What to Start: Initial Combination Antiretroviral Regimens for People with HIV

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Key Considerations and Recommendations

- An initial antiretroviral (ARV) regimen for a person with HIV generally consists of two nucleoside reverse transcriptase inhibitors administered in combination with a third active ARV drug from one of three drug classes: an integrase strand transfer inhibitor (INSTI), a non-nucleoside reverse transcriptase inhibitor, or a protease inhibitor with a pharmacokinetic enhancer (also known as a booster; the two drugs used for this purpose are cobicistat and ritonavir).

- Data also support the use of the two-drug regimen, dolutegravir (DTG) plus lamivudine (3TC), for initial treatment.

- Before initiating antiretroviral therapy (ART) in a person of childbearing potential, clinicians should discuss the person’s intentions regarding pregnancy and a pregnancy test should be performed (AIII). Clinicians should refer to the Perinatal Guidelines for recommendations on initial ARV treatment around the time of conception and during pregnancy.

- The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) classifies the regimens below (in alphabetical order) as Recommended Initial Regimens for Most People with HIV.

  For people with HIV who do not have a history of using long-acting cabotegravir (CAB-LA) as pre-exposure prophylaxis (PrEP), the following regimens are recommended:
  - Bictegravir/tenofovir alafenamide (TAF)/emtricitabine (FTC) (AI)
  - DTG/abacavir/3TC—only for individuals who are HLA-B*5701 negative and without chronic hepatitis B virus (HBV) coinfection (AI)
  - DTG plus (TAF or tenofovir disoproxil fumarate [TDF]) plus (FTC or 3TC) (AI)
  - DTG/3TC (AI)—except for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or when ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available.

  For people with HIV and a history of using CAB-LA as PrEP, INSTI genotypic resistance testing should be done before the start of ART. If treatment is begun prior to results of genotypic testing, the following regimen is recommended:
  - Boosted darunavir plus (TAF or TDF) plus (FTC or 3TC)—pending the results of the genotype test (AIII).

- To address individual patient characteristics and needs, the Panel also provides a list of Recommended Initial Regimens in Certain Clinical Situations (see Table 6 below).

- Given the many excellent options for initial therapy, selection of a regimen for a particular patient should be guided by factors such as virologic efficacy, toxicity, pill burden, dosing frequency, drug–drug interaction potential, resistance-test results, comorbid conditions, access, and cost. For guidance on choosing an ARV regimen based on selected clinical case scenarios, see Table 7. Also see Table 9 for the advantages and disadvantages of different components in an ARV regimen.

- Patients without prior ART use who wish to begin long-acting intramuscular CAB and rilpivirine (RPV) should first achieve viral suppression on another regimen before switching to CAB and RPV (see Optimizing Antiretroviral Therapy in the Setting of Virologic Suppression).
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**Rating of Recommendations:** A = Strong; B = Moderate; C = Weak

**Rating of Evidence:** I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials, observational cohort studies with long-term clinical outcomes, relative bioavailability/bioequivalence studies, or regimen comparisons from randomized switch studies; III = Expert opinion

### Introduction

More than 30 antiretroviral (ARV) drugs in eight mechanistic classes are U.S. Food and Drug Administration (FDA)-approved for treatment of HIV infection. These eight classes are nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), a fusion inhibitor, a CCR5 antagonist, a CD4 T lymphocyte (CD4) post-attachment inhibitor, and a gp120 attachment inhibitor. In addition, two drugs, ritonavir (RTV) and cobicistat (COBI) are used as pharmacokinetic (PK) enhancers (or boosters) to improve the PK profiles of PIs and the INSTI elvitegravir (EVG).

The initial ARV treatment regimen for a person with HIV generally consists of two NRTIs, usually abacavir/lamivudine (ABC/3TC) or either tenofovir alafenamide/emtricitabine (TAF/FTC) or tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), plus a drug from one of three drug classes: an INSTI, an NNRTI, or a boosted PI. As shown in clinical trials and by retrospective evaluation of cohorts of patients in clinical care, this strategy for initial treatment has resulted in suppression of HIV replication and CD4 count increases in most people with HIV. Additional data now support the use of the two-drug regimen dolutegravir/lamivudine (DTG/3TC) for initial treatment of some people with HIV.

### Supporting Evidence and Rationale Used for the Panel’s Recommendations

The Panel on Antiretroviral Guidelines for Adults and Adolescents’ (the Panel) recommendations are primarily based on clinical trial data published in peer-reviewed journals and on data prepared by drug manufacturers for FDA review. In select cases, the Panel considers data from abstracts presented at major scientific meetings. The Panel considers published information from randomized, prospective clinical trials with adequate sample size that demonstrate that an ARV regimen produces high rates of viral suppression, increases CD4 count, and has a favorable safety profile to be the strongest evidence on which to base recommendations. Comparative clinical trials of initial treatments generally show no significant differences in HIV-related clinical endpoints (such as progression to AIDS-defining conditions) or survival. Thus, assessment of regimen efficacy and safety are primarily based on surrogate marker endpoints (i.e., rates of HIV RNA suppression) and the incidence and severity of adverse events.

In some instances, the Panel recommends regimens that include ARV drugs approved by the FDA based on bioequivalence or relative bioavailability studies that demonstrate that the exposure of the drug(s) in the new formulation or combination is comparable to the exposure of a reference drug(s)
that has demonstrated safety and efficacy in randomized clinical trials. When developing recommendations, the Panel may also consider data from randomized switch studies in which a drug in an ARV initial regimen that suppressed patients’ viral loads is replaced by a new drug from the same class. Switch trials do not evaluate the ability of a drug or regimen to induce viral suppression; they only examine the drug or regimen’s ability to maintain suppression. Therefore, results from switch trials may not be directly applicable to the selection of an initial regimen and should be considered in conjunction with other data, including data from bioavailability/bioequivalence studies and from trials conducted in people taking their first ARV treatment regimen. In this section of the guidelines, the definition of an evidence rating of II is expanded to include supporting data from bioavailability/bioequivalence studies or randomized switch studies.

When developing recommendations, the Panel also considers tolerability and toxicity profiles, pill burden and dosing frequency, drug interaction potential, cost and access, post-marketing safety data, observational cohort data published in peer-reviewed publications, the experience of clinicians who are actively engaged in patient care, and the views of community members.

The Panel reviewed the available data to arrive at two classifications for initial ARV treatment regimens: (1) Recommended Initial Regimens for Most People with HIV and (2) Recommended Initial Regimens in Certain Clinical Situations (see Table 6 below). Recommended Initial Regimens for Most People with HIV are those regimens with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use. The Panel also recognizes that, in certain clinical situations, other regimens may be preferred; these options are included in Table 6 in the category of Recommended Initial Regimens in Certain Clinical Situations. See Table 7 for examples of clinical scenarios in which certain drugs in these regimens may be particularly advantageous.

There are many other ARV regimens that are effective for initial therapy but have disadvantages when compared with the regimens listed in Table 6. These disadvantages include greater toxicity, higher pill burden, less supporting data from large comparative clinical trials, or limitations for use in certain patient populations. These regimens are no longer included in Table 6. A person with HIV who has a suppressed viral load and is not experiencing any adverse effects while on a regimen that is not listed in Table 6 need not necessarily change to one that is listed in the table. Clinicians should refer to Optimizing Antiretroviral Therapy in the Setting of Viral Suppression for further guidance if switching to a new regimen is desired.

The ARV drugs and regimens listed in Table 10 are not recommended as initial therapy. In most instances, a clinician is urged to consider switching a patient who is on one of the regimens listed in Table 10 to a recommended regimen.

In addition to these tables, several tables in these guidelines provide clinicians with guidance on selecting and prescribing an optimal regimen for an individual patient. Table 9 lists the potential advantages and disadvantages of the different ARV drug components. Appendix B, Tables 3–9 list characteristics of individual ARV agents (e.g., formulations, dosing recommendations, PKs, common adverse effects). Appendix B, Table 12 provides ARV dosing recommendations for patients who have renal or hepatic insufficiency.
Changes Since the Last Revision of the Guidelines

Since the last revision of these guidelines, the Panel has made several important changes to the recommendations for initial therapy in people with HIV. Among these changes, the following deserve emphasis:

- Long-acting injectable cabotegravir (CAB-LA) was approved by the FDA for HIV pre-exposure prophylaxis (PrEP). Because of the long half-life of CAB-LA, drug levels may be present in some individuals for up to 4 years. This persistent drug exposure at levels suboptimal to prevent infection may select for INSTI-resistant virus. Therefore, in this setting, the Panel recommends that results of an INSTI genotypic resistance test be available before initiating an INSTI-based regimen, because the presence of cabotegravir (CAB)-resistant mutations may have cross-resistance to other INSTIs, including bictegravir (BIC) and dolutegravir (DTG). When antiretroviral therapy (ART) is initiated before an INSTI genotype result is available, a non-INSTI regimen containing boosted darunavir (DRV) plus (tenofovir alafenamide [TAF] or tenofovir disoproxil fumarate [TDF]) plus (emtricitabine [FTC] or lamivudine [3TC]) should be initiated, pending genotype results. If an INSTI-based regimen is initiated and viral suppression is not achieved, genotypic testing for resistance (including for INSTIs) should be repeated.

Table 6. Recommended Antiretroviral Regimens for Initial Therapy

Selection of a regimen should be individualized based on virologic efficacy, potential adverse effects, childbearing potential and use of effective contraception, pill burden, dosing frequency, drug–drug interaction potential, comorbid conditions, cost, access, and resistance-test results. A pregnancy test should be performed in persons of childbearing potential, and choice of ART for pregnant individuals should be guided by recommendations from the Perinatal Guidelines. Drug classes and regimens within each class are arranged first by evidence rating and, when ratings are equal, in alphabetical order. See Table 7 for ARV recommendations based on specific clinical scenarios.

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**For people who do not have a history of CAB-LA use as PrEP, the following regimens are recommended:**

**INSTI plus Two NRTIs**
- BIC/TAF/FTC (AI)\(^a\)
- DTG/ABC/3TC (AI)—if HLA-B*5701 negative
- DTG plus (TAF or TDF)\(^c\) plus (FTC or 3TC) (AI)

**INSTI plus One NRTI**
- DTG/3TC (AI), except for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available

**For people with HIV and a history of CAB-LA use as PrEP, INSTI genotypic resistance testing should be performed before the start of ART. If treatment is begun prior to results of genotypic testing, the following regimen is recommended:**
- DRV/c\(^f\) or DRV/r with (TAF or TDF)\(^c\) plus (FTC or 3TC) pending the results of the genotype test (AIII)
Table 6. Recommended Antiretroviral Regimens for Initial Therapy

These regimens are effective and tolerable but have some disadvantages when compared with the regimens listed above or have fewer supporting data from randomized clinical trials. However, in certain clinical situations, one of these regimens may be preferred (see Table 7 for examples).

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**INSTI plus Two NRTIs**
- EVG/c/(TAF or TDF)c FTC (BI)b
- RAL plus (TAF or TDF)c plus (FTC or 3TC) (BI for TDF/[FTC or 3TC], BII for TAF/FTC)

**Boosted PI plus Two NRTIs**
- In general, boosted DRV is preferred over boosted ATV
  - (DRV/cb or DRV/r) plus (TAF or TDF)c plus (FTC or 3TC) (AI)b
  - (ATV/cb or ATV/r) plus (TAF or TDF)c plus (FTC or 3TC) (BI)b
  - (DRV/cb or DRV/r) plus ABC/3TC— if HLA-B*5701 negative (BII)b

**NNRTI plus Two NRTIs**
- DOR/TDF/3TC (BI) or DOR plus TAFc/FTC (BIII)
- EFV plus (TAF or TDF)c plus (FTC or 3TC)
  - EFV 600 mg plus TDF plus (FTC or 3TC) (BI)
  - EFV 400 mg/TDF/3TC (BI)
  - EFV 600 mg plus TAF/FTC (BII)
- RPV/(TAF or TDF)c/FTC (BII for TAF and BI for TDF)— if HIV RNA <100,000 copies/mL and CD4 count >200 cells/mm³

**Regimens to Consider When ABC, TAF, and TDF Cannot Be Used or Are Not Optimal**
- DTG/3TC (AI), except for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available
- DRV/r plus RAL twice a day (CI)— if HIV RNA <100,000 copies/mL and CD4 count ≥200 cells/mm³
- DRV/r once daily plus 3TC (CI)

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a BIC should not be initiated in pregnant people due to insufficient data.
b COBI should be avoided in pregnancy because lower concentrations of COBI and its boosted drugs—EVG, DRV, and ATV—have been observed during the second and third trimesters. For individuals with viral suppression who become pregnant while on a COBI-containing regimen and wish to remain on that regimen after counseling regarding lower drug concentration, frequent viral load monitoring is recommended. For further information, refer to the Perinatal Guidelines.
c TAF and TDF are two forms of TFV approved by the FDA. TAF has fewer bone and kidney toxicities than TDF, while TDF is associated with lower lipid levels. Safety, cost, and access are among the factors to consider when choosing between these drugs.
Table 6. Recommended Antiretroviral Regimens for Initial Therapy

Note: The following are available as coformulated drugs: ABC/3TC, ATV/c, BIC/TAF/FTC, DOR/TDF/3TC, DRV/c, DRV/c/TAF/FTC, DTG/3TC, DTG/ABC/3TC, EFV (400 mg or 600 mg)/TDF/3TC, EFV/TDF/FTC, Efavirenz/TDF/FTC, Efavirenz/TDF/FTC, TAF/FTC, TDF/3TC, and TDF/FTC.

Key: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; CAB-LA = cabotegravir long-acting; CD4 = CD4 T lymphocyte; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDA = U.S. Food and Drug Administration; FTC = emtricitabine; HBV = hepatitis B virus; HLA = human leukocyte antigen; INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PrEP = pre-exposure prophylaxis; RAL = raltegravir; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TFV = tenofovir

Selecting an Initial Antiretroviral Regimen

The goal of ART is to provide a potent, safe, tolerable, and easy-to-adhere-to regimen in order to achieve sustained virologic control. Initial therapy should be with two NRTIs combined with an INSTI, the combination of DTG/3TC or, in some individuals, a combination including two NRTIs plus an NNRTI or an RTV- or COBI-boosted PI. When selecting a regimen for a person with HIV, a number of patient- and regimen-specific characteristics should be considered. Some of the factors can be grouped into the categories listed below, and these factors may influence the selection of a regimen. See Table 7 for additional regimen recommendations to use in specific clinical scenarios. Individuals without prior ART treatment who wish to use long-acting injectable CAB and rilpivirine (RPV) should first achieve viral suppression on another regimen before shifting to oral, and then injectable, CAB and RPV (see Optimizing Antiretroviral Therapy in the Setting of Virologic Suppression).

Initial Characteristics to Consider in All People with HIV

- Pre-treatment HIV RNA level (viral load)
- Pre-treatment CD4 count
- History of prior exposure to CAB-LA as PrEP
- HIV genotypic drug resistance test results. Based on current rates of transmitted drug resistance to different ARV drugs, standard genotypic drug resistance testing in ARV-naive persons should focus on testing for mutations in the reverse transcriptase and protease genes. If transmitted INSTI resistance is a concern, providers should consider also testing for resistance mutations to this class of drugs. People who acquired HIV after a history of taking CAB-LA as PrEP should have a blood specimen collected for INSTI genotypic resistance testing prior to ART initiation, but they may initiate non–INSTI-based ART prior to receipt of results.
- HLA-B*5701 status. Those who are HLA-B*5701 positive should not receive ABC. Regimens that do not include ABC can be initiated if HLA-B*5701 test results are not yet available; see Table 7 for regimens to initiate.
- Individual preferences
- Anticipated adherence to the regimen
- Whether ART initiation occurs prior to availability of baseline laboratory results
• It should be noted that results of pre-treatment HIV RNA, CD4 count, and resistance testing do not need to be available before starting ART, unless the individual is planning to begin an INSTI-containing regimen and has had prior exposure to CAB-LA as PrEP. See Table 7 for regimens to initiate if these results are not available.

Presence of Specific Conditions

• Comorbid conditions: Cardiovascular disease; hyperlipidemia; renal disease; liver disease; osteopenia, osteoporosis, or other conditions associated with bone mineral density loss; psychiatric illness; neurologic disease; substance use disorder requiring narcotic replacement therapy

• Coinfections: Hepatitis B virus (HBV), hepatitis C virus, tuberculosis (TB)

• Pregnancy and potential for pregnancy: See below, General Considerations for Persons of Childbearing Potential Initiating Antiretroviral Therapy

Regimen-Specific Considerations

• Regimen’s barrier to resistance

• Potential adverse effects and drug toxicities, including risk for development of comorbid diseases

• Known or potential drug interactions with other medications (see Drug–Drug Interactions)

• Convenience (e.g., pill burden, dosing frequency, availability of a fixed-dose combination or single-tablet regimen [STR] formulations, food requirements)

• Cost and access (see Cost Considerations and Antiretroviral Therapy)

General Considerations for Persons of Childbearing Potential Initiating Antiretroviral Therapy

• A pregnancy test should be performed before initiating ART.

• Clinicians should discuss intentions regarding pregnancy with all persons of childbearing potential.

• People with HIV should attain maximum viral suppression before attempting conception in order to protect their own health, prevent sexual HIV transmission to partners without HIV, and minimize the risk of perinatal HIV transmission to the infant.

• A DTG-based regimen is one of the recommended options for persons of childbearing potential initiating ART. Before initiating a DTG-based regimen, clinicians should discuss the risks and benefits of using DTG with persons of childbearing potential to allow them to make an informed decision. Please refer to the Women with HIV section and INSTI-Based Regimens below for additional details.

• For individuals who are trying to conceive, the Panel recommends initiating a regimen designated as a Preferred regimen during pregnancy as detailed in the Perinatal Guidelines.
General Considerations for INSTI-, PI-, or NNRTI-Based Regimens

The choice between an INSTI, PI, or NNRTI in an initial ARV regimen should be guided by the ARV drug’s efficacy, barrier to resistance, and adverse effects profile; convenience; the patient’s comorbidities and concomitant medications; the potential for drug–drug interactions (see Tables 7 and 9); and whether the individual has been exposed to CAB-LA as PrEP prior to HIV acquisition.

Due to concerns about INSTI resistance in the setting of past use of CAB-LA as PrEP, the Panel recommends initiating a boosted PI regimen of darunavir/ritonavir (DRV/r) or darunavir/cobicistat (DRV/c) plus (TAF or TDF) plus (FTC or 3TC) while awaiting availability of INSTI genotype results. In HPTN 083, a study of CAB-LA as PrEP in cisgender men and transgender women, CAB-resistant mutations were reported in one of four cases of persons who received CAB-LA but had undetected HIV infection at baseline and in four of nine cases of incident HIV infection. In this study, there were no cases of infection during the tail phase of CAB decay following the last dose. In this study, there were no cases of infection during the tail phase of CAB decay following the last dose. One additional HIV acquisition with INSTI-resistant mutations occurred during the oral CAB lead-in phase. In HPTN 084, a study of CAB-LA as PrEP in cisgender women, four HIV infections occurred in the CAB-LA arm (one baseline, three incident) and no CAB-resistant mutations were detected. All individuals had low or unquantifiable CAB levels. Two of the three persons with incident infection never received injectable CAB.\textsuperscript{7} HPTN 077, a PK study of CAB-LA, suggested that suboptimal CAB levels could persist for as long as 3 years in men and 4 years in women, suggesting that HIV acquisition following even distant CAB-LA exposure may confer risk of INSTI resistance.\textsuperscript{8}

INSTI-Based Regimens

The Panel’s Recommended Initial Regimens for Most People with HIV as listed in Table 6 include one of two INSTIs (BIC or DTG) plus two NRTIs or DTG/3TC for persons who have not had exposure to CAB-LA as PrEP. In those with prior exposure to CAB-LA as PrEP, these regimens should not be initiated unless a genotype test result showing no INSTI-resistance mutations is available. If an INSTI-based regimen is initiated and viral suppression is not achieved in 8 to 12 weeks, genotypic resistance testing should be repeated, including for INSTIs.

For most patients, these INSTI-containing regimens will be highly effective and have relatively infrequent treatment-limiting adverse effects and few drug interactions. In several head-to-head comparisons between boosted PI- and INSTI-containing regimens, the INSTI-based regimens were better tolerated and caused fewer treatment discontinuations.\textsuperscript{9-11} The Panel recommends a two-drug regimen of DTG/3TC for initial therapy if certain criteria are met. Data from two randomized trials showed that, in terms of virologic efficacy, DTG plus 3TC was noninferior to a three-drug regimen of DTG plus TDF/FTC. No treatment-emergent resistance was seen in either the two-drug or the three-drug group. The study inclusion criteria limited enrollment to participants with HIV RNA levels <500,000 copies/mL; no known major NRTI, PI, or NNRTI resistance; and without active HBV.\textsuperscript{4,12}

Among the INSTI-based regimens, BIC- and DTG-containing regimens have a higher barrier to resistance and lower pill burden than the first-generation INSTI-based regimens that contain EVG or raltegravir (RAL). Treatment-emergent resistance has been reported very rarely in individuals receiving three-drug DTG-based therapy\textsuperscript{13-15} and rarely has been reported in those receiving BIC-based regimens.\textsuperscript{16} In addition, transmitted resistance to BIC and DTG is rare. Because of this high barrier to resistance and tolerability, BIC- and DTG-containing regimens may be considered for
patients who plan to start ART before resistance-test results are available (e.g., with rapid initiation of ART after diagnosis). BIC-based regimens have been shown to be noninferior to DTG-based regimens in clinical trials.\textsuperscript{17,18}

Preliminary data from a birth outcomes surveillance study in Botswana suggested an increased risk of neural tube defects (NTDs) (0.9\%) in infants born to women who were receiving DTG at the time of conception.\textsuperscript{19} Updated data from the same study showed that the prevalence of NTDs in infants born to women on DTG at the time of conception is not significantly different from those on non-DTG regimens at the time of conception.\textsuperscript{20} For persons of childbearing potential who are trying to conceive, DTG-based regimens are among the recommended options for most individuals initiating ART, but clinicians should discuss the risks and benefits of using DTG in persons of childbearing potential to allow them to make an informed decision. BIC/TAF/FTC should not be used in pregnant people due to insufficient data in pregnancy. Because of inadequate drug levels in the second and third trimesters of pregnancy, COBI-boosted EVG should be avoided in a pregnant person. People with suppressed virus on a COBI-boosted regimen who wish to continue the regimen should be followed with frequent viral load monitoring. TAF is now recommended by the Perinatal Guidelines as an alternate drug in pregnancy due to insufficient data on teratogenicity in humans but reassuring data from the Antiretroviral Pregnancy Registry. Clinicians should refer to the Perinatal Guidelines before prescribing ART to a pregnant person or a person of childbearing potential.

There are now data suggesting greater weight gain with certain INSTI-based regimens and TAF than with other ARV drugs. The clinical significance of these findings is still unknown.\textsuperscript{21-27}

EVG- and RAL-based regimens have the disadvantage of having lower barriers to resistance than DTG- or BIC-containing regimens and, therefore, are not recommended regimens for most people with HIV. Also of importance is that EVG-based regimens have a greater potential for drug interactions, because EVG is combined with COBI (EVG/c), a strong cytochrome P 3A4 inhibitor (see Table 7).

**PI-Based Regimens**

PK-enhanced PI-based regimens also are recommended in certain clinical situations. Similar to EVG/c, they have the disadvantage of greater drug interaction potential than other ARV drugs. For those individuals in whom ART needs to begin urgently before resistance-test results are available, boosted DRV may be an appropriate choice because the rate of transmitted PI resistance is low, and boosted DRV has a high barrier to resistance and a low rate of treatment-emergent resistance. DRV/c/TAF/FTC is available as an STR. Boosted atazanavir (ATV), like boosted DRV, has relatively few metabolic adverse effects in comparison to older boosted-PI regimens; however, atazanavir/ritonavir (ATV/r) had a higher rate of adverse effect-associated drug discontinuation than DRV/r or RAL in a randomized clinical trial.\textsuperscript{9} In a substudy of this trial, and in a separate cohort study, ATV/r use was associated with slower progression of atherosclerosis, as measured by carotid artery intima medial thickness.\textsuperscript{28,29} Large observational cohorts found an association between some PIs (DRV/r, fosamprenavir, indinavir, and RTV-boosted lopinavir) and an increased risk of cardiovascular events; however, this association was not seen with ATV.\textsuperscript{30-35} Further study is needed. DRV/c and COBI-boosted ATV should be avoided during pregnancy because of inadequate drug levels.
**NNRTI-Based Regimens**

NNRTI-based regimens (which include doravirine [DOR], efavirenz [EFV], or RPV plus 2-NRTIs) may be options for some patients, although these drugs, especially EFV and RPV, have low barriers to resistance. The emergence of resistance at the time of virologic failure also has been reported with DOR. EFV has a long track record of widespread use, is considered safe in persons of childbearing potential, and has minimal PK interaction with rifamycins, making it an attractive option for patients who require TB treatment. EFV-based regimens (using either 400-mg or 600-mg dosing) have excellent virologic efficacy, including in patients with high HIV RNA (except when EFV is used with ABC/3TC). However, the relatively high rate of central nervous system (CNS)-related side effects reduces the tolerability of EFV-based regimens. As an STR, EFV 600 mg is available with TDF/FTC or TDF/3TC; EFV 400 mg is available with TDF/3TC. RPV has fewer adverse effects than EFV, is available as one of the smallest tablet sizes among STRs that also include TAF/FTC or TDF/FTC, and has a favorable lipid profile. However, RPV has lower virologic efficacy in patients with baseline HIV RNA levels >100,000 copies/mL and CD4 counts <200 cells/mm³. DOR is available both as a single-drug tablet to be used with two NRTIs and as part of an STR with TDF/3TC. In randomized trials, DOR was noninferior to both EFV and DRV/r when either of these drugs were taken in combination with two NRTIs. DOR has CNS tolerability advantages over EFV and more favorable lipid effects than DRV/r and EFV. DOR also has fewer potential drug interactions than EFV or RPV, and unlike RPV, the virologic efficacy of DOR is not compromised in patients with high HIV RNA levels and low CD4 counts. In a cross-trial analysis, DOR was not associated with weight gain compared with EFV 600 mg or boosted DRV.

**Regimens When Abacavir, Tenofovir Alafenamide, and Tenofovir Disoproxil Fumarate Cannot Be Used or Are Not Optimal**

In those patients in whom ABC, TDF, or TAF cannot be used or are not optimal, there are several two-drug options that do not contain these agents. Two-drug ARV options **should not be used** in individuals with HBV coinfection (unless separate HBV treatment is also used) or in those with known pre-existing resistance to any of the ARVs in the combination. Among the two-drug regimens, DTG/3TC is preferred because there are substantial data for this combination in initial therapy, with the caveat that people with HIV RNA >500,000 copies/mL were excluded from the largest trial. Another two-drug treatment option that can be considered is the combination of DRV/r (once daily) plus RAL (twice daily), but this combination should only be used in those with baseline CD4 counts >200 cells/mm³ and HIV RNA levels <100,000 copies/mL. A small randomized trial indicated that once-daily DRV/r plus 3TC had similar efficacy to once-daily DRV/r plus TDF/3TC, although this study has yet to be published.
References


