ART for all individuals diagnosed with HIV-2. (A2†)
- Clinicians should not prescribe any NNRTI for treatment of HIV-2 infection. (A*)
- Clinicians should recommend a single-tablet regimen (STR) that includes 2 nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) plus an integrase strand transfer inhibitor (INSTI) as the initial treatment for adults with HIV-2 who are not pregnant and not planning to become pregnant, including those with acute HIV-2 infection (see *Tables 1 and 2: Preferred and Alternative ART Regimens for Initial Treatment of Nonpregnant Adults with HIV-2*). (A2)
- For individuals with HIV-1/HIV-2 coinfection, clinicians should:
  - Perform HIV-1 drug resistance testing to guide the choice of an initial regimen or to modify a regimen if virologic failure develops. (A2)
  - Recommend an ART regimen that will suppress both viruses effectively. (A*)

Monitoring

- For individuals who are newly diagnosed with HIV-2, clinicians should perform the same laboratory and diagnostic testing currently recommended for individuals with HIV-1, with the exception of drug resistance testing, which is not available. (A3)
  - Testing includes CD4 cell count, HIV-2 viral load, creatinine clearance, and status of coinfections such as hepatitis B and C viruses and tuberculosis (see NYSDOH AI guideline *Selecting an Initial ART Regimen > ART-Initiation Laboratory Testing*).
- Clinicians should use HIV-2 viral load testing and CD4 cell count to determine the effectiveness of an ART regimen in patients with HIV-2. (A2)
- If HIV-2 viral load testing is not available, clinicians should suspect treatment failure if individuals experience a sustained decrease in CD4 cell count or have clinical disease progression. (A2)
- If a clinical practice in New York State cannot obtain HIV-2 viral load testing from the Wadsworth Laboratory, clinicians should refer individuals with HIV-2 to a practice that has the ability to access HIV-2 viral load testing from the Wadsworth Laboratory. (A3)

Management in Pregnancy

- Clinicians should recommend ART for all pregnant individuals with HIV-2. (A2†)
  - Clinicians should recommend one of the ART regimens in Table 3. (A3)
  - Clinicians should not delay initiation of ART in pregnant individuals even if there is no or limited access to HIV-2 viral load testing. (A2†)
- In selecting an ART regimen for a pregnant individual with HIV-2, clinicians should **not** include:
  - Boosted atazanavir, because of its lack of efficacy against HIV-2. (A*)

☑ All RECOMMENDATIONS

- Efavirenz and rilpivirine, the non-nucleoside reverse transcriptase inhibitors recommended for treatment of HIV-1 during pregnancy, because of a lack of efficacy against HIV-2. (A*)

Note: For recommendations regarding administration of zidovudine for prophylaxis during labor and delivery, please see the NYSDOH AI guidance *Good Practices to Prevent Perinatal HIV Transmission* or the U.S. Department of Health and Human Services (DHHS) *Special Populations: HIV-2 Infection and Pregnancy* in the guideline *Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States*.

PrEP and PEP for HIV-2

- Clinicians should recommend TDF/FTC *and* RAL as post-exposure prophylaxis (PEP) after HIV-2 exposure (3TC may be substituted for FTC). (A2†)
  - DTG can be used instead of RAL in a PEP regimen if the exposed individual is not pregnant; if the individual is of childbearing potential, effective birth control should be in use (see *Use of Dolutegravir in Individuals of Childbearing Capacity*).
  - See the NYSDOH AI guideline on *PEP to Prevent HIV Infection*

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Supplement: Guideline Development and Recommendation Ratings

Table S1: Guideline Development: New York State Department of Health AIDS Institute Clinical Guidelines Program	
Developer	New York State Department of Health AIDS Institute (NYSDOH AI) Clinical Guidelines Program
Funding Source	NYSDOH AI
Program Manager	Clinical Guidelines Program, Johns Hopkins University School of Medicine, Division of Infectious Diseases ▪ See Program Leadership and Staff
Mission	To produce and disseminate evidence-based, state-of-the-art clinical practice guidelines that establish uniform standards of care for practitioners who provide prevention or treatment of HIV, viral hepatitis, other sexually transmitted infections, and substance use disorders for adults throughout New York State in the wide array of settings in which those services are delivered.
Expert Committees	The NYSDOH AI Medical Director invites and appoints committees of clinical and public health experts from throughout NYS to ensure that the guidelines are practical, immediately applicable, and meet the needs of care providers and stakeholders in all major regions of NYS, all relevant clinical practice settings, key NYS agencies, and community service organizations. ▪ See Expert Committees
Committee Structure	▪ Leadership: AI-appointed chair, vice chair(s), chair emeritus, clinical specialist(s), JHU Guidelines Program Director, AI Medical Director, AI Clinical Consultant, AVAC community advisor ▪ Contributing members ▪ Guideline writing groups: Lead author, coauthors if applicable, and all committee leaders
Conflicts of Interest Disclosure and Management	▪ Annual disclosure of financial relationships with commercial entities for the 12 months prior and upcoming is required of all individuals who work with the guidelines program and includes disclosure for partners or spouses and primary professional affiliation. ▪ The NYSDOH AI assesses all reported financial relationships to determine the potential for undue influence on guideline recommendations and, when indicated, denies participation in the program or formulates a plan to manage potential conflicts. ▪ Disclosures are listed for each committee member.
Evidence Collection and Review	▪ Literature search and review strategy is defined by the guideline lead author based on the defined scope of a new guideline or update. ▪ A comprehensive literature search and review is conducted for a new guideline or an extensive update using PubMed, other pertinent databases of peer-reviewed literature, and relevant conference abstracts to establish the evidence base for guideline recommendations. ▪ A targeted search and review to identify recently published evidence are conducted for guidelines published within the previous 3 years. ▪ Title, abstract, and article reviews are performed by the lead author. The JHU editorial team collates evidence and creates and maintains an evidence table for each guideline.
Recommendation Development	▪ The lead author drafts recommendations to address the defined scope of the guideline based on available published data. ▪ Writing group members review the draft recommendations and evidence and deliberate to revise, refine, and reach consensus on all recommendations. ▪ When published data are not available, support for a recommendation may be based on the committee's expert opinion.

Table S1: Guideline Development: New York State Department of Health AIDS Institute Clinical Guidelines Program	
	▪ The writing group assigns a 2-part rating to each recommendation to indicate the strength of the recommendation and quality of the supporting evidence. The group reviews the evidence, deliberates, and may revise recommendations when required to reach consensus.
Review and Approval Process	▪ Following writing group approval, draft guidelines are reviewed by all contributors, program liaisons, and a volunteer reviewer from the AI Community Advisory Committee. ▪ Recommendations must be approved by two-thirds of the full committee. If necessary to achieve consensus, full committee deliberation of recommendations is invited to review evidence and revise recommendations when required. ▪ Final approval by the committee chair and the NYSDOH AI Medical Director is required for publication.
External Reviewers	▪ External peer reviewers recognized for their experience and expertise review guidelines for accuracy, balance, clarity, and practicality and provide feedback. ▪ Peer reviewers may include nationally known experts from outside of New York State.
Update Process	▪ JHU editorial staff ensure that each guideline is reviewed and determined to be current upon the 3-year anniversary of publication; guidelines that provide clinical recommendations in rapidly changing areas of practice may be reviewed annually. Published literature is surveilled to identify new evidence that may prompt changes to existing recommendations or development of new recommendations. ▪ If changes in the standard of care, newly published studies, new drug approval, new drug-related warning, or a public health emergency indicate the need for immediate change to published guidelines, committee leadership will make recommendations and immediate updates. ▪ All contributing committee members review and approve substantive changes to, additions, or deletions of recommendations; JHU editorial staff track, summarize, and publish ongoing guideline changes.

Table S2: Recommendation Ratings Scheme			
Strength		**Quality of Evidence**	
Rating	*Definition*	*Rating*	*Definition*
A	Strong	1	Based on published results of at least 1 randomized clinical trial with clinical outcomes or validated laboratory endpoints.
B	Moderate	*	Based on either a self-evident conclusion; conclusive, published, in vitro data; or well-established practice that cannot be tested because ethics would preclude a clinical trial.
C	Optional	2	Based on published results of at least 1 well-designed, nonrandomized clinical trial or observational cohort study with long-term clinical outcomes.
		2†	Extrapolated from published results of well-designed studies (including nonrandomized clinical trials) conducted in populations other than those specifically addressed by a recommendation. The source(s) of the extrapolated evidence and the rationale for the extrapolation are provided in the guideline text. One example would be results of studies conducted predominantly in a subpopulation (e.g., one gender) that the committee determines to be generalizable to the population under consideration in the guideline.
		3	Based on committee expert opinion, with rationale provided in the guideline text.