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Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults

2022 Recommendations of the International Antiviral Society–USA Panel

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IMPORTANCE Recent advances in treatment and prevention of HIV warrant updated recommendations to guide optimal practice.

OBJECTIVE Based on a critical evaluation of new data, to provide clinicians with recommendations on use of antiretroviral drugs for the treatment and prevention of HIV, laboratory monitoring, care of people aging with HIV, substance use disorder and HIV, and new challenges in people with HIV, including COVID-19 and monkeypox virus infection.

EVIDENCE REVIEW A panel of volunteer expert physician scientists were appointed to update the 2020 consensus recommendations. Relevant evidence in the literature (PubMed and Embase searches, which initially yielded 7891 unique citations, of which 834 were considered relevant) and studies presented at peer-reviewed scientific conferences between January 2020 and October 2022 were considered.

FINDINGS Initiation of antiretroviral therapy (ART) is recommended as soon as possible after diagnosis of HIV. Barriers to care should be addressed, including ensuring access to ART and adherence support. Integrase strand transfer inhibitor–containing regimens remain the mainstay of initial therapy. For people who have achieved viral suppression with a daily oral regimen, long-acting injectable therapy with cabotegravir plus rilpivirine given as infrequently as every 2 months is now an option. Weight gain and metabolic complications have been linked to certain antiretroviral medications; novel strategies to ameliorate these complications are needed. Management of comorbidities throughout the life span is increasingly important, because people with HIV are living longer and confronting the health challenges of aging. In addition, management of substance use disorder in people with HIV requires an evidence-based, integrated approach. Options for preexposure prophylaxis include oral medications (tenofovir disoproxil fumarate or tenofovir alafenamide plus emtricitabine) and, for the first time, a long-acting injectable agent, cabotegravir. Recent global health emergencies, like the SARS-CoV-2 pandemic and monkeypox virus outbreak, continue to have a major effect on people with HIV and the delivery of services. To address these and other challenges, an equity-based approach is essential.

CONCLUSIONS AND RELEVANCE Advances in treatment and prevention of HIV continue to improve outcomes, but challenges and opportunities remain.

Multimedia

Supplemental content

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Four decades after the initial cases of HIV were reported, strategies for treating and preventing HIV infection continue to advance. People with HIV should be treated as soon as possible after diagnosis. If they have an opportunistic infection, antiretroviral therapy (ART) should be started shortly after initiation of treatment of the infection. Initial ART options include daily oral therapy, usually with a combination containing an integrase strand transfer inhibitor (InSTI). For patients who have achieved viral suppression, a long-acting injectable regimen (cabotegravir and rilpivirine [RPV]), which can be dosed every 2 months, is an option.

In addition to treatment improvements, there have been major advances in HIV prevention through preexposure prophylaxis (PrEP), including daily oral options and, for the first time, a long-acting injectable option, cabotegravir.

As treatment and prevention of HIV improve, new challenges and opportunities arise. As people with HIV live longer, there are important considerations related to aging that require an integrated approach. Multidisciplinary and holistic care of people with substance use and substance use disorder is required to achieve optimal outcomes in treating and preventing HIV. Other infectious disease outbreaks, such as COVID-19 and now monkeypox virus infection, also present rapidly evolving challenges for clinicians and people with HIV. To effectively address these and other challenges, as well as to realize the opportunity to end the HIV epidemic, efforts must be redoubled, with equity being the guiding principle.

This updated article provides current recommendations for treatment and prevention of HIV as well as an up-to-date discussion of important comorbidities and coinfections in people with HIV as they relate to the use of ART.

Methods

Appointment of the Panel

A volunteer international panel of experts in HIV research and clinical care, and the panel leadership, was appointed by International Antiviral (formerly AIDS) Society–USA (IAS-USA). Members were screened for expertise, involvement in research and care, financial relationships, and ability to work toward consensus. New members were added since the panel's last report to contribute additional expertise, particularly in substance use disorders and antiretroviral drugs. The panel convened in person and by conference calls from October 2021 to October 2022. Teams were appointed for each primary section, which evaluated relevant evidence and drafted recommendations for review by the full panel.

Identification of the Evidence

New evidence on antiretroviral drugs was identified in the published literature, major scientific conference presentations, or safety reports.[1] Literature searches were conducted by a panel member (C.d.R.) in PubMed and Embase for the period January 2020 to October 2022, and the panel monitored for new evidence thereafter. The 7891 unique citations were reviewed by a member (M.S.S.) who identified 834 possibly relevant publications. The substance use disorder team identified and reviewed additional evidence to develop this newly added section. Abstracts presented at scientific conferences between July 2020 and October 2022 were identified by panel members and teams. Additional relevant scientific publications or abstracts presented at peer-reviewed conferences were identified by the panel, and published and presented citations were obtained from drug manufacturers.

Process

The updated recommendations focus on adults with or at risk for HIV infection in settings in which most antiretroviral drugs are available. Each recommendation is rated for the strength of the recommendation and the quality of the supporting evidence (**Table 1**). For recommendations that have not changed substantially or for which few new data have become available since 2020, the previous iterations of the recommendations provide background information and relevant evidence.[1] Key recommendations for each section are listed in a Box or Table. ART drug combinations that are co-formulated are noted with slashes (eg, drug A/drug B/drug C). Detailed tables and further details about the process, panel, evidence identification, and the IAS–USA and its policies are available in the Supplement.

Initiation of ART

Recommendations for when to start ART are reported in **Box 1**. Initiating ART as soon as possible after an HIV diagnosis is a high priority to improve the health and life expectancy of people with HIV and to eliminate HIV transmission to sexual and injection drug use partners, as well as to infants.[1] Rapid ART initiation (within 7 days of diagnosis), including same-day initiation of ART on the day of diagnosis or the first clinic visit, improves the likelihood of persons linking to HIV care and the likelihood of and time to viral suppression.[3-5] In resource-limited settings, rapid ART initiation improved survival and longitudinal engagement in care.[6] In highly resourced settings, there are limited clinical and long-term outcomes from randomized clinical trials of rapid ART initiation. Based on the totality of evidence, ART initiation is recommended within 7 days of diagnosis, including on the day of diagnosis or the first clinic visit, if the patient is ready and there is no evidence of a co-occurring opportunistic infection that might affect the timing of initiation of treatment (evidence rating: AIII). Timing and choice of initial therapy in the presence of an acute opportunistic infection is discussed in the Initiating ART in the Setting of Active Opportunistic Infections and Cancer section below.

The success of ART depends on addressing barriers to care and on reliable ART access and adherence support. Identification and elimination of barriers is especially crucial to the success of rapid ART initiation programs. Barriers often include lack of transportation, housing instability,[7] food insecurity, racism,[8] out-of-pocket drug costs, pharmacy availability, restrictive clinic hours, stigma, and discrimination. Barriers that impair care engagement and ART access and adherence should be identified and addressed using evidence-informed methods (evidence rating: AIIa). These include individual-level interventions such as case management and patient/peer navigation to initiate linkage to care and social services; transportation and accompaniment to visits; appointment reminders; and psychosocial support.[9] Evidence-based structural interventions include "data to care" (using data systems to identify people who are out of care, to provide services), mobile clinics, telehealth, street medicine, use of visiting nurses, expanded clinic hours, pharmacy delivery,

Table 1. Strength of Recommendation and Quality of Evidence Rating Scale[a]

Category, rating	Definition
Strength of recommendation	
A	Strong panel support for the recommendation
B	Moderate panel support for the recommendation
C	Limited or weak panel support for the recommendation
Quality of evidence	
Ia	Evidence from 1 or more randomized clinical trials published in the peer-reviewed literature
Ib	Evidence from 1 or more randomized clinical trials presented in abstract form at peer-reviewed scientific meetings
IIa	Evidence from nonrandomized clinical trials or cohort or case-control studies published in the peer-reviewed literature
IIb	Evidence from nonrandomized clinical trials or cohort or case-control studies presented in abstract form at peer-reviewed scientific meetings
III	Recommendation based on the panel's analysis of the accumulated available evidence

[a] Adapted in part from Canadian Task Force on Periodic Health Examination.[2]

use of community health workers, and use of strategies to eliminate health care–related stigma and discrimination.[10]

The panel recommends initiating ART at the time of diagnosis for persons with acute HIV infection (evidence rating: AIIa). Immediate ART initiation leads to rapid viral suppression, thus decreasing the risk of transmission to others, and preserves immune responses.[4,11,12] Additionally, early ART initiation is associated with a lower viral reservoir.[13] People with HIV who have low or undetectable HIV RNA levels without taking ART ("elite controllers") have elevated levels of inflammation that are reduced after ART is initiated.[14,15] In addition, even those who manifest low viral loads initially often do not maintain control over time.[16] Based on the theoretical benefits of reducing inflammation in people with HIV, treating elite controllers is reasonable.

Initial ART Regimens for Individuals With HIV

Recommended initial ART regimens for individuals with HIV are reported in **Box 2**. Regimens containing the InSTIs bictegravir (BIC) or dolutegravir (DTG) are recommended as initial treatment for most individuals owing to their high efficacy, tolerability, safety, and high barrier to resistance; low pill burden; and low potential for drug-drug interactions (evidence rating: AIa). InSTI-based regimens also result in faster viral suppression than regimens containing a protease inhibitor (PI) (eg, boosted darunavir) or nonnucleoside reverse transcriptase inhibitor (NNRTI).[17]

Tenofovir alafenamide (TAF) or tenofovir disoproxil fumarate (TDF) (herein TXF)/emtricitabine (FTC) or lamivudine (3TC) (herein XTC) are recommended as nucleoside reverse transcriptase inhibitor (nRTI) components of initial ART regimens (when DTG/3TC is not used) (evidence rating: AIa). Abacavir is no longer recommended as initial therapy in most people with HIV owing to concerns about its association with cardiovascular disease,[1,18] the risk of abacavir hypersensitivity, the burden of HLA B*5701 testing, and no substantial advantage over DTG/3TC alone.

Box 1. Key Recommendations for When to Start Antiretroviral Therapy (ART)

- Initiation of ART is recommended as soon as possible after diagnosis, ideally within 7 days, including on the same day as diagnosis or at the first clinic visit if the patient is ready and there is no suspicion for a concurrent opportunistic infection (evidence rating: AIII)
- Structural barriers that could delay receipt of ART (including same-day), and impede care engagement, continuous ART access, and ART adherence should be identified and addressed using evidence-informed strategies (evidence rating: AIIa)
- Initiation of ART at the time of diagnosis of acute HIV infection is recommended (evidence rating: AIIa)
- Initiation of ART is recommended within 2 weeks of initiation of treatment for most opportunistic infections
  - For persons with active tuberculosis without evidence of tuberculous meningitis, ART should be initiated within 2 weeks after initiation of tuberculosis treatment, especially for those with CD4 cell count less than 50/μL (evidence rating: AIa)
  - For those with tuberculous meningitis, high-dose steroids should be initiated along with tuberculosis treatment and ART should be initiated within 2 weeks after starting tuberculosis treatment and steroids (evidence rating: BIa)
  - For individuals with cryptococcal meningitis with access to close monitoring and supportive care for adverse events, ART should be initiated 2 to 4 weeks after starting antifungal therapy (evidence rating: BIIb); ART-naive individuals who have asymptomatic cryptococcal antigenemia and a negative lumbar puncture result with no evidence of cryptococcal meningitis should start ART immediately (evidence rating: BIII)
  - Initiation of ART is recommended immediately in the setting of a new diagnosis of cancer with attention to drug-drug interactions (evidence rating: BIIa)

DTG/3TC is the only 2-drug regimen currently recommended for initial therapy, but it should only be used when HIV RNA level is less than 500 000 copies/mL and neither hepatitis B coinfection nor lamivudine resistance is present (evidence rating: AIa). Accordingly, DTG/3TC should not be used for rapid ART initiation when these laboratory results are not yet available. Long-acting cabotegravir with rilpivirine is not recommended for initial ART, although its use has been explored in a small demonstration project (see Switches to Long-acting Cabotegravir and Rilpivirine section below).[19]

Although InSTIs and tenofovir alafenamide have been implicated in weight gain for some individuals and preliminary data raise concern about metabolic adverse effects with InSTIs, such concerns do not override the potential benefit of these drugs. Clinicians should provide resources and counsel patients regarding lifestyle changes that may ameliorate weight gain and other metabolic concerns (evidence rating: AIII) (see Weight Gain and Metabolic Complications With ART section below).

Initiation of ART in the Setting of PrEP Failure

InSTI resistance has been observed in people who acquire HIV in the setting of cabotegravir PrEP.[20,21] A pharmacokinetic study predicted that concentrations of cabotegravir may persist for up to 2.5 or 4 years in some persons assigned male or female at birth, respectively.[22] If HIV is acquired in the setting of prior cabotegravir

Box 2. Recommended Initial Antiretroviral Therapy (ART) Regimens

Recommended for Most People With HIV

- The following are recommended (in alphabetical order) for most people with HIV:
  - BIC/TAF/FTC (evidence rating: AIa)
  - Dolutegravir plus TXF/XTC (evidence rating: AIa)
  - DTG/3TC (only if HIV RNA <500 000 copies/mL and HBV coinfection not present). This regimen should not be used for rapid initiation when genotype, HIV RNA, and HBV serology results are not yet available (evidence rating: AIa)
- Persons who acquired HIV while receiving preexposure prophylaxis with tenofovir alafenamide or tenofovir disoproxil fumarate with emtricitabine should have a blood sample for genotyping drawn prior to initiating therapy and a 3-drug regimen, preferably dolutegravir or bictegravir plus TXF/XTC, should be initiated if ART is to be started before genotype results are available (evidence rating: AIII)
- Persons who acquired HIV after exposure to cabotegravir for preexposure prophylaxis should have a blood sample for InSTI genotyping drawn prior to beginning therapy with an InSTI-based regimen (evidence rating: AIII)
  - If therapy is desired before genotype results are available or if InSTI-resistance is present, a boosted PI regimen containing darunavir and TXF/XTC should be used (evidence rating: AIII)

Recommended During Pregnancy

- TAF/XTC plus dolutegravir (evidence rating: AIa), withTDF/XTC plus dolutegravir a suitable alternative if tenofovir alafenamide is not available (evidence rating: AIa)
- The following drugs may be used if dolutegravir is not an option:
  - Raltegravir (400 mg twice daily) (evidence rating: AIIa)
  - Atazanavir plus ritonavir (evidence rating: BIIa)
  - Darunavir plus ritonavir (evidence rating: BIIa)
  - Rilpivirine (evidence rating: BIIa)

Not Recommended to Initiate During Pregnancy Because of Inadequate Data to Support Use (Evidence Rating: AIII for All)

- Bictegravir
- Doravirine
- Cabotegravir
- DTG/3TC
- DTG/RPV

If patient is already taking, and stable while taking, bictegravir- or doravirine-containing regimens or the 2-drug regimens DTG/3TC or DTG/RPV and wishes to continue, counsel patient about uncertainties regarding safety during pregnancy and monitor HIV RNA more frequently

Should Not Be Used During Pregnancy Because of Inadequate Drug Levels

- Cobicistat-containing regimens (evidence rating: AIIb)

Recommended During Tuberculosis Treatment (in Alphabetical Order by Anchor Drug)

- TXF/XTC is recommended with 1 of the following[a]:
  - Dolutegravir (50 mg twice daily) (evidence rating: BIa)
  - Efavirenz (600 mg) (evidence rating: AIa)
  - Raltegravir (800 mg twice daily) (evidence rating: BIa)
- A ritonavir-boosted PI regimen with TXF/XTC may be used only if it is not possible to use any of the above regimens. In that case, rifabutin (150 mg) should be substituted for rifampin (evidence rating: BIII)
- Bictegravir, darunavir boosted with ritonavir or cobicistat, doravirine, EVG/COBI, long-acting cabotegravir plus rilpivirine, etravirine, and rilpivirine are not recommended with rifampin because of drug-drug interactions (evidence rating: AIIa)
- DTG/3TC is not recommended with rifampin because of drug-drug interactions and inadequate data (evidence rating: BIII)

Abbreviations: BIC, bictegravir; COBI, cobicistat; DTG, dolutegravir; EVG, elvitegravir; FTC, emtricitabine; HBV, hepatitis B virus; InSTI, integrase strand transfer inhibitor; PI, protease inhibitor; RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; 3TC, lamivudine; TXF, tenofovir alafenamide or tenofovir disoproxil fumarate; XTC, emtricitabine or lamivudine.

[a] There is a pharmacokinetic interaction between rifampin and tenofovir alafenamide; clinical data with coadministration are limited.

PrEP, the results of an InSTI genotype test should be available before starting an InSTI-based regimen (evidence rating: AIII). If ART is to be started before resistance testing results are available, or such testing is not available (owing to resource constraints or inability to amplify with a low viral load), a boosted darunavir regimen with TXF/XTC should be started (evidence rating: AIII).

In persons diagnosed with HIV while receiving TXF-based PrEP, resistance testing should be performed but initiation of ART need not be delayed while awaiting genotype results. A 3-drug regimen, preferably dolutegravir or bictegravir with TXF/XTC, is recommended until genotype results are available (evidence rating: AIII); in the rare but most extreme case of TXF/XTC-induced resistance associated with K65R and M184V mutations, TXF/XTC plus dolutegravir or bictegravir would still be expected to be active.

ART and Pregnancy

All persons with HIV who are pregnant should be receiving ART for their own health and to prevent transmission of HIV to the fetus.[1] Those diagnosed with HIV during pregnancy should begin ART immediately with a recommended 3-drug regimen (evidence rating: AIa). Cobicistat should not be used during pregnancy owing to low drug levels that can impair efficacy (evidence rating: AIIb). At present, there are insufficient data to recommend initiation with bictegravir, doravirine, cabotegravir, and DTG/3TC during pregnancy (evidence rating: AIII). Although bictegravir, doravirine, DTG/3TC, or DTG/RPV should not be initiated during pregnancy, if patients are already stable with these regimens and choose to continue after being informed about the insufficient data, they should be followed up with more frequent HIV RNA monitoring (evidence rating: CIII).[23]

Although preliminary data from the Tsepamo study initially suggested an association between neural tube defects and dolutegravir exposure at the time of conception, updated results now show no statistically significant difference in the incidence of neural tube defects between regimens with and without dolutegravir when taken at the time of conception.[24] Dolutegravir, therefore, is a recommended agent for most people with HIV, including during pregnancy. The IMPAACT 2010 trial found dolutegravir regimens to be virologically superior to efavirenz (EFV)/TDF/FTC and demonstrated that dolutegravir plus TAF/FTC was associated with lower rates of adverse events and improved infant outcomes. Therefore, the recommended regimen for pregnancy is

TAF/XTC plus dolutegravir (evidence rating: AIa), with TDF/XTC plus dolutegravir a suitable alternative if tenofovir alafenamide is not available (evidence rating: AIa). In the same study, efavirenz was associated with higher levels of infant growth stunting than dolutegravir.[25,26] An analysis from the Pediatric HIV/AIDS Cohort and the Swiss Mother and Child HIV Cohort also supports the use of dolutegravir in pregnancy, finding that rates of viral suppression with ritonavir-boosted atazanavir or raltegravir were lower than with dolutegravir.[27]

Initiating ART in the Setting of Active Opportunistic Infections and Cancer

For persons with a concurrent opportunistic infection, initiation of ART within 2 weeks of initiation of treatment for the opportunistic infection is recommended, except where evidence supports delaying ART because of increased risk of morbidity or mortality from immune reconstitution inflammatory syndrome. With the availability of InSTIs and the use of adjunctive corticosteroid therapy, earlier recommendations for delaying *Mycobacterium tuberculosis* treatment have been reconsidered. For persons with active tuberculosis, ART should be initiated within 2 weeks after starting treatment for tuberculosis, particularly if the CD4 cell count is less than 50/μL (evidence rating: AIa). For those with tuberculous meningitis, high-dose steroids along with tuberculosis treatment is recommended, with ART initiation within 2 weeks thereafter (evidence rating: BIa).[28]

For persons with cryptococcal meningitis and with access to close monitoring and supportive care for adverse events, ART should be initiated 2 to 4 weeks after starting antifungal therapy (evidence rating: BIIb). The data supporting a delay in ART initiation for persons with cryptococcal meningitis were largely generated in resource-constrained settings where access to close monitoring and supportive care may not be as readily available and in persons who were not being treated with InSTI-based ART. A cohort study that did not show an increase in adverse outcomes with earlier initiation of ART[29] coupled with the availability of ART regimens with lower rates of adverse effects and drug interactions support earlier ART initiation. ART-naive individuals who have asymptomatic cryptococcal antigenemia and a negative lumbar puncture result should start ART immediately[30] (evidence rating: BIII), as should patients with cancer and untreated HIV (evidence rating: BIIa).

Drug-drug interactions must be considered for all patients, but particularly for those with a diagnosis of HIV and tuberculosis. The only regimens that may be safely used with rifampin include dolutegravir (50 mg twice daily[31]) (evidence rating: BIa), efavirenz (600 mg once daily) (evidence rating: AIa), or raltegravir (800 mg twice daily) (evidence rating: BIa) (but not raltegravir [400 mg twice daily[32]] [evidence rating: AIa]), each given with TXF/XTC.[31-33] (There is a pharmacokinetic interaction between rifampin and tenofovir alafenamide; clinical data with coadministration are limited.) There are inadequate data to support use of DTG/3TC in this setting (evidence rating: BIII). Poorer adherence with twice-daily raltegravir contributed to increased virologic failure in 1 study, underscoring the need for adherence support when twice-daily regimens are used.[34] If none of these regimens can be used, ritonavir-boosted atazanavir or lopinavir with TXF/XTC may be used with rifabutin (150 mg daily).

Table 2. Other Recommended Initial Antiretroviral Therapy (ART) Regimens

Regimen[a,b]	Potential uses and cautions
DRV/COBI/TAF/FTC[c]	Preferred for patients with prior cabotegravir PrEP exposure when an InSTI genotype is not available
Darunavir plus cobicistat or ritonavir plus TXF/XTC	Potential use for known or suspected pretherapy multidrug resistance or InSTI resistance or in people with HIV at high risk of poor adherence
DOR/TDF/3TC[c] or doravirine plus TXF/XTC	May be useful in people with HIV who have intolerance to InSTIs
EFV (600 or 400 mg)/TDF/FTC or 3TC[c]	Potential use for treatment of HIV/tuberculosis coinfection; pregnancy or pregnancy intention
Raltegravir plus TXF/XTC	Potential use for treatment of HIV/tuberculosis; pregnancy or pregnancy intention; when there is high risk of drug-drug interactions
RPV/TAF/FTC[c]	Small pill size; use only if pretreatment HIV RNA level is <100 000 copies/mL and CD4 cell count is >200/μL
Rilpivirine plus TDF/3TC[d]	Use only if pretreatment HIV RNA level is <100 000 copies/mL and CD4 cell count is >200/μL

Abbreviations: COBI, cobicistat; DOR, doravirine; DRV, darunavir; EFV, efavirenz; FTC, emtricitabine; InSTI, integrase strand transfer inhibitor; PrEP, preexposure prohylaxis; RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; 3TC, lamivudine; TXF, tenofovir alafenamide or tenofovir disoproxil fumarate; XTC, emtricitabine or lamivudine.

[a] The recommended initial ART regimens are reported in Box 2.

[b] Regimens are listed in alphabetical order. Drug components separated with a virgule (/) indicate that these are available as coformulations.

[c] Available as a single-tablet coformulation.

[d] Available in generic formulations in many countries.

Other Recommended Regimens

Other recommended regimens appear in **Table 2**. Although InSTI-based regimens are recommended for most persons, there are special circumstances in which other regimens may be considered as initial ART. A boosted darunavir regimen may be used when InSTI or multidrug resistance is a consideration, including when there has been prior exposure to cabotegravir as PrEP (evidence rating: AIIb).

When and How to Switch ART Regimens

Regimen switches can be broadly categorized into those for patients with and for patients without viral suppression. Both indications for switching treatment require careful review of a patient's ART regimen history, medication tolerability, concomitant medications, food requirements, reproductive plans, potential issues with insurance and coverage, and results from all prior resistance testing before switching (evidence rating: AIII).

Regimen changes should also prompt more frequent clinical and laboratory follow-up until it is established that the regimen is well tolerated, not associated with toxicity, and is effective (evidence rating: AIII), with the first assessment of HIV RNA and safety laboratory assays at approximately 1 month after changing therapy. For patients who switched owing to virologic failure, the viral load test should be repeated monthly until suppression to undetectable is documented and then every 6 months thereafter (evidence rating: AIa).

Switching in the Setting of Viral Suppression

Persons with suppressed virus and no history of transmitted or acquired HIV drug resistance can generally switch therapy to any of the recommended initial regimens and maintain viral suppression. Recently, there has been increased interest in 2-drug strategies as a way of reducing drug exposure. Most data supporting this strategy come from prospective randomized trials of persons with no history of treatment failure switching to DTG/3TC[35,36] or DTG/RPV.[37] These studies demonstrated ongoing viral suppression comparable to continued 3-drug treatment, without evidence of loss of virologic control.[38] In addition, InSTI resistance was not observed in these studies, although NNRTI resistance occurred in 1% of participants receiving DTG/RPV. Furthermore, retrospective studies of baseline samples in the trials of DTG/3TC showed no adverse effect from archived resistance mutations, including M184V.[39,40] Thus, unless there is documented or suspected history of treatment failure, proviral resistance testing is not required prior to switching to 2-drug therapy, even if there is no available pretreatment resistance test result (evidence rating: BII).

An important limitation of both 2-drug regimens is that they provide insufficient treatment for people with concomitant chronic hepatitis B who should, therefore, continue 3-drug regimens that include TXF/XTC. Furthermore, all people with HIV who lack immunity to hepatitis B should undergo immunization. Recent data show that hepatitis B CpG oligodeoxynucleotide vaccine (which is being investigated and compared with other vaccines in an ongoing clinical trial) is highly immunogenic in people with HIV who have high CD4 cell counts and suppressed virus while receiving ART.[41] Documenting a seropositive response to the vaccine is recommended prior to switching from a TXF-based 3-drug regimen to a 2-drug regimen that does not include TXF.

Recent clinical trials in persons with viral suppression have demonstrated the safety of switching to dolutegravir plus 2 nRTIs or BIC/FTC/TAF, even in the setting of likely or proven nRTI resistance. In the 2SD study conducted in Kenya, participants receiving second-line regimens consisting of a boosted PI plus nRTIs were randomly assigned to continue their current treatment or switch to dolutegravir plus 2 nRTIs.[42] At 48 weeks, dolutegravir plus 2 nRTIs was noninferior to the continued therapy. Although no prior resistance assessments were performed in that trial, other studies of second-line boosted PI regimens in Africa have shown extensive nRTI resistance, including high rates of M184V and K65R mutations, and such resistance would be expected in the population enrolled in the 2SD trial.

Similar results have been seen with switches to BIC/FTC/TAF in people with resistant virus.[43,44] Preexisting M184V/I mutations had no effect on efficacy in this setting.[45] In addition, prospective studies of people with treatment failure show high rates of viral suppression with dolutegravir plus 2 nRTIs,[46,47] implying that this regimen would maintain suppression regardless of nRTI resistance. By contrast, switches to first-generation InSTIs (raltegravir or elvitegravir) or NNRTIs from high resistance–barrier regimens containing a boosted PI are not recommended (evidence rating: AIa). The use of dolutegravir plus TXF/XTC or BIC/FTC/TAF in patients with current viral suppression and a documented history of M184V and K65R mutations is supported by the existing data from switch and failure studies. Situations where such regimens might be chosen include limited other treatment options, to avoid drug interactions or to maximize treatment simplicity to enhance adherence.

Switches to Long-acting Cabotegravir and Rilpivirine

In persons with no history of treatment failure and no known or suspected resistance to either drug, injectable cabotegravir and rilpivirine, given either every 1 or 2 months, was noninferior to continued oral ART.[48,49] Those interested in non-oral options for ART because of privacy, stigma, or convenience reasons will usually have greater satisfaction with cabotegravir and rilpivirine than continued oral ART.[50] One recent report described use of this regimen in 15 people with viremia not receiving oral ART.[19] Despite the short-term success of this approach in this study, cabotegravir plus rilpivirine is not recommended in the setting of viremia outside of a research setting and should be started only after viral suppression has been achieved with oral ART.

Cabotegravir plus rilpivirine injections can be started after an oral lead-in to ensure tolerability or, alternatively, without an oral cabotegravir plus rilpivirine lead-in based on patient preference.[51] Since the regimen is administered by clinic staff, cabotegravir plus rilpivirine requires more clinical resources than oral ART. Staff must be trained in proper administration techniques; in addition, the prescribing clinician will need to ensure that pharmacy, insurance, and scheduling logistics are in place prior to offering this therapy. Moreover, patients need to travel to and from sites of administration, which may pose a barrier for some individuals.

Even among patients who receive all of the scheduled injections in a timely fashion, there is a risk of treatment failure with emergent resistance, including both InSTI and NNRTI mutations in some. Although this risk is small (approximately 1%-2% in clinical trials), it is higher than for continued oral ART with dolutegravir- or bictegravir-based regimens, and patients should be informed of this risk prior to switching to long-acting injectable ART. The risk appears to be higher when giving cabotegravir plus rilpivirine every 8 weeks than every 4 weeks. Treatment options for those who experience treatment failure with long-acting cabotegravir plus rilpivirine and develop resistance will be limited, because neither NNRTI-based nor InSTI-based regimens are optimal choices.

If scheduled doses of cabotegravir plus rilpivirine are missed, resumption of therapy should follow redosing guidance as outlined in the product prescribing information. For patients who have maintained viral suppression, switching from long-acting injectable cabotegravir plus rilpivirine back to daily oral therapy can be done without the need for proviral DNA resistance testing (evidence rating: BIII).

Switching for Virologic Failure

Virologic failure (defined as HIV RNA level >200 copies/mL) should be confirmed by repeating a viral load measurement as soon as possible. If virologic failure is confirmed, genotype resistance testing should be performed, preferably while patients are taking the failing therapy. Resistance testing is still recommended even if a regimen has been discontinued or a person acknowledges poor medication adherence (evidence rating: AIII).

Proviral DNA resistance testing can identify resistance even if HIV RNA level is less than 500 copies/mL (including undetectable levels), but results of such testing do not correlate reliably with

Table 3. Recommendations for Laboratory Monitoring for Persons With HIV

Description of monitoring	At HIV diagnosis and start of ART	During ART	At virologic failure
HIV RNA level	Yes (evidence rating: AIII)	Every 3 mo until suppressed and then every 6 mo (evidence rating: AIa)	Yes (evidence rating: AIa)
CD4 cell count	Yes (evidence rating: AIII)	Every 6 mo until >250 cells/uL for 1 y, then stop provided viral suppression is maintained (evidence rating: BIII)	Yes (evidence rating: AIII)
HIV RT-pro genotype test	Yes (evidence rating: AIII)	If switching to injectable ART when patient has viral suppression, proviral RT-pro genotype can be collected for those who do not have a documented pre-ART RT-pro genotype (evidence rating: BIII)	Yes (evidence rating: AIa)
HIV integrase genotype test	If a patient's partner is known to have a failing ART regimen that includes an InSTI or individual has received cabotegravir for PrEP (evidence rating: BIII)		If failing ART regimen included an InSTI (evidence rating: AIII)
Viral tropism test			Before start of maraviroc (evidence rating: AIa)
HLA B*5701 test	Before start of abacavir (evidence rating: AIa)		
Cryptococcal antigen test if CD4 cell count <100 cells/μL	Yes (evidence rating: AIa)		
Safety laboratory and coinfection screening (eg, STIs, viral hepatitis)	Yes (evidence rating: AIa)	Yes (evidence rating: AIII)	Yes (evidence rating: AIII)

Abbreviations: ART, antiretroviral therapy; InSTI, integrase strand transfer inhibitor; PrEP, preexposure prophylaxis; RT-pro, reverse transcriptase–protease; STI, sexually transmitted infection.

standard genotypes and may miss important mutations, so results should be interpreted with caution.[52]

The most common reason for virologic failure is poor medication adherence. Additional potential causes such as food effects, drug interactions, and pharmacy dispensing errors should be investigated. If no resistance mutations are found, clinicians should offer tools to improve adherence and regimen change to improve simplicity or tolerability, if indicated. Based on the results of prospective clinical trials, dolutegravir plus 2 nRTIs (with at least 1 active nRTI as determined by genotypic testing) is recommended after treatment failure with an NNRTI plus 2 nRTIs (evidence rating: AIa).[1] Although not studied in virologic failure, BIC/FTC/TAF should have similar activity to dolutegravir plus TXF/XTC. If no active nRTIs are present after virologic failure and a boosted PI and an InSTI remain fully active, then treatment choices include boosted darunavir plus TXF/XTC (evidence rating: AIa) or dolutegravir plus a boosted PI with or without additional agent(s) (evidence rating: BIII). Dolutegravir plus TXF/XTC (evidence rating: AIa) is an alternative option to avoid drug interactions and maximize treatment simplicity, although this regimen has an approximate 4% risk of emergence of dolutegravir resistance.[47]

Management of InSTI resistance can be difficult. Owing to the rarity of such resistance, the common presence of extensive resistance to other drug classes, and relative paucity of prospective studies evaluating treatment outcomes in this population, guidance from an expert in HIV drug resistance is recommended for selection of an optimal regimen (evidence rating: AIII).

If InSTI resistance is relatively limited (as commonly occurs after treatment failure with raltegravir or elvitegravir) and a new ART regimen is to include an InSTI, dolutegravir should be administered twice daily.[53] This regimen should also include at least 1 and preferably 2 other fully active drugs, optimally from drug classes not previously used. These might include fostemsavir (except for treatment of HIV subtype CRF01_AE, because available data suggest that this subtype has naturally occurring resistance to fostemsavir),[54] lenacapavir (currently approved in the European Union and under US Food and Drug Administration [FDA] review), maraviroc (if the patient's virus is documented to be R5 tropic when tested), ibalizumab, or enfuvirtide. Recycling of nRTIs with partial antiretroviral activity may also be warranted.

If there is both high-level InSTI resistance and decreased PI susceptibility, then a multidrug regimen with at least 2 fully active agents from these novel drug classes should be used, along with recycled nRTIs because of their ongoing partial antiviral activity (evidence rating: AIII).

Laboratory Monitoring in Individuals With Established HIV at HIV Diagnosis and Starting ART

Recommendations are summarized in **Table 3**. Recommended laboratory monitoring before ART is started (evidence rating: AIII) should characterize (1) HIV stage (HIV RNA level, CD4 cell count), (2) general health (kidney and liver function, lipid levels, complete blood cell count, glucose level, and pregnancy), (3) ART resistance (reverse transcriptase–protease [RT-pro] genotype), and (4) presence of coinfections (viral hepatitis A, B, and C; tuberculosis; and sexually transmitted infections [STIs]). Unless there is a history of preexisting kidney or liver injury or a high likelihood of transmitted drug resistance, the results of these laboratory tests should not delay starting ART (evidence rating: BIII), but follow-up of these results should occur quickly to maximize safety. Given the low prevalence of transmitted InSTI resistance,[55] InSTI genotyping prior to ART initiation is not recommended unless there is suspicion that infection was transmitted from a partner with InSTI failure or if the patient previously received PrEP with cabotegravir (evidence rating: BIII).[1,56] An assessment for latent tuberculosis (initially, after immune reconstitution, and then if there is exposure) and, if the

Box 3. Weight Gain and Metabolic Complications While Receiving Antiretroviral Therapy (ART)

- Documentation of weight and BMI at baseline and every 6 months is recommended for people with HIV initiating or switching regimens to identify those with excessive weight gain (evidence rating: AIIa)
- Counseling regarding possibility of weight gain and potential cardiometabolic complications is recommended for people with HIV initiating or switching ART (evidence rating: AIII)
- Yearly diabetes screening and assessment of cardiovascular risk score of patients receiving InSTI-based ART is recommended (evidence rating: BIII)
- Lifestyle changes (exercise and diet) are recommended to support people with HIV who gain greater than 5% body weight (evidence rating: AIII)

Abbreviations: BMI, body mass index; InSTI, integrase strand transfer inhibitor.

CD4 cell count is less than 100 cells/μL, cryptococcal antigen testing at presentation should be performed.

During ART

Within 6 weeks of starting ART, assessment of treatment adherence and tolerability is recommended, along with the measurement of HIV RNA level (evidence rating: BIII). Although suppression of HIV RNA levels to undetectable may occur faster with InSTI-based regimens, it may take up to 24 weeks of continuous therapy.[57,58] If the HIV RNA level has not declined by 2 $\log_{10}$ copies/mL within 12 weeks of therapy and adherence appears to be sufficient, then a genotype based on the patient's regimen is recommended (evidence rating: AIII).[1]

If the patient remains virally suppressed, clinically stable, and adherent to medications, then HIV RNA levels should be monitored every 3 months until virally suppressed for at least 1 year. Afterward, the frequency of viral monitoring can be changed to every 6 months (evidence rating: AIII).

Before starting an injectable ART regimen for a patient with viral suppression, proviral RT-pro genotype should be collected for those who do not have a documented pre-ART RT-pro genotype (evidence rating: BIII). Of note, NNRTI resistance may not always be detected by a proviral genotype, and proviral genotyping has not yet been validated as a method to decide whether it is safe to switch to injectable cabotegravir plus rilpivirine. If a patient has rilpivirine-associated mutations on genotypic testing or a history of virologic failure while receiving an NNRTI, injectable cabotegravir plus rilpivirine should be avoided (evidence rating: BIa).[48,59]

Once viral suppression occurs with ART, CD4 cell counts should be measured every 6 months until they are greater than 250 cells/μL for at least 1 year (evidence rating: AIII).[1] Afterward, CD4 cell counts do not need to be measured unless ART failure is identified or the patient experiences an immunosuppressive condition (evidence rating: AIII). Patients receiving tenofovir disoproxil fumarate should also have urinary glucose and protein monitoring when starting tenofovir disoproxil fumarate and at least every year thereafter (evidence rating: BIII).[60-64]

Patients should have regular age- and risk-appropriate screening for coinfections such as STIs (at all exposed mucosal sites), tuberculosis, and viral hepatitis; cancer screening (including for cervical and anal cancer); general health maintenance assessments; vaccinations; and evaluation for medication toxicity at each visit.[65]

At the Time of Virologic Failure and Before Starting New ART Regimen

If an HIV RNA level greater than 20 to 50 copies/mL is detected during ART after previous viral suppression, then an early repeat HIV RNA level and assessment of medication adherence, drug-drug interactions, and tolerability is recommended (evidence rating: AIa).[1] If HIV RNA level is greater than 200 copies/mL on 2 consecutive measurements, then HIV RT-pro genotype and InSTI genotype (if the patient was receiving an InSTI) testing are recommended (evidence rating: AIII).[1] For patients with intermittent or persistent low-level viremia between 50 and 200 copies/mL, assessments for ART adherence, tolerability, and toxic effects are recommended (evidence rating: CI), but changing ART regimens is not recommended unless ART toxicity or intolerability are identified (evidence rating: AIII). Of note, a common cause of low-level viremia in patients receiving an InSTI are interactions with multivalent cations (Ca^{2+}, Fe^{3+}, Mg^{2+}, Al^{3+}, Zn^{2+}), such as those in mineral supplements and antacids.[1] Before starting maraviroc, testing for viral CCR5 tropism is recommended each time (unless X4 virus was previously detected), in which case maraviroc should not be used (evidence rating: AIa).

Weight Gain and Metabolic Complications With ART

Recommendations are summarized in **Box 3**. Weight gain is generally observed within the first year following initiation of most ART regimens, but treatment with InSTI- and tenofovir alafenamide–based regimens is associated with greater weight gain than regimens containing tenofovir disoproxil fumarate, efavirenz, or a boosted PI. Weight gain can occur with (1) initiation of InSTI- or tenofovir alafenamide–containing ART in previously ART-naive individuals[66]; (2) switch to InSTI- or tenofovir alafenamide–containing ART in individuals with viral suppression[67]; or (3) initiation of tenofovir alafenamide or InSTI for PrEP.[68] This weight gain with ART is more likely to occur in women and Black and Hispanic individuals and appears to occur mostly within the first year of ART initiation[69] or switch.[70] In the ADVANCE trial, most of the weight gain in dolutegravir groups was fat gain in trunk and limbs, and it was higher with concomitant tenofovir alafenamide use.[71]

Exposure to efavirenz or tenofovir disoproxil fumarate for ART or PrEP is associated with weight suppression, compared with other antiretroviral drugs or no ART exposure.[72] This might complicate assessment of weight gain after switching from tenofovir disoproxil fumarate to tenofovir alafenamide or after changing efavirenz to an InSTI.

Weight gain while receiving an InSTI is likely mediated by adipocyte dysfunction, inducing adipogenesis, lipogenesis, oxidative stress, fibrosis, and insulin resistance.[73,74] CYP2B6 genotypes have been associated with greater weight gain after switch from efavirenz to InSTI-based ART.[75] Mechanism(s) of tenofovir alafenamide–associated weight gain remain incompletely elucidated. A switch from tenofovir disoproxil fumarate to tenofovir

alafenamide is associated with increases in lipid levels and cardiovascular risk score, perhaps because tenofovir disoproxil fumarate lowers lipid levels.[76]

Although decreased in the general population, the risk of cardiovascular disease has not declined among people with HIV.[77] In addition to traditional risk factors and the chronic inflammation associated with HIV itself, some ART regimens may contribute to this risk, but more research is needed. Recent cohort studies suggest that InSTI-based ART may be associated with an increased risk of incident cardiovascular disease, new-onset diabetes, hyperglycemia,[78-80] elevated blood pressure,[80] and de novo hepatic steatosis. These cardiometabolic effects were not observed in other studies, and it remains unclear whether they are transient or sustained or whether InSTI exposure is causative. The retrospective nature and lack of availability of weight measurements in most data make it difficult to ascertain whether this risk (if confirmed) is a direct InSTI toxic effect or the result of InSTI-related weight gain. In one study, the InSTI-diabetes association was attenuated when accounting for 12-month weight change.[81] Nonetheless, data suggest that diabetes risk with weight gain at ART initiation is significant.[82] Further research is needed to evaluate the role of appetite, caloric intake, and energy expenditure in InSTI- and tenofovir alafenamide–related weight gain.

Whether weight gain is reversible with switch to non-InSTI or non–tenofovir alafenamide regimens is unclear and under investigation (ClinicalTrials.gov Identifier: NCT04636437). Data from the SALSA[83] and TANGO[39] studies suggest that switching off of tenofovir alafenamide does not lead to weight loss. Until there are data proving benefit, switching regimens because of weight gain is not recommended (evidence rating: BIIa); instead, lifestyle modifications, like exercise and diet intervention, are recommended (evidence rating: AIII). Semaglutide and other glucagon-like peptide 1 analogues that decrease weight in people without HIV are being studied in people with HIV.[84,85]

HIV and Aging

Recommendations for older people with established HIV are summarized in **Box 4**. Not only is the prevalence of HIV and diagnoses of new infections in people older than 50 years increasing, but more than half of older people with HIV are diagnosed at a late stage of disease (ie, CD4 cell count <350/μL).[86,87] Delayed diagnosis is a lost opportunity to initiate ART early for maximal health benefits and for prevention of transmission.

Early diagnosis and initiation of ART is particularly important in older persons because they are more likely to have a blunted immune response following ART initiation[88] and have a higher risk of serious non-AIDS complications. Choice of initial ART requires consideration of the background risk and burden of non-AIDS comorbidity, drug-drug interactions, and polypharmacy to manage multimorbidity in older people with HIV (evidence rating: BIII). Recommended initial ART includes InSTI-based regimens with TAF/FTC or DTG/3TC (see Initiation of ART section). Caution should be exercised in the use of tenofovir disoproxil fumarate because of its associated kidney and bone toxicity.[89] Studies of pharmacokinetics of ART are limited in older people with HIV. Whether clinically relevant pharmacokinetic changes and potential increased toxicity associated with aging require dose adjustment in older people with HIV remains unclear and is currently not warranted (evidence rating: AIII).[90]

Box 4. Recommendations for Older People With HIV

- Screening for HIV is recommended in older individuals to prevent late diagnosis with advanced disease (evidence rating: AIIa)
- Initiation of ART is recommended as soon as possible after diagnosis, either the same day of diagnosis, first clinic visit, or within 7 days. Assessment of comorbidities, kidney function, and medications will influence the choice of ART (evidence rating: AIa)
- Assessment of polypharmacy and simplification of complex regimens, both ART and comorbidity treatments, is recommended to improve adherence, prevent adverse drug-drug interactions, reduce falls risk, and reduce costs (evidence rating: AIIb)
- Screening for comorbidities, impaired cognitive and function, poor mobility, frailty, and falls risk is recommended for older people with HIV, using validated tools. The frequency of assessment is determined by the baseline assessment (evidence rating: BIII)[1]
- Consideration of integrated care models and Antiretroviral Stewardship models is recommended to improve outcomes and quality of life for people aging with HIV (evidence rating: BIII)

Abbreviation: ART, antiretroviral therapy.

Polypharmacy occurs more frequently in older people with HIV and is associated with increased risk of adverse health outcomes such as falls, frailty, hospitalization and mortality, and drug-drug interactions.[91] Management of polypharmacy includes (1) optimization of ART, including simplification of ART when possible (see When and How to Switch ART Regimens section), and (2) regular medication review with "pruning" of nonessential medications.[92,93] Antiretroviral stewardship programs effectively reduce medication errors, dose antiretroviral drugs appropriately for kidney and liver dysfunction, manage drug-drug interactions, and offer an opportunity to assess and deprescribe potentially inappropriate medication.[94]

There is an ongoing growing burden of neurocognitive dysfunction and frailty in people aging with HIV, which results in decreased quality of life, greater health care utilization, and higher mortality.[95,96] Recommendations for screening and management of comorbidities in older people with HIV, assessment of functional impairment and frailty, and evaluation of neurocognitive impairment are unchanged since the previous report.[1] Recent studies have shown that accumulation of comorbidities had greater negative effect on neurocognitive performance than did HIV disease parameters.[97,98] Intensification of ART with either dolutegravir or maraviroc did not improve cognitive impairment, despite lower cerebrospinal fluid HIV viral loads in the intensified group.[99] Aggressive management of comorbidities, rather than ART modification, may be the most beneficial strategy for improving neurocognitive function.

By the end of this decade, the proportion of people with HIV who will be older than 65 years is projected to be almost 25%.[100] The aging of people with HIV has highlighted the need for integrated care

models, including multidisciplinary teams of geriatricians, HIV specialists, pharmacists, and allied health practitioners (such as physiotherapists) offering holistic patient-centered care.[101-103]

Prevention of HIV Infection

Recommendations for HIV prevention are summarized in **Table 4**. Tools to prevent the acquisition of HIV infection are highly effective and continue to increase in breadth. Strategies to test, identify, link to care, and quickly treat and virally suppress individuals with HIV are crucial to prevention efforts (evidence rating: AIa); such efforts have health benefit for the individual and eliminate sexual transmission of HIV. Use of condoms continues to be recommended as the cornerstone of STI prevention efforts for all penetrative sex acts (evidence rating: AIIa). Medical circumcision for heterosexual males and harm reduction interventions (including but not limited to medication treatment for opioid use disorder and syringe access) are effective prevention strategies for applicable populations.

PrEP should be discussed with all sexually active adolescents and adults and anyone who injects nonprescription drugs (eg, opioids, methamphetamine) or who has a substance use disorder, without specific criteria for risk behaviors or screening tools (evidence rating: AIII).[105] Populations with disproportionately high HIV incidence rates should be particularly encouraged to consider PrEP as part of their HIV prevention plans; these include cisgender men and transgender individuals who have sex with men; young adults and adolescents; people whose sexual partners are from regions of generalized HIV epidemic; persons who use nonprescription drugs and alcohol; individuals who exchange sex for money, goods, or services; partners of incarcerated individuals; and anyone with a recent bacterial STI. Prescription of PrEP for adolescents should be done with specific attention to their additional support and adherence needs (evidence rating: AIa) and with care around potential disclosure of sexual behaviors and gender identity to parents or guardians (evidence rating: AIII).

Choosing the PrEP Regimen

The optimal PrEP regimen for a given person is the one most acceptable to that person and congruent with their sexual behavior, ability to take medications reliably, likelihood of anticipating sexual activity, and adverse effect profile. The choice of PrEP regimen made initially may need to be reconsidered over time. For example, someone challenged by taking daily oral tablets is likely to have better prevention effectiveness from an injectable regimen; for someone who prefers to take an oral medication, that preference should be respected.

Oral PrEP Regimens

Daily oral TDF/FTC (including generic tenofovir formulations) remains a recommended PrEP regimen for all populations at risk (evidence rating: AIa). For cisgender males, oral dosing should be initiated with a double dose of TDF/FTC for the first day, followed by daily single tablets, and should not be discontinued until at least 2 doses after last sexual activity[1]; this approach is anticipated to provide protection within 24 hours of initial dosing. For non–cisgender male populations, 7 days of daily dosing is likely required to reach maximal protection and is recommended for at least 7 days after last risk activity.[1] This daily regimen is also recommended for people who are pregnant or breastfeeding (evidence rating: AIIa).

On-demand (2-1-1) oral dosing is recommended for cisgender men of any sexual orientation, but there are insufficient data to support its use to prevent HIV acquisition via receptive vaginal sex (including neovaginal sex) or injection drug use. TDF/FTC 2-1-1 dosing is initiated with a double dose 2 to 24 hours before planned sexual activity and single additional doses 24 and 48 hours subsequent to the first dose; if additional sexual activity occurs within 7 days of the initial planned activity, daily single dosing should be continued until 2 doses after the last planned activity. The 2-1-1 regimen should be used with caution in transgender women receiving gender-affirming hormone therapy, particularly with first use, or reinitiation of TDF/FTC after prolonged hiatus, because rectal tissue concentrations may be somewhat lower early after starting 2-1-1 regimens and may have reduced efficacy.[106,107]

Daily oral TAF/FTC is preferred over TDF/FTC for individuals with creatinine clearance between 30 and 60 mL/min or when there is known osteopenia or osteoporosis. (Bone density scans are not necessary before starting TDF/FTC.) Further, TAF/FTC use should be limited to cisgender men of any sexual orientation and anyone whose risks do not include receptive vaginal sex (including neovaginal sex) or those whose risk is exclusively posed by injection drug use. Data on efficacy of TAF/FTC for preventing HIV acquisition through receptive vaginal sex are not available.

Prescribing for all oral PrEP regimens (including the 2-1-1 regimen) should be for no more than 1 month initially and 3 months thereafter to ensure appropriate HIV testing intervals. Tenofovir-based oral PrEP regimens have extremely low failure rates when taken as prescribed.

Same-Day or Rapid PrEP Start

Delaying PrEP is not recommended for individuals at risk. If HIV test results are available from samples drawn within 7 days of initiation or if the result of a rapid (point-of-care) HIV antibody test is negative, then PrEP should be initiated while awaiting the results of HIV, hepatitis B, and kidney function testing, as long as the patient is willing to take such an approach. Clinicians should follow up on test results and make adjustments as needed. If a high-risk encounter occurred within the past 72 hours, then a 3-drug postexposure prophylaxis (PEP) regimen is recommended (evidence rating: AIa) (see below), which can be changed to PrEP on PEP completion.

Injectable PrEP Regimen

Long-acting injectable cabotegravir was approved by the FDA for the prevention of sexual acquisition of HIV infection in December 2021 and is recommended for prevention of sexual transmission of HIV across populations (evidence rating: AIa).[20,108] There are insufficient data to recommend its use for injection drug exposures, but if a person who injects drugs is also at risk for acquiring HIV through sex, cabotegravir is a recommended option (evidence rating: AIII). An oral lead-in of cabotegravir of approximately 1 month duration should be limited to those with severe atopic histories or concerns, because potential nonadherence to oral dosing may create a period

Table 4. Recommendations for Biomedical HIV Prevention by Population and Transmission Risk Behavior[a]

	TDF/FTC (evidence rating)[b]		Daily oral TAF/FTC (evidence rating)	Intramuscular cabotegravir (evidence rating)
	Daily oral	On-demand oral		
Cisgender men/women				
Insertive sex (vaginal/anal)	Yes (AIa)	Yes (BIa)	Yes (AIa)	Yes (AIa)
Receptive vaginal sex	Yes (AIa)	Insufficient data	Insufficient data	Yes (AIa)
Receptive anal sex	Yes (AIa)	Yes (AIa)	Yes (AIa)	Yes (AIa)
Injection drug use (if sexual risk as well, apply appropriate category above)[c]	Yes (AIa)	Insufficient data	Insufficient data	Insufficient data
Transgender women				
Insertive sex (vaginal/anal)	Yes (AIa)	Yes (AIII/CIII)[d]	Yes (AIa)	Yes (AIa)
Receptive (neo) vaginal sex	Yes (BIII)	Insufficient data	Insufficient data	Yes (BIII)
Receptive anal sex	Yes (AIa)	Yes (AIII/CIII)[d]	Yes (BIa)	Yes (AIa)
Injection drug use (if sexual risk as well, apply appropriate category above)[c]	Yes (AIa)	Insufficient data	Insufficient data	Insufficient data
Transgender men				
Receptive vaginal ("front-hole") sex	Yes (AIII)	Insufficient data	Insufficient data	Yes (AIII)
Receptive anal sex	Yes (AIII)	Yes (AIII)	Yes (AIII)	Yes (AIII)
Injection drug use (if sexual risk as well, apply appropriate category above)[c]	Yes (AIII)	Insufficient data	Insufficient data	Insufficient data
Prerequisites and safety considerations				
Creatinine clearance, mL/min	>60	>60	>30	No restrictions; caution with end-stage kidney disease not yet receiving dialysis
Drug-drug interactions	NA	NA	NA	Do not use with certain anticonvulsants and antimycobacterials[e] Adjust dosing if using with rifabutin[f]
Other	Avoid use if individual has known osteopenia or osteoporosis	Avoid use if individual has known osteopenia or osteoporosis; caution during first use for transgender woman who uses exogenous estrogens or androgen blockers	Not applicable	Use caution if gluteal fillers or implants are present or if patient is using anticoagulants or has bleeding diathesis or thrombocytopenia
Prescribing				
Initial	30-d supply	30-d supply	30-d supply	30 d of oral (optional) First and second injections separated by 4 wk
Follow-up	90-d supply	90-d supply	90-d supply	One injection every 8 wk[g]
Dosing	TDF (300 mg)/FTC (200 mg)	TDF (300 mg)/FTC (200 mg)	TAF (25 mg)/FTC (200 mg)	Oral: 30 mg
				Injection: 600 mg (3 mL)
Laboratory tests				
Initiation[h]	HIV Ag/Ab[i] HIV RNA[j] Creatinine HAV IgG[k] HBsAg HBsAb HCV IgG Gonorrhea/chlamydia NAAT[l] Syphilis test Pregnancy test[m]	HIV Ag/Ab[i] HIV RNA[j] Creatinine HAV IgG[k] HBsAg HBsAb HCV IgG Gonorrhea/chlamydia NAAT[l] Syphilis test Pregnancy test[m]	HIV Ag/Ab[i] HIV RNA[j] Creatinine HAV IgG[k] HBsAg HBsAb HCV IgG Gonorrhea/chlamydia NAAT[l] Syphilis test Pregnancy test[m]	HIV Ag/Ab[i] HIV RNA[j] HAV IgG[k] HBsAg HBsAb HCV IgG Gonorrhea/chlamydia NAAT[l] Syphilis test Pregnancy test[m]
After 1 mo	HIV Ag/Ab	HIV Ag/Ab	HIV Ag/Ab	HIV Ag/Ab HIV RNA[j,n]
Every 2 mo				HIV Ag/Ab HIV RNA

(continued)

Table 4. Recommendations for Biomedical HIV Prevention by Population and Transmission Risk Behavior[a] (continued)

	TDF/FTC (evidence rating)[b]		Daily oral TAF/FTC (evidence rating)	Intramuscular cabotegravir (evidence rating)
	Daily oral	On-demand oral		
Every 3-4 mo[o]	HIV Ag/Ab Creatinine[p] Gonorrhea/chlamydia NAAT[l] Syphilis[q] Pregnancy test[m]	HIV Ag/Ab Creatinine[p] Gonorrhea/chlamydia NAAT[l] Syphilis[q] Pregnancy test[m]	HIV Ag/Ab Creatinine[p] Gonorrhea/chlamydia NAAT[l] Syphilis[q] Pregnancy test[m]	HIV Ag/Ab HIV RNA Gonorrhea/chlamydia NAAT[1] Syphilis[q] Pregnancy test[m]
Annually	Creatinine HCV IgG[r]	Creatinine HCV IgG[r]	Creatinine HCV IgG[r]	HCV IgG[r]
HIV testing considerations	If discordant or difficult-to-interpret HIV test results, call CDC (800-232-4636) for additional guidance	If discordant or difficult-to-interpret HIV test results, call CDC (800-232-4636) for additional guidance	If discordant or difficult-to-interpret HIV test results, call CDC (800-232-4636) for additional guidance	Results of HIV Ag/Ab test and HIV RNA are not needed before administering follow-up injections If discordant or difficult-to-interpret HIV test results, call CDC (800-232-4636) for additional guidance
Other considerations				
Late or missed doses	When starting or after 7 or more consecutive missed doses, restart with double dose of TDF/FTC and resume 1 tablet daily	NA	Resume with single-tablet daily dosing	If any injection is more than 7 d late, consider oral "bridging" with daily oral TDF/FTC or TAF/FTC as appropriate for sexual risk factors until injections can be resumed If any injection is ≥8 wk late, reload with 4-wk interval before resuming with 8-wk interval injections
ART regimen in the event of HIV acquisition	Bictegravir or dolutegravir + TXF/XTC	Bictegravir or dolutegravir + TXF/XTC	Bictegravir or dolutegravir + TXF/XTC	TXF/XTC/RTV/DRV (or COBI/DRV) unless a genotype exonerates NNRTI resistance, in which case TXF/XTC/EFV, rilpivirine, or doravirine can be considered

Abbreviations: Ab, antibody; Ag, antigen; ART, antiretroviral therapy; BIC, bictegravir; CDC, Centers for Disease Control and Prevention; COBI, cobicistat; DRV, darunavir; EFV, efavirenz; FTC, emtricitabine; HAV, hepatitis A virus; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; NA, not applicable; NAAT, nucleic acid amplification testing; NNRTI, nonnucleoside reverse transcriptase inhibitor; RTV, ritonavir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; 3TC, lamivudine; TXF, tenofovir alafenamide or tenofovir disoproxil fumarate; XTC, emtricitabine or lamivudine.

[a] Recommendations in this table are based on currently available data.

[b] This applies equally to generic tenofovir disoproxil formulations.

[c] Consider individual balance of risk behaviors—persons who inject drugs are frequently also sexually active within the same networks; therefore, the absence of data for an agent's protective efficacy in the setting of parenteral exposures should not preclude the agent's use if demonstrated to have efficacy for that individual's predominant route of sexual exposure. In such cases, refer to the relevant sexual risk category

[d] Evidence rating AIII if patient is using no gender-affirming hormone therapy, CIII if using therapy.

[e] Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifampin, rifapentine, and St. John's Wort.

[f] When rifabutin is started before or concomitantly with the first initiation injection, the recommended dosing is one 600-mg (3-mL) injection, followed 2 weeks later by a second 600-mg (3-mL) initiation injection and monthly thereafter while receiving rifabutin. When rifabutin is started at the time of the second initiation injection or later, the recommended dosing schedule is 600 mg (3 mL) monthly while receiving rifabutin.

[g] The first 2 injections on injection initiation are separated by 4 weeks.

[h] If results for the following tests have not been received, preexposure prophylaxis initiation should not be delayed: creatinine, HAV IgG, HBsAg, HBsAb, HCV IgG, GC/CT NAAT, and syphilis.

[i] Within 7 days of preexposure prophylaxis initiation or if not available, rapid test on site and blood drawn for a fourth-generation assay the same day.

[j] When initiating oral preexposure prophylaxis regimens, HIV RNA testing is recommended if high-risk exposure in last 4 weeks or signs and symptoms of HIV infection. When initiating cabotegravir, HIV RNA testing is recommended in all cases. If HIV RNA not available, use the most sensitive assay that is implementable and feasible.

[k] For men who have sex with men and persons who inject drugs (if not known to be immune).

[l] Test all sites used for sexual activity (vaginal, rectal, urethral (via urine testing), and pharyngeal).

[m] For individuals of childbearing potential.

[n] After 1 month of oral (if oral lead-in is used, before first injection) and 4 weeks after first injection.

[o] Laboratory testing conducted every 3 months for oral tenofovir disoproxil fumarate–based preexposure prophylaxis and every 4 months for injectable cabotegravir.

[p] Estimated creatinine clearance rate at first quarterly visit and annually thereafter; every 3 to 6 months for patients with or at risk for kidney injury (>50 y and/or estimated glomerular filtration rate <90 mL/min/1.73 m^2).

[q] Syphilis screening per CDC guidelines with consideration of both conventional and "reverse" screening algorithms.[104]

[r] Every 3 to 6 months for men who have sex with men and persons who inject drugs who use recreational drugs and alcohol at the time of sex or if liver function test results are incidentally found to be abnormal (assays are not part of routine monitoring).

of vulnerability to HIV acquisition (evidence rating: AIII). Injections should be administered gluteally at a dose of 600 mg (3 mL). The first 2 injections should be separated by 4 weeks, and subsequent injections by 8 weeks. Because the timing of onset of protection is unknown but is likely to be approximately 7 days after first injection, barrier protection is recommended in the first week of the first injection cycle. If an individual is more than 7 days late for any injection, it is recommended to "bridge" the period from that 7-day delay until the next injection can be given with an oral PrEP regimen (see Oral PrEP Regimens section above) (evidence rating: BIII). If a resumed injection schedule is 8 or more weeks late (that is, 12 or more weeks from previous for injection 2, or 16 or more weeks from previous for injections 3 and beyond), a "reloading" dose should be given with a 4-week interval between the 2 injections after the hiatus, before returning to every-8-weeks dosing (evidence rating: AIa). The recommended HIV testing algorithm at dispensation of oral bridging and at the time of injection resumption includes both antigen/antibody and HIV RNA testing (evidence rating: AIII).

Because of the prolonged pharmacologic "tail" phase after discontinuation of cabotegravir injections (median 43.7 weeks for males, 67.3 weeks for females),[109] there has been concern for InSTI resistance should infection occur during this period. Individuals who are stopping injectable cabotegravir but who remain at risk for HIV acquisition should be transitioned to an oral PrEP regimen (see Oral PrEP Regimens section above), and that regimen should be continued during the period of ongoing risk (evidence rating: AIa). Injectable cabotegravir should be dose-adjusted for coadministration with rifabutin and should not be used with potent inducers of UDP-glucuronosyltransferase 1A1. It should be used with particular caution in individuals with gluteal implants or fillers. Strategies to optimize on-time injections should be implemented and may include reminder communications, clinic transportation support, or home visiting nursing services (evidence rating: AIII).

Laboratory Testing in People Receiving PrEP

Recommendations on frequency and type of laboratory testing are reported in Table 4. In patients initiating an oral TXF-based regimen, recommended HIV screening includes a fourth- or fifth-generation laboratory-based, antigen-antibody assay. For cabotegravir-based regimens, HIV testing at initiation and at all visits should ideally include an HIV RNA test with a lower limit of quantification of 50 copies/mL or lower AND a laboratory-based antigen-antibody test (evidence rating: AIa). If RNA testing is not available, cabotegravir PrEP can still be considered using antigen/antibody screening only (evidence rating: BIa). Results of such testing do not need to be available to provide injections. Injectable cabotegravir may "mask" or delay the reactivity/positivity of conventional HIV testing owing to its high potency and prolonged pharmacokinetics, making breakthrough infections (ie, PrEP failures) challenging to identify. Such failures are often asymptomatic and characterized by inconsistent HIV assay results with very low levels of HIV RNA.[110] A high degree of suspicion for HIV infection should be maintained for any reactive/detectable HIV testing results in the setting of a recent HIV exposure or when there are delays in dosing.

Discordant or difficult-to-interpret combinations of HIV test results should be discussed with experts, including the PrEP Warmline at the National Clinician Consultation Center, available at (855) HIV-PrEP.[111]

Adherence to PrEP and Persistence/Retention

Individuals most at risk for acquiring HIV are often challenged by adhering to and persisting with oral PrEP medication and services, with high rates of loss to follow-up.[112,113] Numerous structural barriers contribute to this and are also likely to be applicable to long-acting cabotegravir PrEP.[22] Strategies to enhance adherence and persistence include PrEP navigators, telehealth or telephone check-ins, smartphone reminders, mobile service delivery, and pillboxes.

ART Choice for PrEP Breakthrough Infections

In instances of breakthrough infections, which can occur rarely with oral or injectable PrEP, see the Initiation of ART in the Setting of PrEP Failure section above.

Postexposure Prophylaxis for HIV and Bacterial STIs

A 3-drug fully suppressive ART regimen for 28 days is recommended to be administered as rapidly as possible but within 72 hours of a percutaneous, mucous membrane, or sexual exposure to known or suspected HIV-positive blood, genital secretions, or visibly bloody secretions. The recommended regimen is TXF/XTC plus dolutegravir or bictegravir (evidence rating: AIII). PEP should be initiated even if awaiting results of HIV testing on the source person (evidence rating: BIII). If there is concern for drug-resistant HIV or in the setting of pregnancy or breastfeeding, expert consultation is advised (evidence rating: AIII) (for example, through the National Clinician Consultation Center).[111]

Randomized studies suggest benefit of postexposure doxycycline (200 mg once after condomless intercourse) to prevent acquisition of gonorrhea, chlamydia, and syphilis in men who have sex with men (MSM) and in transgender women.[114,115] Importantly, data on its use for cisgender women and its effects on antimicrobial resistance and the microbiome are still pending. Until more information is available, this strategy should be considered only on a case-by-case basis for individuals at high risk for acquiring syphilis, chlamydia, or gonorrhea.

Substance Use in Persons at Risk for and With HIV

Recommendations for persons at risk for and with HIV who use substances and who have substance use disorders (SUDs) are summarized in **Box 5**. Substance use (eg, opioids, stimulants, alcohol) and SUD can interfere with all stages of the HIV prevention and treatment care continuum.[116] Substance use increases the risk of acquiring HIV through sharing injection drug use equipment and condomless sexual intercourse and may adversely affect HIV outcomes by interfering with ART adherence and the ability to achieve or maintain HIV suppression.[117-119]

Substance use and SUDs are more common among people with HIV than among the general population. Despite the high prevalence of SUDs, only a small number of people with HIV are linked to or initiate treatment for SUD. To increase diagnosis and treatment

Box 5. Recommendations for Persons at Risk for and With HIV Who Use Substances and Who Have Substance Use Disorders

- Provide screening and treatment for substance use disorders to all persons at risk for and living with HIV (evidence rating: AIa)
- Substance use treatment should be integrated into HIV prevention and treatment services (evidence rating: AIa)
- Persons with substance use disorders and HIV infection or risk for HIV should receive integrated addiction treatment with:
  - Pharmacotherapy for opioid and alcohol use disorders (evidence rating: AIa)
  - Contingency management for stimulant use disorders (evidence rating: AIII)
- Persons with opioid use and alcohol use disorders should be offered timely initiation of medications for substance use disorder regardless of HIV and HCV treatment plans (evidence rating: AIa)
- Peer/patient support staff, telehealth, extended hours, mobile clinics, and walk-in clinic options should be available to persons with substance use disorders who are receiving HIV treatment or prevention (evidence rating: AIIb)
- Peer/patient support staff, mobile health units, and pharmacy delivery services should be available to persons with substance use disorders who are receiving HIV treatment or prevention (evidence rating: AIIb)

Abbreviation: HCV, hepatitis C virus.

of SUDs, screening for and linkage to SUD treatment should be integrated into HIV prevention and treatment services (evidence rating: AIa) (eTable 4 in the Supplement).[120,121] Reducing substance use (even if abstinence is not achieved) is associated with improved HIV outcomes.[122] Therefore, offering addiction treatment, including pharmacotherapy and behavioral-based therapies, is recommended for all people with HIV with SUDs (evidence rating: AIa).[118]

Medication treatments for opioid use disorder (OUD), including buprenorphine, methadone, and extended-release naltrexone, reduce nonmedical opioid use and reduce risk for HIV and hepatitis C virus (eTable 5 in the Supplement).[123-125] For persons with alcohol use disorder (AUD), medications (extended-release naltrexone, oral naltrexone) reduce alcohol use, thereby reducing HIV risk (eTable 6 in the Supplement).[126] For those with HIV, medication treatment of OUD and AUD improves ART adherence and viral suppression and thus is recommended with ART (eFigure in the Supplement) (evidence rating: AIa).[127-130] Clinically significant drug-drug interactions between ART or hepatitis C virus direct-acting antiviral medications and medications used to treat SUDs are infrequent[131,132]; neither ART nor medication treatments for SUDs should be withheld (evidence rating: AIII). Although there are as yet no FDA-approved medications to treat stimulant use disorders (eg, methamphetamine, cocaine), there are data supporting the use of contingency management to promote reduced stimulant use.[133-136]

Interventions that reduce substance use, including medication treatments for OUD and AUD, may also improve PrEP outcomes for HIV prevention. Although oral PrEP is approved for reducing HIV transmission via injection drug use, TAF/FTC and injectable cabotegravir have not yet been evaluated for injection drug use–related risk among persons who inject drugs.[137] However, persons who use drugs may acquire HIV via condomless sexual intercourse; therefore, if they are at sexual risk of HIV acquisition, they should be offered PrEP (evidence rating: AIa).[138-140]

Among persons engaged in HIV prevention or treatment services, SUD can create an additional hurdle for retention in care. Structural barriers to retention, including lack of transportation, insurance, and housing, as well as criminal legal barriers, poverty, mental illness, racism, and stigma should be evaluated and addressed.[141] Innovative service delivery options, including telehealth, extended hours, mobile clinics, walk-in clinics, and staff who are peers or near-peers with lived experience with addiction, are recommended as ways to improve access for patients (evidence rating: AIIb).[9,142,143] Rapid HIV testing combined with rapid ART or PrEP provision among persons at risk should be available to persons who use substances and who have SUDs (see above).

COVID-19 and HIV

Recommendations are summarized in **Box 6**. The COVID-19 pandemic disrupted access to and delivery of HIV care and services.[144-147] An extended review is beyond the scope of this document, but several key points should be considered.[148,149] Recent studies indicate that people with HIV are not at increased risk of acquisition of SARS-CoV-2 compared with people without HIV after controlling for underlying immunosuppression, viral suppression while receiving ART, and comorbidities.[149,150] Data are conflicting and influenced by regional heterogeneity about the independent contribution of HIV to higher risk of severe disease and mortality due to COVID-19.[151] The preponderance of data suggests that people with HIV who are receiving effective ART, virally suppressed with a CD4 cell count greater than 200/μL (or in some studies >350 cells/μL), and without key comorbidities do not appear to be at substantially increased risk for severe disease or death compared with people without HIV.[152] There are 3 potential explanations for some of the contradictory findings. First, published reports did not control for (or may have been confounded by) higher prevalence among people with HIV of underlying comorbidities such as cardiovascular disease, diabetes, chronic kidney disease, chronic pulmonary disease, and obesity, all of which are associated with increased risk of severe COVID-19 and mortality.[153-155] Second, published reports had not accounted for HIV RNA, residual HIV-associated inflammation, or incomplete CD4 cell reconstitution in some people with HIV despite receiving ART. Third, social determinants of poor COVID-19 outcomes also intersect with higher prevalence of HIV among racial and ethnic minority populations.

Primary COVID-19 vaccination and vaccine boosting is recommended for all people with HIV (evidence rating: AIa). For those who have untreated HIV infection or a CD4 cell count less than 200/μL, the primary vaccination series should include at least 3 primary vaccine doses, and vaccine booster doses are recommended regardless of age (evidence rating: AIIa). For persons with HIV with viral suppression while receiving ART and with CD4 cell counts greater than 350/μL, antibody responses to SARS-CoV-2 infection or vaccines are not substantially different than among those without HIV. People with HIV also do not have higher rates of adverse events related to SARS-CoV-2 vaccines.[156-158] However, some studies suggest that vaccine efficacy, as measured by reduction in hospitalizations and mortality, and antibody response rates are lower for people with HIV with advanced immunosuppression, especially those with CD4 cell counts less than 200/μL or without viral suppression, than those without HIV.[159-162] Many of the large phase 3 vaccine trials excluded people with HIV or enrolled numbers too small to draw firm

conclusions. Again, some published data on vaccine immunogenicity in people with HIV are conflicting, possibly owing to small numbers, insufficient controls for underlying age, comorbidities, HIV RNA levels, or other factors that may affect antibody responses.[163,164] People with HIV who have CD4 cell counts less than 200/μL or untreated HIV may benefit from PrEP with tixagevimab plus cilgavimab, but only if the circulating SARS-CoV-2 variants are susceptible (evidence rating: BIII). People with HIV, particularly those with CD4 cell counts less than 200/μL, do appear to be at increased risk of vaccine breakthrough infections.[165] This risk was lower for those with CD4 cell counts greater than 500/μL.

Current COVID-19 treatment guidelines do not recommend that treatment be intensified, withheld, or altered based on HIV-related immunosuppression or ART.[166-168] One emerging issue is whether postacute sequelae of COVID-19 ("long COVID") is more prevalent among people with HIV. Risk factors for postacute sequelae in people with HIV appear to be the same as for people without HIV.[169] The degree to which underlying immunosuppression, viral suppression while receiving ART, or other factors affect the risk of postacute sequealae remains to be determined.

Monkeypox Virus Infection

A global surge in monkeypox virus infections, primarily among MSM and with up to 50% occurring among people with HIV, was first identified in 2022. Most cases are related to skin-to-skin transmission during sexual encounters. Although the infection can be asymptomatic,[170] the predominant symptoms are skin lesions that progress from papules to pustules and ulcers, often associated with fever, lymphadenopathy, myalgias, headache, or fatigue.[171,172] Skin lesions are typically painful and can coalesce. Patients also often have anogenital or oral lesions, although lesions may exist without any symptoms. People with HIV and low CD4 cell counts or with no viral suppression may experience more severe disease.[173] Coinfection with other STIs is frequent and should be screened for when monkeypox is first recognized or suspected (evidence rating: AIII).

Diagnosis of monkeypox currently requires nucleic acid amplification testing of lesions. Treatment recommendations are evolving, but those patients who are immunosuppressed or otherwise at high risk for progression or those with severe disease should receive oral or intravenous tecovirimat (evidence rating: BIII), an investigational agent with activity against smallpox and monkeypox viruses. Oral dosing is every 8 or 12 hours (depending on weight) for 14 days, administered within 30 minutes of a full fatty meal. Potential drug interactions exist between tecovirimat and rilpivirine, doravirine, and maraviroc, but dose adjustment is not required.[174]

The incubation time for monkeypox virus is approximately 12 days. For individuals with a known exposure, the JYNNEOS vaccine (smallpox and monkeypox vaccine, live, nonreplicating [Bavarian Nordic]) should be administered to asymptomatic contacts ideally within 4 days but up to 14 days (evidence rating: AIII). Primary JYNNEOS vaccination with 2 doses given at least 28 days apart is recommended for individuals at high risk (evidence rating: AIII) (eg, MSM with multiple sexual partners). It is crucial that health messaging center on an equity approach to ensure that education and services reach the most affected populations while simultaneously fighting the stigma increasingly directed toward these communities.

Box 6. Recommendations for COVID-19 and People With HIV

- Primary COVID-19 vaccination and vaccine boosting is recommended for all people with HIV (evidence rating: AIa). For those who have untreated HIV infection or a CD4 cell count less than 200/μL, the primary vaccination series should include at least 3 vaccine doses, and vaccine booster doses are recommended regardless of age (evidence rating: AIIa)
- If circulating SARS-CoV-2 variants anticipated to be susceptible, preexposure prophylaxis for susceptible subvariants with tixagevimab (300 mg) plus cilgavimab (300 mg) to prevent COVID-19 is recommended for adults and adolescents (aged ≥12 years and weighing ≥40 kg) with HIV who have untreated HIV infection or a CD4 cell count less than 200/μL or those not able to be fully vaccinated owing to a history of severe adverse reactions to a COVID-19 vaccine or its components (evidence rating: BIII)
- Postexposure prophylaxis is not recommended for people with HIV (evidence rating: AIII). Currently available monoclonal antibody agents have not been shown to be sufficiently effective against the predominant circulating Omicron variants and subvariants
- People with HIV who develop COVID-19 should be treated according to current guidelines for management of COVID-19, regardless of CD4 cell count or viral suppression (evidence rating: AIa)
- People with HIV with CD4 cell counts less than 200/μL or without viral suppression who develop mild-moderate COVID-19 infection should be treated with ritonavir-boosted nirmatrelvir (evidence rating: AIIa). With the exception of maraviroc, ART can be co-administered with ritonavir-boosted nirmatrelvir without dose adjustment (except as needed for estimated glomerular filtration rate <60 mL/min), but people with HIV should be monitored closely for adverse effects while receiving this treatment. Drug-drug interactions may still limit the use of this treatment if medications used for underlying comorbidities or opportunistic infections are contraindicated with ritonavir-boosted nirmatrelvir
- People with HIV who recover from severe COVID-19 should be monitored for postacute sequelae of SARS-CoV-2 (long COVID) and HIV treatment should be optimized to the extent possible to further reduce inflammatory responses to COVID-19 and HIV (evidence rating: AIII)

Abbreviation: ART, antiretroviral therapy.

Promoting Equity in HIV Treatment and Prevention

Despite advances in HIV treatment and prevention, large disparities exist in the global HIV epidemic. The 2021 Global AIDS Update titled "Confronting Inequalities" describes the inequity that continues to drive the HIV epidemic in all regions of the world, with a focus on low- and middle-income countries.[175] However, HIV epidemics in high-income countries also are characterized by ongoing disparities. The US epidemic is a prime example: HIV disproportionately affects people who are Black or Hispanic, those who live in the US South, MSM, transgender individuals, and people who use drugs, compared with the general population.[176] In 2020, HIV testing and services were disrupted by the COVID-19 pandemic in the US, particularly among priority populations including men who have sex with men, transgender persons, and Black or African American and Hispanic persons.[177] In addition, Black/African American people were furthest from the

Ending the HIV Epidemic Initiative targets for linkage to care (80%), viral suppression (60%), and PrEP coverage (9%).[178] Among Black people with HIV in the US, 52% reside in geographic areas with high social vulnerability index scores.[179] The greatest burden of HIV in the US is in the South, driven by structural factors including long-standing inequitable policies based in racism, and resulting in high levels of poverty, failure to expand health care access through Medicaid expansion, low educational attainment, intersectional stigma and discrimination, and clinician shortages that result in inequitable access to HIV prevention and treatment services. Striking disparities also exist across other high-income settings. For example, in the European Union and European Economic Area, 44% of new diagnoses in 2019 were among the migrant populations.[180]

Global disparities in PrEP utilization limit its ability to reduce HIV transmission,[181,182] and there is serious concern that, although long-acting cabotegravir for PrEP has the potential for considerable benefit,[183] its cost and implementation complexity will only widen disparities.

The United Nations General Assembly Political Declaration on HIV and AIDS, titled "Ending Inequalities and Getting on Track to End AIDS by 2030," offers roadmaps to address global health disparities, including those associated with HIV status, sex, gender, race, ethnicity, disability, age, income level, education, occupation, geographic disparities, migratory status, and incarceration.[184] Ending the HIV epidemic will require an equity approach that focuses resources on addressing societal disparities (for example, tackling poverty as an HIV prevention strategy), addressing stigma as a root cause of HIV risk, eliminating laws that target people with HIV, and ensuring access to care for all.

Limitations

First, this article is meant to provide general recommendations and is not designed as mandates or to replace clinical judgment. Second, the recommendations are based on the body of evidence that was available at the time of preparation and may change as new data become available. Third, the recommendations were developed for high- and medium-income settings, for which most of the drugs and tools are available. The specific recommendations may not be applicable in all resource-limited settings.

Conclusions

Advances in treatment and prevention of HIV continue to improve outcomes, but challenges and opportunities remain.

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