

What to Start: Initial Combination Regimens for the Antiretroviral-Naive Patient

(Last updated June 3, 2021; last reviewed June 3, 2021)

Key Considerations and Recommendations

- An antiretroviral (ARV) regimen for a treatment-naive patient generally consists of two nucleoside reverse transcriptase inhibitors (NRTIs) 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 (NNRTI), or a protease inhibitor (PI) with a pharmacokinetic (PK) 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 plus lamivudine, 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 regimen for an ART-naive person around the time of conception and during pregnancy.**
- The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) classifies the following regimens as *Recommended Initial Regimens for Most People with HIV* (in alphabetical order):
 - Bictegravir/tenofovir alafenamide/emtricitabine **(AI)**^a
 - Dolutegravir/abacavir/lamivudine—**only** for individuals who are HLA-B*5701 negative and without chronic hepatitis B virus (HBV) coinfection **(AI)**
 - Dolutegravir plus (emtricitabine or lamivudine) plus (tenofovir alafenamide [TAF] or tenofovir disoproxil fumarate [TDF])^b **(AI)**
 - Dolutegravir/lamivudine **(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.
- 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 such factors as virologic efficacy, toxicity, pill burden, dosing frequency, drug-drug interaction potential, resistance test results, comorbid conditions, access, and cost. [Table 7](#) provides guidance on choosing an ARV regimen based on selected clinical case scenarios. [Table 9](#) highlights the advantages and disadvantages of different components in a regimen.
- **Patients without prior ART who wish to begin long-acting intramuscular cabotegravir (CAB) and rilpivirine (RPV) should first achieve viral suppression on another regimen before switching to oral, and then injectable, CAB and RPV (see [Optimizing Antiretroviral Therapy in the Setting of Virologic Suppression](#)).**

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

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

^a **Bictegravir should not be prescribed to people who are pregnant because of insufficient data in pregnancy.**

^b TAF and TDF are two forms of tenofovir that are approved by the Food and Drug Administration. TAF has fewer bone and kidney toxicities than TDF, whereas TDF is associated with lower lipid levels. Safety, cost, and access are among the factors to consider when choosing between these drugs.

Introduction

More than 30 antiretroviral (ARV) drugs in **eight** mechanistic classes are Food and Drug Administration (FDA)-approved for treatment of HIV infection. These **eight** classes include the 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 regimen for a treatment-naive patient 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.¹⁻³ Additional data now support the use of the two-drug regimen dolutegravir/lamivudine (DTG/3TC) for initial treatment of some people with HIV.⁴

Supporting Evidence and Rationale Used for the Panel’s Recommendations

Recommendations made by the Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) are based primarily on clinical trial data published in peer-reviewed journals and 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 a randomized, prospective clinical trial with an adequate sample size that demonstrates 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 based primarily on surrogate marker endpoints (especially rates of HIV RNA suppression) and the incidence and severity of adverse events.

In some instances, the Panel recommends regimens that include medications approved by the FDA, based on bioequivalence or relative bioavailability studies demonstrating 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 also may consider data from randomized switch studies in which a medication in an initial regimen that suppressed patients’ viral loads is replaced by a new medication from the same class. Switch trials do not evaluate the ability of a drug or regimen to induce viral suppression; they examine only 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 trials conducted in treatment-naive patients and bioequivalence/bioavailability studies. 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 regimen classifications for ARV-naive patients: (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*. Examples of clinical scenarios in which certain drugs in these regimens may be particularly advantageous are outlined in [Table 7](#).

Many other ARV regimens 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 other 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.

Regimens and medications 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 other tables 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 3–10 list characteristics of individual ARV agents (e.g., formulations, dosing recommendations, PKs, common adverse effects). [Appendix B, Table 11](#) 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:

- Raltegravir (RAL), in combination with FTC or 3TC and TDF or TAF, is now recommended as an *Initial Regimen in Certain Clinical Circumstances*. This change is made primarily because RAL has a lower barrier to resistance than DTG or bictegravir (BIC), it is not part of any single-tablet regimen (STR), and RAL-containing regimens have a higher pill burden than those containing DTG or BIC.
- The Panel previously recommended DTG as an alternative ARV in individuals of childbearing potential who are trying to conceive or who are sexually active and not using effective contraception, because preliminary data from a birth outcome surveillance study in Botswana raised concern that DTG use around the time of conception may be associated with an increased risk of infant neural tube defects (NTDs).⁵ Additional results from the same study have shown that the prevalence of infant NTDs, in association with DTG exposure at conception, is substantially lower than in the preliminary data.^{6,7} This rate was slightly higher than with non-DTG containing regimens, but the difference was not statistically significant. Because of these newer data, the Panel now considers DTG a recommended option for people of childbearing potential. Before initiating a DTG-based regimen, clinicians should discuss the risks and benefits of using DTG with people of childbearing potential to allow them to make an informed decision. Clinicians should refer to the [Perinatal Guidelines](#) for more detailed recommendations on the safety and effectiveness of ARV drugs during conception and throughout pregnancy.
- Data from studies showing increased weight gain with particular ARV medications, including some INSTIs and TAF and especially in certain patient populations (i.e., women, Black and Hispanic populations), are updated.

Table 6. Recommended Antiretroviral Regimens for Initial Therapy (Last updated June 3, 2021; last reviewed June 3, 2021)

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 people of childbearing potential, and choice of antiretroviral therapy (ART) for individuals who are pregnant 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. [Table 7](#) provides ARV recommendations based on specific clinical scenarios.

Recommended Initial Regimens for Most People with HIV

Recommended regimens are those with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use. Choice of ART during pregnancy should be guided by recommendations from the [Perinatal Guidelines](#).

INSTI plus 2 NRTIs:

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

INSTI plus 1 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

Recommended Initial Regimens in Certain Clinical Situations

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

INSTI plus 2 NRTIs:

- EVG/c/(TAF or TDF)^a/FTC (BI)^b
- RAL plus (TAF or TDF)^a plus (FTC or 3TC) (BI for TDF/[FTC or 3TC], BII for TAF/FTC)

Boosted PI plus 2 NRTIs:

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

NNRTI plus 2 NRTIs:

- DOR/TDF^c/3TC (BI) or DOR plus TAF^c/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^a (CI)

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

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

^a Because of insufficient data, BIC should not be prescribed to people who are pregnant.

^b Because lower concentrations of COBI and its boosted drugs EVG, DRV, and ATV have been observed during the second and third trimesters, it should be avoided during pregnancy. For women with viral suppression who become pregnant while on a COBI-containing regimen but wish to remain on this regimen after counseling regarding its lower-drug concentration, frequent viral load monitoring is recommended. For further information, refer to the [Perinatal Guidelines](#).

° TAF and TDF are two forms of TFV approved by the FDA. TAF has fewer bone and kidney toxicities than TDF, whereas TDF is associated with lower lipid levels. Safety, cost, and access are among the factors to consider when choosing between these drugs.

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, EVG/c/TAF/FTC, EVG/c/TDF/FTC, RPV/TAF/FTC, RPV/TDF/FTC, TAF/FTC, TDF/3TC, and TDF/FTC.

Key: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; 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 = Food and Drug Administration; FTC = emtricitabine; HLA = human leukocyte antigen; INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; STR = single-tablet regimen; TAF = tenofovir alafenamide; TFV = tenofovir; TDF = tenofovir disoproxil fumarate

Selecting an Initial Antiretroviral Regimen

The goal of ART is to provide a potent, safe, tolerable, and easy-to-adhere-to regimen 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 factors can be grouped into the categories listed below and may influence the selection of a regimen. [Table 7](#) includes recommendations for additional regimens to use in specific clinical scenarios. **Individuals without prior ARV treatment who wish to use long-acting injectable CAB and RPV should first achieve viral suppression on another regimen before switching 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

- Pretreatment HIV RNA level (viral load)
- Pretreatment CD4 count
- HIV genotypic drug resistance test results. Based on current rates of transmitted drug resistance to different ARV medications, standard genotypic drug-resistance testing in ARV-naive persons should focus on testing for mutations in the reverse transcriptase (RT) and protease (PR) genes. If transmitted INSTI resistance is a concern, providers should consider also testing for resistance mutations to this class of drugs.
- 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
- Timing of ART initiation after diagnosis (i.e., immediate versus delayed)

Note that results of pretreatment HIV RNA, CD4 count, and resistance testing do not need to be available before starting ART. 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; drug abuse or dependency requiring narcotic replacement therapy
- Coinfections: HBV, hepatitis C virus, tuberculosis (TB)
- Pregnancy and potential for pregnancy (see below, **General Considerations for People 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 STR formulations, food requirements)
- Cost and access (see [Cost Considerations and Antiretroviral Therapy](#))

General Considerations for People of Childbearing Potential Initiating Antiretroviral Therapy

- A pregnancy test should be performed before initiating ART.
- Clinicians should discuss intentions regarding pregnancy with all people of childbearing potential.
- People with HIV should attain maximum viral suppression for their own health before attempting conception to prevent sexual HIV transmission to partners without HIV and to minimize the risk of perinatal HIV transmission.
- A DTG-based regimen is one of the recommended options for women initiating ART. Before initiating a DTG-based regimen, clinicians should discuss the risks and benefits of using DTG with people of childbearing potential to allow them to make an informed decision. Please refer to the [Women with HIV](#) section, [Selecting an Initial Antiretroviral Regimen](#) (see above), and [INSTI-Based Regimens](#) (see 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; and the potential for drug-drug interactions (see [Tables 7](#) and [9](#)).

[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 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.⁸⁻¹⁰ 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 hepatitis B.^{4, 11}

Among the INSTI-based regimens, BIC- and DTG-containing regimens have a higher barrier to resistance and lower pill burden than the first generation INSTIs, EVG- or RAL-containing regimens. Treatment-emergent resistance has been reported very rarely in individuals receiving three-drug DTG-based therapy¹²⁻¹⁴ and rarely has been reported in those receiving BIC-based regimens.¹⁵ 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.^{16, 17}

Recent studies have shown that the prevalence of infant NTDs associated with DTG exposure at conception is slightly higher than with non-DTG containing regimens (1.9 per 1,000 versus 1.1 per 1,000, respectively), but the prevalence difference was not statistically significant.^{6,7} For individuals of childbearing potential who are trying to conceive, DTG-based regimens are among the recommended options for most people initiating ART, acknowledging that clinicians should discuss the risks and benefits of using DTG with people of childbearing potential to allow them to make an informed decision. Because of insufficient data in pregnancy, BIC/TAF/FTC should not be used in people who are pregnant. Because of inadequate drug levels in the second and third trimesters of pregnancy, COBI-boosted EVG should be avoided in someone who is pregnant. People with suppressed virus on a COBI-boosted regimen who wish to continue the regimen should be followed with frequent viral load monitoring. 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 alternative drug in pregnancy because of 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 person who is pregnant or a person of childbearing potential.

Data now suggest greater weight gain with certain INSTI-based regimens and TAF than with other ARV drugs. The clinical significance of these findings is still unknown.¹⁸⁻²⁵

EVG- and [RAL](#)-based regimens have the disadvantages 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, a strong cytochrome P (CYP) 3A4 inhibitor (see [Table 7](#)).

Protease Inhibitor-Based Regimens

PK-enhanced PI-based regimens are recommended in certain clinical situations. Similar to elvitegravir/cobicistat (EVG/c), these regimens carry 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 ATV, like boosted DRV, has relatively few metabolic adverse effects in comparison to older boosted-PI regimens; however, ATV/r had a higher rate of adverse effect-associated drug discontinuation than darunavir/ritonavir (DRV/r) or RAL in a randomized clinical trial.⁸ 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.^{26,27} Large observational cohorts found an association between some PIs (DRV/r, fosamprenavir [FPV], indinavir [IDV], and LPV/r) and an increased risk of cardiovascular events; however, this association was not seen with ATV.²⁸⁻³³ Further study is needed. Cobicistat-boosted DRV and cobicistat-boosted ATV should be avoided during pregnancy because of inadequate drug levels.

NNRTI-Based Regimens

NNRTI-based regimens (which include doravirine [DOR], 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 people 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,³⁴ 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 was taken in combination with two NRTIs.^{35,36} 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 with 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.**³⁷

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

For those patients in whom ABC, TDF, or TAF cannot be used or are not optimal, several two-drug options do not contain these agents. Two-drug options **should not be used** in individuals with HBV coinfection or known preexisting resistance to either ARV in the combination. Among the two-drug regimens, DTG/3TC is preferred because substantial data support this combination in initial therapy, with the caveat that people with HIV RNA >500,000 copies/mL were excluded from the largest trial.^{4,11} 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 be used only in those with baseline CD4 counts >200 cells/mm³ and HIV RNA levels <100,000 copies/mL.³⁸ 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.³⁹

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