



CLINICAL GUIDELINES PROGRAM

NEW YORK STATE DEPARTMENT OF HEALTH AIDS INSTITUTE | HIV • HCV • STIs • SUBSTANCE USE • LGBTQ+ HEALTH

Diagnosis and Management of HIV-2 in Adults

Updates, Authorship, and Related Resources

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Purpose of This Guideline

The New York State Department of Health AIDS Institute (NYSDOH AI) developed this guideline for primary care providers and other clinicians who may diagnose and treat adults with HIV-2 infection. The guideline is designed to achieve the following goals:

- 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 patients 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 New York State 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 New York State.

Note on “experienced” HIV care providers: The NYSDOH AI Clinical Guidelines Program defines an “experienced HIV care provider” as a practitioner who has been accorded HIV Specialist status by the American Academy of HIV Medicine. Nurse practitioners (NPs) and licensed midwives who provide clinical care to individuals with HIV in collaboration with a physician may be considered experienced HIV care providers if all other practice agreements are met; NPs with more than 3,600 hours of qualifying experience do not require collaboration with a physician (8 NYCRR 79-5.1; 10 NYCRR 85.36; 8 NYCRR 139-6900). Physician assistants who provide clinical care to individuals with HIV under the supervision of an HIV Specialist physician may also be considered experienced HIV care providers (10 NYCRR 94.2).

HIV-2 Overview

The HIV-2 virus was first isolated in West Africa in the mid-1980s among individuals 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, et al. 2018]. An HIV testing surveillance analysis covering the period 2010 to 2017 reported that among 327,700 HIV cases diagnosed in the United States, 102 were confirmed HIV-2 infections and 11 were dual HIV-1/HIV-2 infections [Peruski, et al. 2020]. The report also confirmed that the cases of HIV-2 were diagnosed predominantly in people from West Africa who were living in the northeast United States and had acquired HIV-2 through heterosexual transmission. The number of HIV-2 cases was proportionate between males and females [Peruski, et al. 2020]. An analysis of New York State surveillance data covering the period 2010 to 2020 found that among 34,949 diagnosed HIV cases, 43 had HIV-2 infection, 3 had dual HIV-1/HIV-2 infection, and 25 had probable HIV-2 infection. Among the 71 HIV-2 cases, 54% were male, 79% were non-Hispanic Black, and 31% were aged ≥ 55 years at diagnosis [NYSDOH 2022].

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. Elevated markers of B-cell perturbations and colonic damage were observed in treatment-naive individuals with HIV-2 and no detectable virus; these findings were not observed in antiretroviral therapy (ART)-treated individuals with HIV-1 and viral suppression [Johansson, et al. 2022]. In addition, the majority of individuals with HIV-2, if untreated, will eventually progress to AIDS and death [Esbjornsson, et al. 2019].

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 ART initiation. As noted in the guideline section [Treatment of HIV-2](#), ART should be recommended for all individuals 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 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 on 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 of HIV-2

- To diagnose HIV-2 infection, clinicians should follow the standard [HIV laboratory testing algorithm](#). (A1)
- In individuals who are confirmed to have HIV-2 antibodies [a], clinicians should perform a clinical evaluation for HIV-2 infection that is similar in scope to the evaluation of patients with HIV-1. (A1)

Abbreviations: Ab, antibody; Ag, antigen; FDA, U.S. Food and Drug Administration.

Note:

- a. HIV-2 antibodies are confirmed by a reactive result to an HIV-1/2 Ag/Ab combination immunoassay and a positive result for HIV-2 Abs on an FDA-approved supplemental HIV-1/HIV-2 Ab differentiation immunoassay. See NYSDOH AI guideline [HIV Testing > Figure 2: HIV Laboratory Testing Algorithm](#).

Before the HIV-1/2 Ag/Ab combination and HIV-1/HIV-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 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 Centers for Disease Control and Prevention (CDC)/Association of Public Health Laboratories algorithm begins with an FDA-approved HIV-1/2 Ag/Ab combination immunoassay [CDC 2018], which detects HIV-1 p24 Ag and HIV-1 and HIV-2 antibodies but not HIV-2 Ag. If the combination immunoassay is reactive, a supplemental HIV-1/HIV-2 Ab differentiation immunoassay is performed. HIV-2 infection should be considered in the 4 scenarios below.

HIV-1/HIV-2 Ab differentiation immunoassay is reactive for HIV-2 Abs only: The individual is considered HIV-2 Ab positive; clinical evaluation for HIV-2 infection should be initiated.

HIV-1/HIV-2 Ab differentiation immunoassay is reactive for both HIV-1 and HIV-2 Abs: The individual is considered HIV positive, undifferentiated; clinical evaluation for HIV-1/HIV-2 coinfection should be initiated.

- Both HIV-1 RNA testing and HIV-2 RNA or DNA testing should be performed to determine the presence of either or both viruses.
- Although a qualitative HIV-1/HIV-2 nucleic acid test (NAT) is now available, HIV-2 viral load and DNA testing are not routinely available in commercial laboratories. If these tests are not available, contact the [NYSDOH Wadsworth Center Bloodborne Viruses Laboratory](#) for qualitative and quantitative HIV-2 viral load testing.
- A minority of individuals with HIV-2 are coinfecting with HIV-1.

HIV-1/HIV-2 Ab differentiation immunoassay is nonreactive or indeterminate for HIV-1 and/or HIV-2 Abs: HIV-1 RNA NAT should be performed to confirm or exclude acute HIV-1 infection [CDC 2018].

- If the HIV-1/HIV-2 Ab differentiation immunoassay is nonreactive or HIV-1 indeterminate and HIV-1 RNA is not detected, the individual is considered negative for both HIV-1 and HIV-2 infection.
- If the HIV-1/HIV-2 Ab differentiation immunoassay is HIV-2 indeterminate or HIV indeterminate and HIV-1 RNA is not detected, HIV-2 RNA testing may be warranted if there is clinical suspicion for HIV-2 infection.
 - Because HIV-2 RNA levels can be low or undetectable in a person with HIV-2 infection, a negative HIV-2 RNA NAT does not rule out HIV-2 infection. In these cases, especially for individuals at elevated risk of HIV-2 infection, ordering HIV-2 DNA testing or repeating the HIV testing algorithm in 2 to 4 weeks, beginning with the HIV-1/2 Ag/Ab immunoassay, should be considered.
 - If results remain unclear, obtaining other HIV-2-specific tests through public health or commercial laboratories or consulting the CDC should be considered.
- If available, the FDA-approved cobas HIV-1/HIV-2 Qualitative NAT may be used to detect both HIV-1 and HIV-2 RNA.

Nonreactive HIV-1/2 Ag/Ab immunoassay and suspected recent exposure to HIV-2 (e.g., sex partner from an HIV-2 endemic area):

- HIV testing algorithm should be repeated, beginning with the HIV-1/2 Ag/Ab immunoassay at 4 weeks (but no later than 12 weeks) after the initial test.
- HIV-2 RNA NAT may also be considered.

Box 1: NYSDOH Wadsworth Center Bloodborne Viruses Laboratory

- The [NYSDOH Wadsworth Center Bloodborne Viruses Laboratory](#) offers HIV-2 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 and qualitative HIV-2 viral load testing, and quantitative detection of HIV-2 RNA in plasma samples for baseline and subsequent monitoring of response to antiretroviral therapy in patients with confirmed HIV-2 infection
 - HIV-2 RNA viral load testing during pregnancy: Contact the lab 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 the person submitting the sample indicates that the newborn has been exposed to HIV-2, Pediatric HIV Testing (518-486-9605) will perform a reverse transcription polymerase chain reaction test for qualitative detection of HIV-2 RNA in all samples.
- HIV-2 phenotypic and genotypic resistance testing is not offered at the Wadsworth Center or commercially available in the United States.

Treatment of HIV-2

RECOMMENDATIONS

Treatment of HIV-2

- Clinicians should recommend ART for all individuals diagnosed with HIV-2. (A2+)
- Before initiating ART in patients with HIV-2, clinicians should perform all of the [standard laboratory testing](#) recommended for patients with HIV-1 except for HIV drug resistance testing, which is not available. (A3)
 - Testing includes CD4 count, HIV-2 viral load, creatinine clearance, and status of coinfections such as hepatitis B and C viruses and tuberculosis.
- Clinicians should not prescribe any NNRTI for the treatment of HIV-2 infection, including long-acting injectable rilpivirine in combination with cabotegravir. (A*)
- Clinicians should recommend a single-tablet regimen that includes 2 NRTIs plus an INSTI as the initial treatment for adults with HIV-2, including those with acute HIV-2 infection (see Tables 1 and 2 for [preferred](#) and [alternative](#) ART regimens; see Table 4 for ART regimens [preferred during pregnancy](#)). (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*)

Abbreviations: ART, antiretroviral therapy; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor.

Table 1: Preferred ART Regimens for Initial Treatment of Nonpregnant Adults With HIV-2 [a]

(listed alphabetically; for specific details, see prescribing information; for full recommendations on initiating ART in patients with HIV-1, see NYSDOH AI guideline [Selecting an Initial ART Regimen](#))

Regimen	Comments	Rating
<i>Available as a Single-Tablet Formulation</i>		
Tenofovir alafenamide/emtricitabine/bictegravir [b,c] (TAF 25 mg/FTC/BIC; Biktarvy)	<ul style="list-style-type: none"> • Do not initiate a tenofovir-based regimen in patients with CrCl <30 mL/min [d]. • 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. 	A2
<i>Available as a Multi-Tablet Regimen</i>		
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)	<ul style="list-style-type: none"> • Do not initiate a tenofovir-based regimen in patients with CrCl <30 mL/min [d]. • TAF/FTC is strongly preferred over TDF/FTC in patients with CrCl <50 mL/min [d]. • For TDF/FTC in patients with CrCl 30 to 49 mL/min: 1 tablet every 48 hours. • For TDF/FTC, consider bone mineral density. • 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. 	A2

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

Regimen	Comments	Rating
<p>Abbreviations: 3TC, lamivudine; ART, antiretroviral therapy; CrCl, creatinine clearance; INSTI, integrase strand transfer inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; PrEP, pre-exposure prophylaxis.</p> <p>Notes:</p> <p>a. For recommended ART regimens in pregnant patients with HIV-2, see Table 4: ART Regimens for Initial Treatment of Pregnant Adults With HIV-2.</p> <p>b. Substitutions:</p> <ul style="list-style-type: none"> – In all cases, FTC and 3TC are interchangeable. – TAF 10 mg and TAF 25 mg are not interchangeable. <p>c. If a patient acquires HIV-2 while receiving long-acting injectable cabotegravir for PrEP, the initial regimen should be non-INSTI-based (e.g., a boosted PI and 2 NRTIs).</p> <p>d. For dose adjustments, refer to NYSDOH AI guideline Selecting an Initial ART Regimen > ARV Dose Adjustments for Hepatic or Renal Impairment.</p>		

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

Regimen	Comments	Rating
<i>Available as a Single-Tablet Formulation</i>		
Tenofovir alafenamide/emtricitabine/darunavir/cobicistat [b] (TAF 10 mg/FTC/DRV/COBI; Symtuza)	<ul style="list-style-type: none"> • Do not initiate a tenofovir-based regimen in patients with CrCl <30 mL/min [c]. • Carefully consider drug-drug interactions with COBI [Eron, et al. 2018]. 	B2
Tenofovir alafenamide/emtricitabine/elvitegravir/cobicistat [b,d] (TAF 10 mg/FTC/EVG/COBI; Genvoya)	<ul style="list-style-type: none"> • Do not initiate a tenofovir-based regimen in patients with CrCl <30 mL/min [c]. • Carefully consider drug-drug interactions with COBI. • Separate dosing of aluminum-, calcium-, and magnesium-containing antacids by 2 hours, either before or after EVG. 	B2
<i>Available as a Multi-Tablet Regimen</i>		
Tenofovir alafenamide/emtricitabine or tenofovir disoproxil fumarate/emtricitabine and high-dose raltegravir [b,d] (TAF 25 mg/FTC or TDF 300 mg/FTC and RAL HD; Descovy or Truvada and Isentress HD)	<ul style="list-style-type: none"> • Do not initiate a tenofovir-based regimen in patients with CrCl <30 mL/min [c]. • TAF/FTC is strongly preferred over TDF/FTC in patients with CrCl <50 mL/min [c]. • For TDF/FTC in patients with CrCl 30 to 49 mL/min: 1 tablet every 48 hours. • For TDF/FTC, consider bone mineral density. • Administer as TAF/FTC or TDF/FTC once daily and RAL HD 1,200 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. 	B2

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

Regimen	Comments	Rating
Tenofovir alafenamide/emtricitabine or tenofovir disoproxil fumarate/emtricitabine <i>and</i> raltegravir [b,d] (TAF 25 mg/FTC or TDF 300 mg/FTC and RAL; Descovy or Truvada <i>and</i> Isentress)	<ul style="list-style-type: none"> Do not initiate a tenofovir-based regimen in patients with CrCl <30 mL/min [c]. TAF/FTC is strongly preferred over TDF/FTC in patients with CrCl <50 mL/min [c]. For TDF/FTC in patients with CrCl 30 to 49 mL/min: 1 tablet every 48 hours. 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. 	B2
Tenofovir alafenamide/emtricitabine or tenofovir disoproxil fumarate/emtricitabine <i>and</i> darunavir/ritonavir [b] (TAF 25 mg/FTC or TDF 300 mg/FTC <i>and</i> DRV 800 mg and RTV 100 mg; Descovy or Truvada <i>and</i> Prezista/Norvir)	<ul style="list-style-type: none"> Do not initiate a tenofovir-based regimen in patients with CrCl <30 mL/min. TAF/FTC is strongly preferred over TDF/FTC in patients with CrCl <50 mL/min [c]. For TDF/FTC in patients with CrCl 30 to 49 mL/min: 1 tablet every 48 hours. For TDF/FTC, consider bone mineral density. 	B2

Abbreviations: 3TC, lamivudine; ART, antiretroviral therapy; CrCl, creatinine clearance; INSTI, integrase strand transfer inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; PrEP, pre-exposure prophylaxis.

Notes:

- a. For recommended ART regimens in pregnant patients with HIV-2, see [Table 4: ART Regimens for Initial Treatment of Pregnant Adults With HIV-2](#).
- b. Substitutions:
 - In all cases, FTC and 3TC are interchangeable.
 - TAF 10 mg and TAF 25 mg are not interchangeable.
 - COBI and ritonavir should not be considered interchangeable because of their drug-interaction profiles.
- c. For dose adjustments, refer to NYSDOH AI guideline [Selecting an Initial ART Regimen > ARV Dose Adjustments for Hepatic or Renal Impairment](#).
- d. If a patient acquires HIV-2 while receiving long-acting injectable cabotegravir for PrEP, the initial regimen should consist of a non-INSTI-based regimen (e.g., a boosted PI and 2 NRTIs).

Table 3: Other Initial ART Regimen Not Included as Preferred or Alternative for Nonpregnant Adults with HIV-2 [a]
(for specific details, see prescribing information; for full recommendations on initiating ART in patients with HIV-1, see NYSDOH AI guideline [Selecting an Initial ART Regimen](#))

Regimen	Comments	Rating
<i>Available as a Single-Tablet Formulation</i>		
Abacavir/lamivudine/dolutegravir [b,c] (ABC/3TC/DTG; Triumeq)	<ul style="list-style-type: none"> Abacavir is likely associated with CVD, even among individuals with low-to-moderate risk for atherosclerotic CVD and should be avoided in an initial ART regimen. Initiate only in patients confirmed to be negative for HLA-B*5701. Do not use regimen for rapid-start or test-and-treat initiation of ART. Do not initiate in patients with CrCl <30 mL/min [d]. Consider underlying risk of coronary heart disease. Documented DTG resistance after initiation in treatment-naïve 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. 	B2

Table 3: Other Initial ART Regimen Not Included as Preferred or Alternative for Nonpregnant Adults with HIV-2 [a]
(for specific details, see prescribing information; for full recommendations on initiating ART in patients with HIV-1, see NYSDOH AI guideline [Selecting an Initial ART Regimen](#))

Regimen	Comments	Rating
<p>Abbreviations: ART, antiretroviral therapy; CVD, cardiovascular disease; CrCl, creatinine clearance.</p> <p>Notes:</p> <p>a. For recommended ART regimens in pregnant patients with HIV-2, see Table 4: ART Regimens for Initial Treatment of Pregnant Adults With HIV-2.</p> <p>b. Substitution: FTC and 3TC are interchangeable.</p> <p>c. Not recommended as a preferred or alternative ART regimen. ABC is likely associated with CVD even among individuals with low-to-moderate risk for atherosclerotic CVD and should be avoided in an initial ART regimen. See NYSDOH AI guideline Selecting an Initial ART Regimen > Special Considerations for Comorbid Conditions > Cardiovascular risks.</p> <p>d. For dose adjustments, refer to NYSDOH AI guideline Selecting an Initial ART Regimen > ARV Dose Adjustments for Hepatic or Renal Impairment.</p>		

Resistance testing: Although baseline genotypic drug resistance testing is recommended for all individuals with HIV-1 before ART initiation, HIV-2 resistance tests are not commercially available in the United States.

ART regimen options: All U.S. Food and Drug Administration-approved NRTIs effectively inhibit HIV-2 reverse transcriptase [Menendez-Arias and Alvarez 2014]. Three HIV protease inhibitors (PIs) effectively inhibit HIV-2, but given the availability of darunavir (DRV), the 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 PI is being considered as part of an ART regimen for HIV-2 treatment, boosted DRV 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 (EVG), raltegravir (RAL), and dolutegravir (DTG), a retrospective observational study with bictegravir (BIC), and in vitro data [Le Hingrat, et al. 2019; Smith, et al. 2019; Tsiang, et al. 2016], INSTIs as a class are shown to be active against HIV-2; a DTG- or BIC-based regimen with 2 NRTIs can be used for treatment-naive patients with HIV-2. In one study of a single-tablet regimen (elvitegravir/cobicistat/tenofovir disoproxil fumarate/emtricitabine [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]. A retrospective observational study from Spain among participants with HIV-2 reported that after approximately 13 months of follow-up on INSTI-based regimens (including DTG), 89% of treatment-naive and 65% of treatment-experienced participants achieved an undetectable viral load [Requena, et al. 2019]. A similar study from India showed that on a DTG-based regimen, 86% of treatment-naive participants with HIV-2 achieved an undetectable viral load [Pujari, et al. 2020]. At the 48-week follow-up of a phase 2 study of DTG with 2 NRTIs (ABC/3TC or TDF/FTC), 27 of 30 treatment-naive patients with HIV-2 demonstrated viral suppression (<40 copies/mL), with a median CD4 count increase of 101 cells/mL [Pacheco, et al. 2023]. In a retrospective study of 24 patients with HIV-2, including 5 who were treatment-naive, all participants maintained or achieved viral suppression for a median duration of 37.5 months after switching to or initiating treatment with TAF/FTC/BIC [Joly, et al. 2025]. However, without genotypic resistance testing, the 2-drug regimen of lamivudine/DTG should not be used by patients with HIV-2 because using this regimen requires advance confirmation that they do not have virus with the M184V mutation.

In treatment-experienced patients with HIV-2, the antiretrovirals (ARVs) listed in Tables 1 and 2, above, 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 cases of virologic failure. Algorithms are available to interpret HIV-2 genetic sequences obtained from research laboratories for the presence of resistance-associated mutations and coreceptor use; however, clinical decisions should not be made solely on these predictions. See:

- Stanford University HIV Resistance Database: [HIVdb Program for HIV-2 \(beta\)](#)
- Collaborative HIV and Anti-HIV Drug Resistance Network: [HIV2EU Algorithm](#) [Charpentier, et al. 2025]
- Max Planck Institute for Informatics: [Geno2pheno \[coreceptor-hiv2\] 1.0](#)

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 attachment inhibitor fostemsavir has no activity against HIV-2 [FDA 2024].

Ibalizumab (IBA), 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 [Le Hingrat, et al. 2022]. However, the in vivo efficacy of an IBA-containing regimen in individuals with ARV-resistant HIV-2 infection has not been established.

Lenacapavir (LEN), a multistage inhibitor of HIV-1 capsid function, is active against HIV-2 isolates but 11- to 16-fold less potent against HIV-2 compared to HIV-1 [Smith, et al. 2024]. In patients with HIV-2 and limited antiretroviral options, treatment with a LEN-based regimen would require careful monitoring to assess virologic and immunologic responsiveness.

In patients with 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.

→ KEY POINT

The following ARVs do not have activity against HIV-2:

- All NNRTIs
- Certain PIs (atazanavir, fosamprenavir, tipranavir, and nelfinavir)
- Attachment inhibitor fostemsavir

Monitoring ART in Individuals With HIV-2

✓ RECOMMENDATIONS

Monitoring ART

- Clinicians should monitor the [virologic and immunologic status](#) of patients with HIV-2 by performing viral load and CD4 count testing at the same intervals recommended for patients with HIV-1.
 - Because HIV-2 viral load testing is available in New York State only through the Wadsworth Center, clinicians who do not have access to Wadsworth Center laboratory testing services should refer patients to practices that do. (A3)
 - Clinicians should continue to monitor CD4 count every 6 months in all patients with HIV-2, even those with persistent viral suppression. (B2)
- If HIV-2 viral load testing is not available, clinicians should suspect treatment failure if patients experience a sustained decrease in CD4 count, defined as a 30% decrease in CD4 count or a 3-point decrease in CD4%, confirmed by repeat testing (B2), or have clinical disease progression. (A2)
- If patients with HIV-2 have either virologic or immunologic treatment failure, clinicians should consult with an experienced HIV-2 clinical management specialist. (A3) Contact the NYSDOH [Clinical Education Initiative \(CEI\) Clinician Line](#), by website or phone: 866-637-2342 (press 2) to consult with an expert clinician.

There is no U.S. Food and Drug Administration-approved, HIV-2 quantitative viral load assay commercially available. However, an HIV-2 quantitative viral load test is available by contacting the Wadsworth Center Bloodborne Viruses Laboratory (see [Box 1](#)). In New York State, HIV-2 viral load testing should be used to determine the effectiveness of an antiretroviral therapy (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 a patient with HIV-2 has a sustained or progressive decline in CD4 count or experiences clinical disease progression on therapy. Data from a multicohort study indicate that patients with HIV-2 who were initiated on a first-line combination ART regimen had less robust CD4 count increases than those with HIV-1, even after adjustment for plasma viral load levels [Wittkop, et al. 2017]. In HIV-2, a muted CD4 count increase from baseline after treatment initiation may not necessarily imply that the regimen is ineffective.

HIV-2 disease progression has been reported in individuals with undetectable HIV-2 viral loads [Raugi, et al. 2021], and resistance mutations have been reported in the presence of suppressive ART (viral load <25 copies/mL) [Gottlieb, et al. 2009]. Therefore, even with persistent undetected or unquantifiable viral load, CD4 count monitoring is recommended for all patients with HIV-2 at least every 6 months.

HIV-2 treatment failure is defined as a persistent increase in viral load. In the absence of HIV-2 viral load testing, treatment failure can be assessed using changes in CD4 count (e.g., a 30% decrease in CD4 count or a 3-point decrease in CD4%, confirmed by repeat testing [StatPearls 2023]) or clinical disease progression. In cases of treatment failure, it is critically important to address adherence to therapy and to eliminate drug interactions that could adversely affect antiretroviral efficacy, especially given the limited number of ART regimen options. A retrospective observational assessment of patients with HIV-2 showed integrase resistance mutations often followed treatment failure with raltegravir (RAL) [Treviño, et al. 2015]. In the absence of HIV-2 genotypic resistance testing, it is reasonable to recommend that a patient with HIV-2 taking a failing integrase strand transfer inhibitor (INSTI)-based regimen switch to an active boosted protease inhibitor (PI)-based regimen. Twice-daily dolutegravir, in combination with other presumptively active agents such as darunavir (DRV)/ritonavir or DRV/cobicistat, could be used with caution in patients with HIV-2 who have experienced virologic failure on a RAL- or elvitegravir (EVG)-based ART regimen [Descamps, et al. 2015]. Similarly, it is reasonable to recommend that a patient with HIV-2 on a failing boosted PI-based regimen switch to an INSTI-based regimen. This approach is preferable to switching to other drugs within the INSTI or PI drug class. As noted above, other antiretrovirals, such as maraviroc, ibalizumab, and lenacapavir (LEN), have in vitro activity against HIV-2 and may be included in subsequent treatment regimens. In a report of highly treatment-experienced patients with HIV-2, 5 of 8 who received LEN in addition to an optimized background regimen that had few active agents rapidly developed capsid resistance mutations after treatment failure [Montrouge, et al. 2024]. If patients with HIV-2 have either immunologic or virologic treatment failure, clinicians are strongly urged to refer them to or consult with an experienced HIV-2 clinical management specialist.

In addition to monitoring ART, patients with HIV-2 require the same laboratory and diagnostic testing, use and appropriate discontinuation of prophylaxis for opportunistic infections, and use of [immunizations](#) as patients with HIV-1.

→ KEY POINT

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

Management of HIV-2 in Pregnancy

RECOMMENDATIONS

Management of HIV-2 in Pregnancy

- Clinicians should recommend ART for all pregnant individuals with HIV-2. (A2+)
 - Clinicians should recommend one of the ART regimens in [Table 4: ART Regimens for Initial Treatment of Pregnant Adults With HIV-2](#) [a]. (A3)
 - Clinicians should not delay ART initiation in pregnant individuals even if there is no or limited access to HIV-2 viral load testing. (A2+)
 - If a patient is already on an effective ART regimen that is active against HIV-2 at the time of pregnancy, clinicians should continue the ART regimen with monitoring. (A3)
- In selecting an ART regimen for a pregnant individual with HIV-2, clinicians should **not** include:
 - Boosted ATV, because of its lack of efficacy against HIV-2 (A*)
 - EFV and RPV, the NNRTIs recommended for treatment of HIV-1 during pregnancy, because of a lack of efficacy against HIV-2 (A*)
 - EVG/COBI and DRV/COBI, because of the potential for lower levels of drug exposure during the third trimester (A*)

Abbreviations: ART, antiretroviral therapy; ATV, atazanavir; COBI, cobicistat; DHHS, U.S. Department of Health and Human Services; DRV, darunavir; EFV, efavirenz; EVG, elvitegravir; NNRTI, non-nucleoside reverse transcriptase inhibitor; RPV, rilpivirine.

Note:

- a. See DHHS [Recommendations for the Use of Antiretroviral Drugs During Pregnancy and Interventions to Reduce Perinatal HIV Transmission in the United States > Special Populations > HIV-2 Infection and Pregnancy](#).

See Table 4, below, for the preferred and alternative ART regimens recommended for pregnant adults with HIV-2. For individuals with HIV-2, viral load monitoring during pregnancy, labor, and delivery and prophylactic ART for the HIV-2-exposed infant should follow the recommendations for pregnancy and infant exposure to HIV-1 (see DHHS [Recommendations for the Use of Antiretroviral Drugs During Pregnancy and Interventions to Reduce Perinatal HIV Transmission in the United States > Special Populations > HIV-2 Infection and Pregnancy](#)). 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 Bloodborne Viruses Laboratory Services (see [Box 1](#)). 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 4: ART Regimens for Initial Treatment of Pregnant Adults With HIV-2 [a]			
Regimen			Rating
<i>Preferred</i>			
Tenofovir alafenamide/emtricitabine/bictegravir (TAF/FTC/BIC; Biktarvy)			A3
Tenofovir alafenamide/emtricitabine (TAF/FTC; Descovy) OR Tenofovir disoproxil fumarate/emtricitabine (TDF/FTC; Truvada) OR Tenofovir disoproxil fumarate/lamivudine (TDF/3TC; multiple brands)	AND	Dolutegravir [b,c] (DTG; Tivicay)	A3
<i>Alternative</i>			
Tenofovir alafenamide/emtricitabine (TAF/FTC; Descovy) OR Tenofovir disoproxil fumarate/emtricitabine (TDF/FTC; Truvada) OR Tenofovir disoproxil fumarate/lamivudine (TDF/3TC; multiple brands)	AND	Ritonavir-boosted darunavir twice daily (DRV/r; Prezista and Norvir) OR Raltegravir twice daily (RAL; Isentress)	B3
Notes:			
<p>a. Listed alphabetically; for specific details, see NYSDOH AI guideline Selecting an Initial ART Regimen > Specific Factors to Consider and Discuss With Patients and prescribing information.</p> <p>b. A single-tablet regimen of abacavir/lamivudine/dolutegravir is available but is not recommended as a preferred or alternative ART regimen. Abacavir is likely associated with cardiovascular disease (CVD) even among individuals with low-to-moderate risk for atherosclerotic CVD and should be avoided in an initial ART regimen. See NYSDOH AI guideline Selecting an Initial ART Regimen > Special Considerations for Comorbid Conditions > Cardiovascular risks.</p> <p>c. DTG has been shown to be safe throughout pregnancy [Zash, et al. 2022].</p>			

Pre- and Post-Exposure Prophylaxis for HIV-2

RECOMMENDATIONS

PEP for HIV-2

- Clinicians should recommend TAF/FTC/BIC as PEP after HIV-2 exposure. (A2†)
 - TAF/FTC or TDF/FTC and either DTG or RAL can be used instead of TAF/FTC/BIC in a PEP regimen (3TC may be substituted for FTC) [a]. (A3)

Abbreviations: 3TC, lamivudine; BIC, bictegravir; DTG; dolutegravir; FTC, emtricitabine; PEP, post-exposure prophylaxis; RAL, raltegravir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Note:

- a. The recommendation regarding discussion of the small risk of teratogenicity with DTG in the first trimester and the need for birth control while using DTG has been removed. DTG has been shown to be safe throughout pregnancy [Zash, et al. 2022].

As with HIV-1, TDF/FTC, TAF/FTC, cabotegravir, and lenacapavir are active against HIV-2 [Smith, et al. 2018; Menendez-Arias and Alvarez 2014] and could be used as part of a pre-exposure prophylaxis (PrEP) regimen to prevent HIV-2 infection. See the NYSDOH AI guideline [PrEP to Prevent HIV and Promote Sexual Health](#).

For more information on evaluating patients for PEP and PrEP, see the NYSDOH AI guideline [PEP to Prevent HIV Infection](#).

All Recommendations

ALL RECOMMENDATIONS: DIAGNOSIS AND MANAGEMENT OF HIV-2 IN ADULTS

Diagnosis of HIV-2

- To diagnose HIV-2 infection, clinicians should follow the standard [HIV laboratory testing algorithm](#). (A1)
- In individuals who are confirmed to have HIV-2 antibodies [a], clinicians should perform a clinical evaluation for HIV-2 infection that is similar in scope to the evaluation of patients with HIV-1. (A1)

Treatment of HIV-2

- Clinicians should recommend ART for all individuals diagnosed with HIV-2. (A2†)
- Before initiating ART in patients with HIV-2, clinicians should perform all of the [standard laboratory testing](#) recommended for patients with HIV-1 except for HIV drug resistance testing, which is not available. (A3)
 - Testing includes CD4 count, HIV-2 viral load, creatinine clearance, and status of coinfections such as hepatitis B and C viruses and tuberculosis.
- Clinicians should not prescribe any NNRTI for the treatment of HIV-2 infection, including long-acting injectable rilpivirine in combination with cabotegravir. (A*)
- Clinicians should recommend a single-tablet regimen that includes 2 NRTIs plus an INSTI as the initial treatment for adults with HIV-2, including those with acute HIV-2 infection (see Tables 1 and 2 for [preferred](#) and [alternative](#) ART regimens; see Table 4 for ART regimens [preferred during pregnancy](#)). (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 ART

- Clinicians should monitor the [virologic and immunologic status](#) of patients with HIV-2 by performing viral load and CD4 count testing at the same intervals recommended for patients with HIV-1.
 - Because HIV-2 viral load testing is available in New York State only through the Wadsworth Center, clinicians who do not have access to Wadsworth Center laboratory testing services should refer patients to practices that do. (A3)
 - Clinicians should continue to monitor CD4 count every 6 months in all patients with HIV-2, even those with persistent viral suppression. (B2)
- If HIV-2 viral load testing is not available, clinicians should suspect treatment failure if patients experience a sustained decrease in CD4 count, defined as a 30% decrease in CD4 count or a 3-point decrease in CD4%, confirmed by repeat testing (B2), or have clinical disease progression. (A2)
- If patients with HIV-2 have either virologic or immunologic treatment failure, clinicians should consult with an experienced HIV-2 clinical management specialist. (A3) Contact the NYSDOH [Clinical Education Initiative \(CEI\) Clinician Line](#), by website or phone: 866-637-2342 (press 2) to consult with an expert clinician.

Management of HIV-2 in Pregnancy

- Clinicians should recommend ART for all pregnant individuals with HIV-2. (A2†)
 - Clinicians should recommend one of the ART regimens in [Table 4: ART Regimens for Initial Treatment of Pregnant Adults With HIV-2](#) [b]. (A3)
 - Clinicians should not delay ART initiation in pregnant individuals even if there is no or limited access to HIV-2 viral load testing. (A2†)
 - If a patient is already on an effective ART regimen that is active against HIV-2 at the time of pregnancy, clinicians should continue the ART regimen with monitoring. (A3)
- In selecting an ART regimen for a pregnant individual with HIV-2, clinicians should **not** include:
 - Boosted ATV, because of its lack of efficacy against HIV-2 (A*)
 - EFV and RPV, the NNRTIs recommended for treatment of HIV-1 during pregnancy, because of a lack of efficacy against HIV-2 (A*)
 - EVG/COBI and DRV/COBI, because of the potential for lower levels of drug exposure during the third trimester (A*)

ALL RECOMMENDATIONS: DIAGNOSIS AND MANAGEMENT OF HIV-2 IN ADULTS

PEP for HIV-2

- Clinicians should recommend TAF/FTC/BIC as PEP after HIV-2 exposure. (A2⁺)
 - TAF/FTC or TDF/FTC and either DTG or RAL can be used instead of TAF/FTC/BIC in a PEP regimen (3TC may be substituted for FTC) [c]. (A3)

Abbreviations: 3TC, lamivudine; Ab, antibody; Ag, antigen; ART, antiretroviral therapy; ATV, atazanavir; BIC, bictegravir; COBI, cobicistat; DHHS, U.S. Department of Health and Human Services; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; EVG, elvitegravir; FDA, U.S. Food and Drug Administration; FTC, emtricitabine; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PEP, post-exposure prophylaxis; RAL, raltegravir; RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Notes:

- HIV-2 antibodies are confirmed by a reactive result to an HIV-1/2 Ag/Ab combination immunoassay and a positive result for HIV-2 Abs on an FDA-approved supplemental HIV-1/HIV-2 Ab differentiation immunoassay. See NYSDOH AI guideline [HIV Testing > Figure 2: HIV Laboratory Testing Algorithm](#).
- See DHHS [Recommendations for the Use of Antiretroviral Drugs During Pregnancy and Interventions to Reduce Perinatal HIV Transmission in the United States > Special Populations > HIV-2 Infection and Pregnancy](#).
- The recommendation regarding discussion of the small risk of teratogenicity with DTG in the first trimester and the need for birth control while using DTG has been removed. DTG has been shown to be safe throughout pregnancy [Zash, et al. 2022].

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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 New York State to ensure that the guidelines are practical, immediately applicable, and meet the needs of care providers and stakeholders in all major regions of New York State, all relevant clinical practice settings, key New York State agencies, and community service organizations.
Committee structure	<ul style="list-style-type: none"> • 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
Disclosure and management of conflicts of interest	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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 is 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	<ul style="list-style-type: none"> • 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. • 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.

Table S1: Guideline Development: New York State Department of Health AIDS Institute Clinical Guidelines Program

Review and approval process	<ul style="list-style-type: none"> • 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, the full committee is invited to deliberate, review the evidence, and revise recommendations. • Final approval by the committee chair and the NYSDOH AI Medical Director is required for publication.
External reviews	<ul style="list-style-type: none"> • External review of each guideline is invited at the developer’s discretion. • External reviewers recognized for their experience and expertise review guidelines for accuracy, balance, clarity, and practicality and provide feedback.
Update process	<ul style="list-style-type: none"> • 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 and will invite full committee review as indicated.

Table S2: Recommendation Ratings and Definitions

Strength	Quality of Evidence	
A: Strong B: Moderate C: Optional	1	Based on published results of at least 1 randomized clinical trial with clinical outcomes or validated laboratory endpoints.
	*	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.
	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.