

# Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults 2020 Recommendations of the International Antiviral Society-USA Panel

Michael S. Saag, MD; Rajesh T. Gandhi, MD; Jennifer F. Hoy, MBBS; Raphael J. Landovitz, MD; Melanie A. Thompson, MD; Paul E. Sax, MD; Davey M. Smith, MD; Constance A. Benson, MD; Susan P. Buchbinder, MD; Carlos del Rio, MD; Joseph J. Eron Jr, MD; Gerd Fätkenheuer, MD; Huldrych F. Günthard, MD; Jean-Michel Molina, MD; Donna M. Jacobsen, BS; Paul A. Volberding, MD

 Supplemental content

**IMPORTANCE** Data on the use of antiretroviral drugs, including new drugs and formulations, for the treatment and prevention of HIV infection continue to guide optimal practices.

**OBJECTIVE** To evaluate new data and incorporate them into current recommendations for initiating HIV therapy, monitoring individuals starting on therapy, changing regimens, preventing HIV infection for those at risk, and special considerations for older people with HIV.

**EVIDENCE REVIEW** New evidence was collected since the previous International Antiviral (formerly AIDS) Society-USA recommendations in 2018, including data published or presented at peer-reviewed scientific conferences through August 22, 2020. A volunteer panel of 15 experts in HIV research and patient care considered these data and updated previous recommendations.

**FINDINGS** From 5316 citations about antiretroviral drugs identified, 549 were included to form the evidence basis for these recommendations. Antiretroviral therapy is recommended as soon as possible for all individuals with HIV who have detectable viremia. Most patients can start with a 3-drug regimen or now a 2-drug regimen, which includes an integrase strand transfer inhibitor. Effective options are available for patients who may be pregnant, those who have specific clinical conditions, such as kidney, liver, or cardiovascular disease, those who have opportunistic diseases, or those who have health care access issues. Recommended for the first time, a long-acting antiretroviral regimen injected once every 4 weeks for treatment or every 8 weeks pending approval by regulatory bodies and availability. For individuals at risk for HIV, preexposure prophylaxis with an oral regimen is recommended or, pending approval by regulatory bodies and availability, with a long-acting injection given every 8 weeks. Monitoring before and during therapy for effectiveness and safety is recommended. Switching therapy for virological failure is relatively rare at this time, and the recommendations for switching therapies for convenience and for other reasons are included. With the survival benefits provided by therapy, recommendations are made for older individuals with HIV. The current coronavirus disease 2019 pandemic poses particular challenges for HIV research, care, and efforts to end the HIV epidemic.

**CONCLUSION AND RELEVANCE** Advances in HIV prevention and management with antiretroviral drugs continue to improve clinical care and outcomes among individuals at risk for and with HIV.

**Author Affiliations:** Author affiliations are listed at the end of this article.

**Corresponding Author:** Michael S. Saag, MD, School of Medicine, University of Alabama at Birmingham, 845 19th St S, BBRB 256, Birmingham, AL 35294 (msaag@uabmc.edu).

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**A**dvan­ces regard­ing the use of antiretroviral drugs for the treat­ment and pre­ven­tion of HIV infec­tion have emerged since the last ver­sion of these recom­men­da­tions in 2018,<sup>1</sup> war­rant­ing an update.

All per­sons with HIV who have detectable viremia, regard­less of their CD4 cell count, should begin antiretroviral therapy (ART) as soon as pos­si­ble after diag­no­sis. New data demon­strate the effi­cacy of 2-drug dolutegravir/lamivudine therapy as initial and sub­se­quent treat­ment. Novel long-act­ing injectable ART regimens admin­is­tered once every 4 weeks, and poten­tially every 8 weeks, have demon­strated effec­tiveness for treat­ment. Sim­i­larly, a long-act­ing injectable antiretroviral drug admin­is­tered every 8 weeks is effec­tive in pre­ven­ting HIV.

The suc­cess of ART has led to a sub­stan­tial increase in sur­vival such that per­sons with HIV now live a near-normal life­span. As a result, increas­ing num­bers of per­sons with HIV are living to the age of 50 years and older. In this update, a sec­tion on aging has been added to provide guid­ance on the opti­mal man­age­ment of older per­sons with HIV. How­ever, a remain­ing chal­lenge is reduc­ing the num­ber of new cases of HIV in the com­mu­nity. This has led to an increas­ing focus on ending the HIV epi­dem­ic.

At this time, the world has been devas­tated by the corona­virus disease 2019 (COVID-19) pan­dem­ic, and severe acute respi­ra­tory syn­drome corona­virus 2 (SARS-CoV-2) infec­tion has had major effects on the ability of HIV clin­ic­ians and re­searchers to man­age their pa­tients and con­duct stud­ies, re­spec­tively. Emerg­ing data on the inter­sec­tion of COVID-19 and HIV are dis­cussed.

As in pre­vious updates of the recom­men­da­tions, this Special Communication provides updates on current knowl­edge regard­ing when to start ART, what regimen to initiate, when and how to switch ART, con­sid­er­a­tions for when and how to use pre­ex­posure prophylaxis (PrEP), and mon­i­tor­ing dur­ing therapy as well as issues in aging with HIV.

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## Methods

The volun­teer inter­na­tional panel of experts in HIV re­search and care was appointed by the Inter­na­tional Antiviral (formerly AIDS) Society—USA (IAS-USA; eBoxes 1-3 in the [Supplement](#)). Mem­bers were screened for expertise, in­volvement in re­search and patient care, financial relationships, and ability to work toward consensus. The panel convened from Octo­ber 2019 to August 2020. Teams for each sec­tion evaluated relevant evi­dence and drafted recom­men­da­tions for full-panel review.

New evi­dence that was published in the liter­ature, pre­sent­ed at relevant peer-reviewed sci­en­tific confer­ences, or released as safety reports was reviewed.<sup>1</sup> Literature searches were con­ducted in PubMed and EMBASE for Jan­uary 2018 to August 22, 2020 (addi­tional details appear in the eMethods in the [Supplement](#)). Overall, 5316 unique cita­tions were reviewed by 2 of the authors (C.d.R. and P.A.V.) who identified a total of 549 poten­tially relevant pub­lica­tions. There were 336 addi­tional unique cita­tions for aging and HIV. Abstracts pre­sent­ed at relevant peer-reviewed sci­en­tific confer­ences since July 2018 were identified by panel mem­bers. Relevant pub­lica­tions, data pre­sent­ed at peer-reviewed confer­ences, and safety

reports were requested from drug man­u­fac­turers (eTable 1 in the [Supplement](#)).

The updated recom­men­da­tions focus on adults (aged  $\geq 18$  years) with or at risk for HIV infec­tion in settings in which most antiretroviral drugs are available or are in the late-stage develop­ment process. The strength of the panel's recom­men­da­tions and the quality of the evi­dence to support the recom­men­da­tions are rated (Table 1). For recom­men­da­tions or ratings that have not changed sub­stan­tially or for which few new data have become available since 2018, the pre­vious iterations of the recom­men­da­tions provide background infor­ma­tion and relevant evi­dence.<sup>1</sup> Key recom­men­da­tions for each sec­tion are listed in a Box or Table. Co-formulated drug combinations are indicated with vir­gules (eg, drug A/drug B/drug C).

Details about the develop­ment process, the panel, evi­dence col­lec­tion and liter­ature searches, and the study's sponsor (IAS-USA) and its policies appear in the eMethods and eTables 2 and 3 in the [Supplement](#).

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## When to Start ART

Recom­men­da­tions for when to start ART have not changed from the pre­vious report (Box 1).<sup>1</sup> The goals of ART are to maintain opti­mal health for the individual and eliminate HIV trans­mis­sion through rapid and durable viral sup­pres­sion in all per­sons with HIV. Accomplish­ing these goals requires strategies that facilitate im­mediate entry into care, remove barriers to initiation of ART, and support continuous care engagement.

One strategy has been called rapid ART, im­mediate ART, or same-day ART. The term *rapid ART* refers to initiation of ART as soon as pos­si­ble (within 7 days) after HIV diag­no­sis. Im­mediate ART and same-day ART refer to starting HIV treat­ment on the day of diag­no­sis or at the first clinic visit. Such an approach is feasible and stud­ies from several resource-limited settings demonstrate that im­ple­ment­ing rapid treatment protocols can increase care retention and population-level viral sup­pres­sion.<sup>3</sup> As previously described,<sup>1</sup> 3 ran­domized clinical trials con­ducted in South Africa and Haiti showed that rapid initiation of ART was associated with higher rates of viral sup­pres­sion. How­ever, a new study<sup>4</sup> sug­gested that this favorable virological outcome may not be sus­tained beyond 12 months.

No data from clinical trials of im­mediate initiation of treat­ment from resource-rich settings have been published, but several observational stud­ies have shown decreased time to viral sup­pres­sion compared with standard of care and high rates of viral sup­pres­sion at 1 year.<sup>1,5,6</sup> Such a strategy can be used if the resources required, such as staff­ing, readily available drugs, and no concerns for payer source, are available. Because of the urgent need for viral sup­pres­sion in per­sons with acute HIV infec­tion, im­mediate ART is recom­men­ded if feasible (evidence rating: AIIa). Im­ple­ment­ation of im­mediate ART alone may not improve long-term care retention or durable viral sup­pres­sion over standard of care and longer-term outcomes are needed.<sup>1,4,7</sup> Robust, cultur­ally sensitive care engagement strategies are required, including attention to essential needs such as housing and food. Im­ple­ment­ing rapid ART is a way to address and remove struc­tural barriers to accessing HIV care.<sup>8</sup>

Table 1. Strength of Recommendation and Quality of Evidence Rating Scale<sup>a</sup>

Evidence rating	Definition
<b>Strength of recommendation</b>	
A	Strong panel support
B	Moderate panel support
C	Limited or weak panel support
<b>Quality of evidence</b>	
Ia	Evidence from ≥1 RCTs published in the peer-reviewed literature
Ib	Evidence from ≥1 RCTs presented in abstract form at peer-reviewed scientific meetings
IIa	Evidence from cohort or case-control studies published in the peer-reviewed literature
IIb	Evidence from cohort or case-control studies presented in abstract form at peer-reviewed scientific meetings
III	Based on the panel's analysis of the available evidence

Abbreviation: RCT, randomized clinical trial.

<sup>a</sup> Adapted in part from the Canadian Task Force on the Periodic Health Examination.<sup>2</sup>

### Initiating ART in the Setting of Active Opportunistic Infections and Cancer

Recommendations for initiating ART in the setting of active opportunistic infections remain largely unchanged.<sup>1</sup> ART should be started within the first 2 weeks after initiation of treatment for most opportunistic infections (evidence rating: A1a), within 2 weeks after tuberculosis treatment initiation in individuals with a CD4 cell count below 50 cells/μL when tuberculosis meningitis is not suspected, within 2 to 8 weeks after starting tuberculosis treatment in those with higher CD4 cell counts (evidence rating: A1a), and within 4 to 6 weeks after starting antifungal therapy for those with cryptococcal meningitis (evidence rating: A1a).<sup>1,9</sup> The timing of ART initiation in the setting of tuberculosis meningitis (although uncommon in resource-rich settings) remains controversial; however, most experts recommend that ART be started within 2 weeks after initiating treatment for the opportunistic infection with close monitoring for people with tuberculosis meningitis and CD4 cell counts below 50 cells/μL. For individuals with HIV and a cancer diagnosis, immediate ART initiation is recommended (evidence rating: B11a) with special attention to drug-drug interactions and monitoring for early ART adverse events while cancer assessments are being conducted.

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

- Initiation of ART is recommended as soon as possible after HIV diagnosis, including immediately after diagnosis if the patient is ready to commit to treatment (evidence rating: A1a)
- Structural barriers that delay receipt of ART should be removed to allow newly diagnosed persons to receive ART at the first clinic visit after diagnosis if they and their clinicians determine that this approach is appropriate (evidence rating: A1a)
- Initiation of ART is recommended within 2 weeks of initiation of treatment for most opportunistic infections (evidence rating: A1a), except:
  - For individuals with tuberculosis and CD4 cell counts of 50/μL or above, ART should be initiated within 2 to 8 weeks of initiation of tuberculosis treatment (evidence rating: A1a)
  - For individuals with cryptococcal meningitis, ART should be initiated within 4 to 6 weeks after starting antifungal therapy (evidence rating: B1a)
- Initiation of ART is recommended immediately in the setting of a new diagnosis of cancer with attention to drug-drug interactions (evidence rating: B11a)

### Initial ART for Individuals With HIV

#### Recommended Initial ART Regimens

Recommended initial ART regimens for individuals with HIV appear in Box 2. Optimal regimens have a high rate of viral suppression, minimal toxicity, low pill burden, and few drug interactions. Regimens that are less likely to be associated with emergence of HIV resistance, even when treatment adherence is not optimal, are favored over combinations that have a lower barrier to resistance.

Recommended initial regimens consist of 3 drugs: 2 nucleoside reverse transcriptase inhibitors (nRTIs) and an integrase strand transfer inhibitor (InSTI) or a 2-drug regimen of dolutegravir/lamivudine. When choosing between comparable regimens, cost and health care access are important considerations.

#### InSTIs as Components of the Initial ART Regimen

Dolutegravir and bictegravir are recommended for InSTI-containing ART owing to their high (and comparable) rates of viral suppression, minimal toxicity, low risk of drug interactions, and high barrier to resistance. Raltegravir-containing regimens have a higher

pill burden (≥3 pills per day) and a lower barrier to resistance. Elvitegravir is the least-favored InSTI because the co-formulated pharmacological booster, cobicistat, a potent CYP3A4 inhibitor, results in more drug interactions than other InSTIs.

#### Choice of nRTIs

Tenofovir alafenamide-containing regimens and tenofovir disoproxil fumarate-containing regimens have similar virological efficacy. Compared with tenofovir disoproxil fumarate-containing regimens, tenofovir alafenamide-containing regimens have fewer tenofovir-associated adverse effects, such as proximal renal tubular toxicity and reductions in bone mineral density. However, these differences are most pronounced when tenofovir disoproxil fumarate is used with pharmacological boosters, such as ritonavir or cobicistat, which increase tenofovir levels. Tenofovir decreases plasma lipid levels and, as a result, people who receive tenofovir disoproxil fumarate have lower lipid levels than those who receive tenofovir alafenamide because tenofovir disoproxil fumarate results in higher plasma tenofovir levels than tenofovir alafenamide. It is unknown if the lipid-lowering effect of tenofovir disoproxil fumarate has clinical significance. Tenofovir alafenamide is associated with greater

## Box 2. Recommended Initial Antiretroviral Therapy (ART) Regimens

**Recommended for Most People With HIV<sup>a</sup>**

- Bictegravir/tenofovir alafenamide/emtricitabine (evidence rating: Ala)
- Dolutegravir plus (all evidence ratings: Ala)
  - Tenofovir alafenamide/emtricitabine
  - Tenofovir disoproxil fumarate/emtricitabine
  - Tenofovir disoproxil fumarate/lamivudine
- Dolutegravir/lamivudine with caveats<sup>b</sup> (evidence rating: Ala)

**Recommended in the Setting of Opportunistic Infection Treatment**

- Dolutegravir (50 mg twice daily), efavirenz (600 mg/d), or raltegravir (800 mg twice daily) plus 2 nucleoside reverse transcription inhibitors is recommended for initial ART in people with HIV who have active tuberculosis and are receiving a rifamycin-based tuberculosis treatment regimen (evidence rating: Ala)
- Bictegravir with rifampin is not recommended due to drug-drug interactions (evidence rating: Alla)
- Boosted protease inhibitors are recommended only if an integrase strand transfer inhibitor–based or efavirenz–based regimen is not an option (evidence rating: Ala); if possible, rifabutin (150 mg/d) should be substituted for rifampin in the tuberculosis treatment regimen if a protease inhibitor–based regimen must be used (evidence rating: BIII)

**Recommended During Pregnancy<sup>c</sup>**

- Atazanavir/ritonavir (evidence rating: Alla)<sup>d</sup>
- Darunavir/ritonavir (evidence rating: Alla)<sup>d</sup>
- Dolutegravir (evidence rating: Alb)<sup>d,e</sup>

- Efavirenz (evidence rating: BIIa)<sup>d</sup>
- Raltegravir (evidence rating: Alla)<sup>d</sup>
- Rilpivirine (evidence rating: BIIa)<sup>f</sup>

<sup>a</sup> Listed in alphabetical order by integrase strand transfer inhibitor component. Drug components separated with a virgule indicate these are available as co-formulations.

<sup>b</sup> Not recommended for rapid start because baseline laboratory evaluation results must be reviewed before initiation. Also not recommended for patients with chronic hepatitis B or HIV RNA level above 500 000 copies/mL, and perhaps a CD4 cell count below 200/μL, although the latter is unclear. Close monitoring for adherence and virological response is needed. Not recommended for patients being treated for an active opportunistic infection.

<sup>c</sup> Listed in alphabetical order. Drug components separated with a virgule indicate these are available as co-formulations.

<sup>d</sup> Combined with either tenofovir disoproxil fumarate/emtricitabine or tenofovir disoproxil fumarate/lamivudine. There are data supporting the use of dolutegravir plus tenofovir alafenamide/emtricitabine during pregnancy (evidence rating: Alb).

<sup>e</sup> Women who are taking this drug when they become pregnant do not necessarily have to switch ART.

<sup>f</sup> May be used as a component of the regimen during pregnancy. Abacavir/lamivudine (evidence rating: BIIa) may be used in place of one of the other dual-nucleoside reverse transcription inhibitor components during pregnancy, but data and experience for either are more limited.

weight gain than tenofovir disoproxil fumarate (additional details appear below). The cost of tenofovir disoproxil fumarate–containing regimens is likely to decrease as generic formulations increase in availability, which should result in greater access for a larger number of persons with HIV.

With the recognition that the 2-drug regimen of dolutegravir/lamivudine provides comparable results with the 3-drug therapy (important caveats appear below), the role of abacavir in initial therapy is limited. In addition to the efficacy data for dolutegravir/lamivudine, there are lingering concerns regarding a link between abacavir and an increased risk of myocardial infarction. There is also a requirement to confirm absence of HLA-B\*5701 before abacavir can be safely administered.

**Two-Drug Initial Therapy**

For decades, a combination of 2 nRTIs plus a third agent has been the mainstay of HIV therapy.<sup>1</sup> In recent years, combinations that contain only a single nRTI (lopinavir/ritonavir plus lamivudine) or no nRTI (darunavir/ritonavir plus raltegravir) have shown comparable virological results as 3-drug regimens, but both regimens have disadvantages. Lopinavir/ritonavir plus lamivudine has a larger pill burden and greater toxicity than other regimens and darunavir/ritonavir plus raltegravir is not as effective as a 3-drug regimen in people with a CD4 cell count below 200/μL or an HIV RNA level above 100 000 copies/mL. In the GEMINI studies,<sup>10</sup> dolutegravir plus lamivudine demonstrated rates of viral suppression that were noninferior to the rates of viral suppression achieved with dolutegravir plus tenofovir disoproxil fumarate/emtricitabine. Importantly, no virological resistance was seen in either the 2- or 3-drug regimens. Like many recent initial ART

studies, only a small proportion (8%) of participants in the trials had a CD4 cell count below 200/μL; in this subset, there was a numerically lower rate of viral suppression in the 2-drug group vs the 3-drug group (79% vs 93%, respectively) but the difference was not related to a higher rate of virological failure.

Dolutegravir/lamivudine is recommended as an initial ART regimen (evidence rating: Ala), but with several caveats. First, the GEMINI studies<sup>10</sup> enrolled participants with screening HIV RNA levels below 500 000 copies/mL, so the efficacy of the 2-drug regimen in people with higher HIV RNA levels is unknown. Second, HIV genotypic testing should confirm the absence of resistance to either of the 2 drugs before dolutegravir/lamivudine is initiated. Because the results from resistance testing take several days, this regimen should not be started on the same day of HIV diagnosis. Third, people with hepatitis B co-infection should not receive dolutegravir/lamivudine because lamivudine could select for hepatitis B virus resistance. Fourth, there was a lower treatment response rate in people with CD4 cell counts below 200/μL. Except for these caveats, dolutegravir/lamivudine is an appealing option for the treatment of HIV and it may offer cost or safety advantages over 3-drug regimens. Given the limited use of this regimen in clinical practice to date, clinicians should monitor patients closely to ensure optimal adherence and virological response.

**Other Recommended Initial ART Regimens**

Several other ART regimens are safe and suppress HIV RNA level in the majority of patients who are adherent to therapy (Table 2). These other ART regimens may be chosen for a given patient based on individual clinical characteristics, preferences, financial considerations, or lack of availability of other options.

Table 2. Other Recommended Initial Antiretroviral Therapy (ART) Regimens<sup>a</sup>

Regimens <sup>b</sup>	Potential uses and cautions
<ul style="list-style-type: none"> <li>Darunavir/cobicistat/tenofovir alafenamide/emtricitabine<sup>c</sup></li> <li>Darunavir/cobicistat plus tenofovir disoproxil fumarate/lamivudine<sup>d</sup></li> </ul>	<ul style="list-style-type: none"> <li>Potential use for patients with known or suspected pretherapy multidrug resistance</li> <li>Potential use for patients who have resistance to INSTIs</li> <li>Potential use for patients at high risk of poor adherence<sup>e</sup></li> </ul>
<ul style="list-style-type: none"> <li>Dolutegravir/abacavir/lamivudine</li> </ul>	<ul style="list-style-type: none"> <li>Caution for patients with kidney insufficiency<sup>f</sup></li> </ul>
<ul style="list-style-type: none"> <li>Doravirine/tenofovir disoproxil fumarate/lamivudine<sup>c</sup></li> <li>Doravirine plus tenofovir alafenamide/emtricitabine</li> <li>Doravirine plus tenofovir disoproxil fumarate/lamivudine<sup>c</sup></li> </ul>	<ul style="list-style-type: none"> <li>Potential use for patients who are intolerant to INSTIs</li> </ul>
<ul style="list-style-type: none"> <li>Efavirenz (400 mg or 600 mg) plus tenofovir disoproxil fumarate/lamivudine<sup>c,d</sup></li> <li>Efavirenz (400 mg or 600 mg) plus tenofovir disoproxil fumarate/emtricitabine</li> </ul>	<ul style="list-style-type: none"> <li>Potential use for patients being treated for co-infection with HIV and tuberculosis</li> <li>Potential use for patients who are pregnant or intend to become pregnant</li> </ul>
<ul style="list-style-type: none"> <li>Raltegravir plus tenofovir alafenamide/emtricitabine</li> <li>Raltegravir plus tenofovir disoproxil fumarate/emtricitabine</li> <li>Raltegravir plus tenofovir disoproxil fumarate/lamivudine<sup>d</sup></li> </ul>	<ul style="list-style-type: none"> <li>Potential use for patients at high risk of drug-drug interactions</li> <li>Potential use for patients who are intolerant to other INSTI initial regimens</li> <li>Potential use for patients with child-bearing potential who are trying to conceive</li> <li>Potential use for patients who are sexually active and not consistently using contraception</li> </ul>
<ul style="list-style-type: none"> <li>Rilpivirine/tenofovir alafenamide/emtricitabine<sup>c,g</sup></li> <li>Rilpivirine plus tenofovir disoproxil fumarate/lamivudine<sup>d,g</sup></li> </ul>	<ul style="list-style-type: none"> <li>Potential use for patients who are intolerant to INSTIs</li> <li>Small pill size is an advantage for some patients</li> </ul>

Abbreviation: INSTI, integrase strand transfer inhibitor.

<sup>a</sup> The recommended initial ART regimens appear in Box 2.

<sup>b</sup> The regimens are listed in alphabetical order. Drug components separated with a virgule indicate these are available as co-formulations.

<sup>c</sup> Available as a single-tablet co-formulation.

<sup>d</sup> Available in generic formulations in many countries.

<sup>e</sup> Darunavir has a high barrier to resistance.

<sup>f</sup> Fixed-dose combination should not be used if creatinine clearance rate is below 50 mL/min.

<sup>g</sup> Use this regimen only if pretreatment HIV RNA level is below 100 000 copies/mL and CD4 cell count is 200/μL.

## Important Considerations

### Treatment for Sexually Active Individuals of Childbearing Potential

The optimal HIV treatment for both maternal and child outcomes remains unknown. In Botswana, a small but statistically significant increased risk of neural tube defects was initially observed among infants who were conceived while the mothers were receiving dolutegravir-based regimens compared with the mothers receiving regimens without dolutegravir (mostly efavirenz) or mothers without HIV.<sup>11</sup> However, updated data from this cohort show a reduced risk of neural tube defects over time and the difference is no longer significant compared with other ART regimens.<sup>12</sup> A randomized comparative trial demonstrated that dolutegravir-based regimens initiated during pregnancy led to higher rates of viral suppression at delivery compared with efavirenz. This same study showed that there were fewer adverse pregnancy or infant outcomes with tenofovir alafenamide/emtricitabine than with tenofovir disoproxil fumarate/emtricitabine.<sup>13</sup> Therefore, dolutegravir plus either tenofovir disoproxil fumarate/emtricitabine or tenofovir alafenamide/emtricitabine is recommended as a safe option when started during pregnancy (evidence rating: Alb).

Recommended regimens for pregnant individuals include dolutegravir, raltegravir, atazanavir/ritonavir, darunavir/ritonavir, or efavirenz and each is combined with either tenofovir disoproxil fumarate/emtricitabine or tenofovir disoproxil fumarate/lamivudine. The data summarized above also support the use of dolutegravir plus tenofovir alafenamide/emtricitabine during pregnancy. Rilpivirine or the nRTI pair abacavir/lamivudine may be used during pregnancy, but data and experience are more limited. Insufficient data exist to recommend bictegravir use during pregnancy. Treatment-experienced pregnant women taking an ART regimen not recommended during pregnancy should switch to a recommended regimen after review of geno-

type results and ART history. Raltegravir should be given in its original twice-daily formulation and darunavir/ritonavir should be dosed twice daily once the pregnancy is confirmed. Cobicistat should not be used during pregnancy due to potential suboptimal drug concentrations.

The best regimen to start for individuals of childbearing potential who are not trying to conceive is uncertain. With the understanding that some pregnancies are unplanned, a shared decision-making approach is recommended (evidence rating: AIII). This approach entails communicating the favorable characteristics of the optimal initial ART regimens that include dolutegravir, along with a potentially very small excess risk of neural tube defects and ensuring folate supplementation for women trying to become pregnant. Notifying the patient that the data are insufficient to advise on the safety of bictegravir at the time of conception is also warranted.

### Weight Gain

Initiation of ART often leads to weight gain. In certain individuals, especially those with weight loss directly due to HIV and its complications, this weight gain represents an ART-induced reversal of HIV-associated inflammation, accelerated catabolism, and alleviation of disease-related anorexia, and is considered a return to health. However, ART can induce weight gain that leads to obesity among individuals with HIV who start treatment with a normal or greater baseline weight.<sup>14</sup> Several risk factors for excess weight gain have been identified, including low pretreatment CD4 cell count and high viral load, Black race, and female sex.<sup>15</sup>

Randomized clinical trials of initial therapy demonstrate significant differences in weight gain based on the specific ART regimen.<sup>16-19</sup> Regimens that include INSTIs induce greater weight gain than comparator regimens. Regimens that include dolutegravir

or bictegravir are associated with greater weight gain than regimens that include efavirenz. Among nRTIs, tenofovir alafenamide is associated with greater weight gain than tenofovir disoproxil fumarate or abacavir.

The clinical consequences and the mechanisms inducing the differences in weight gain between regimens remain unknown. Specifically, it is not known whether InSTIs lead to greater weight gain because of fewer adverse effects or due to a direct effect on appetite or metabolism. A placebo-controlled study of PrEP showed that tenofovir disoproxil fumarate may inhibit weight gain, which may partially explain the excess weight gain observed with tenofovir alafenamide vs tenofovir disoproxil fumarate.<sup>20</sup>

The data on weight gain are insufficient to prompt a change in the primary recommendations for initial therapy. Persons with HIV should be counseled about the potential for weight gain and should be given information about diet, exercise, and behavior modifications that minimize this problem.

### Recommended Initial ART in the Setting of Opportunistic Infections

The choice of ART regimen in the setting of opportunistic infections, which has largely remained unchanged since the last report,<sup>1</sup> is guided by the principles articulated for the initiation of ART but also should consider drug-drug interactions associated with agents used for the treatment or prevention of opportunistic infections. The 2-drug regimen dolutegravir/lamivudine has not been studied for initiating ART in persons with HIV who are being treated for an active opportunistic infection and this regimen is not recommended for initial ART in this setting at this time (evidence rating: BIII).

Drug-drug interactions largely affect individuals with HIV and tuberculosis co-infection. Initial ART in people with active tuberculosis and who are receiving a rifamycin-based tuberculosis treatment regimen should include 2 nRTIs plus either efavirenz (600 mg/d), raltegravir (800 mg twice daily), or dolutegravir (50 mg twice daily) (evidence rating: A1a).<sup>21</sup> A pharmacokinetic study in healthy volunteers suggested that tenofovir alafenamide may be administered with rifampin without dose adjustment, although no clinical trials of tuberculosis treatment using tenofovir alafenamide-containing regimens exist.<sup>22</sup> Administration of bictegravir with rifampin is not recommended due to a significant drug-drug interaction (evidence rating: AIIa). Boosted protease inhibitors (PIs) only should be used if an InSTI-based or efavirenz-based regimen is not an option (evidence rating: A1a). If possible, rifabutin (150 mg/d) should be substituted for rifampin if a PI-based regimen must be used (evidence rating: BIII).

A 1-month course of daily rifapentine plus isoniazid was equivalent to 9 months of isoniazid for prevention of tuberculosis in persons with HIV at high risk.<sup>1</sup> Regimens recommended for treatment of latent tuberculosis and HIV co-infection include once-weekly rifapentine and isoniazid for 12 weeks, daily rifampin for 4 months, or daily isoniazid and rifampin for 3 months. The recommended alternative regimens are daily isoniazid for 6 or 9 months or daily rifapentine and isoniazid for 1 month.<sup>23</sup> Rifapentine can be safely administered with an efavirenz-based ART regimen. Dolutegravir-based regimens can be safely used with the once-weekly rifapentine plus isoniazid regimen for 12 weeks for the prevention of tuberculosis.<sup>23</sup>

## When and How to Switch ART Regimens

Recommendations for when and how to switch ART regimens appear in **Box 3**. The most common reasons for switching therapy remain regimen simplification (either to a single-tablet regimen or from a 3-drug to a 2-drug regimen); management or prevention of toxic effects or comorbidities; avoidance or management of interactions with drugs, food, or dietary supplements; and economic factors and considerations.<sup>1</sup>

Switching from older ART regimens is recommended to reduce pill burden and to manage or prevent toxicity and drug-drug interactions, especially in older people with HIV (evidence rating: BIII).<sup>1</sup> Antiretroviral drugs that require boosting should be avoided when not required. Adverse economic consequences may result from switching from older ART (many are now available in generic formulations) to more expensive brand-name regimens. Among people who have been receiving treatment and have at least 6 months of viral suppression, no history of treatment failure, and no evidence of archived resistance mutations, maintenance of viral suppression has been demonstrated after switching to a single-tablet regimen for most fixed-dose combination regimens compared with regimens prior to switching.<sup>1,24</sup>

### Simplification to a 2-Drug Regimen in the Setting of Viral Suppression and Without Drug Resistance

Given the equivalent efficacy, switching to a 2-drug regimen may reduce the potential nRTI-related bone, kidney, and cardiovascular complications and reduce costs. Simplifying initial 3-drug ART regimens to 2-drug regimens has been documented to maintain viral suppression in individuals without prior virological failure or evidence of drug resistance (evidence rating: A1a).<sup>25</sup>

Maintenance of viral suppression was achieved among patients without prior virological failure, nRTI resistance, or hepatitis B co-infection who were receiving a tenofovir alafenamide-based 3-drug or 4-drug regimen and randomized to the 2-drug dolutegravir and lamivudine regimen compared with those continuing the tenofovir alafenamide-based regimen.<sup>25</sup> Cost-effectiveness has been demonstrated for the induction maintenance strategy of dolutegravir/abacavir/lamivudine by switching to dolutegravir/lamivudine in individuals who had viral suppression at 48 weeks. Dolutegravir/lamivudine is recommended if contraindications are excluded (evidence rating: A1a).

The switch to dolutegravir/rilpivirine among individuals without concurrent hepatitis B virus infection, without prior virological failure, and without resistance to dolutegravir or rilpivirine was associated with durable viral suppression for 2 years, improvement in bone mineral density, reduced bone turnover, and improved kidney tubular function.<sup>26</sup> Rilpivirine-associated resistance occurred in less than 1% of participants.

Monthly intramuscular injections of the long-acting combination of cabotegravir and rilpivirine (after a 4-week induction period with daily oral cabotegravir and rilpivirine) were noninferior at 48 weeks to remaining on a stable virologically suppressive regimen of either InSTI-based, nonnucleoside reverse transcriptase inhibitor (NNRTI)-based, or PI-based ART in individuals without prior virological failure or archived InSTI resistance mutations.<sup>27</sup> Monthly injections of this regimen were also noninferior in treatment-naive

**Box 3. Key Recommendations for When and How to Switch Antiretroviral Therapy (ART) Regimens**

- Review of the patient's ART regimen history, regimen tolerability, co-medications, food requirements, cost, and results from prior resistance tests is recommended before any treatment changes are made (evidence rating: A1a).
- HIV viral load assessment is recommended 1 month after switching regimens (evidence rating: BIII).

**Switching When the Patient Has Achieved Viral Suppression**

- Patients with HIV and hepatitis B virus (HBV) co-infection who are switching therapy should continue taking tenofovir alafenamide or tenofovir disoproxil fumarate (evidence rating: AIII) unless these drugs are contraindicated. Switching to a regimen including lamivudine or emtricitabine and excluding tenofovir alafenamide or tenofovir disoproxil fumarate will not maintain suppression of chronic HBV and is not recommended; alternative HBV suppressive therapy is recommended (evidence rating: AIIa).
- In patients with nucleoside reverse transcriptase inhibitor (nRTI) resistance mutations, switching from a boosted protease inhibitor (PI) to a regimen containing a drug with a low genetic barrier to resistance (eg, nonnucleoside reverse transcriptase inhibitor [NNRTI] or raltegravir) is not recommended (evidence rating: A1a).
- In the setting of viral suppression, switching from a 3-drug regimen to an oral 2-drug regimen is an appropriate strategy to manage toxic effects, intolerance, adherence, or patient preference provided both agents are fully active (evidence rating: A1a). Recommended regimens include dolutegravir/rilpivirine (evidence rating: A1a), a boosted PI with lamivudine (evidence rating: A1a), dolutegravir/lamivudine (evidence rating: A1a) or a long-acting injectable 2-drug regimen of cabotegravir and rilpivirine dosed every 4 weeks (evidence rating: A1a) or every 8 weeks (evidence rating: B1b) pending approval by regulatory bodies and availability.
- Monotherapy with boosted PIs or dolutegravir is not recommended (evidence rating: AIIa).

- Review of co-medications is recommended to ensure no change in tenofovir alafenamide dosing is needed (evidence rating: BIII).

**Switching for Virological Failure**

- Resistance testing is recommended while the patient is taking the failing ART regimen (evidence rating: A1a) or within 4 weeks of stopping ART (evidence rating: AIIa).
- Virological failure (defined as HIV RNA level >200 copies/mL) should be confirmed and, if resistance is identified, a prompt switch to another active regimen using the results of current and past resistance testing is recommended (evidence rating: BIIa).
- Adding a single active agent to a failing regimen is not recommended (evidence rating: A1a).
- Dolutegravir plus 2 nRTIs (with  $\geq 1$  active drug determined by genotypic testing) is recommended after initial treatment failure with an NNRTI (evidence rating: A1a).
- A boosted PI plus 2 nRTIs (with  $\geq 1$  active nRTI) is recommended for initial treatment failure of an integrase strand transfer inhibitor-containing regimen (evidence rating: AIII).
- Dolutegravir (dosed twice daily) plus at least 1 fully active other agent is recommended in the setting of raltegravir or elvitegravir resistance (evidence rating: BIII).
- Virological failure due to resistance mutations is rare with PIs (evidence rating: A1a). Support for adherence or an alternative regimen that improves adherence, tolerability, or both is recommended (evidence rating: AIII).
- In the setting of multiclass resistance (3-class resistance), the next regimen should be constructed using drugs from new classes if available (evidence rating: BIII); eg, fostemsavir (evidence rating: A1b) or ibalizumab (evidence rating: BII) with at least 1 additional active drug in an optimized ART regimen.

individuals who had viral suppression after 20 weeks of treatment with dolutegravir/abacavir/lamivudine.<sup>28</sup> Rates of viral suppression approached 95% in both studies.<sup>27,28</sup> Injection site reactions are common, are generally mild to moderate, and rarely result in treatment discontinuation. Most participants preferred the long-acting injectable over their previous regimen. Persons with HIV and poor adherence to care are unlikely to be good candidates for this combination given the potential for prolonged periods of subtherapeutic levels if a dose is missed. Higher doses (eg, 600 mg of cabotegravir or 900 mg of rilpivirine) given every 8 weeks was reported to be noninferior to 4-week dosing at 48 weeks. However, among the 1.5% of people with confirmed virological failure in the every 8-week dosing group, 6 of 8 (75%) developed rilpivirine resistance and 60% had INSTI resistance. These data underscore the need for adherence to the injection schedule for the 8-week dosing regimen, which is not yet approved by regulatory authorities.<sup>29</sup> Either the dosing interval of every 4 weeks (evidence rating: A1a) or every 8 weeks (evidence rating: B1b) is recommended once approved by regulatory bodies and is available (evidence rating: B1b).

Dual-therapy regimens that include a boosted PI (lopinavir, atazanavir, or darunavir) and lamivudine were noninferior to 3-drug regimens for the maintenance of viral suppression in small studies and may be an option when other nRTIs or dolutegravir cannot be used.<sup>1</sup> A 2-drug regimen including lamivudine or emtricitabine is not recommended in individuals with concomitant hepatitis B virus in-

fection, in those with known or archived M184V/I mutations, or in those who are pregnant.

**Treatment Simplification in the Setting of Viral Suppression and Archived Drug Resistance Mutations**

For patients with viral suppression and previous ART treatment failure, simplification of the ART regimen may be more challenging due to the presence of preexisting nRTI, NNRTI, or PI resistance mutations. However, bictegravir/tenofovir alafenamide/emtricitabine or dolutegravir plus tenofovir alafenamide/emtricitabine or abacavir/lamivudine may be effective in patients with an archived M184V/I mutation detected by proviral DNA genotyping (evidence rating: A1a).<sup>30-32</sup> Limited data in a small number of patients only suggest bictegravir/tenofovir alafenamide/emtricitabine may be effective when the K65R mutation is present.<sup>32</sup> More data are needed before this can be recommended.

In people with archived 2-class drug resistance ( $\leq 3$  thymidine analogue-associated resistance mutations but no Q151 mutation complex, T69 insertion complex, or darunavir resistance mutations), elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide combined with darunavir taken once daily effectively maintained viral suppression at rates higher than observed in individuals continuing baseline ART (90% vs 72%, respectively).<sup>1</sup> Darunavir/cobicistat/emtricitabine/tenofovir alafenamide maintained viral suppression to 96 weeks in individuals without a history of

darunavir treatment failure or darunavir resistance mutations who had been switched from a boosted PI plus emtricitabine/tenofovir disoproxil fumarate and is recommended in this setting (evidence rating: Ala).<sup>24</sup>

Among patients with previous virological failure, switching from a boosted PI-based regimen to raltegravir plus 2 nRTIs or elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine is not recommended because of the relative lower barrier to resistance compared with the boosted PI (evidence rating: Ala).<sup>1</sup>

### Adjusting Regimens in the Setting of Treatment of Concomitant Disease

Switching ART regimens is sometimes required due to risk of or established comorbid conditions. Screening for and addressing modifiable risk factors remains as important as switching ART regimens to prevent and manage comorbid conditions.<sup>33</sup>

#### Kidney Disease

The development of proximal tubulopathy while receiving a tenofovir disoproxil fumarate-containing regimen should result in a switch to a tenofovir alafenamide-containing regimen or to dolutegravir/lamivudine to prevent progression to chronic kidney disease.<sup>1</sup> Most InSTIs block the tubular secretion of creatinine resulting in a 10% increase in the estimated glomerular filtration rate but no change in the true glomerular filtration rate. When considering an ART switch from tenofovir disoproxil fumarate it is important to exclude other common causes of kidney dysfunction. For individuals with progressive kidney dysfunction, tenofovir should be avoided, but in instances where this is not feasible, tenofovir alafenamide/emtricitabine can be used when the creatinine clearance rate is above 30 mL/min/1.73 m<sup>2</sup>.<sup>1,34</sup> If the glomerular filtration rate falls below 50 mL/min/1.73 m<sup>2</sup>, most fixed-dose ART formulations are contraindicated and dose adjustment of individual components (eg, lamivudine or emtricitabine) of the regimen may be required.

#### Liver Disease

Among patients with hepatitis C co-infection, drug-drug interactions are an important consideration when selecting an ART regimen. Current InSTI-based ART regimens do not have substantial drug-drug interactions with recommended hepatitis C treatment regimens. Non-InSTI-based ART regimens may require a temporary regimen switch (eg, during the course of hepatitis C treatment) or a permanent switch.

Among patients with cirrhosis (from any cause), reduction in hepatic cytochrome enzymes may result in decreased metabolism of some antiretroviral drugs. Although there are few pharmacokinetic data to support dosing recommendations for most antiretroviral drugs, PIs and InSTIs should be used with caution for patients with severe hepatic impairment (Child-Pugh C disease), and no dose adjustment is required for patients with mild to moderate impairment (evidence rating: BIII). Tenofovir, lamivudine, raltegravir, and rilpivirine do not require dose adjustment in patients with severe hepatic impairment.

#### Cardiovascular Disease

Among patients at moderate to high risk for a cardiovascular event or among those who have experienced a cardiovascular event,

switching from abacavir-based or PI-containing regimens (except atazanavir) is recommended (evidence rating: Alla).<sup>1</sup>

#### Bone Disease

Bone loss is observed with initiation of all ART regimens, and is greater with tenofovir disoproxil fumarate-containing and PI-containing ART. There is less bone loss associated with initiation of InSTI-based ART than with older regimens. In the presence of established osteopenia or osteoporosis and toxicity, a switch from tenofovir disoproxil fumarate-based or PI-based ART is recommended (evidence rating: Ala).<sup>35</sup>

#### Weight Gain

Proactive switching from tenofovir disoproxil fumarate-based to tenofovir alafenamide-based regimens may result in modest weight gain and an increase in lipid levels.<sup>36,37</sup> It is unknown whether ART-induced weight gain translates into significant metabolic and cardiovascular adverse outcomes, or whether the InSTI-induced and tenofovir alafenamide-induced weight gain is reversible after switching regimens.

#### Cancer and Autoimmune Disease

Chemotherapy for a new diagnosis of cancer or the use of immune-based therapy in the setting of transplantation or autoimmune disease may require adjustment of the ART regimen. Any antiretroviral drugs that are metabolized independently of the CYP450 pathway (eg, raltegravir-, dolutegravir- or bicitegravir-based regimens) are recommended to minimize drug-drug interactions (evidence rating: Alla).<sup>1</sup> If chemotherapy-induced severe mucositis is likely to be prolonged, switching ART to a regimen that can be crushed or delivered in a liquid formulation can mitigate swallowing difficulty. Crushing bicitegravir/tenofovir alafenamide/emtricitabine is not recommended.

#### Solid Organ Transplantation

Drug-drug interactions between PIs and boosters with required immunosuppressive medication (especially tacrolimus) cause difficulty in designing an ART regimen. Known drug interactions can be checked on the University of Liverpool HIV Drug Interactions website (<https://www.hiv-druginteractions.org/>). If a switch to a nonboosted regimen is unlikely to maintain viral suppression, more careful monitoring of tacrolimus/cyclosporine levels is recommended (evidence rating: CIII). For individuals without archived drug resistance, the 2-drug combinations of dolutegravir/lamivudine and dolutegravir/rilpivirine will minimize risks of drug-drug interactions and may be used depending on history of virological failure and resistance. In patients with nRTI resistance mutations but no virological failure while receiving an NNRTI regimen, dolutegravir/rilpivirine or dolutegravir/doravirine should maintain viral suppression; however, data are limited with the latter regimen.

#### Virological Failure

In the modern ART era it is uncommon to encounter virological failure, especially among individuals receiving an InSTI-based regimen.<sup>38</sup> Virological failure is defined as a confirmed HIV RNA level above 200 copies/mL on 2 consecutive measurements in an individual receiving ART. In contrast, a virological blip (an isolated increase in HIV RNA levels to <1000 copies/mL with a return to



undetectable levels while receiving ART), is rarely associated with progression to virological failure. Switching ART in this setting is not recommended.<sup>1</sup> The principles and practice of detecting and managing potential reasons for regimen failure (psychosocial or financial circumstances, inconsistent adherence, drug interactions) and construction of a new effective regimen remain unchanged.<sup>1</sup> Collation of all resistance mutations identified by available genotypes, along with the ART history, should be used to inform selection of a new treatment regimen.

For failure of an initial NNRTI-based regimen, dolutegravir plus 1 or 2 active nRTIs was superior to lopinavir plus 2 nRTIs regardless of the presence of an M184V/I mutation found in 80% of study participants and is recommended in this setting (evidence rating: Aa).<sup>39</sup> Bictegravir/tenofovir alafenamide/emtricitabine is likely to have similar activity but there are no data to support such a recommendation.

Poor adherence is the most likely reason for failure of a PI-based regimen, and therefore continuation of the boosted PI-regimen is recommended initially with adherence support rather than switching to a new regimen (evidence rating: Aa). Alternatively, the regimen can be replaced by another boosted PI, dolutegravir plus 1 or 2 active nRTIs, or bictegravir/tenofovir alafenamide/emtricitabine (evidence rating: BIII).

There are no clinical trial data to guide treatment changes for the management of virological failure with initial INSTI regimens. For virological failure after initial raltegravir- or elvitegravir-based regimens in patients with integrase resistance mutations, 50 mg of dolutegravir taken twice daily with at least 1 other active drug may be effective. Alternatively, a boosted PI regimen with 2 nRTIs (at least 1 fully active) is likely to be effective (evidence rating: BIII). Virological failure while receiving bictegravir- or dolutegravir-based regimens occurred rarely in the clinical trials, as did emergence of drug resistance.

For virological failure among patients with a more complex treatment history, therapy with at least 2 fully active drugs from different antiretroviral drug classes is recommended (evidence rating: Aa). Consultation with an expert may be needed in this setting. For individuals with virological failure while receiving a PI-based regimen, it is not necessary to include nRTIs in salvage regimens (ART regimens used when a treatment regimen is no longer effective and standard treatment options are limited) as long as there are 2 or more fully active drugs in the regimen (evidence rating: Aa).<sup>40</sup> In the uncommon setting of virological failure with multidrug resistance,<sup>38</sup> optimization of the ART regimen to keep the HIV viral load as low as possible is desirable. Adding a single active drug to the failing regimen is not recommended (evidence rating: AIIa).

Ibalizumab (an anti-CD4 monoclonal antibody that inhibits HIV cell entry via CD4 binding) is administered intravenously every 2 weeks. Almost 50% of adults with virological failure and multidrug-resistant HIV achieved undetectable HIV RNA levels at 12 months when ibalizumab was used with at least 1 other active drug.<sup>41,42</sup> Although adding ibalizumab to an optimized ART regimen has been lifesaving for some patients, it is not cost-effective for general use.<sup>43</sup>

Fostemsavir, the prodrug of temsavir, binds to the HIV envelope gp120-blocking viral attachment regardless of HIV tropism (an attachment inhibitor). Fostemsavir had durable activity to 96 weeks in the setting of multidrug-resistant HIV with 60% of patients achiev-

ing an HIV RNA level below 40 copies/mL when combined with at least 1 fully active agent.<sup>44</sup> Although ideally used with another fully active drug, approximately one-third of individuals taking fostemsavir without other fully active agents in the ART regimen achieved undetectable viral loads at 96 weeks. Ibalizumab (evidence rating: BIIa) or fostemsavir (evidence rating: Aa) can be used when creating a salvage regimen for individuals with extremely limited treatment options. The prevalence of resistance mutations associated with in vitro resistance to doravirine is lower in ART-experienced patients than the prevalence of resistance mutations associated with other NNRTIs.<sup>45</sup> Doravirine may be used as an additional active agent in this setting but clinical data are lacking.

## Laboratory Monitoring in Individuals With HIV

### HIV Screening

Recommendations for laboratory monitoring of persons with HIV appear in **Table 3**. All persons who have ever been sexually active or injected drugs should be tested for HIV at least once during their lives (evidence rating: AIII). Ongoing risk for HIV should be assessed regularly, and men who have sex with men (MSM), trans-feminine persons, people who inject drugs outside needle sharing programs, and people newly diagnosed with other sexually transmitted infections (STIs) or hepatitis C should be tested every 3 months as long as risk continues (evidence rating: BIII).<sup>49</sup> Screening for HIV is best performed with assays that can detect recent HIV infection (eg, the combined HIV antibody and antigen test or HIV RNA assay).<sup>50</sup> Third-generation HIV antibody and home-based testing is recommended for people who do not have access to testing otherwise (evidence rating: BIIb).

Persons identified with high-risk exposure within the previous 72 hours should be screened for HIV infection, preferably by a rapid HIV antibody test. If this test is negative, then postexposure prophylaxis (PEP) should be offered (evidence rating: AIIa).<sup>51,52</sup> At the time of prescribing PEP, recommended testing includes measurement of the creatinine level, hepatitis B surface antigen, STIs, and a combined HIV antibody and antigen test or HIV RNA assay; however, initiation of PEP should not be delayed while waiting for the test results (evidence rating: AIII). Similarly, persons identified with an ongoing high risk for infection should be screened with a rapid HIV antibody test or a combined HIV antibody and antigen test (additional information appears in the PrEP section). If an initial HIV test is negative, then PrEP should be offered without waiting for confirmatory or other safety or STI testing results (evidence rating: AIII; additional information appears below).

### After HIV Diagnosis

Before starting ART, recommended laboratory monitoring should characterize (1) the HIV stage (using HIV RNA level and CD4 cell count), (2) general health (kidney and liver function, lipid levels, complete blood cell count, blood glucose level, and pregnancy), and (3) any co-infections (viral hepatitis A, hepatitis B, hepatitis C, tuberculosis, and STIs) (evidence rating: AIIa). Unless there is pre-existing kidney or liver damage or a high likelihood of transmitted drug resistance, the results of these tests should not delay the start of ART (evidence rating: AIII); however, follow-up for these test results should occur quickly to ensure safety.

**Table 3. Key Recommendations for Laboratory Monitoring Across the HIV Continuum**

Description of monitoring	Strength of recommendation	Quality of evidence	When HIV negative	PrEP	PEP	At HIV diagnosis	During ART	At virological failure
Rapid HIV antibody test	A	Ila	Yes	Yes (before PrEP)	Yes (before PEP)	No	No	No
Combined HIV antibody and antigen test	A	Ila	Yes	Yes <sup>a</sup>	Yes <sup>a</sup>	No	No	No
HIV RNA test	A	Ia	Yes <sup>b</sup>	Yes	Yes <sup>a</sup>	Yes	Yes	Yes
Measure CD4 cell count	B	III	No	No	No	Yes	Every 6 mo until >250/μL for 1 y and then stop	Yes
HIV RT-PCR genotype test	A	Ia	No	No	No	Yes	No	Yes
HIV integrase genotype test	B	III	No	No	No	Yes <sup>c</sup>	No	If failing ART regimen included an InSTI
Cryptococcal antigen test if CD4 cell count is <100/μL	A	Ilb	No	No	No	Yes	No	No
Safety laboratory tests, and co-infection screening (eg, STI, viral hepatitis)	A	Ila	No	Yes	Yes	Yes	Yes	Yes
Vaccinations	NA	NA	Yes <sup>d</sup>	Yes <sup>d</sup>	Yes <sup>d</sup>	Yes <sup>d</sup>	Yes <sup>d</sup>	Yes <sup>d</sup>

Abbreviations: ART, antiretroviral therapy; InSTI, integrase strand transfer inhibitor; NA, not applicable; PEP, postexposure prophylaxis; PrEP, preexposure prophylaxis; RT-PCR, reverse transcriptase-polymerase chain reaction; STI, sexually transmitted infection.  
<sup>a</sup> Before and after PEP.  
<sup>b</sup> For persons at higher risk.  
<sup>c</sup> If a patient's partner has a failing ART regimen that includes an InSTI.  
<sup>d</sup> Should be updated regularly and include serological screening per current recommendations.<sup>46-48</sup>

For individuals newly diagnosed with HIV who have CD4 cell counts below 100/μL, a baseline serum cryptococcal antigen test is recommended even in people without symptoms suggestive of cryptococcal meningitis (evidence rating: AIIa). This test is highly accurate and inexpensive, and a positive result may facilitate pre-emptive treatment of disseminated cryptococcal disease before the development of cryptococcal meningitis.

Because of high rates of transmitted drug resistance from nRTI, NNRTI, and PI exposure, baseline reverse transcriptase-pro-drug resistance genotype testing is recommended before initiating ART for ART-naive persons (evidence rating: AIIa).<sup>53</sup> Given the low prevalence of transmitted InSTI resistance, InSTI genotyping at baseline is not recommended unless there is suspicion that HIV was transmitted from a partner with InSTI failure (evidence rating: BIII).<sup>54,55</sup> Testing for viral CCR5 tropism is recommended each time before starting maraviroc (unless X4 virus has been previously detected) and testing for HLA-B\*5701 (to be performed only once) is recommended before starting abacavir (evidence rating: AIIa). After HIV diagnosis, the general health screening should be updated, including the vaccination record, the substances used, and any mental health conditions.

**During ART**

Within 6 weeks of starting ART, adherence and tolerability of therapy along with the measurement of HIV RNA level are recommended (evidence rating: AIII). Although suppression of HIV RNA to undetectable levels may occur faster with InSTI-based regimens, it may take up to 24 weeks of continuous therapy.<sup>56</sup> If HIV RNA levels have not declined considerably within 4 to 6 weeks of therapy and adherence appears to be sufficient, then genotypic resistance testing (per the patient's ART regimen) is recommended (evidence rating: AIII).

If the patient continues to have viral suppression, is considered clinically stable, and is adherent to all prescribed medications, HIV RNA levels should be monitored every 3 months until the patient has achieved viral suppression for at least 1 year and monitored every 6 months thereafter (evidence rating: AIII). If an HIV RNA level above 50 copies/mL is detected after a patient previously had viral suppression, then measurement of the HIV RNA level should be quickly repeated and medication adherence and tolerability should be reassessed (evidence rating: AIIa).<sup>1</sup> If HIV RNA levels are above 200 copies/mL on 2 consecutive measurements, then an HIV reverse transcriptase-polymerase chain reaction genotype should be obtained and an integrase resistance test should be performed if the patient was receiving an InSTI (evidence rating: AIII).<sup>55</sup> If plasma HIV genotypic resistance tests are unsuccessful, a proviral DNA analysis may be used (evidence rating: BIIa). Patients with intermittent or persistent low-level viremia between 50 copies/mL and 200 copies/mL should be assessed for treatment adherence, tolerability, and toxicity; however, changing ART regimens is not recommended unless ART toxicity or intolerability are identified (evidence rating: BIII).

While receiving ART, regular age- and risk-appropriate screening for STIs at exposed mucosal sites, anal or cervical dysplasia, tuberculosis, general health issues, and medication toxicity are recommended (evidence rating: AIIa). Hepatitis C screening is recommended at least yearly for persons with ongoing risk, including MSM, persons who use injection drugs, or those who have been

diagnosed with a new STI (evidence rating: BIII). Once viral suppression is achieved and maintained, CD4 cell counts should be measured every 6 months until measurements are above 250 cells/ $\mu$ L for at least 1 year (evidence rating: BIII). After 1 year, CD4 cell counts do not need to be measured unless ART failure is identified or if the patient experiences an immunosuppressive condition (evidence rating: AIII).

The COVID-19 pandemic has disrupted many aspects of medical care. Owing to patients' and practitioners' concerns regarding the risk of acquisition of SARS-CoV-2 infection, the COVID-19 pandemic has created a new normal in medical care. Many outpatient visits are being conducted via telemedicine, which can create barriers for laboratory testing and access to other point-of-care services within the clinic. Thus, adequate care delivery will require robust telemedicine systems and additional practices to ensure appropriate laboratory monitoring. Many clinics have made accommodations for these gaps, but the gaps are mostly addressed on an individual basis.

## Prevention of HIV Infection

Maximizing prevention of HIV transmission requires a multimodal approach. Crucial to success is wide dissemination of information and activities that support immediate or early ART treatment in persons with HIV (evidence rating: AIIa), which eliminates sexual transmission once viral load is undetectable for 6 months and remains undetectable (evidence rating: AIIa). Condoms are recommended for all genital penetrative sex acts (evidence rating: AIIa) to prevent other STIs. Testing for and treatment of bacterial STIs, male medical circumcision for heterosexual males (in areas with generalized epidemics), and harm reduction interventions such as opioid substitution therapy and needle exchange services should be used when available.

Recommendations for the use of PrEP appear in **Box 4**. PrEP for HIV prevention should be discussed with all sexually active adults and adolescents and individuals who inject drugs (evidence rating: AIII). PrEP has high levels of protection when used as prescribed and has a powerful influence on reducing incident HIV transmission events at the population level when implemented broadly in locally defined at-risk populations.<sup>57-60</sup> Identification of at-risk individuals for whom PrEP is recommended requires individualized approaches that take into consideration past and future anticipated risk. Such populations include but are not limited to MSM, men who have sex with men and women, and those who do not use condoms; transgender individuals; individuals from or whose partners are from any location where HIV incidence is 3% or greater<sup>61</sup>; and individuals who have traded sex for money, goods, or services; individuals who have multiple partners; individuals who have had STIs; individuals who have been or their partners have been incarcerated; and individuals who share injection drug needles, syringes, or other equipment.

### PrEP Regimens

Tenofovir disoproxil fumarate/emtricitabine is the recommended oral PrEP regimen for all populations at risk (evidence rating: AIIa). For MSM, initiation with a double dose (2 tablets) of tenofovir disoproxil fumarate/emtricitabine on the first day followed by

once daily dosing is recommended to reduce time to anticipated maximal protection, which is achieved within 24 hours of double dose ingestion; and at cessation or interruption, tenofovir disoproxil fumarate/emtricitabine should be continued for 2 days after the last at-risk exposure (evidence rating: AIIa). For others at risk, maximum protection is likely to be achieved in approximately 7 days after initiation; and at cessation or interruption, tenofovir disoproxil fumarate/emtricitabine should be continued for 7 days after the last at-risk exposure (evidence rating: BIIa). Daily tenofovir disoproxil fumarate/emtricitabine is recommended for at-risk individuals who are pregnant or breastfeeding (evidence rating: AIIa).

The 2-1-1 (or on demand) oral dosing schedule is recommended only for MSM (evidence rating: AIIa).<sup>1,61</sup> The 2-1-1 dosing schedule requires a double dose of tenofovir disoproxil fumarate/emtricitabine taken 2 to 24 hours prior to sexual activity, a second (single) dose 24 hours later, and a final (single) dose 24 hours after that. Daily (single) doses are therefore continued until 48 hours after the last sexual contact. Prescribing should be sufficient to accommodate daily dosing over the desired time interval of the prescription.<sup>1</sup> Daily tenofovir alafenamide/emtricitabine<sup>20</sup> is recommended for the subset of MSM with a creatinine clearance rate between 30 mL/min and below 60 mL/min who have a history of osteopenia or osteoporosis, or who are at high risk for these complications (evidence rating: BIIa).

The efficacy of tenofovir alafenamide/emtricitabine is not superior to tenofovir disoproxil fumarate/emtricitabine; clinical correlates of kidney biomarker differences and dual-energy X-ray absorptiometry differences have not been demonstrated. There are no data supporting event-driven use of tenofovir alafenamide/emtricitabine or tenofovir alafenamide/emtricitabine in individuals other than MSM. Tenofovir disoproxil fumarate/lamivudine (evidence rating: BIII) and tenofovir disoproxil fumarate (evidence rating: BIIa) alone are not recommended as PrEP agents because of absence of and less compelling efficacy data, respectively.

In a randomized clinical trial, long-acting cabotegravir injected every 8 weeks was compared with daily oral tenofovir disoproxil fumarate/emtricitabine PrEP in 4570 MSM and transgender women. The study was stopped by an independent data safety and monitoring board for early determination of superiority and a comparable safety profile (other than injection site reactions). A similarly designed comparative trial in cisgender women is nearly fully enrolled and ongoing in Sub-Saharan Africa (NCT03164564).

Long-acting injectable cabotegravir (pending approval by regulatory agencies and availability) is recommended as PrEP for cisgender men and transgender women who have sex with men (evidence rating: AIIa); injections are to be provided at 8-week intervals with 600 mg administered intramuscularly after an initial 4-week interval separating the first 2 injections (evidence rating: AIIa).<sup>62</sup> An oral lead-in period to establish tolerability is optional (evidence rating: BIIb).

### Baseline Testing

The goal of baseline laboratory testing is to prevent the administration of PrEP in persons with undiagnosed acute or chronic HIV. If a combined HIV antibody and antigen test performed within 7 days of the first visit was negative, and there were no symptoms of primary HIV infection, PrEP could be initiated at the first visit

**Box 4. Key Recommendations for the Use of Preexposure Prophylaxis (PrEP) and Postexposure Prophylaxis (PEP)**

- PrEP is recommended for individuals at risk for HIV infection (evidence rating: A1a)
- Initiation of PrEP is recommended as soon as feasible for individuals who have chosen to use it (evidence rating: AIII)
- Tenofovir disoproxil fumarate/emtricitabine once daily is recommended for oral PrEP (evidence rating: A1a).
- For men who have sex with men (MSM), a double dose (2 pills) of tenofovir disoproxil fumarate/emtricitabine is recommended on the first day (evidence rating: A1a)
- For MSM with or at risk for kidney dysfunction, osteopenia, or osteoporosis, daily tenofovir alafenamide/emtricitabine is recommended (evidence rating: B1a)
- Oral PrEP dosing using the 2-1-1 (or on-demand) method is recommended only for MSM (evidence rating: A1a)
- Injectable cabotegravir every 8 weeks (see text for details) is recommended (pending approval by regulatory agencies and availability) as PrEP for cisgender men and transgender women who have sex with men (evidence rating: A1b)<sup>a</sup>

**Recommended Monitoring for Oral PrEP<sup>a</sup>****Prior to Initiation**

- Combined HIV antibody and antigen testing (HIV RNA level if clinical suspicion of acute HIV)<sup>b</sup> (evidence rating: A1a)
- Serum creatinine level (evidence rating: A1a)
- Hepatitis B surface antigen (evidence rating: A1a)
- Hepatitis C IgG antibody (if not known to be previously positive; if known positive, hepatitis C virus RNA should be confirmed if not recently known; evidence rating: A1a)
- Hepatitis A IgG antibody for MSM and people who inject drugs (if not known to be immune; evidence rating: A1a)
- Genital and nongenital *Neisseria gonorrhoea* and *Chlamydia trachomatis* testing by nucleic acid amplification test (NAAT) (evidence rating: A1a)
- Syphilis testing (evidence rating: A1a)

**During PrEP**

- At 1 month:
  - Combined HIV antibody and antigen test (evidence rating: BIII)
- Quarterly:
  - Combined HIV antibody and antigen test (evidence rating: A1a)
  - Estimated creatinine clearance rate (at first quarterly visit and annually thereafter; evidence rating: A1a); every 3 to 6 months for patients with or at risk for kidney injury (evidence rating: B1a)

- Genital and nongenital *N gonorrhoea* and *C trachomatis* testing by NAAT (evidence rating: A1a)
- Syphilis testing (evidence rating: A1a)
- Pregnancy testing for individuals of childbearing potential (evidence rating: A1a)
- Annually:
  - Combined HIV antibody and antigen test (evidence rating: A1a)
  - Estimated creatinine clearance rate (evidence rating: A1a)
  - Hepatitis C virus antibody test (every 3-6 months for people who inject drugs and MSM who use recreational drugs at the time of sex if liver function test results are abnormal) (evidence rating: B1a)
- For individuals who have ceased PrEP for 7 or more consecutive days, the combined HIV antibody and antigen test is recommended prior to restarting PrEP (evidence rating: BIII)
- In the setting of substantial nonadherence to PrEP<sup>c</sup> and high-risk exposure, discontinuation of PrEP and initiation of a 28-day course of 3-drug PEP is recommended (evidence rating: CIII)
- Use of exogenous estrogens or androgen blockers by transfeminine persons may result in a reduction of approximately 30% in tenofovir/tenofovir metabolite concentrations and reduced protection is possible; additional measures to support maximal adherence to daily dosing is recommended (evidence rating: BIII)

**For PEP**

- A 3-drug ART regimen is recommended for PEP within the first 24 hours (ideally) to 72 hours after an exposure and continued for 28 days (evidence rating: B1a)
- In the event of HIV acquisition while receiving PrEP, a transition to a dolutegravir-, bicitegravir-, or ritonavir-boosted darunavir-based regimen is recommended initially (evidence rating: A1b), which can be subsequently tailored according to clinical resistance test results

<sup>a</sup> Laboratory-based testing unless otherwise indicated. Monitoring recommendations for injectable PrEP appear in Box 5.

<sup>b</sup> PrEP should not be initiated until HIV RNA test results confirm uninfected status for HIV in the setting of clinical suspicion or clinical signs or symptoms consistent with acute or primary HIV infection (evidence rating: A1a).

<sup>c</sup> Details regarding definition of substantial nonadherence appear in the text.

(ie, same day) (evidence rating: B1a). If the test result was not available, then a rapid point-of-care test should be performed at the first visit, and PrEP started only if the test result is negative; however, a laboratory-based HIV antibody and antigen test should also be performed.

If there is clinical suspicion of acute HIV infection, HIV RNA testing should be performed and PrEP withheld pending the test results (evidence rating: A1a). Administration of a fully suppressive ART regimen (early treatment) is recommended in cases where clinical suspicion is extremely high while awaiting confirmatory test results (evidence rating: AIII). Administration of early ART has the added advantages of providing supererogatory PrEP activity while awaiting laboratory results and not missing prevention opportunities.

Additional testing that should be ordered prior to PrEP initiation includes serum creatinine level, hepatitis B surface antigen,

hepatitis C antibody (if not previously known to be positive), and genital and nongenital *Neisseria gonorrhoea* and *Chlamydia trachomatis* testing by a nucleic acid amplification test, and syphilis testing. PrEP can be administered prior to these results returning. People who inject drugs and MSM should be tested for hepatitis A if not previously known to be immune. All nonimmune individuals should be offered hepatitis A and B vaccination (evidence rating: A1a); however, 2-1-1 PrEP is not recommended for individuals testing positive for the hepatitis B surface antigen.

**PrEP Initiation**

PrEP should be initiated as soon as feasible in individuals choosing to use it (evidence rating: BIII). For oral PrEP, no more than a 30-day supply should be prescribed initially and 90-day supplies are recommended thereafter (evidence rating: BIII). A visit is recommended 30 days after initiation with repeated HIV antibody and

antigen testing and quarterly thereafter. Among patients who are deemed stable, on time with refills, and doing well, telemedicine visits may substitute for in-person visits, assuming required laboratory testing can be completed remotely and results will be available for the visit.

### Considerations in the Setting of Recent Exposure

If a PrEP candidate reports a high-risk exposure without condom use within the past 72 hours, a 3-agent course of PEP for 1 month is recommended, followed by seamless simplification to a 2-agent PrEP regimen (evidence rating: AIII). Combined HIV antibody and antigen testing and HIV RNA testing at the conclusion of PEP treatment should yield negative results. If an exposure is reported more than 72 hours from the clinical visit, PrEP should be initiated according to the above guidelines.

### Monitoring

At the 1-month visit after initiation of oral PrEP, a combined HIV antibody and antigen test should be performed (evidence rating: AIII). At the first quarterly follow-up visit, the estimated creatinine clearance rate should be calculated and the creatinine clearance rate should be evaluated annually thereafter (evidence rating: AIIa). Patients at increased risk for kidney injury, including those older than aged 50 years, those with a prior creatinine clearance rate below 90 mL/min before PrEP initiation, and those with comorbidities predisposing them to kidney dysfunction (diabetes, hypertension) should be monitored every 3 to 6 months (evidence rating: BIIa).

Hepatitis C virus antibody should be tested annually, and more frequently (eg, every 3-6 months) in people who inject drugs or MSM who engage in sex while using drugs. If there is clinical suspicion of hepatitis, or if incidental liver function abnormalities are found, a workup for all nonimmune types of viral hepatitis is recommended (evidence rating: BIIa). Laboratory-based HIV antibody and antigen testing, genital and nongenital *N gonorrhoea* and *C trachomatis* nucleic acid amplification testing, and syphilis serology testing should be performed quarterly (evidence rating: AIIa), with adjustments based on individual risk. Routine testing for *Mycoplasma genitalium* in asymptomatic individuals is not recommended (evidence rating: BIII). Interim recommendations for monitoring specifically for long-acting cabotegravir outside assessments for HIV, STIs, and hepatitis appear in Box 5.

The COVID-19 pandemic has disrupted many aspects of daily living and medical care and PrEP is similarly prone to disruption.<sup>63</sup> Some PrEP users may be less sexually active due to physical distancing, whereas others may maintain or even increase sexual activity during shelter-in-place mandates. Standard guidance for quarterly follow-up for HIV and STI testing and oral PrEP medication dispensation is recommended, but if clinical services are limited or unavailable, or patient transit to clinical locations is infeasible or impractical, leverage of home-based HIV, STI, or both types of testing as locally available is appropriate, with concomitant telehealth follow-up for discussion of test results and support. Treatment of incident STIs should follow standard-of-care treatment regimens. If in-person and remote laboratory assessments are not available, extending oral PrEP medication provision for up to 6 months at a time is reasonable. Such decisions should be individualized based on careful review of previous adherence patterns and

#### Box 5. Interim Guidance on Monitoring for Injectable Cabotegravir as Preexposure Prophylaxis (PrEP)

- Intramuscular gluteal injections with 600 mg of cabotegravir every 8 weeks after an initial 4-week interval between the first 2 injections (evidence rating: AIIb)
- Rapid point-of-care HIV testing should be done on the day of each injection prior to the provision of the injection; the combined antibody and antigen test should be performed and sent to the laboratory but injections should not be delayed pending the results (evidence rating: AIIb)
- If an injection is missed, resume as soon as possible after HIV testing results are available (same algorithm as above; evidence rating: AIIb)
- If an injection is 8 or more weeks late from its due date after HIV testing results are available, the first 2 injections should again be separated by 4 weeks before returning to the 8-week interval (evidence rating: AIIb)
- Sexually transmitted infection testing as with oral PrEP but every 4 months (every second injection) (evidence rating: AIIa)
- Liver enzyme tests should be administered every 6 months (evidence rating: BIIb)
- For discontinuation of injectable PrEP if an individual is still at risk for HIV infection, the patient should transition to another recommended PrEP regimen (evidence rating: AIII)
- If seroconversion occurs, acquire genotypic testing including for integrase resistance and begin a protease inhibitor or nonnucleoside reverse transcriptase inhibitor-based antiretroviral regimen (evidence rating: BIII)
- Injection site reactions should be managed aggressively with topical and systemic analgesics and hot or cold packs (evidence rating: AIIb)

refill requests, ongoing inconsistent condom use during sexual activity, and demonstrated clinical stability of serum creatinine levels or creatinine clearance rate (evidence rating: AIII).

### Persistence and Retention

Patients who discontinue PrEP because their self-assessed risk profile has changed and they no longer consider themselves at risk for HIV acquisition should have those assumptions reviewed and discussed by a practitioner (evidence rating: BIII) and be reminded about the efficacy of PrEP, options for PEP, and that use of condoms should be resumed. Patients who discontinue PrEP use due to economic or structural barriers such as loss of insurance, complexity of attending visits or accessing required laboratory testing, adverse effects, or stigma or medical mistrust should have individualized assistance directed at minimizing or eliminating such barriers. Individuals persistently at risk for HIV acquisition who discontinue PrEP have high rates of HIV acquisition (evidence rating: BI). Patients who have ceased daily PrEP for 7 consecutive days or longer should be retested for HIV using a laboratory-based antibody and antigen test prior to restarting PrEP (evidence rating: BIII).

### Adherence Support Strategies

Individuals with challenges to adherence either by self-report or refill timing should be provided individualized counseling to minimize or eliminate barriers. Those who are willing to use technology should be considered for alarms, pill boxes, electronic reminders, or automated text messaging services (evidence rating: BIIa).

**Box 6. Recommendations for Polypharmacy, Frailty, and Cognitive Function Screening for Older People With HIV**

- Close and sustained attention to polypharmacy is recommended in the management of older people with HIV (evidence rating: AIII)
- Assessment of mobility and frailty is recommended for patients aged 50 years or older using a frailty assessment that is validated in all persons with HIV (evidence rating: BIa); the frequency of frailty assessment is guided by the baseline assessment and should be more frequent (every 1-2 years) in patients who are frail or before becoming frail, and less frequent (up to 5 yearly) in patients who are robust (evidence rating: BIII)
- In patients who are frail or prefrail, management of polypharmacy, referral for complete geriatric assessment, exercise and physical therapy, and nutrition advice is recommended (evidence rating: AIII)
- Routine assessment of cognitive function every other year using a validated instrument is recommended for people with HIV who are older than 60 years (evidence rating: BIII)

**Postexposure Prophylaxis**

Although most effective within 24 hours after exposure, PEP initiation with 3-drug ART is generally recommended up to 72 hours after an exposure and should be continued for 28 days (evidence rating: BIa) unless absence of HIV infection in the source individual is confirmed. PEP reduces HIV acquisition by 80% to 90%.<sup>64</sup>

In the setting of substantial nonadherence to PrEP, discontinuation of PrEP and initiation of a 28-day course of PEP is recommended if high-risk exposures are reported (evidence rating: CIII). For daily PrEP users, substantial nonadherence may be defined as fewer than 4 of 7 doses per week on average taken for MSM and transgender women, and fewer than 6 of the past 7 doses per week taken for cisgender women, people who inject drugs, and heterosexual men (evidence rating: CIa).

**Considerations for Transfeminine Individuals**

Use of exogenous estrogens or androgen blockers may produce up to a 27% reduction in tenofovir/tenofovir metabolite concentrations in blood plasma and tissue.<sup>65</sup> The clinical importance of these reduced concentrations is unclear. Additional measures to support maximal adherence to daily dosing is recommended (evidence rating: BIII).

**Testing and Diagnostic Considerations in the Use of Antiretroviral Drugs for Prevention**

The use of PrEP agents can attenuate or delay HIV seroconversion diagnostic assays, including antigen, antibody, and nucleic acid detection. Reactive test results, in contrast, may represent true HIV infection or false-positive results. These scenarios are challenging to differentiate. A reactive rapid point-of-care HIV assay should be confirmed by a combined antibody and antigen testing and subsequent confirmation with HIV RNA testing (evidence rating: AIII). If such tests are not available, multiple rapid point-of-care assays should be used to adjudicate initial results. In the event of discrepant results, repeat testing using assays that evaluate antibodies to distinguish HIV antigens should be used.

Clinical management decisions should be predicated on the pretest probability of infection and the pattern of HIV diagnostic test reactivity. Management may range from cessation of PrEP agents

for 3 to 4 weeks followed by retesting, intensifying to a fully suppressive combination ART regimen (if clinical suspicion is high for acute HIV infection), or continuing PrEP agents if suspicion for false-positive testing is high. Expert consultation is recommended for complicated cases (eg, with the National Clinician Consultation Center).<sup>66</sup>

**Choice of ART in the Setting of HIV Acquisition While Taking PrEP**

The majority of HIV acquisitions in the context of PrEP use occur among individuals with poor medication adherence, and, therefore, most infection is with wild-type HIV. Even if M184V or K65R/M184V variants are present, dolutegravir-based, bictegravir-based, or darunavir-based regimens boosted with ritonavir or cobicistat in combination with tenofovir disoproxil fumarate or tenofovir alafenamide plus emtricitabine or lamivudine would still be expected to achieve high rates of viral suppression (evidence rating: AIIb). The treatment regimen should be adjusted based on the genotype results prior to ART initiation.

**Aging and HIV**

Owing to effective ART, the lifespan of people with HIV is increasing<sup>67-70</sup> and approaches that of people without HIV.<sup>71</sup> However, people with HIV who are in their sixth and seventh decade of life are at higher risk of poorer health outcomes.<sup>67,68,72</sup> Despite achieving durable viral suppression, older persons with HIV are at increased risk of cardiovascular disease, chronic kidney disease, neurocognitive impairment, and mental health disorders, all of which may be associated with polypharmacy and frailty syndrome (**Box 6**). In addition, loneliness, social isolation, and stigma are associated with poorer outcomes in this population.

**Polypharmacy**

Among persons with HIV, comorbid conditions appear to occur at a younger age and polypharmacy is present earlier than in people without HIV.<sup>73,74</sup> Commonly prescribed medications in older persons with HIV include lipid-lowering agents, antihypertensive agents, antidepressants, analgesics (nonopioid and opioid), hypoglycemic agents, proton pump inhibitors, and steroid and nonsteroid inhalers.<sup>75</sup>

A common complication of polypharmacy is drug-drug interactions between antiretroviral drugs and commonly used drugs. Most notably, pharmacological boosters, such as ritonavir and cobicistat, inhibit CYP3A4, an enzyme that metabolizes many medications, including statins, inhaled and injectable steroids, and phosphodiesterase type 5 inhibitors (eg, sildenafil).<sup>74</sup> INSTIs must be dosed separately from multivalent cations (eg, calcium, magnesium, aluminum, or iron) for optimal absorption. It is essential to check for drug interactions prior to initiating ART and, conversely, when starting a new drug for another condition among individuals receiving ART. All persons with HIV should be cautioned not to initiate over-the-counter medications without first checking with their HIV clinician.

Polypharmacy in persons with HIV may result in overlapping toxic effects between antiretroviral drugs and other drugs. For example, efavirenz may result in neuropsychiatric effects among individuals taking psychotropic medications or in people with neurocognitive impairment, and INSTIs have been associated with

insomnia. Polypharmacy may lead to an increased risk of ART non-adherence owing to pill fatigue or confusion among older individuals taking numerous medications. Close and sustained attention to polypharmacy is recommended in the management of older persons with HIV (evidence rating: AIII).<sup>75</sup>

### Frailty

HIV is an independent predictor of incident frailty and as persons with HIV age, they are more prone to frailty.<sup>76-79</sup> Frailty is associated with increased falls, hospitalization, and mortality. There is no gold standard method used to assess frailty.<sup>76-80</sup> The Fried Frailty Phenotype and the Frailty Index are the most frequently used. The Short Performance Physical Battery, which is used to assess physical capacity, and the Edmonton Frail Scale are feasible to administer in the clinic (eTables 4 and 5 in the Supplement).<sup>81</sup> The frailty state is dynamic; people can transition between the stages of frail, pre-frail, and not frail (robust) with treatment of comorbidities, improved physical function (strength and balance), and better nutrition.<sup>80</sup> Identifying frailty is the first step in the implementation of a range of interventions to prevent further functional decline and improve the quality of life and quality of HIV care.

Assessment of mobility and frailty is recommended at aged 50 years and older using a frailty assessment that is validated in persons with HIV (evidence rating: BIa). The frequency of frailty assessments is guided by the baseline assessment and should be more frequent (every 1-2 years) in individuals who are frail or prefrail and less frequent (up to every 5 years) in those who are robust (evidence rating: BIll). In individuals who are frail or prefrail, management of polypharmacy, referral for complete geriatric assessment, exercise and physical therapy, and nutrition advice is recommended (evidence rating: AIII).<sup>80</sup> Healthy aging may require lifestyle changes for many persons with HIV, including cessation of smoking and reduction in the use of alcohol and recreational drugs.

### Neurocognitive Impairment, Mental Health, and Stigma

Persons with HIV are more likely to have neurocognitive impairment than people without HIV.<sup>82</sup> A case-control study found that persons with HIV older than aged 55 years were at higher risk for neurocognitive impairment than age-matched controls. The largest proportion of cases had asymptomatic neurocognitive impairment.<sup>79</sup> Although there is no specific treatment for neurocognitive impairment, early recognition by clinicians can affect patient management. Periodic assessment of cognitive function using a validated instrument is recommended for persons with HIV who are older than aged 60 years (evidence rating: BIll).

Loneliness and social isolation in persons with HIV is associated with depression, anxiety, poorer cognition, decreased quality of life, and a higher risk of hospitalization and death.<sup>79,83,84</sup> Loneliness and social isolation are common in older persons with HIV due to diminishing social networks, especially among individuals who identify as lesbian, gay, bisexual, transgender, queer, gender diverse, and in those with smaller or nonexistent family networks. Larger social networks, as measured by the Lubben Social Network Scale, were associated with better physical function and greater purpose in life, suggesting that interventions to increase social interactions might have broad effects.<sup>85</sup>

Interactions are complex between stigma and health parameters. Among women with HIV, stigma associated with HIV status,

sex, or race was associated with worse mental and physical health-related quality of life. This was mediated, in part, by social support and financial status.<sup>86</sup> Stigma also was associated with cognitive dysfunction and decreased physical function in older Canadian men with well controlled HIV.<sup>87</sup> Interventions to address stigma could result in improved quality of life as well as improved clinical outcomes.

### Cost

HIV medications are costly, accounting for a high proportion of the costs associated with HIV care. Antiretroviral regimens in resource-rich countries cost up to \$48 000 per month,<sup>88</sup> whereby in resource-limited countries the cost of the same regimens are as low as \$27 per month.<sup>89</sup> In some countries, the price of HIV treatment has increased faster than the rate of inflation, making this an ever-increasing challenge in clinical care.<sup>87</sup>

The high cost of medicines can be a deterrent to successful therapy. In a study of 3948 patients in the US, 7% of the participants reported using cost-saving practices that would lead to sub-optimal adherence, such as skipping doses, taking less medication, and delaying pharmacy refills.<sup>90</sup> Those reporting such practices had a lower rate of engagement in care and had a significantly lower likelihood of viral suppression. By contrast, other studies have shown that reducing patient costs can improve adherence to treatments for many chronic conditions.<sup>91</sup>

Although the per-capita costs of medications are higher in the US than in other countries, studies done in diverse socioeconomic settings have demonstrated a correlation between higher out-of-pocket costs and lower adherence. Hence, although the first priority for clinicians is finding the most effective and safest treatments for their patients, it is also essential to assess issues related to the cost. Strategies to reduce treatment costs include prescribing generic antiretroviral drugs when available, splitting up co-formulations (providing this does not reduce adherence or increase co-pays), and assisting with applications for government- and industry-funded patient assistance programs.

### Ending the HIV Epidemic

Efforts to end the HIV epidemic began in 2014 with the 90-90-90 initiative, whereby 90% of people living with HIV would know their status, 90% of those individuals would be receiving treatment, and 90% of those receiving treatment would achieve viral suppression by 2020.<sup>92,93</sup> Although achievement of the 90-90-90 initiative will not end the HIV epidemic, population-based studies provide strong evidence that achievement of 90-90-90 goals leads to decreases in HIV incidence and mortality<sup>94</sup> and this construct has been useful to measure progress across the world. Important gains toward achieving those targets have been made globally: 79% (range, 67%-92%) of persons with HIV know their status, 78% (range, 69%-82%) have access to treatment, and 86% (range, 72%-92%) have achieved viral suppression. This means that 54% of persons with HIV worldwide have achieved viral suppression, and that the gap to achieving 73% of persons with HIV achieving viral suppression is approximately 7.7 million people.<sup>95</sup> Despite this progress, it is clear that the 90-90-90 goals will not be achieved globally by the end of 2020.

However, some countries that have already reached 90-90-90 are now raising the bar to 95-95-95 and incorporating PrEP because this will be necessary to end HIV transmission in high-burden countries.<sup>96</sup>

In February 2019, a commitment was made to end the HIV epidemic in the US with goals of reducing the 40 000 new infections per year by 75% within 5 years and by 90% within 10 years.<sup>97</sup> Clinicians around the world can contribute to ending the HIV epidemic by routinely testing for HIV in clinical settings, rapidly linking persons with HIV to care and prevention services, supporting patients so they can continue receiving ART and continue to have viral suppression, and prescribing PrEP so that people at highest risk can avoid acquiring HIV.

## New Directions and Emerging Trends

Many new therapies are being developed, most of which focus on novel agents that work through new mechanisms of action, have prolonged serum half-lives, or both. A list of selected agents in development appears in eTable 6 in the [Supplement](#).

In addition, the COVID-19 pandemic has had tremendous effects on all individuals worldwide, including persons with HIV. Whether HIV is an independent risk factor for worse COVID-19 outcomes is still under evaluation. Comorbidities that are known to increase the risk of severe COVID-19, such as increasing age, cardiovascular disease, obesity, diabetes, chronic lung disease, and smoking, are common among persons with HIV. For all these reasons, persons with HIV should be prioritized for SARS-CoV-2 testing and closely monitored for complications.

Persons with HIV should be counseled regarding measures to prevent COVID-19 such as wearing a mask, physical distancing, avoiding crowds greater than 10 people, and hand hygiene. Uninterrupted access to ART should be ensured, and 90-day rather than 30-day refills are recommended (evidence rating: BIII).

Persons with HIV and active SARS-CoV-2 infection should receive the same treatment as people without HIV (evidence rating: AIII). HIV status should not influence triage of lifesaving interventions. Studies regarding drug-drug interactions with common antiretroviral medications are underway and patients should be included in clinical trials whenever possible.<sup>98</sup> There is no evidence that any particular antiretroviral drug is clinically active against SARS-CoV-2. For this reason, persons with HIV should not change their ART regimen in the hope that any specific antiretroviral drug will prevent or treat COVID-19 (evidence rating: AIII).

## Limitations

These recommendations have some limitations. First, scientific advances and new therapies in HIV medicine are continually emerging. It is inevitable, therefore, that changes will emerge during the interval between updates, such as the anticipated availability of long-acting antiretroviral drugs for HIV treatment and prevention. Yet the panel expects that the principles set forth in this guideline will remain durable and relevant to these new situations.

Second, the recommendations are the result of a review of articles listed in PubMed and EMBASE and abstracts presented at relevant scientific conferences. Data that were not presented at conferences and are now in press may not be included in the evidence used by the panel.

Third, these guidelines were developed based on clinical care in high- and medium-income countries and thus the recommendations may not necessarily be applicable to resource-limited settings.

## Conclusions

Advances in HIV prevention and management with antiretroviral drugs continue to improve clinical care and outcomes among individuals at risk for and with HIV.

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**Author Affiliations:** University of Alabama at Birmingham (Saag); Harvard Medical School and Massachusetts General Hospital, Boston (Gandhi); Monash University and Alfred Hospital, Melbourne, Australia (Hoy); University of California, Los Angeles (Landovitz); AIDS Research Consortium of Atlanta, Atlanta, Georgia (Thompson); Harvard Medical School and Brigham and Women's Hospital, Boston, Massachusetts (Sax); University of California, San Diego, La Jolla (Smith, Benson); San Francisco Department of Public Health and University of California, San Francisco (Buchbinder); Emory University School of Medicine, Atlanta, Georgia (del Rio); School of Medicine, University of North Carolina, Chapel Hill (Eron); University Hospital Cologne, Cologne, Germany (Fätkenheuer); University Hospital Zurich and Institute of Medical Virology, University of Zurich, Zurich, Switzerland (Günthard); University of Paris and Saint-Louis/Lariboisière Hospitals, APHP, Paris, France (Molina); International Antiviral Society—USA, San Francisco, California (Jacobsen); University of California, San Francisco (Volberding).

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**Concept and design:** Saag, Gandhi, Hoy, Landovitz, Thompson, Sax, Smith, Benson, del Rio, Eron, Fätkenheuer, Günthard, Jacobsen, Volberding.

**Acquisition, analysis, or interpretation of data:** Saag, Hoy, Landovitz, Thompson, Sax, Smith, Benson, Buchbinder, del Rio, Fätkenheuer, Günthard, Molina, Volberding.

**Drafting of the manuscript:** Saag, Gandhi, Hoy, Landovitz, Thompson, Sax, Smith, Benson, del Rio, Fätkenheuer, Jacobsen, Volberding.

**Critical revision of the manuscript for important intellectual content:** Saag, Hoy, Landovitz, Thompson, Sax, Smith, Benson, Buchbinder, Eron, Fätkenheuer, Günthard, Molina.

**Statistical analysis:** Fätkenheuer.

**Obtained funding:** Jacobsen.

**Administrative, technical, or material support:** Saag, Sax, Smith, Fätkenheuer, Jacobsen, Volberding.

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