WHAT TO START

Initial Combination Antiretroviral Regimens for People With HIV

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Introduction

More than 30 antiretroviral (ARV) drugs in nine mechanistic classes have been U.S. Food and Drug Administration (FDA)–approved for treatment of HIV. These nine classes include nucleos(t)ide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), a fusion inhibitor (no longer available), a CCR5 antagonist, a CD4 T lymphocyte (CD4) cell post-attachment inhibitor, a gp120 attachment inhibitor, and a capsid inhibitor. In addition, two drugs—ritonavir (RTV) and cobicistat (COBI)—are used as pharmacokinetic (PK) enhancers (or boosters) to improve the PK profiles of select PIs and the INSTI elvitegravir (EVG).

Over time, incremental improvements in potency, tolerability, safety, convenience, drug interactions, and genetic barriers to the emergence of drug resistance have led to streamlined recommendations for initial ARV regimens for most people with HIV. For more information, see Principles of Antiretroviral Therapy.

The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) now recommends initial ARV regimens based on an oral second-generation INSTI plus one or two NRTIs for most people with HIV **(**see **Table 6a** below**).** When INSTI resistance is possible, such as after exposure to long-acting injectable cabotegravir (CAB-LA) as pre-exposure prophylaxis (PrEP) and INSTI resistance results are not yet available, a boosted PI in combination with two NRTIs is recommended. The tables below outline the Panel's initial recommended regimens for most people with HIV (**Table 6a**) and for certain clinical scenarios (**Table 6b**).

Table 6a. Recommended Initial Regimens for Most People With HIV

Selection of an ARV regimen should be based on the regimen's virologic efficacy, potential adverse effects, pill burden, dosing frequency, drug–drug interaction potential, cost, access, resistance test results, and select comorbid conditions of the person with HIV. A pregnancy test should be performed in women of childbearing potential, and choice of ART for pregnant women 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. Additional initial ARV regimen options for certain clinical scenarios are listed in Table 6b below.

Table 6a. 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.

For people who do not have a history of using CAB-LA as PrEP, one of the following regimens is recommended[a]:

- BIC/TAF/FTC **(AI)**
- DTG plus (TAF or TDF)[b] plus (FTC or 3TC) **(AI)**
- DTG/3TC **(AI),** except for individuals—
  - With HBV coinfection.
  - With unknown HBV serostatus.
  - Without results from genotypic resistance testing for reverse transcriptase.
  - For whom rapid ART initiation is planned.

For people who have a history of CAB-LA use as PrEP, INSTI genotypic resistance testing should be performed before starting INSTI-based ART. If ART is to be started before results of genotypic testing, the following regimen is recommended:

- DRV/c[c] or DRV/r plus (TAF or TDF)[b] plus (FTC or 3TC)—pending the results of the genotype test **(AIII)**

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*

[a] Because of the current low rates of transmitted INSTI resistance in the United States, even when there is suspicion that HIV was acquired from a partner with virologic failure while on an INSTI, an INSTI-based regimen can be started pending the results of the INSTI genotype.

[b] TAF and TDF are two forms of TFV approved by the U.S. Food and Drug Administration. 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.

[c] COBI should be avoided in pregnancy because lower concentrations of COBI and DRV have been reported during the second and third trimesters. For further information, refer to the Perinatal Guidelines.

Note: Of regimens listed in Table 6a, the following are available as coformulated drugs: BIC/TAF/FTC, DRV/c/TAF/FTC, DTG/3TC, TAF/FTC, TDF/3TC, and TDF/FTC.

Key: 3TC = lamivudine; ART = antiretroviral therapy; BIC = bictegravir; CAB-LA = long-acting cabotegravir; COBI = cobicistat; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; FTC = emtricitabine; HBV = hepatitis B virus; INSTI = integrase strand transfer inhibitor; PrEP = pre-exposure prophylaxis; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TFV = tenofovir

Table 6b. Initial Antiretroviral Regimens for Certain Clinical Scenarios

Several antiretroviral regimens are found to be effective and tolerable as initial regimens but have some disadvantages or have fewer supporting data from randomized clinical trials compared with the recommended regimens listed in Table 6a. However, one of these regimens may be preferred for an individual with HIV in certain clinical situations (also see Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios). These regimens are listed below.

Type of Regimen	ARV Regimen	Rapid Start	For Certain Clinical Scenarios	Other Considerations
INSTI Plus Two NRTIs	DTG/ABC/3TC **(BI)** (if HLA-B*5701-negative)	No	When concern about renal- or bone-associated AEs precludes the use of TDF or TAF or when DTG/3TC cannot be used	Test for HLA-B*5701 before prescribing ABC; ABC is **contraindicated** if HLA-B*5701-positive. Consider alternative ARV medications in place of ABC in people with HIV and higher underlying ASCVD risk or known CVD. Do not use in people with HBV unless an HBV-active drug other than 3TC (i.e., entecavir) is also used. Do not use following exposure to CAB-LA unless INSTI genotype shows sensitivity to DTG.
Boosted PI Plus Two NRTIs	(DRV/c[a] or DRV/r) plus (TAF or TDF[b]) plus (FTC or 3TC) **(BI)**	Yes	To avoid an INSTI-based regimen (e.g., suspected or documented INSTI resistance)	Assess for potential RTV- or COBI-related DDIs (see the Liverpool HIV Drug Interaction Checker). Needs to be taken with a meal.
	(DRV/c[a] or DRV/r) plus ABC/3TC **(BII)** (if HLA-B*5701-negative)	No	To avoid an INSTI-based regimen (e.g., with suspected or documented INSTI resistance), *and* When concerns about renal or bone-associated AEs preclude the use of TDF or TAF	Test for HLA-B*5701 before prescribing ABC; do not prescribe if HLA-B*5701-positive. Consider alternative ARV medications in place of ABC in people with HIV and higher underlying ASCVD risk or known CVD. Do not use in people with HBV unless used with an HBV-active drug other than 3TC (i.e., entecavir). Assess for potential RTV- or COBI-related DDIs. Needs to be taken with a meal.

Table 6b. Initial Antiretroviral Regimens for Certain Clinical Scenarios

Type of Regimen	ARV Regimen	Rapid Start	For Certain Clinical Scenarios	Other Considerations
Boosted PI Plus One NRTI	DRV/r plus (3TC **[BI]** or FTC **[BII]**), *or* DRV/c plus (3TC or FTC) **(BII)**	No	To avoid TFV and ABC in people who are not candidates for DTG/3TC	Do not use if genotypic resistance testing for reverse transcriptase is not yet available. Do not use in people with HBV unless used with an HBV-active drug other than 3TC (i.e., entecavir). Assess for potential RTV- or COBI-related DDIs (see the Liverpool HIV Drug Interaction Checker). Needs to be taken with a meal.
NNRTI Plus Two NRTIs	DOR/TDF/3TC[b] **(BI)** *or* DOR plus TAF/FTC[b] **(BIII)**	No	To avoid an INSTI-based regimen (e.g., with suspected or documented INSTI resistance), *and* To avoid a PI-based regimen (e.g., with significant DDIs with concomitant medications)	
	RPV/TAF/FTC **(BII)** Only if HIV RNA ≤100,000 copies/mL **and** CD4 count ≥200 cells/mm^3	No	To avoid an INSTI-based regimen (e.g., with suspected or documented INSTI resistance), *and* To avoid a PI-based regimen (e.g., with significant DDIs with concomitant medications), *and* When a single-tablet regimen containing an NNRTI and TAF is desired	**Contraindicated** with PPI; space apart from H2 antagonist or antacids. Needs to be taken with a meal.

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*

[a] COBI-boosted DRV **is not recommended** as part of initial therapy in pregnancy because lower concentrations of COBI and DRV have been observed during the second and third trimesters. For further information, refer to the Perinatal Guidelines.

Table 6b. Initial Antiretroviral Regimens for Certain Clinical Scenarios

[b] TAF and TDF are two forms of TFV approved by the U.S. Food and Drug Administration. 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.

Note: The following are available as coformulated drugs: ABC/3TC, DOR/TDF/3TC, DRV/c, DRV/c/TAF/FTC, DTG/ABC/3TC, RPV/TAF/FTC, TAF/FTC, TDF/3TC, and TDF/FTC.

Key: 3TC = lamivudine; ABC = abacavir; AE = adverse event; ARV = antiretroviral; ASCVD = atherosclerotic cardiovascular disease; CAB-LA = long-acting cabotegravir; CD4 = CD4 T lymphocyte; COBI = cobicistat; CVD = cardiovascular disease; DDI = drug–drug interaction; DOR = doravirine; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; FTC = emtricitabine; H2 = histamine type 2; 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; PPI = proton pump inhibitor; RPV = rilpivirine; RTV = ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TFV = tenofovir

Supporting Evidence and Rationale Used for the Panel's Recommendations

The Panel's 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 are not designed to show significant differences in HIV-related clinical endpoints (such as progression to AIDS-defining conditions) or survival. Thus, the assessment of regimen efficacy and safety is 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 initial ARV 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 the evidence rating **"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, postmarketing 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* (Table 6a) and (2) *Initial Antiretroviral Regimens for Certain Clinical Scenarios* (Table 6b). *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 *Initial Antiretroviral Regimens for Certain Clinical Scenarios*. See Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios for examples of clinical scenarios in which certain drugs in these regimens may be particularly advantageous.

Many other ARV regimens are effective for initial therapy but have disadvantages when compared with the regimens listed in Tables 6a and 6b. These disadvantages include greater toxicity, higher pill burden, less supporting data from large comparative clinical trials, and limitations for use in certain populations. As such, these regimens are no longer included in Tables 6a and 6b. For people with HIV who have a suppressed viral load and are not experiencing any adverse effects while on a regimen that is not listed, changing to a regimen listed in Table 6a or 6b is not necessary. Clinicians should refer to Optimizing Antiretroviral Therapy in the Setting of Viral Suppression for further guidance if switching to a new regimen is desired.

Several tables in these guidelines provide clinicians with guidance on selecting and prescribing an optimal regimen for a person with HIV, including Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios and Advantages and Disadvantages of Antiretroviral Components of Initial Antiretroviral Therapy. Appendix A, Tables 3–10, lists characteristics of individual ARV agents for initial therapy (e.g., formulations, dosing recommendations, PK, common adverse effects). Appendix B provides ARV dosing recommendations for people who have renal or hepatic insufficiency. See the Liverpool HIV Drug Interaction Checker for potential drug interactions.

Changes Since the Last Revision of the Guidelines

The Panel has made several important changes since the last revision of these guidelines, as outlined below.

Changes to the Recommended Initial Regimens for Most People With HIV

- The single-tablet regimen (STR) dolutegravir (DTG)/lamivudine (3TC) is now recommended for initial therapy regardless of baseline plasma HIV RNA if there is no evidence of genotypic resistance to 3TC and there is documented absence of chronic hepatitis B virus (HBV) infection (see *Recommended Initial Regimens for Most People With HIV*). This change is based upon the DOLCE study, which showed similar efficacy for DTG/3TC compared with DTG and tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) or TDF/3TC for initial therapy among people with advanced HIV infection. There was no significant difference between the DTG/3TC arm and the three-drug arm in the subgroup with HIV viral load >500,000 copies/mL.[1]

Changes to Initial Antiretroviral Regimens for Certain Clinical Scenarios

- The two-drug combinations of (darunavir/ritonavir [DRV/r] or darunavir/cobicistat [DRV/c) plus (3TC or FTC) are now recommended two-drug regimens for people with HIV who need to avoid tenofovir (TFV) and abacavir (ABC) and who are not candidates for DTG/3TC. This change is based on the ANDES study showing similar efficacy in those receiving DRV/r plus 3TC compared with those receiving DRV/r plus TDF/FTC or TDF/3TC.[2]

Other Additions

- DTG/3TC is now classified as an *Alternative* regimen in pregnancy. See the Perinatal Guidelines for more information.

- Doravirine (DOR) is noted to have a distinct resistance pathway and potentially higher barrier to resistance compared with other NNRTIs, although not comparable to that of boosted PIs or second-generation INSTIs.
- Refer to the Liverpool HIV Drug Interaction Checker for drug–drug interaction guidance between ARV drugs and concomitant medications.

Selecting an Initial Antiretroviral Regimen

The goal of antiretroviral therapy (ART) is to improve health and prolong life for people with HIV and to prevent the transmission of HIV to others by maximizing virologic suppression. This is achieved by initiating therapy with a potent, safe, tolerable, and easy-to-adhere-to ARV regimen as soon as possible after diagnosis. Table 6a provides a list of Panel-recommended ARV regimens for most people with HIV. Some factors listed below may influence the selection of a regimen. See Table 6b and Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios for additional regimen recommendations to use in specific clinical scenarios.

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 or oral TDF/FTC or tenofovir alafenamide (TAF)/FTC as PrEP, or use of INSTI-based post-exposure prophylaxis (PEP)
- Suspected drug resistance (prior to availability of genotypic testing results)
- HIV genotypic drug resistance test results
    - Genotypic drug resistance testing in people without prior ARV exposure should include testing for mutations in the reverse transcriptase and protease genes.
    - If transmitted INSTI resistance is a concern, providers should also test for resistance mutations to this class of drugs.
- Individual preferences
- Anticipated adherence to the regimen

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: HBV, hepatitis C virus, tuberculosis
- Pregnancy and potential for pregnancy: See below in General Considerations for Women of Childbearing Potential Initiating Antiretroviral Therapy

Regimen-Specific Considerations

- Regimen's barrier to resistance
- HLA-B*5701 status (only for those considering initiation of ABC). ABC **is contraindicated** in those who are HLA-B*5701 positive. See Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios for regimens to initiate.

- Potential adverse effects and drug toxicities, including risk for the development of comorbid diseases
- Known or potential drug interactions with other medications (see Drug–Drug Interactions and the Liverpool HIV Drug Interaction Checker)
- Convenience (e.g., pill burden, dosing frequency, availability of a fixed-dose combination or of STR formulations, food requirements)
- Cost and access (see Cost Considerations and Antiretroviral Therapy)

Considerations for People With Prior Use of Pre- or Post-Exposure Prophylaxis

- For people who acquired HIV after taking oral PrEP with TAF/FTC or TDF/FTC, there is concern for transmitted or acquired resistance, especially related to FTC or 3TC with the M184V/I mutation. In a cohort of people in New York City with newly diagnosed HIV, 2% had the M184V/I mutation. People who had used prior oral PrEP were four to seven times more likely to harbor resistance than people who had never used oral PrEP.[3]
- For people who acquired HIV after exposure to CAB-LA as PrEP, there is concern for INSTI resistance. CAB-LA may remain detectable after treatment discontinuation for up to 3 years in men and 4 years in women.[4] This long PK tail may contribute to the selection of drug-resistant variants in the setting of incident infection. In the HPTN 083 trial of CAB-LA as PrEP in cisgender men and transgender women, 10 of 32 people who acquired HIV after exposure to CAB-LA were found to harbor major INSTI resistance mutations.[5] This is the basis for the Panel's recommendation to obtain INSTI genotypic drug resistance testing in people with prior CAB-LA exposure and not to initiate INSTIs before these results are available and show INSTI sensitivity. If therapy is initiated before INSTI sensitivity is confirmed, the Panel recommends initiating a boosted darunavir (DRV) regimen with TAF/FTC or TDF/FTC while awaiting INSTI genotype results; once INSTI sensitivity is confirmed by genotypic resistance testing, a switch to an INSTI-based regimen can occur **(AIII).**
- For people with no history of using CAB-LA for PrEP and who acquire HIV despite INSTI-based PEP use, an INSTI genotype should be obtained prior to beginning an INSTI-based regimen. However, because selection of INSTI-resistant virus is likely to be uncommon in this setting, an INSTI-based regimen could be started prior to the return of genotype results. This recommendation is based largely on the fact that although INSTI resistance could occur in the setting of INSTI-based PEP failure, it is likely to be uncommon. In addition, transmitted INSTI resistance remains low in the United States.

General Considerations for Women of Reproductive Potential Initiating Antiretroviral Therapy

- A pregnancy test should be performed before initiating ART.
- Clinicians should discuss intentions regarding pregnancy with all women 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.
- 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

Except when HIV is acquired after exposure to CAB-LA as PrEP and results from INSTI genotypic resistance testing are not available, INSTIs (specifically bictegravir [BIC] and DTG) are recommended for initial therapy in most people because of their demonstrated efficacy, high barrier to resistance, tolerability, low potential for drug–drug interactions, convenience, and better adverse effects profile compared with NNRTIs and boosted PIs (see Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios and Advantages and Disadvantages of Antiretroviral Components of Initial Antiretroviral Therapy).

INSTI-Based Regimens

The Panel's *Recommended Initial Regimens for Most People With HIV* include one of two INSTIs: BIC coformulated with TAF/FTC **(AI);** or DTG plus TAF or TDF plus FTC or 3TC **(AI);** or DTG coformulated with 3TC **(AI)** for people 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 recent 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 people, these INSTI-containing regimens are 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.[6-8]

The Panel recommends a two-drug regimen of DTG/3TC for initial therapy in those with documented absence of both transmitted NRTI resistance and chronic HBV infection. 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. A third randomized trial demonstrated similar outcomes in patients with advanced HIV infection, as defined by CD4 counts ≤200 cells/mm^3, many of whom had very high viral loads.[1] Moreover, no treatment-emergent resistance was seen in any of these two-drug or three-drug study groups.[9] Based on the need for resistance testing and HBV serology, DTG/3TC is not currently recommended for rapid ARV initiation before the availability of HBV serology and an HIV genotypic test demonstrating sensitivity to NRTIs. Although not *Preferred*, DTG/3TC is recommended as an *Alternative* treatment option for pregnant women with HIV (see the Perinatal Guidelines for more information).

Among the INSTI-based regimens, BIC- and DTG-containing regimens have a higher barrier to resistance than the first-generation INSTI-based regimens containing EVG or raltegravir (RAL) and do not require a PK booster. Transmitted resistance to BIC or DTG is rare. Treatment-emergent resistance has been reported in individuals who failed three-drug DTG-based therapy[10-13] and BIC-based regimens.[14-17] Because of this high barrier to resistance and tolerability, BIC- and DTG-containing regimens with two NRTIs may be used in people who have not previously used CAB-LA for PrEP and plan to start ART before resistance testing 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.[18-20]

Some data suggest greater weight gain after initiating therapy with certain INSTI-based regimens and TAF than with other ARV drugs. The reasons for differences in weight gain are unclear and should not be a reason to withhold an INSTI- or TAF-based regimen.[21-28] See Weight Gain in People With Treated HIV for more information.

EVG- and RAL-based regimens have the disadvantage of having lower barriers to resistance than DTG- or BIC-containing regimens and therefore are no longer recommended as initial therapy. Additionally, the pill burden with RAL is higher than for other INSTI-based regimens, whereas EVG-based regimens have a greater potential for drug interactions because EVG is combined with COBI, a strong cytochrome P450 3A4 inhibitor (see Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios).

PI-Based Regimens

In the setting of HIV acquisition following CAB-LA exposure, a regimen of RTV- or COBI-boosted DRV containing TAF or TDF plus FTC or 3TC is recommended as initial therapy if a genotypic drug resistance test indicating INSTI sensitivity is not available at the time of ART initiation **(AIII),** or in certain clinical situations when INSTIs must be avoided (e.g., suspected or documented INSTI resistance) **(BI).** DRV/c/TAF/FTC is available as an STR. Large observational cohorts found an association between some PIs, including DRV/r, and an increased risk of cardiovascular events; however, further study is needed.[29-34] COBI-boosted regimens should not be initiated during pregnancy because of inadequate drug levels. Boosted ATV is no longer recommended as initial therapy because of frequent adverse events (e.g., hyperbilirubinemia) and high rates of drug–drug interactions, including with TFV and acid-suppressive therapy.

NNRTI-Based Regimens

NNRTI-based regimens are not recommended for initial therapy in most people with HIV, but selected regimens may be useful in some circumstances. The NNRTI-based regimens that are currently recommended by the Panel to be used in certain clinical scenarios include DOR/TDF/3TC **(BI),** DOR plus TAF/FTC **(BIII),** and rilpivirine (RPV)/TAF/FTC **(BII).** The emergence of drug resistance at the time of virologic failure has been reported with all NNRTIs, which generally have a lower barrier to resistance than boosted PIs or second-generation INSTIs.

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 efavirenz (EFV) and DRV/r when either of these drugs was taken in combination with two NRTIs,[35,36]. DOR has fewer central nervous system (CNS) side effects than EFV and more favorable lipid effects than both 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 people with high HIV RNA levels and low CD4 counts. DOR also has a distinct resistance pathway and a potentially higher barrier to resistance than earlier NNRTIs, although not comparable to that of boosted PIs or second-generation INSTIs.[37-40]

RPV has fewer adverse effects than EFV, and RPV/TAF/FTC is available as one of the smallest tablet sizes among STRs. However, RPV has lower virologic efficacy in people with baseline HIV RNA levels >100,000 copies/mL and/or CD4 counts <200 cells/mm^3 and is subject to numerous drug–drug interactions.[41] EFV is no longer recommended for initial therapy due to a relatively high rate of CNS-related side effects, reported suicidality, high rates of drug discontinuation, and numerous drug–drug interactions.

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

For people in whom ABC, TDF, or TAF cannot be used or are not optimal, the Panel recommends DTG/3TC **(AI).** For the unique situation of individuals needing to avoid TFV and ABC and who are not candidates for DTG/3TC, the Panel recommends DRV/r plus 3TC **(BI)** or FTC **(BII),** or DRV/c plus 3TC **(BII)** or FTC **(BII).** Several other NRTI-sparing two-drug regimens have been evaluated in clinical trials but are not currently recommended for initial therapy due to insufficient data. For more information on these regimens, see Other Antiretroviral Regimens for Initial Therapy. Tenofovir-

sparing regimens **should not be used** in individuals with HBV unless entecavir is taken along with the ARV regimen.

Knowledge Gaps

- Research is needed on the efficacy of boosted DRV plus DTG as an initial two-drug regimen.
- Further research is needed to determine whether certain ARV medications or regimens have fewer cardiometabolic complications.
- Research is needed on the safety and efficacy of ARV regimens with extended dosing intervals as initial therapy.

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