Prevention and Treatment of HIV-1 Infection: Guidelines

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# Table of Contents

Overview ............................................................................................................................................................................. 1  
Key Findings ...................................................................................................................................................................... 1  
  Prevention of HIV-1 ................................................................................................................................................... 1  
  Treatment of HIV-1 .................................................................................................................................................... 1  
Background ....................................................................................................................................................................... 2  
Key Questions ................................................................................................................................................................... 3  
Methods .............................................................................................................................................................................. 3  
Findings ............................................................................................................................................................................... 3  
  Overview of Clinical Practice Guidelines Ratings and Recommendations ............................................ 5  
  Recommendations for the Prevention of HIV-1 ............................................................................................. 7  
  Recommendations for the Treatment of HIV-1 ........................................................................................... 11  
Discussion ....................................................................................................................................................................... 17  
References ....................................................................................................................................................................... 20  
Appendix A. Methods ................................................................................................................................................. 24  
  Clinical Practice Guidelines Methods ............................................................................................................... 24  
  Quality Assessment ................................................................................................................................................. 25  
Appendix B. Antiretroviral Treatment Options for Patients with HIV-1 .................................................. 26
Overview

More than 1.1 million people in the U.S. were living with HIV in 2015, and of those, an estimated 38,500 Americans were newly infected.1,2 HIV-1, 1 of the 2 types of HIV, is responsible for the majority of HIV infections worldwide, and takes less time to progress to symptomatic HIV/AIDS than HIV-2.3,4 Medicaid administrators are interested in current recommendations for the prevention and treatment of HIV-1 in adults and adolescents. In this report, we summarize 8 relevant clinical practice guidelines from U.S. and international professional societies and organizations, 3 of which were rated good methodological quality; 2 were rated fair methodological quality; and 3 were rated poor methodological quality. The good-methodological-quality guideline by the U.S. Preventive Services Task Force (USPSTF) is in draft form and recommendations might be modified before it is finalized. The 8 guidelines are consistent in their recommendations of HIV prophylaxis regimens, although the strength of recommendations and evidence ratings vary across guidelines. The guidelines agree on 3 optimal antiretroviral therapies (ART) for treatment-naïve individuals, but recommendations largely vary for ART regimens in treatment-experienced individuals. Table 1 lists the guidelines and their methodological quality.

Key Findings

Prevention of HIV-1

- Seven of 8 identified guidelines provide recommendations on HIV pre-exposure prophylaxis (PrEP). These guidelines recommend the use of daily, continuous, oral emtricitabine and tenofovir disoproxil fumarate (FTC/TDF) 200 mg/300 mg (Truvada) for a maximum of 90 days at a time for all populations meeting eligibility criteria for PrEP. In general, the guideline authors rated the PrEP recommendations as strong and supported by underlying evidence from randomized controlled trials (RCTs), but there is some variation across guidelines.
- On-demand dosing of FTC/TDF 200 mg/300 mg (Truvada) is recommended as an alternative PrEP dosing schedule for men who have sex with men (MSM) and transgender or gender-diverse individuals. TDF alone (Viread) is recommended as an alternative PrEP regimen for sexually active heterosexual men and women and people who inject drugs (PWID).
- The guidelines recommend baseline assessment of HIV status, renal function, use of contraindicated medications, and hepatitis B virus (HBV) infection prior to initiation of PrEP. The guidelines also recommend follow-up assessment of HIV status, bacterial sexually transmitted infection (STI) and hepatitis C virus (HCV) screening, renal function, and administration of services such as medication adherence counseling, behavioral risk reduction support, and safe injection and drug treatment services as appropriate.

Treatment of HIV-1

- Three of the 8 guidelines provide recommendations on initial ART regimens for the treatment of HIV infection in treatment-naïve patients. These guidelines center on 3 recommended treatment regimens for most people with HIV: bictegravir, FTC, and tenofovir
alafenamide (BIC/FTC/TAF); abacavir, dolutegravir, and lamivudine (ABC/DTG/3TC); and DTG with coformulated FTC/TAF (DTG + FTC/TAF). The guidelines also agree on the use of cobicistat/elvitegravir/FTC/TAF or TDF (c/EVG/FTC/TAF [or TDF]) or efavirenz with coformulated FTC/TDF (EFV + FTC/TDF) for ART in certain clinical situations, such as in patients with low CD4 cell counts (< 200 cells/mm³) or HIV RNA greater than 100,000 copies/mL, or in certain conditions such as HCV coinfection, chronic kidney disease, liver disease with cirrhosis, osteoporosis, or psychiatric illnesses. The guideline authors rated these recommendations as strong and supported by evidence from RCTs. Recommendations for other ART regimens vary across guidelines in terms of the strength of recommendations and quality of the underlying evidence.

- The guidelines cite numerous reasons for switching ART regimens in treatment-experienced patients, including regimen simplification, the need to respond to newly diagnosed comorbidities or to prevent comorbid conditions, and managing drug-drug interactions. In patients who are virologically suppressed, switching ART regimens might be beneficial in minimizing renal or bone adverse events. The guidelines recommend conducting resistance testing and using the results to guide ART regimen changes for patients experiencing virologic failure.

- The guidelines encourage patients and clinicians to weigh the benefits and risks of using ART therapy in individuals with childbearing potential. Preliminary data suggest that DTG might lead to an increased risk of neural tube defects in infants born to individuals receiving this drug at the time of conception.

**Background**

HIV is a major public health concern. By the end of 2015, more than 1.1 million people in the U.S. were living with HIV, of which approximately 1 in 7 were unaware of their infection. An estimated 38,500 Americans became newly infected with HIV in 2015; the number of new HIV infections declined by 8% between 2010 and 2015. HIV-1 accounts for approximately 95% of all HIV infections worldwide. Since the beginning of the HIV epidemic in the early 1980s, more than 40 antiretroviral drugs have been developed to help control HIV infection when used in various combinations. The use of ART has improved immune responses and substantially reduced the morbidity and mortality associated with HIV infection. Currently, HIV-1 infected individuals have a life expectancy that is only slightly shorter than that of non-HIV infected individuals. Because of the numerous options available and potential benefits and harms of each strategy, determining which treatments to prescribe can be a difficult task. Additionally, populations have different risk factors for acquiring HIV, and consideration of these risk factors is crucial for the determination of appropriate prophylactic measures.

The most recent Drug Effectiveness Review Project (DERP) report on HIV-1 treatment relied on guidelines produced by the U.S. Department of Health and Human Services (DHHS) in 2016. DHHS has since updated these guidelines to reflect changes in the evidence and to include newly approved drugs. Medicaid administrators are interested in a synthesis of the newly
updated DHHS guidelines as well as other relevant guidelines on prophylaxis and treatment of HIV-1 infection.

**Key Questions**

1. What recommendations do clinical practice guidelines make for preventing and treating HIV-1 infection among adults and adolescents?
2. Do these recommendations differ by patient characteristics (e.g., MSM, PWID)?

**Methods**

We searched core clinical guidelines sources, conducted a literature search in Ovid MEDLINE, and conducted targeted searches using Google and Google Scholar for clinical practice guidelines for preventing and treating HIV-1 infection in adults and adolescents. One researcher independently assessed the methodological quality of eligible guidelines and a second rater reviewed each assessment. Disagreements were resolved through consensus. We contacted the Australasian Society for HIV, Viral Hepatitis, and Sexual Health (ASHM); the European AIDS Clinical Society (EACS); and DHHS for additional information on guideline methods. We received additional information on methods from only EACS, which we used to inform our methodological quality assessment. We present quality of evidence ratings as reported by each eligible guideline. Please refer to Appendix A for a list of core guidelines sources, search terms, and the literature search strategy for this report.

**Findings**

We identified 8 clinical practice guidelines developed by professional societies and organizations that were published within the last 2 years on the prevention and treatment of HIV-1 infection (Table 1).¹⁰⁻¹⁷ Seven guidelines¹⁰⁻¹²,¹⁴⁻¹⁷ include recommendations on PrEP and 3 guidelines¹³⁻¹⁵ include recommendations for the treatment of HIV-1 infection. Six guidelines¹⁰⁻¹³,¹⁵,¹⁷ provide strength of recommendation ratings and quality of evidence ratings for their recommendations; 2 guidelines (ASHM¹⁶ and EACS¹⁴) do not provide strength of recommendation or quality of evidence ratings for their recommendations (Table 1). We rated 3 guidelines¹⁰,¹²,¹⁷ as good methodological quality because of clear and appropriate literature searching and evidence grading methods meeting quality standards for a systematic review, clear and appropriate methods on the development of recommendations, and accounting of funding and disclosures of interest (Table 1). We rated 2 guidelines¹¹,¹⁵ as fair methodological quality and 3 guidelines¹³,¹⁴,¹⁶ as poor methodological quality because of unclear reporting of methods and potential for numerous biases (Table 1). The good-methodological-quality guideline by the USPSTF is in draft form and recommendations might be modified before it is finalized.¹⁷
<table>
<thead>
<tr>
<th>Organization</th>
<th>Focus</th>
<th>Methodological Quality</th>
<th>Rating System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australasian Society for HIV, Viral Hepatitis, and Sexual Health Medicine (ASHM)(^{16}) 2018</td>
<td>PrEP</td>
<td>Poor</td>
<td>No grading of evidence or recommendations</td>
</tr>
<tr>
<td>British HIV Association/British Association for Sexual Health and HIV (BHIVA/BASHH)(^{10}) 2018</td>
<td>PrEP</td>
<td>Good</td>
<td>GRADE methodology</td>
</tr>
<tr>
<td>Canadian Medical Association (CMA)(^{11}) 2018</td>
<td>PrEP</td>
<td>Fair</td>
<td>GRADE methodology</td>
</tr>
<tr>
<td>Centers for Disease Control and Prevention (CDC)(^{12}) 2017</td>
<td>PrEP</td>
<td>Good</td>
<td>Strength of recommendations ranges from A to C; quality of evidence for recommendations ranges from I to III</td>
</tr>
<tr>
<td>DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents (DHHS)(^{13}) 2018</td>
<td>Treatment</td>
<td>Poor</td>
<td>Strength of recommendations ranges from A to C; quality of evidence for recommendations ranges from I to III</td>
</tr>
<tr>
<td>European AIDS Clinical Society (EACS)(^{14}) 2018</td>
<td>PrEP and Treatment</td>
<td>Poor</td>
<td>No grading of evidence or recommendations</td>
</tr>
<tr>
<td>International Antiviral Society-USA Panel (IAS-USA)(^{15}) 2018</td>
<td>PrEP and Treatment</td>
<td>Fair</td>
<td>Adapted from Canadian Task Force on Periodic Health Examination</td>
</tr>
<tr>
<td>US Preventive Services Task Force (USPSTF) Draft Recommendation(^{17}) 2018</td>
<td>PrEP</td>
<td>Good</td>
<td>USPSTF rating system</td>
</tr>
</tbody>
</table>

**Abbreviations.** GRADE: Grading of Recommendations Assessment, Development and Evaluation; PrEP: pre-exposure prophylaxis.
Overview of Clinical Practice Guidelines Ratings and Recommendations

Two guidelines (ASHM and EACS) do not provide strength of recommendation or quality of evidence ratings for their recommendations.14,16 Six of the 8 guidelines do provide strength of recommendations and quality of evidence ratings for their recommendations, using multiple methods and rating systems.

The British HIV Association/British Association for Sexual Health and HIV (BHIVA/BASHH)10 and the Canadian Medical Association (CMA)11 guidelines used the GRADE system for specifying the strength of recommendations and the quality of evidence on which the recommendations were based. These professional organizations rated the strength of recommendations as:

- **Strong (or Grade 1):** a recommendation to do (or not do) something for which the guideline panel is confident that the benefits of an intervention outweigh the risks (or vice versa), across the range of patients for whom the recommendation is intended.10,11
- **Weak (or Grade 2):** a recommendation where the benefits and risks are more closely balanced or are more uncertain, and where alternative strategies may be reasonable depending on the individual patient’s circumstances, preferences, and values.10,11

Both BHIVA/BASHH10 and CMA11 rated the quality of evidence using the following categories:

- **High (or Grade A):** high-quality evidence from consistent results from well-performed RCTs, or overwhelming evidence from another source (e.g., well-executed nonrandomized studies with consistent strong effects and exclusion of potential sources of bias).10 The true effect lies close to the estimate of effect.10
- **Moderate (or Grade B):** moderate-quality evidence from randomized trials that has serious flaws in conduct, inconsistency, indirectness, imprecise estimates, reporting bias, or some combination of these limitations; or from other study designs with specific strengths such as nonrandomized studies with consistent effects and exclusion of the majority of potential sources of bias.10
- **Low (or Grade C):** low-quality evidence from controlled trials with several serious limitations, or nonrandomized studies with limited evidence on effects and exclusion of most potential sources of bias.10
- **Very low (or Grade D):** evidence based only on case studies, expert judgement or observational studies with inconsistent effects and a potential for substantial bias, such that there can be little confidence in the effect estimate.10

One difference between the quality of evidence ratings for these 2 guideline groups is that in the CMA guidelines, high quality of evidence is the starting point for assessing the quality of evidence from RCTs and low quality of evidence is the starting point for assessing the quality of evidence from nonrandomized studies.11 This approach is consistent with GRADE methods.18,19 The BHIVA/BASHH guidelines do not specify a starting point for quality of evidence ratings based on study design, but specify that the risk of bias for each study was an important factor in the overall quality of evidence rating.10
The Centers for Disease Control and Prevention (CDC)\textsuperscript{12} and DHHS\textsuperscript{13} guidelines used similar rating systems for their recommendations (Table 2).

<table>
<thead>
<tr>
<th>Strength of Recommendation</th>
<th>Quality of Evidence for Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A:</strong> Strong recommendation for the statement</td>
<td>I: One or more randomized trials with clinical outcomes and/or validated laboratory endpoints</td>
</tr>
<tr>
<td><strong>B:</strong> Moderate recommendation for the statement</td>
<td>II: One or more well-designed, nonrandomized studies with long-term clinical outcomes</td>
</tr>
<tr>
<td><strong>C:</strong> Optional recommendation for the statement</td>
<td>III: Expert opinion</td>
</tr>
</tbody>
</table>

Abbreviations. CDC: Centers for Disease Control and Prevention; DHHS: U.S. Department of Health and Human Services.

The CDC guidelines clearly state that for quality of evidence ratings, RCTs and nonrandomized studies needed to be well-executed;\textsuperscript{12} however, this is not specified in the DHHS guidelines.

The International Antiviral Society-USA Panel (IAS-USA) guidelines\textsuperscript{15} utilized a rating system adapted from the Canadian Task Force on Periodic Health Examination (Table 3).\textsuperscript{20} This rating system provides more detail by indicating whether evidence is from published or unpublished studies and specifies whether the evidence is peer-reviewed.\textsuperscript{15} The grading of the strength of recommendations is consistent with the CDC and DHHS guidelines.

<table>
<thead>
<tr>
<th>Strength of Recommendation</th>
<th>Quality of Evidence for Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A:</strong> Strong support for the recommendation</td>
<td>1a: Evidence from at least 1 randomized clinical trial published in the peer-reviewed literature</td>
</tr>
<tr>
<td><strong>B:</strong> Moderate support for the recommendation</td>
<td>1b: Evidence from at least 1 randomized clinical trial presented in abstract form at peer-reviewed scientific meetings</td>
</tr>
<tr>
<td><strong>C:</strong> Limited support for the recommendation</td>
<td>1la: Evidence from nonrandomized clinical trials or cohort or case-control studies published in the peer-reviewed literature</td>
</tr>
<tr>
<td></td>
<td>1lb: Evidence from nonrandomized clinical trials or cohort or case-control studies presented in abstract form at peer-reviewed scientific meetings</td>
</tr>
<tr>
<td></td>
<td>III: Recommendation based on the panel’s analysis of the accumulated available evidence</td>
</tr>
</tbody>
</table>

Abbreviations. IAS-USA: International Antiviral Society-USA Panel. Note. \textsuperscript{a} Adapted in part from the Canadian Task Force on Periodic Health Examination.\textsuperscript{20}

The USPSTF guidelines provide grades to aid in interpreting their recommendations (Table 4).\textsuperscript{17} These grades reflect consideration of both certainty and magnitude of net benefit, including assessment of the internal validity of individual studies.\textsuperscript{17}
Table 4. USPSTF Recommendation Grades\textsuperscript{17}

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition and Suggestions for Practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>The USPSTF recommends the service. There is high certainty that the net benefit is substantial. Offer or provide this service.</td>
</tr>
<tr>
<td>B</td>
<td>The USPSTF recommends this service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial. Offer or provide this service.</td>
</tr>
<tr>
<td>C</td>
<td>The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgement and patient preferences. There is at least moderate certainty that the net benefit is small. Offer or provide this service for selected patients depending on individual circumstances.</td>
</tr>
<tr>
<td>D</td>
<td>The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits. Discourage the use of this service.</td>
</tr>
<tr>
<td>I</td>
<td>Statement of insufficient evidence. The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined. Read the Clinical Considerations section of the USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.</td>
</tr>
</tbody>
</table>

Abbreviations. USPSTF: US Preventive Services Task Force.

Recommendations for the Prevention of HIV-1

Seven guidelines evaluated in this report provide recommendations on PrEP.\textsuperscript{10-12,14-17} These guidelines are consistent in recommending the use of daily, continuous, oral FTC/TDF 200 mg/300 mg as PrEP for all populations who meet eligibility criteria (Table 5); the guidelines recommend a maximum 90-day supply of medication when initiating PrEP.\textsuperscript{10,12,14-17} The guideline authors rated recommendations for PrEP as strong and supported by underlying evidence from RCTs, but there is some variation across guidelines (Table 5).

Guidelines included in this report specify clinical criteria for patients to be eligible for PrEP therapy, including a documented negative HIV test result prior to prescribing PrEP,\textsuperscript{10-12,14,16} no signs or symptoms of acute HIV infection,\textsuperscript{10,12,16} normal renal function,\textsuperscript{10-12,16} no use of contraindicated medications,\textsuperscript{12,16} and documented negative test for HBV infection or proof of vaccination status.\textsuperscript{10-12,14,16} The guidelines recommend some follow-up services to be provided to ensure the success of PrEP treatment. Follow-up services include regular HIV testing, medication adherence counseling, behavioral risk reduction support, renal function testing, side effect assessment, testing for bacterial STIs (i.e., chlamydia, gonorrhea, and syphilis), and screening for HCV (especially in MSM).\textsuperscript{10-12,15-17} The guidelines also recommend testing for pregnancy in individuals of childbearing age\textsuperscript{11,12,16} and for PWID, ensuring access to clean needles and syringes and drug treatment services.\textsuperscript{10,12,16}
### Table 5. Summary of Recommended PrEP Regimens by Population

<table>
<thead>
<tr>
<th>Regimen</th>
<th>MSM</th>
<th>Heterosexual Men and Women</th>
<th>PWID</th>
<th>Transgender and Gender-Diverse People</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Recommended Regimen</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily, continuous, oral FTC/TDF 200 mg/300 mg</td>
<td>ASHM\textsuperscript{16}</td>
<td>• Not rated</td>
<td>ASHM\textsuperscript{16}</td>
<td>• Not rated</td>
</tr>
<tr>
<td></td>
<td>BHIVA/BASHH\textsuperscript{10}</td>
<td>• Rating 1A</td>
<td>BHIVA/BASHH\textsuperscript{10}</td>
<td>• Rating 1A</td>
</tr>
<tr>
<td></td>
<td>CDC\textsuperscript{12}</td>
<td>• Rating IA</td>
<td>CDC\textsuperscript{12}</td>
<td>• Rating IA</td>
</tr>
<tr>
<td></td>
<td>CMA\textsuperscript{11}</td>
<td>• Strong recommendation; high-quality evidence</td>
<td>CMA\textsuperscript{11}</td>
<td>• Strong recommendation; high-quality evidence</td>
</tr>
<tr>
<td></td>
<td>EACS\textsuperscript{14}</td>
<td>• Not rated</td>
<td>EACS\textsuperscript{14}</td>
<td>• Not rated</td>
</tr>
<tr>
<td></td>
<td>IAS-USA\textsuperscript{15}</td>
<td>• Rating A</td>
<td>IAS-USA\textsuperscript{15}</td>
<td>• Rating A</td>
</tr>
<tr>
<td></td>
<td>USPSTF\textsuperscript{17}</td>
<td>• Rating A</td>
<td>USPSTF\textsuperscript{17}</td>
<td>• Rating A</td>
</tr>
</tbody>
</table>

| **Alternative Regimens** | | | | |
| On-demand (“2-1-1” or event-driven) dosing of FTC/TDF 200 mg/300 mg | ASHM\textsuperscript{16} | • Not rated | NR | ASHM\textsuperscript{16} |
| | BHIVA/BASHH\textsuperscript{10} | • Rating 1A | NR | • Transgender women: not rated |
| | CMA\textsuperscript{11} | • Weak recommendation; high quality of evidence | NR | |

\(\text{ASHM} = \text{American Society for HIV Medicine} \quad \text{BHIVA/BASHH} = \text{British HIV Association/British Association for Sexual Health and HIV} \quad \text{CDC} = \text{Centers for Disease Control and Prevention} \quad \text{CMA} = \text{Canadian Medical Association} \quad \text{EACS} = \text{European AIDS Clinical Society} \quad \text{IAS-USA} = \text{International AIDS Society-USA} \quad \text{USPSTF} = \text{United States Preventive Services Task Force} \)
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NR</td>
<td></td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations. ASHM: Australasian Society for HIV, Viral Hepatitis and Sexual Medicine; BASHH: British Association for Sexual Health and HIV; BHIVA: British HIV Association; CDC: Centers for Disease Control and Prevention; CMA: Canadian Medical Association; EACS: European AIDS Clinical Society; FTC: emtricitabine; IAS-USA: International Antiviral Society-USA Panel; MSM: men who have sex with men; NR: not recommended; PWID: people who inject drugs; TDF: tenofovir disoproxil fumarate; USPSTF: US Preventive Services Task Force.
Men Who Have Sex With Men

Seven guidelines (ASHM, BHIVA/BASHH, CDC, CMA, EACS, IAS-USA, and USPSTF) recommend the use of PrEP for HIV-negative MSM who are at a high risk\(^{10-12,14-17}\) and the consideration of PrEP for MSM who are at moderate risk of HIV infection.\(^{16}\) The guidelines generally consider MSM to be at high risk if they have had condomless sex with a partner of unknown HIV status or with a partner who is HIV-positive but not on treatment or with a detectable viral load within the last 3 to 12 months or likely to within the next 3 months.\(^{10-12,14-17}\) The ASHM guideline considers MSM to be at moderate risk if, in the last 3 months or likely in the next 3 months, they had more than 1 episode of sex with condom failure with a partner of unknown HIV status or an HIV-positive partner not on treatment or with a detectable viral load, with or without sharing intravenous drug equipment.\(^{16}\) The BHIVA/BASHH guideline recommends PrEP in adolescent and young adults (15 to 25 years old) as well as adult MSM.\(^{10}\) Three guidelines (BHIVA/BASHH, CMA, and EACS) further specify the use of PrEP for MSM who report condomless anal sex within the last 6 months\(^{10}\) and have a bacterial STI (particularly in the last 12 months), recurrent use of nonoccupational postexposure prophylaxis (nPEP), an ongoing sexual relationship with an HIV-positive partner with substantial risk of transmissible HIV, or an HIV Incidence Risk Index-MSM (HIRI-MSM) risk score of at least 11.\(^{11,14}\) HIRI-MSM is a 7-item screening index (scores range from 0 to 47) with a cutoff (score of 10) that is predictive of substantial risk of HIV infection (HIV seroconversion) in 2 large nonrandomized studies conducted in the U.S. in MSM.\(^{21}\) Developers of the HIRI-MSM index propose that MSM who score less than 10 should be counseled with basic HIV/STI risk-reduction messages; however, patients who score 10 or greater are eligible for PrEP and should receive an in-depth assessment of sexual behaviors and the context of risk behaviors by a health care provider.\(^{21}\) For MSM not meeting the eligibility criteria for high or moderate risk of HIV infection, PrEP may still be considered necessary by clinician discretion after taking a detailed history.\(^{16}\) The BHIVA/BASHH guideline specifies that PrEP is not recommended for HIV-negative MSM with HIV-positive partners if the infected partner has been on ART for at least 6 months and their plasma viral load is low (< 200 copies/mL).\(^{10}\) The BHIVA/BASHH guideline recommends that MSM should be advised that daily PrEP is likely to be ineffective if fewer than 4 doses are taken per week.\(^{10}\)

Another option for PrEP dosing in MSM with infrequent sexual exposures is on-demand oral FTC/TDF 200 mg/300 mg, also known as pericoital, event-driven, or “2-1-1” dosing.\(^{10,11,14,15}\) This type of dosing involves a loading dose of 2 tablets of FTC/TDF taken 2 to 24 hours before first sexual exposure, followed by a third tablet 24 hours and a fourth tablet 48 hours later.\(^{10,11,14}\) When potential exposure is sustained for more than a 24-hour period, the BHIVA/BASHH guideline recommends that patients take 1 pill per day until the last sexual exposure followed by 2 postexposure pills.\(^{10}\) The EACS guideline recommends that if a dosed on-demand regimen is used, the total dose per week should not exceed 7 tablets.\(^{14}\) On-demand dosing of PrEP is not recommended by the IAS-USA Panel guidelines in patients with active HBV infection because of the risk of hepatitis flare and hepatic decompensation.\(^{15}\) The USPSTF guideline does not clearly recommend event-driven dosing, despite evidence from 1 good-methodological-quality RCT.
showing a lower risk of HIV infection with event-driven dosing compared with a placebo in MSM. However, MSM randomized to PrEP took an average of 4 doses of PrEP per week (15 doses per month); therefore, it is uncertain whether this finding would apply to less frequent use or on-demand dosing. The BHIVA/BASHH and CDC guidelines do not recommend the use of TDF alone for PrEP for MSM because of a lack of evidence in this population.

**Heterosexual Men and Women**

Seven guidelines (ASHM, BHIVA/BASHH, CDC, CMA, EACS, IAS-USA, and USPSTF) agree that PrEP should be recommended as one preventive option for HIV-negative sexually active heterosexual adult men and women who are at substantial risk of HIV infection. These guidelines recommend offering daily oral FTC/TDF to HIV-negative heterosexual men and women having condomless sex with partners who are HIV positive and have substantial or low but non-negligible risk of having transmissible HIV, unless the partner has been on ART for at least 6 months and has a low plasma viral load (< 200 copies/mL). The BHIVA/BASHH guideline recommends offering PrEP with daily oral FTC/TDF on a case-by-case basis to heterosexual men and women exposed to current factors that could increase their risk of acquiring HIV. The ASHM guideline recommends considering PrEP for heterosexual men and women if the risk of acquiring HIV infection is rated as medium. For sexually active heterosexual men and women who do not meet the eligibility criteria for high or medium risk of acquiring HIV, PrEP can still be recommended if a clinician deems it necessary after conducting a detailed history. The CDC guideline recommends discussing PrEP with heterosexually active women and men whose partners are known to have HIV infection as one of several options to protect the uninfected partner during conception and pregnancy, balancing the risks and benefits of PrEP for mother and fetus. The ASHM guideline recommends assessing pregnancy intent and conducting pregnancy tests every 3 months, if needed.

In the absence of data, the BHIVA/BASHH guideline does not recommend on-demand PrEP dosing as an alternative in sexually active heterosexual men and women. However, 4 guidelines (ASHM, BHIVA/BASHH, CDC, and USPSTF) recommend that TDF alone can be offered to sexually active heterosexual men and women when FTC is contraindicated because TDF monotherapy has shown substantial efficacy and safety in trials in this population. These guidelines do not specify contraindications to FTC, but the U.S. Food and Drug Administration (FDA) has stated that FTC is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the product.

**People Who Inject Drugs**

Five guidelines (ASHM, CDC, CMA, IAS-USA, and USPSTF) recommend PrEP as one preventive option for PWID at substantial risk of HIV infection. Three of these guidelines (ASHM, CDC, and USPSTF) state that TDF alone can be considered as an alternative regimen for PWID because this regimen has shown substantial efficacy and safety in trials in this population. The CMA and USPSTF guidelines state that PrEP can be considered for PWID if the individual shares drug use paraphernalia with a person who has a non-negligible risk of HIV infection.
The ASHM guideline recommends offering PrEP to PWID with a high risk of acquiring HIV infection, and to consider PrEP for PWID at a medium risk of acquiring HIV.\textsuperscript{16} For PWID who do not meet the eligibility criteria for high or medium risk of acquiring HIV, PrEP can still be recommended if a clinician deems it necessary after conducting a detailed history because PWID may have high or medium risk of HIV acquisition through other factors such as sexual exposure.\textsuperscript{16} Four guidelines (ASHM, BHIVA/BASHH, CDC, and USPSTF) recommend that harm-reduction strategies, such as needle exchange and opiate substitution or other drug treatment services, should be encouraged for PWID.\textsuperscript{10,12,16,17} When these services are available and accessed by PWID, the BHIVA/BASHH guideline states that PrEP is not recommended.\textsuperscript{10}

**Transgender and Gender-Diverse People**

Six guidelines (ASHM, BHIVA/BASHH, CMA, EACS, IAS-USA, and USPSTF) agree that PrEP with daily oral FTC/TDF is the recommended PrEP regimen for transgender individuals, and should be offered to HIV-negative adult and young adult transgender men and women who are identified as being at elevated risk of HIV acquisition through condomless anal sex in the previous 6 months and through ongoing condomless sex.\textsuperscript{10,11,14-17} The CDC does not specifically provide PrEP recommendations for transgender or gender-diverse people in its guideline, but includes evidence on this population in the context of risk of HIV infection in MSM.\textsuperscript{12} The USPSTF guideline notes that evidence of PrEP in transgender or gender-diverse individuals is lacking because studies have generally enrolled few individuals from these populations.\textsuperscript{17} The BHIVA/BASHH guideline specifies that PrEP is recommended in HIV-negative transgender men and women having condomless sex with partners who are HIV positive, unless the partner has been on ART for at least 6 months and their plasma viral load is less than 200 copies/mL.\textsuperscript{10} In addition to risk from sexual activity, the CMA guideline recommends PrEP for transgender and gender-diverse individuals with infectious syphilis or rectal bacterial STI (especially in the preceding 12 months), or recurrent use of nPEP.\textsuperscript{11} The ASHM guideline recommends offering PrEP to transgender and gender-diverse people at high-risk for HIV acquisition and considering PrEP for those at medium-risk for HIV acquisition.\textsuperscript{16} Transgender and gender-diverse people who do not meet these criteria may be eligible for PrEP according to a clinician’s discretion after taking a detailed history.\textsuperscript{16} The BHIVA/BASHH guideline advises that daily PrEP is likely to be ineffective if fewer than 4 doses are taken per week.\textsuperscript{10} As an alternative to daily oral FTC/TDF, the ASHM guideline recommends that on-demand FTC/TDF may be appropriate for transgender women.\textsuperscript{16}

**Recommendations for the Treatment of HIV-1**

**Treatment-Naïve Individuals**

Recommended initial antiretroviral regimens for treating HIV-1 are divided into 2 categories: regimens that are recommended for most people with HIV and regimens that are recommended in certain clinical situations. Regimens that are recommended for most people with HIV are classified as such because they have demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use.\textsuperscript{13} Regimens that are recommended in certain
clinical situations are to be used when none of the preferred regimens are feasible or available. The guidelines recommend individualizing the selection of an antiretroviral regimen based on virologic efficacy, potential adverse effects, childbearing potential and the use of effective contraception, pill burden, dosing frequency, potential for drug-drug interactions, comorbid conditions, cost, access, adherence, and resistance test results. Please see Table B1 in Appendix B for recommended ART dosing frequencies in treatment-naive patients.

Three guidelines (DHHS, EACS, and IAS-USA Panel) provide recommendations for treating patients with HIV infection. These 3 guidelines are consistent in recommending 3 initial ART regimens that are suitable for most people with HIV (Table 6): BIC/FTC/TAF, ABC/DTG/3TC, and DTG with coformulated FTC/TAF. The DHHS and IAS-USA Panel rated these recommendations as strong and supported by evidence from RCTs. ART regimens including BIC and DTG are optimal because these two drugs do not require pharmacological boosting and are components of regimens with a low pill burden. These drugs also have a high barrier to resistance, which is important in the event of inconsistent or low adherence to medication.

The DHHS and EACS guidelines both recommend DTG with coformulated FTC/TDF, as well as raltegravir (RAL) with either coformulated FTC/TDF or FTC/TAF, as additional treatment options (Table 6). Of these 2 guideline groups, only the DHHS rated the recommendations and underlying evidence. The DHHS rated these recommendations as strong to moderate and supported by evidence from RCTs, well-designed nonrandomized studies with or without long-term clinical outcomes, relative bioavailability/bioequivalence studies, or regimen comparisons from randomized switch studies. Of the integrase strand transfer inhibitor (INSTI) drugs, RAL has the longest clinical experience and has been shown to have durable virologic efficacy; however, regimens containing RAL have a higher pill burden than BIC- or DTG-containing regimens and RAL has a lower barrier to resistance.

Only the EACS guideline recommends the use of FTC/rilpivirine (RPV)/TAF (or TDF) and cobicistat- or ritonavir-boosted darunavir (DRV/c or DRV/r) with either coformulated FTC/TAF or FTC/TDF (Table 6). The EACS did not provide ratings for recommendations or underlying evidence.
Table 6. Recommended Initial ART Regimens for Most People with HIV

<table>
<thead>
<tr>
<th>Regimen</th>
<th>U.S. Trade Name</th>
<th>Guideline Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>IAS-USA&lt;sup&gt;15&lt;/sup&gt;</td>
</tr>
<tr>
<td>INSTI + 2 NRTIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIC/TAF/FTC</td>
<td>Biktarvy</td>
<td>✓ (rating Al)</td>
</tr>
<tr>
<td>DTG/ABC/3TC</td>
<td>Triumeq</td>
<td>✓ (rating Al)</td>
</tr>
<tr>
<td>DTG + TAF/FTC</td>
<td>Tivicay + Descovy</td>
<td>✓ (rating Al)</td>
</tr>
<tr>
<td>DTG + TDF/FTC</td>
<td>Tivicay + Truvada</td>
<td>✓ (rating Al)</td>
</tr>
<tr>
<td>RAL + TDF/FTC</td>
<td>Isentress + Truvada</td>
<td>✓ (rating Bl)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>RAL + TAF/FTC</td>
<td>Isentress + Descovy</td>
<td>✓ (rating Bl)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>NNRTI + 2 NRTIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RPV/TAF (or TDF)/FTC</td>
<td>Odefsey or Complera</td>
<td>✓</td>
</tr>
<tr>
<td>PI/r or PI/c + 2 NRTIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(DRV/c or DRV/r) + TAF (or TDF)/FTC</td>
<td>Prezobix or Prezista + Norvir + Descovy or Truvada</td>
<td>✓</td>
</tr>
</tbody>
</table>

Abbreviations. 3TC: lamivudine; ABC: abacavir; BIC: bictegravir; c: cobicistat; DTG: dolutegravir; FTC: emtricitabine; INSTI: integrase strand transfer inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI/c: cobicistat-boosted protease inhibitor; PI/r: ritonavir-boosted protease inhibitor; r: ritonavir; RAL: raltegravir; RPV: rilpivirine; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate. Notes. a EACS did not provide ratings for recommendations or evidence underlying the guidelines. b Preliminary data suggest that there is an increased risk of neural tube defects in infants born to women receiving DTG at the time of conception. There are no safety data on BIC, which has a similar chemical structure to DTG. There are limited data on the use of RAL and fetal malformations. A class effect of INSTI and neural tube defects is currently unknown. c If HLA-B*5701 negative.

In terms of ART regimens for certain clinical conditions, 3 guidelines (DHHS, EACS, and IAS-USA Panel) consistently recommend the use of c/EVG/FTC/TAF (or TDF) or EFV with coformulated FTC/TDF (Table 7).<sup>13-15</sup> Ratings for these recommendations range from strong support for the recommendations based on RCT evidence<sup>15</sup> to moderate support for the recommendations based on well-designed nonrandomized studies with or without long-term clinical outcomes, relative bioavailability/bioequivalence studies, or regimen comparisons from randomized switch studies.<sup>13</sup> Guidelines diverged when recommending other regimens (Table 7). One striking difference between guideline recommendations is that the IAS-USA Panel guideline recommends RAL with either coformulated FTC/TDF or FTC/TAF as alternative PrEP regimens to be used in certain clinical situations (Table 7), but the DHHS and EACS guidelines both recommend these regimens as initial regimens for most people with HIV (Table 6). The IAS-USA Panel rated the recommendation for the use of RAL with coformulated FTC/TDF as strong based on evidence from at least 1 RCT, but did not specifically cite the underlying evidence.<sup>15</sup> This guideline group did not rate the recommendation or evidence for the use of RAL with
coformulated FTC/TAF.\textsuperscript{15} In comparison, the DHHS\textsuperscript{13} rated the recommendation for the use of RAL with coformulated FTC/TDF as moderate based on evidence from 2 double-blind RCTs (STARTMRK\textsuperscript{23} and SPRING-2\textsuperscript{24}), 1 open-label randomized trial (ACTG A5257\textsuperscript{25}), and 1 phase 3 randomized, double-blind active-controlled trial (ONCEMRK\textsuperscript{26}). TDF has been associated with lower lipid levels than TAF, but is more likely to cause bone and kidney toxicities than TAF.\textsuperscript{13}

The IAS-USA Panel recommendations for other regimens to be used for certain clinical conditions were all rated as strong and supported by evidence from RCTs. The DHHS recommendations were rated as largely moderate to optional with evidence from nonrandomized studies or expert opinion (Table 7).

### Table 7. Initial ART Regimens Recommended in Certain Clinical Conditions

<table>
<thead>
<tr>
<th>Regimen</th>
<th>U.S. Trade Name</th>
<th>Guideline Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>IAS-USA\textsuperscript{15}</td>
</tr>
<tr>
<td>INSTI + 2 NRTIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EVG/c/TAF (or TDF)/FTC</td>
<td>Genvoya or Stribild</td>
<td>✓ (rating AlA)</td>
</tr>
<tr>
<td>RAL + ABC/3TC</td>
<td>Isentress + Epzicom</td>
<td>✓ (rating CII)\textsuperscript{b,c,d}</td>
</tr>
<tr>
<td>PI/c or PI/r + 2 NRTIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(DRV/c or DRV/r) + TAF (or TDF)/FTC</td>
<td>Prezocibix or Prezista + Norvir + Descovy or Truvada</td>
<td>✓ (rating AlA)</td>
</tr>
<tr>
<td>(ATV/c or ATV/r) + TAF (or TDF)/FTC</td>
<td>Evotaz or Reyataz + Norvir + Descovy or Truvada</td>
<td>✓ (rating BI)</td>
</tr>
<tr>
<td>(DRV/c or DRV/r) + ABC/3TC</td>
<td>Prezocibix or Prezista + Norvir + Epzicom</td>
<td>✓ (rating BII)\textsuperscript{c}</td>
</tr>
<tr>
<td>(ATV/c or ATV/r) + ABC/3TC</td>
<td>Evotaz or Reyataz + Norvir + Epzicom</td>
<td></td>
</tr>
<tr>
<td>NNRTI + 2 NRTIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EFV + TDF/FTC</td>
<td>Sustiva + Truvada</td>
<td>✓ (rating AlA)</td>
</tr>
<tr>
<td>DOR/TDF/3TC</td>
<td>Delstrigo</td>
<td>✓ (rating BI)</td>
</tr>
<tr>
<td>DOR + TAF/FTC</td>
<td>Pifeltro + Descovy</td>
<td>✓ (rating BIII)</td>
</tr>
<tr>
<td>RPV/TAF (or TDF)/FTC</td>
<td>Odefsey or Complera</td>
<td>✓ (rating AlA)</td>
</tr>
<tr>
<td>EFV + ABC/3TC</td>
<td>Sustiva + Epzicom</td>
<td>✓ (rating BI)</td>
</tr>
<tr>
<td>Other Combinations\textsuperscript{a}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regimen</td>
<td>U.S. Trade Name</td>
<td>Guideline Organization</td>
</tr>
<tr>
<td>------------------</td>
<td>----------------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IAS-USA(^{15})</td>
</tr>
<tr>
<td>DRV/r + RAL</td>
<td>Prezista + Norvir + Isentress</td>
<td>✓ (rating CI)(^{3,e})</td>
</tr>
<tr>
<td>DRV/c + RAL</td>
<td>Prezcobix + Isentress</td>
<td>✓</td>
</tr>
<tr>
<td>DRV/r + 3TC</td>
<td>Prezista + Norvir + Epivir</td>
<td>✓ (rating CI)</td>
</tr>
<tr>
<td>RAL + TDF/FTC</td>
<td>Isentress + Truvada</td>
<td>✓ (rating Ala)</td>
</tr>
<tr>
<td>RAL + TAF/FTC</td>
<td>Isentress + Descovy</td>
<td>✓ (not rated)</td>
</tr>
</tbody>
</table>

Abbreviations. 3TC: lamivudine; ABC: abacavir; c: cobicistat; DTG: dolutegravir; FTC: emtricitabine; INSTI: integrase strand transfer inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI/c: cobicistat-boosted protease inhibitor; PI/r: ritonavir-boosted protease inhibitor; r: ritonavir; RAL: raltegravir; RPV: rilpivirine; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate. Note. \(^a\) Other combinations are regimens that should be considered when ABC, TAF, and TDF cannot be used or are not optimal. \(^b\) There are limited data on the use of INSTIs and neural tube defects or other fetal malformations. \(^c\) If HLA-B*5701 negative, \(^d\) If HIV RNA <100,000 copies/mL, \(^e\) If CD4 cell count >200 cells/mm\(^3\).

**Treatment-Experienced Individuals**  
**Switching Antiretroviral Regimens**

There are numerous reasons for switching ART regimens in individuals with HIV-1. The most common reasons for switching therapy are to simplify the regimen, to respond to newly diagnosed comorbidities, to prevent comorbid conditions, or to manage interactions with drugs or supplements.\(^{14,15}\) The EACS and IAS-USA Panel guidelines suggest that switching from older ARV regimens should be considered when there is evidence of or potential for chronic toxicity, drug-drug interactions, or emergent adverse effects with current regimens.\(^{14,15}\)

Virologic suppression is defined as an HIV viral load of less than 50 copies/mL for at least 6 months.\(^{14}\) The IAS-USA Panel guidelines offer the following considerations when switching ART regimens in virologically suppressed patients:

- **Proactive switching from TDF- and TAF-containing regimens might be beneficial in minimizing renal or bone adverse effects (strength of recommendation: B; quality of evidence rating: Ia).\(^{15}\)**
- **When switching from 3-drug regimens to certain 2-drug regimens, the following can be used in patients with no prior virologic failure or transmitted drug resistance, although longer-term follow-up is needed to assess the durability of these strategies\(^{15}\):**
  - DTG/RPV (strength of recommendation: A; quality of evidence rating: Ia)
  - A boosted protease inhibitor with 3TC (strength of recommendation: A; quality of evidence rating: Ila)
  - DTG with 3TC (strength of recommendation: A; quality of evidence rating: IIa)
- **Patients who are coinfected with HIV and HBV should receive a regimen that contains 2 drugs that are active against HBV (i.e., TAF or TDF plus lamivudine or emtricitabine) in**
addition to a third ART drug (strength of recommendation: A; quality of evidence rating: IIa). These patients generally should not be switched to a 2-drug ART regimen.15

Monotherapy with boosted protease inhibitors or DTG is not recommended.15

Switching ART regimens is indicated if a patient experiences virologic failure, which the DHHS guideline defines as the inability to achieve or maintain suppression of viral replication to an HIV RNA level of less than 200 copies/mL.13 Virologic failure can be caused by patient-related factors (e.g., comorbidities), adherence-related factors (e.g., high pill burden), HIV infection-related factors (e.g., innate or acquired resistance to ARVs), and ARV regimen-related factors (e.g., suboptimal pharmacokinetics).13 The treatment goal for ART-experienced patients with drug resistance who are experiencing virologic failure is to establish virologic suppression, which the DHHS guideline defines as HIV RNA levels below the lower limits of detection of currently used assays (strength of recommendation: A; quality of evidence rating: I).13 The DHHS guideline highlights the importance of continuous adherence support for all patients before and after regimen changes because of virologic failure.13 Please see Table B2 in Appendix B for detailed recommendations of ARV options for patients with virologic failure in specific clinical scenarios.

The DHHS and IAS-USA Panel guidelines offer the following considerations when switching ART regimens in patients with virologic failure:

- Resistance testing is recommended while the patient is taking the failing ART regimen or within 4 weeks of stopping (strength of recommendation: A; quality of evidence rating: IIa), although resistance testing can provide useful information even if more than 4 weeks have elapsed since discontinuation.13,15

- Clinicians should confirm virologic failure and if resistance is identified, promptly switch the patient to another active regimen using results of resistance testing to prevent the accumulation of additional resistance mutations (strength of recommendation: B; quality of evidence rating: IIa).15 A fully active agent is expected to have uncompromised activity on the basis of the patient’s ART history and current and past drug-resistance test results or to have a novel mechanism of action.13

- DTG plus 2 nucleoside reverse transcriptase inhibitors (NRTIs) with at least 1 active by genotype is recommended after initial treatment failure with a non-NRTI (strength of recommendation: A; quality of evidence rating: Ia).15

- A boosted protease inhibitor plus 2 NRTIs (with at least 1 active NRTI) are recommended for initial treatment failure of an INSTI-containing regimen (strength of recommendation: A; quality of evidence rating: III).15

- DTG plus at least 1 fully active other agent may be effective in patients with RAL or EVG resistance. DTG should be dosed twice daily (strength of recommendation: B; quality of evidence rating: III).15

- A single active agent added to a failing regimen is not recommended (strength of recommendation: A; quality of evidence rating: Ia).15

- For multiclass resistance, the next regimen should be constructed using drugs from new classes if available (strength of recommendation: B; quality of evidence rating: III).15
• Maximal virologic suppression might not be possible in patients with extensive drug resistance. In this case, ART should be continued (strength of recommendation: A; quality of evidence rating: I) with regimens designed to minimize toxicity, preserve CD4 cell counts, and delay clinical progression.\textsuperscript{13}

• When it is not possible to construct a viable suppressive regimen for a patient with multidrug-resistant HIV, the clinician should consider enrolling the patient in a clinical trial of investigational agents or contacting pharmaceutical companies that might have investigational agents available.\textsuperscript{13}

**Risks of Antiretroviral Use in Pregnancy**

Three guidelines (DHHS, EACS, and IAS-USA Panel) cite preliminary data suggesting an increased risk of neural tube defects in infants born to individuals receiving DTG at the time of conception.\textsuperscript{13-15} The DHHS guideline recommends that pregnancy testing should be performed before starting a patient on DTG if the patient has virologic failure and is of childbearing age (strength of recommendation: A; quality of evidence rating: III).\textsuperscript{13} For patients who are pregnant and within 12 weeks postconception, or those who are of childbearing age and who are not using effective contraception or who are contemplating pregnancy, the DHHS guideline recommends that clinicians consider the following factors:

• If an alternative active ARV option to DTG exists, DTG should not be prescribed (strength of recommendation: A; quality of evidence rating: II).\textsuperscript{13}

• If no alternative exists, providers and individuals of childbearing age should discuss the possible association between neural tube defects and DTG use during conception, and the risks of persistent viremia in the patient and HIV transmission to the fetus during pregnancy if the patient is not on effective ART.\textsuperscript{13} The decision of whether to initiate or continue DTG should be made after careful consideration of these risks.\textsuperscript{13}

The IAS-USA Panel guideline recommends the use of RAL for individuals who are already pregnant.\textsuperscript{15} The DHHS guideline states that the rate of fetal malformations in patients who receive RAL during pregnancy is within the expected range for pregnancy outcomes in the U.S., although data on RAL use in the first trimester is limited to fewer than 300 deliveries.\textsuperscript{13} Cobicistat-boosted elvitegravir (c/EVG) should not be used during pregnancy (strength of recommendation: A; quality of evidence rating: IIA).\textsuperscript{15} Pregnant women already taking c/EVG should be switched to a recommended regimen.\textsuperscript{15} Finally, BIC should not be used during pregnancy because available safety data are insufficient.\textsuperscript{15}

**Discussion**

We identified 8 eligible clinical practice guidelines: 7 with recommendations on PrEP and 3 with recommendations on ARV treatment. The guidelines that cover PrEP recommend the use of daily, continuous, oral FTC/TDF 200 mg/300 mg in concert with medication adherence counseling, behavioral risk reduction support, and drug-treatment services, as needed. On-demand PrEP with FTC/TDF is recommended as an alternative dosing schedule for MSM and
transgender or gender-diverse individuals; TDF alone is recommended as an alternative for sexually active heterosexual men and women and PWID. The guidelines consistently recommend BIC/FTC/TAF, ABC/DTG/3TC, and DTG + FTC/TAF as initial treatment for most people with HIV and the use of c/EVG/FTC/TAF (or TDF) or EFV + FTC/TDF for treatment in certain clinical conditions. The guidelines vary in terms of recommendations for other ART regimens. The guidelines also provide numerous considerations for switching ART regimens in virologically suppressed individuals and those experiencing virologic failure.

Of the 8 included guidelines, we rated the BHIVA/BASHH, CDC, and USPSTF guidelines as good methodological quality. We rated the CMA and IAS-USA Panel guidelines as fair methodological quality and the ASHM, DHHS, and EACS guidelines as poor methodological quality because of multiple methodological limitations. The CMA guideline provides good reporting of methods, but states that panelists with competing interests were permitted to participate in panel discussions without restriction.\(^1\)\(^1\) It is unclear whether panelists with conflicts of interest may have influenced the recommendations for this guideline through voting or other participation. The IAS-USA Panel guideline provides limited reporting of methods, but did provide detail on rating recommendations and assessing the quality of the evidence. We rated the ASHM, DHHS, and EACS guidelines as poor methodological quality because of a lack of reporting of methods including literature searching, inclusion criteria for studies, and assessment of strengths and limitations of the evidence. These guidelines also lack external peer review and provide little to no information on funding or disclosures of interest of the guideline panel members. For guidelines that provide disclosures, many panel members reported affiliations with pharmaceutical companies who have developed HIV prevention and treatment drugs and regimens, highlighting potential conflicts of interest.

The included guidelines vary considerably in terms of the metrics used to assess the strength of recommendations and the quality of the underlying evidence. As previously described, the BHIVA/BASHH and CMA guidelines used GRADE methods for rating recommendations; the CDC, DHHS, IAS-USA, and USPSTF guidelines used adapted or modified rating systems. The ASHM and EACS did not formally rate the recommendations or provide assessment of the quality of the underlying evidence.

Despite the extensive research in this field, there are gaps in the evidence that are worth noting. Research is needed to develop and validate tools for identifying individuals at high risk of HIV acquisition who would benefit from PrEP.\(^1\)\(^1\)\(^1\)\(^7\) Risk assessment instruments should include populations most at risk for HIV infection, especially racial and ethnic minorities.\(^1\)\(^7\) Research is needed on different drug regimens, dosing strategies, and optimal timing of PrEP discontinuation.\(^1\)\(^1\)\(^7\) Research is also needed on factors associated with adherence to PrEP and methods to increase uptake and adherence, particularly in populations with low adherence such as adolescents and racial and ethnic minorities.\(^1\)\(^7\) Additional trials or demonstration projects of PrEP in U.S. populations of sexually active heterosexual men and women, PWID, and transgender women and men are needed to better quantify effectiveness in these populations.\(^1\)\(^7\) Data are
needed on the safety and effectiveness of PrEP during pregnancy and breastfeeding.\textsuperscript{11,17} Finally, research is needed on the long-term safety and effectiveness of PrEP.\textsuperscript{17}

Numerous factors contribute to the success of implementing effective PrEP interventions. To fully optimize PrEP, the CMA guideline offers important considerations for implementing PrEP using a health systems approach. PrEP is recommended as part of a combination prevention strategy that includes behavioral interventions (e.g., condoms, risk reduction counseling, partner reduction), biomedical interventions (e.g., treatment of HIV-positive partners, testing and treatment of STI), and attention to synergistic epidemic conditions that may predispose people to increased risk-taking behavior (e.g., depression and substance abuse).\textsuperscript{11} Health systems should ensure the availability of other harm-reduction interventions for PWID, including programs that distribute sterile equipment for drug use and medication-assisted treatments for opioid use disorders.\textsuperscript{11} Health systems should strive to engage a broad range of qualified clinical providers in administration and follow-up of PrEP, including family and specialist physicians, nurses, nurse practitioners, and pharmacists, where scope of practice allows, or under appropriate delegation of responsibility.\textsuperscript{11} In addition, nonprescribing health care and health service providers should be encouraged to play roles in PrEP delivery, including clinical monitoring, screening and management of STIs, risk reduction counseling, and adherence support.\textsuperscript{11} Studies indicate that there is a strong relationship between medication adherence and effectiveness of PrEP: greater adherence is associated with greater reduction in risk of HIV acquisition; therefore, it is important to provide adherence support to individuals on PrEP.\textsuperscript{17}

Recommendations for optimal HIV prevention and treatment strategies will continue to shift as new drugs are approved and longer-term studies become available. Since the last update of the DERP report on treatment of HIV, 1 new drug (doravirine [DOR]; Pifeltro), 6 new drug combinations (BIC/FTC/TAF [Biktarvy], 3TC/TDF [Cimduo], DOR/3TC/TDF [Delstrigo], DTG/RPV [Juluca], EFV/3TC/TDF [Symfi], and c/DRV/FTC/TAF [Symtuza]), and 2 new drug formulations (RAL [Isentress HD] and EFV/3TC/TDF [Symfi Lo]) have been approved by the FDA for treatment of HIV-1. The guidelines that cover treatment have been updated to include the BIC/FTC/TAF combination as a recommended initial regimen for most people with HIV, and DOR-containing regimens were included as recommended regimens for certain clinical conditions. In addition, 1 new biological therapy (ibalizumab [Trogarzo]; monoclonal antibody) was recently approved, further highlighting the changing landscape of treatment in this field. Research is ongoing for alternative, non-oral modes of PrEP that require infrequent dosing (i.e., long-acting injectables and an intravaginal ring), which could lead to changes in PrEP guidelines in the future.\textsuperscript{17} These changes underscore the need for continued timely evaluation of new evidence to identify benefits and harms of HIV prevention and treatment regimens as well as where new regimens fit in the constellation of management strategies for individuals with HIV.
References


Appendix A. Methods

Clinical Practice Guidelines Methods

Search Strategy
We searched Center for Evidence-based Policy (Center) core clinical practice guidelines sources to identify guidelines using the terms human immunodeficiency virus, HIV, prevention, pre-exposure prophylaxis, PrEP, treatment, antiretroviral therapy/treatment, ARV, and ART. We limited searches of core sources to citations published in 2016 and later.

We searched for clinical practice guidelines published in the last 2 years, using the following sources:
- Ovid MEDLINE
- Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM)
- Australian National Health and Medical Research Council (NHMRC)
- British HIV Association (BHIVA)
- Canadian Medical Association (CMA)
- Centers for Disease Control and Prevention (CDC)
- European AIDS Clinical Society (EACS)
- International Antiviral Society (IAS)
- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guidelines Network (SIGN)
- U.S. Department of Health and Human Services (DHHS)
- U.S. Preventive Services Task Force (USPSTF)
- VA/DoD Clinical Practice Guidelines

Ovid MEDLINE Search Strategy
Database: Ovid MEDLINE(R) <1946 to July Week 5 2018>

1  exp HIV/ or exp HIV-1/ (92643)
2  guidelines.mp. or GUIDELINE/ or PRACTICE GUIDELINE/ (327775)
3  clinical practice guideline.mp. (2276)
4  2 or 3 (328139)
5  1 and 4 (1341)
6  limit 5 to yr="2016 -Current" (151)
Exclusion Criteria
We excluded guidelines if they were not published in English, if they did not present recommendations on treatment or prevention of HIV, and if they were published before 2016.

Quality Assessment

Methodological Quality of Clinical Practice Guidelines
We assessed the methodological quality of the included clinical practice guidelines using standard instruments developed and adapted by the Center that are modifications of instruments used by several renowned, respected organizations.27-29 One experienced researcher independently rated the methodological quality of included clinical practice guidelines. A second experienced researcher reviewed each assessment. Disagreement was managed by discussion.

We assessed the methodological quality of the guidelines using an instrument adapted from the Appraisal of Guidelines Research and Evaluation (AGREE) Collaboration.27-29 Each rater assigned the study a rating of good, fair, or poor based on its adherence to recommended methods and potential for biases. A good-methodological-quality guideline fulfills all or most of the criteria outlined in the instrument. A fair-methodological-quality guideline fulfills some of the criteria, and its unfulfilled criteria are not likely to alter the recommendations. A poor-methodological-quality guideline met few or none of the criteria.
# Appendix B. Antiretroviral Treatment Options for Patients with HIV-1

Table B1. Antiretroviral Therapy Options for Treatment-Naïve Patients

<table>
<thead>
<tr>
<th>Drug or Combination</th>
<th>Dosing Frequency</th>
<th>Dual-NRTIs</th>
</tr>
</thead>
</table>
| ABC/3TC             | Once daily      | • ABC/3TC
|                     |                 | • DTG/ABC/3TC                                                           |
| TAF/FTC             | Once daily      | • TAF 25 mg/FTC                                                          |
|                     |                 | • BIC/TAF 25 mg/FTC                                                      |
|                     |                 | • DRV/c/TAF 10 mg/FTC                                                    |
|                     |                 | • EVG/c/TAF 10 mg/FTC                                                    |
|                     |                 | • RPV/TAF 25 mg/FTC                                                     |
| TDF/FTC             | Once daily      | • TDF/FTC                                                               |
|                     |                 | • EVF/TDF/FTC                                                            |
|                     |                 | • EVG/c/TDF/FTC                                                          |
|                     |                 | • RPV/TDF/FTC                                                            |
| TDF/3TC             | Once daily      | • TDF/3TC                                                               |
|                     |                 | • DOR/TDF/3TC                                                            |
|                     |                 | • EFV 600 mg/TDF/3TC                                                     |
|                     |                 | • EFV 400 mg/TDF/3TC                                                    |

**Integrase Strand Transfer Inhibitors**

<table>
<thead>
<tr>
<th>Drug or Combination</th>
<th>Dosing Frequency</th>
<th>Single Tablet Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIC</td>
<td>Once daily</td>
<td>BIC/TAF/FTC</td>
</tr>
<tr>
<td>DTG</td>
<td>Once daily</td>
<td>DTG/ABC/3TC</td>
</tr>
</tbody>
</table>
|                     | • Once daily: in ART-naïve or INSTI-naïve persons
|                     | • Twice daily: if used with certain CYP3A4 and UGT1A1 inducers or in INSTI-experienced persons with certain INSTI DRMs |
| EVG                 | Once daily; requires boosting with cobicistat | EVG/c/TAF/FTC
|                     |                  | EVG/c/TDF/FTC          |
| RAL                 | • Once daily: 1,200 mg (two 600 mg tablets)
|                     | • Twice daily: 400 mg | No single tablet regimen available for ART-naïve patients. RAL available as a single drug tablet. |

**Non-Nucleoside Reverse Transcriptase Inhibitors**

<table>
<thead>
<tr>
<th>Drug or Combination</th>
<th>Dosing Frequency</th>
<th>Single Tablet Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOR</td>
<td>Once daily</td>
<td>DOR/TDF/3TC</td>
</tr>
<tr>
<td>EFV</td>
<td>Once daily</td>
<td>EFV 600 mg/TDF/FTC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EFV 600 mg/TDF/3TC</td>
</tr>
<tr>
<td>Drug or Combination</td>
<td>Dosing Frequency</td>
<td>Formulations, Coformulations, or Single Tablet Regimens</td>
</tr>
<tr>
<td>---------------------</td>
<td>------------------</td>
<td>--------------------------------------------------------</td>
</tr>
<tr>
<td>RPV</td>
<td>Once daily</td>
<td>• EFV 400 mg/TDF/3TC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• RPV/TAF/FTC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• RPV/TDF/FTC</td>
</tr>
<tr>
<td>Protease Inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATV</td>
<td>Once daily</td>
<td>• ATV/c</td>
</tr>
<tr>
<td>DRV</td>
<td>• Once daily for PI-naïve patients</td>
<td>• DRV/c</td>
</tr>
<tr>
<td></td>
<td>• Twice daily for PI-experienced patients with certain PI mutations</td>
<td>• DRV/c/TAF/FTC</td>
</tr>
</tbody>
</table>

Abbreviations. 3TC: lamivudine; ABC: abacavir; ART: antiretroviral therapy; ATV: atazanavir; BIC: bictegravir; c: cobicistat; CYP3A4: cytochrome P450 3A4 enzyme; DRV: darunavir; DOR: doravirine; DRM: drug resistance mutation; DTG: dolutegravir; EFV: efavirenz; EVG: elvitegravir; FTC: emtricitabine; INSTI: integrase strand transfer inhibitor; PI: protease inhibitor; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate; RAL: raltegravir; RPV: rilpivirine. UGT1A1: UDP Glucuronosyltransferase Family 1 Member A1 gene.
<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Type of Failing Regimen</th>
<th>Resistance Considerations</th>
<th>New Regimen Optionsa,b</th>
<th>Goal of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First Regimen Failure</strong></td>
<td>NNRTI + 2 NRTIs</td>
<td>Most likely resistant to NNRTI ± 3TC/FTC (i.e., NNRTI mutations ± M184V/I). Additional NRTI mutations may also be present.</td>
<td>• Boosted PI + 2 NRTIs (at least 1 active) (AI), or</td>
<td>Resuppression</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• DTGd + 2 NRTIs (at least 1 active) (AI), or</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Boosted PI + INSTI (AI)</td>
<td></td>
</tr>
<tr>
<td>Boosted PI + 2 NRTIs</td>
<td></td>
<td>Most likely no resistance, or resistance only to 3TC/FTC (i.e., M184V/I, without resistance to other NRTIs).</td>
<td>• Continue same regimen (AI), or</td>
<td>Resuppression</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Another boosted PI + 2 NRTIs (at least 1 active) (AI), or</td>
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<tr>
<td></td>
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<td></td>
<td>• INSTI + 2 NRTIs (at least 1 active; if only 1 of the NRTIs is fully active, or, if adherence is a concern, DTGd is preferred over the other INSTIs) (AI), or</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Another boosted PI + INSTI (BII)</td>
<td></td>
</tr>
<tr>
<td>INSTI + 2 NRTIs</td>
<td></td>
<td>No INSTI resistance (can have 3TC/FTC resistance, i.e., only M184V/I, usually without resistance to other NRTIs).</td>
<td>• Boosted PI + 2 NRTIs (at least 1 active) (AI), or</td>
<td>Resuppression</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• DTGd + 2 NRTIs (at least 1 active) (AI), or</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Boosted PI + INSTI (BIII)</td>
<td></td>
</tr>
<tr>
<td>EVG or RAL ± 3TC/FTC</td>
<td></td>
<td>Resistance to first-line BIC or DTG is rare.</td>
<td>• Boosted PI + 2 NRTIs (at least 1 active) (AI), or</td>
<td>Resuppression</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• DTGd,e twice daily (if patient is sensitive to DTG) plus 2 active NRTIs (AI), or</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• DTGd,e twice daily (if patient is sensitive to DTG) + a boosted PI (AI)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• BIC has not been studied in this setting and cannot be recommended.</td>
<td></td>
</tr>
<tr>
<td><strong>Second Regimen Failure</strong></td>
<td>Drug resistance with active treatment options</td>
<td>Use past and current genotypic ± phenotypic resistance testing and ART history in designing new regimen.</td>
<td>• At least 2, and preferably 3, fully active agents (AI).</td>
<td>Resuppression</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Partially active drugs may be used when no other options are available.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Consider using an ARV with a different mechanism of action.</td>
<td></td>
</tr>
<tr>
<td>Multiple or extensive drug resistance with few treatment options</td>
<td>Use past and current genotypic and phenotypic resistance testing to guide therapy.</td>
<td>• Identify as many active or partially active drugs as possible based on resistance test results.</td>
<td>Resuppression, if possible; otherwise, keeping viral load</td>
<td></td>
</tr>
<tr>
<td>Clinical Scenario</td>
<td>Type of Failing Regimen</td>
<td>Resistance Considerations</td>
<td>New Regimen Options&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>Goal of Treatment</td>
</tr>
<tr>
<td>-------------------</td>
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<td>---------------------------</td>
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<td>-------------------</td>
</tr>
</tbody>
</table>
| Previously on treatment, suspected drug resistance, limited or incomplete ART and resistance history | Unknown | Obtain medical records if possible. Resistance testing may be helpful in identifying drug resistance mutations, even if the patient has been off ART. Keep in mind that resistance mutations may not be detected in the absence of drug pressure. | - Consider restarting the old regimen, and obtain viral load and resistance testing 2 to 4 weeks after reintroduction of therapy.  
- If there is no available ARV history, consider initiating a regimen with drugs with high genetic barriers to resistance (e.g., DTG<sup>d,e</sup> and/or boosted DRV). | Resuppression |

**Abbreviations.** 3TC: lamivudine; ART: antiretroviral therapy; ARV: antiretroviral; BIC: bictegravir; DTG: dolutegravir; DRV: darunavir; EVG: elvitegravir; FTC: emtricitabine; INSTI: integrase strand transfer inhibitor; M184V/I: methionine replacing mutation; MVC: maraviroc; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; RAL: raltegravir.  
**Notes.**<sup>a</sup> There are insufficient data to provide a recommendation for the continuation of 3TC/FTC in the presence of M184V/I.  
<sup>b</sup> When switching an ARV regimen in a patient with HIV/HBV coinfection, ARV drugs that are active against HBV should be continued as part of the new regimen. Discontinuation of these drugs may lead to the reactivation of HBV, which may result in serious hepatocellular damage.  
<sup>c</sup> If other NNRTI resistance mutations are present, use resistance test results to guide NRTI usage in the new regimen.  
<sup>d</sup> Preliminary data from Botswana have suggested that there is an increased risk of neural tube defects in infants born to individuals who were receiving DTG at the time of conception.  
<sup>e</sup> Pregnancy testing should be performed for women of childbearing potential prior to initiation of DTG.  
<sup>f</sup> Response to DTG depends on the type and number of INSTI mutations.

Conflict of Interest Disclosures: No authors have conflicts of interest to disclose. All authors have completed and submitted the Oregon Health & Science University form for Disclosure of Potential Conflicts of Interest, and none were reported.