



CLINICAL GUIDELINES PROGRAM

NEW YORK STATE DEPARTMENT OF HEALTH AIDS INSTITUTE | HIV · HCV · SUBSTANCE USE · LGBT HEALTH

Selecting an Initial ART Regimen

Lead Author: Samuel T. Merrick, MD, with the Medical Care Criteria Committee, updated January 2019

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SELECTING AN INITIAL ART REGIMEN

Purpose of this Guideline

Lead Author: Samuel T. Merrick, MD, with the Medical Care Criteria Committee, updated January 2019

This guideline was developed by the New York State Department of Health (NYSDOH) AIDS Institute (AI) for primary care providers and other practitioners who are initiating therapy in nonpregnant, antiretroviral therapy (ART)-naive adults living with HIV. The guideline aims to achieve the following goals:

- Provide a clear and concise roadmap to choosing from among several equally efficacious ART regimens based on individual patient characteristics and preferences.
- Provide a list of regimens to avoid.
- Provide dosing considerations for individuals with renal or hepatic impairment and important drug-drug and food interactions.
- Encourage clinicians to seek the assistance of an experienced HIV care provider when treating patients with extensive comorbidities.
- Integrate current evidence-based clinical recommendations into the healthcare-related implementation strategies of the *Ending the Epidemic Initiative*, which seeks to end the AIDS epidemic in NYS by the end of 2020.

The NYSDOH AI is publishing this guideline at a critical time: 1) initiation of ART is now recommended for all individuals diagnosed with HIV; 2) identifying and linking individuals with HIV to care and treatment that achieves optimal virologic suppression are crucial to the success of *New York State's Ending the Epidemic initiative*; and 3) the ability of primary care providers and other clinicians in NYS to properly select initial ART is key to the successful treatment of individuals with HIV.

Introduction: The NYSDOH AI Medical Care Criteria Committee recommendations for prescribing ART regimens for treatment-naive, nonpregnant adults (age ≥ 18 years) with HIV-1 and without acquired resistance are based on a comprehensive review of available clinical trial data. (For guidelines specific to treatment of adolescents with HIV, please consult the U.S. Department of Health and Human Services (DHHS) *Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV*). In formulating its recommendations for NYS, this Committee balanced the strength of published evidence regarding efficacy of treatment regimens with factors that influence adherence, including pill burden, tolerability, and dosing schedule. Preferred regimens are supported by evidence and have favorable adherence profiles, with lower pill burdens, fewer adverse effects, and dosing schedules that may be easier for individuals to manage. Ranking of regimens in this manner is designed to inform discussion and decision-making with patients.

How to use this guideline: Tables presenting preferred and alternative regimens appear first (see the *Available ART Regimens* section of this guideline: Tables 1 and 2). To help guide the choice among regimens of similar efficacy, each table includes comments that address selected pertinent issues regarding each regimen, such as limitations based on a patient's kidney function and drug-drug interactions.

Other sections of the guideline include a review of relevant issues, patient considerations, essential laboratory assessments, and the rationale for the recommendations. Reference to the expanded information is crucial for addressing factors that may be of particular importance when individualizing a patient's treatment, such as loss of bone mineral density with a regimen that includes tenofovir disoproxil fumarate (TDF) and the conflicting data on cardiac risk with abacavir (ABC); see the *Specific Factors to Consider and Discuss with Patients* section of this guideline.

Scope: This guideline addresses initial treatment of HIV-1 infection with ART in **nonpregnant adults**. For information regarding ART in individuals who are or who may become pregnant, please refer to the DHHS guideline *Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States* [AIDSinfo 2017b]. Please refer to the NYSDOH AI guideline *HIV-2 Infection* for recommendations regarding treatment of HIV-2 infection. For recommendations regarding second-line regimens, please refer to the DHHS *guideline on management of the treatment-experienced patient* [AIDSinfo 2017a]. For the NYSDOH definition of "experienced HIV care provider," see *HIV Care Provider Definitions*.

References

- AIDSinfo. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. 2017a Oct 17. <https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/16/regimen-switching-in-the-setting-of-virologic-suppression> [accessed 2018 May 1]
- AIDSinfo. Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States. 2017b Mar 27. <https://aidsinfo.nih.gov/guidelines/html/3/perinatal-guidelines/0> [accessed 2018 May 1]

Available ART Regimens

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Note: The recommendations in this guideline pertain to initial antiretroviral therapy (ART) regimens for adults with HIV who are not pregnant.

Dolutegravir (DTG) Safety Statement, May 2018

- On May 18, 2018, the FDA and the DHHS Antiretroviral Guidelines Panels issued statements in response to preliminary results from a study that reported increased risk of neural tube defects in babies born to mothers taking DTG-based ARV drug regimens at the time of conception [AIDSinfo 2018; FDA 2018].
- Until more data become available, **DTG-containing regimens should be avoided in any HIV-exposed individual who is pregnant in the first trimester or could become pregnant and is not using effective contraception.** If there are no alternatives to DTG for individuals of child-bearing potential, then clinicians should strongly advise the use of effective contraception and should obtain a pregnancy test before initiating treatment.
- For more information, see: *DHHS Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*

RECOMMENDATIONS: SELECTING AN INITIAL ART REGIMEN

- Clinicians should involve their patients when deciding which ART regimen is most likely to result in adherence. (A3)
- Clinicians should perform the following when initiating ART:
 - Assessment for comorbidities and chronic co-administered medications that may affect the choice of regimen for initial therapy. (A3)
 - Genotypic resistance testing for the protease and reverse transcriptase genes at diagnosis or at the initial visit if not done previously. (A2) See the *Specific Factors to Consider and Discuss with Patients* section of this guideline.
- Baseline testing is currently not recommended for either integrase resistance (unless transmitted integrase strand transfer inhibitor [INSTI] resistance is suspected) or tropism. (A3)
- For individuals who have delayed initiation of ART and have engaged in high-risk behaviors associated with acquisition of HIV superinfection, genotypic resistance testing should be repeated before choosing the ART regimen. (B3)
- Clinicians should consult with a care provider experienced in ART management when:
 - Baseline resistance indicates the need for treatment with a regimen other than the listed preferred or alternative regimens. (A3)
 - Selecting a regimen for individuals with extensive comorbidities and/or comedications, impaired renal function, hepatitis B virus or hepatitis C virus coinfection, or active opportunistic infections. (B3)
- Clinicians should ask individuals about their reproductive plans and discuss the use of contraception. (A3)
 - Refer to the DHHS guideline when choosing an initial regimen for individuals of childbearing potential: *Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*.
- For ART-naïve individuals, clinicians should select an initial ART regimen that is preferred; see *Table 1: Preferred Initial ART Regimens for Nonpregnant Adults*. (A1)
 - A single-tablet regimen or regimen with once-daily dosing is preferred unless contraindicated by resistance, drug-drug interactions, intolerance, allergy, or access. (A2)
 - In general, a preferred regimen should be selected (see *Table 1: Preferred Initial ART Regimens for Nonpregnant Adults*), although there may be times when an alternative regimen may be a better choice for an individual patient (*Table 2: Alternative Initial ART Regimens for Nonpregnant Adults*).
- Clinicians should not prescribe two-drug regimens as initial therapy. (A2)
- Clinicians or clinic staff should follow up, by telephone or other methods, within 2 weeks after treatment initiation to assess tolerance and adherence. Adherence should be reinforced at regular intervals. (A3)
- Clinicians should obtain a viral load test within 4 weeks after ART initiation to assess initial response to therapy (A3); see the NYSDOH AI guideline *Virologic and Immunologic Monitoring* for more information.

Available Antiretroviral Agents and Regimens

Each regimen listed below in Tables 1 and 2, preferred and alternative initial ART regimens, and *Table 3: Other ART Regimens Not Included as Preferred or Alternative for Nonpregnant Adults*, is expected to produce full viral suppression; however, they differ in tolerability, possible toxicities, convenience, and the potential for drug–drug interactions, all of which can affect overall adherence and, therefore, suppression rates.

This Committee recommends tenofovir alafenamide (TAF) over tenofovir disoproxil fumarate (TDF) as part of the backbone in preferred regimens based on renal toxicity and bone mineral density data from randomized trials of TAF/emtricitabine/cobicistat/elvitegravir (TAF/FTC/COBI/EVG) versus TDF/emtricitabine/cobicistat/elvitegravir (TDF/FTC/COBI/EVG) in ART-naïve patients or those previously suppressed on TDF/FTC/COBI/EVG [Sax, et al. 2015; Mills, et al. 2016a; Pozniak, et al. 2016]. These data, combined with data from bioequivalence and switch studies [Zack, et al. 2016a; Zack, et al. 2016b], provide support for the use of TAF/FTC rather than TDF/FTC when combined with DTG or raltegravir (RAL) as part of a preferred regimen. In a study of ART-naïve individuals, RAL HD 1200 mg once daily was non-inferior to 400 mg tablets dosed twice daily and is thus preferred [Cahn, et al. 2017]. This Committee does not yet recommend TAF at a dose of 25 mg in combination with boosted protease inhibitors (PIs), as noted below (see the *Special Considerations for Comorbid Conditions* section of this guideline). Studies have shown that TDF-related renal toxicity is more common when using TDF in a regimen containing COBI or ritonavir (RTV) [Goicoechea, et al. 2008; Ryom, et al. 2013; Cuzin, et al. 2017; Hill, et al. 2018]; therefore, this Committee does not recommend TDF use with boosted regimens when initiating therapy. TDF-containing regimens combined with an INSTI or non-nucleoside reverse transcriptase inhibitor (NNRTI) remain safe and efficacious as alternative regimens (Table 2, below). An INSTI as the third drug is preferred over PIs and NNRTIs based on tolerability and a lower incidence of drug–drug interactions. Because the use of TAF/FTC/rilpivirine (RPV) is limited by viral load and CD4 parameters and is contraindicated with proton-pump inhibitors (PPIs), this combination is listed as an alternative regimen (Table 3, below).

Efavirenz (EFV)-containing regimens (see Table 3, below), although efficacious, have been shown to be less well tolerated than the preferred or alternative regimens in Tables 1 and 2, below. Lopinavir (LPV)/RTV-containing regimens are no longer included among the options for initial treatment because of pill burden and reduced tolerability in comparison with other boosted PIs.

When initiating ART at the time of HIV diagnosis (i.e., “rapid start” or “test and treat”), avoid regimens containing ABC unless results of HLA-B*5701 testing are known to be negative. Similarly, RPV is not appropriate for patients whose viral load is not confirmed to be <100,000 copies/mL and whose CD4 count is not confirmed to be ≥ 200 cells/mm³.

Initial regimens should be selected on the basis of patient preferences and clinical characteristics, and a preferred regimen should be used whenever possible (Table 1, below). Regimens in the tables below are listed alphabetically. For more information, including drug trade names, see *All FDA-Approved HIV Medications*.

Single-Tablet Regimens Versus Multi-Tablet Regimens

The advantages of single-tablet regimens (STR) compared with multi-tablet regimens (MTR) include simplicity, convenience, and lower chance of selective nonadherence [Gardner, et al. 2008]. A recent meta-analysis demonstrated that STR regimens had better adherence rates when compared with MTRs of any frequency (daily or twice daily) and had higher 48-week viral suppression rates with comparable side effects [Clay, et al. 2015]. In another retrospective study, INSTI-based regimens generally had greater rates of suppression and a lower probability of viral rebound after suppression in comparison to NNRTI-based regimens, regardless of whether an STR or MTR was used, but STR-based INSTI therapy was more durable [Mills, et al. 2016b]. In the same study, STR NNRTI-based therapy led to greater rates of suppression than MTR NNRTI therapy [Mills, et al. 2016b]. Other studies have demonstrated better efficacy and adherence, lower cost to patients, and fewer hospital admissions associated with STRs than with MTRs [Bangalore, et al. 2007; Raboud, et al. 2011; Cohen, et al. 2013; Colombo, et al. 2013; Hanna, et al. 2014; Nachege, et al. 2014; Sweet, et al. 2014; Armstrong, et al. 2015; Maggiolo, et al. 2015; Griffith, et al. 2016; Mills, et al. 2016b]. Another study examined once-daily dosing of LPV/RTV and found better adherence than with twice-daily dosing [Molina, et al. 2007].

There are 2 STRs listed below as preferred regimens: ABC/3TC/DTG and TAF/FTC/bictegravir (BIC). It is possible that these regimens may contain 1 or more components that are not appropriate for an individual patient, do not allow for adjustment of individual components for renal function, have significant drug interactions, are poorly tolerated, or may be more expensive than the individual components prescribed separately, particularly if available as generic formulations. With full adherence, any of the preferred or alternative regimens should lead to full suppression, including MTRs, which can be used when an STR is not possible or not tolerated. Cost and access may also be determinative factors. For patients with impaired baseline renal function, separating the drugs into individual components and adjusting each may be appropriate. For more detailed instructions on dosage adjustments for impaired renal function, see Table 8: ARV Dose Adjustments for Renal and Hepatic Impairment.

Table 1, below, includes initial ART regimens preferred by this Committee; Table 2 lists alternative initial regimens. Table 3 lists other available ART regimens that this Committee considers neither preferred nor alternative. Within each table, regimens are

listed alphabetically. For specific details on choosing a regimen, see the discussions in other sections of this guideline and/or the package inserts for the drugs listed below.

| Table 1: Preferred Initial ART Regimens for Nonpregnant* Adults (listed alphabetically; for specific details, see <i>Specific Factors to Consider</i> or drug package inserts) | | |
|--|--|--------|
| Regimen | Comments | Rating |
| <i>Available as a Single-Tablet Formulation</i> | | |
| Abacavir/lamivudine/dolutegravir (ABC/3TC/DTG; Trimeq) | <ul style="list-style-type: none"> Initiate only in patients confirmed to be negative for HLA-B*5701, including when a “rapid-start” or “test-and-treat” initiation of ART occurs before baseline laboratory test results are available. Initiate only in patients with CrCl ≥50 mL/min. Consider underlying risk of coronary heart disease. Documented DTG resistance after initiation in treatment-naive patients is rare. Take magnesium- or aluminum-containing antacids 2 hours before or 6 hours after DTG; calcium-containing antacids or iron supplements may be taken simultaneously if taken with food. | A1 |
| Tenofovir alafenamide/emtricitabine/bictegravir (TAF 25 mg/FTC/BIC; Biktarvy) | <ul style="list-style-type: none"> Initiate only in patients with CrCl ≥30 mL/min. Contains 25 mg of TAF, unboosted. Take magnesium- or aluminum-containing antacids 2 hours before or 6 hours after BIC; calcium-containing antacids or iron supplements may be taken simultaneously if taken with food. | A1 |
| <i>Available as a Multi-Tablet Regimen with Once-Daily Dosing</i> | | |
| Tenofovir alafenamide/emtricitabine and dolutegravir (TAF 25 mg/FTC and DTG; Descovy and Tivicay) | <ul style="list-style-type: none"> Initiate only in patients with CrCl ≥30 mL/min. Documented DTG resistance after initiation in treatment-naive patients is rare. Contains 25 mg of TAF, unboosted. Take magnesium- or aluminum-containing antacids 2 hours before or 6 hours after DTG; calcium-containing antacids or iron supplements may be taken simultaneously if taken with food. | A1 |
| Tenofovir alafenamide/emtricitabine and raltegravir (TAF 25 mg/FTC and RAL HD; Descovy and Isentress HD) | <ul style="list-style-type: none"> Initiate only in patients with CrCl ≥30 mL/min. To date, no clinical trials have been conducted with TAF and RAL; data are based on bioequivalence pharmacokinetic studies. Contains 25 mg of TAF, unboosted. Administer as TAF/FTC once daily and RAL HD 1200 mg once daily, dosed as two 600 mg HD tablets. Magnesium- or aluminum-containing antacids are contraindicated; co-administration of calcium-containing antacids is not recommended with RAL HD. | A2 |
| <ul style="list-style-type: none"> Additional abbreviations: ART, antiretroviral therapy; CrCl, creatinine clearance. ART Regimens for individuals of childbearing potential: Refer to the DHHS guideline: Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. Substitutions: 1) In all cases, FTC and 3TC are interchangeable. 2) TAF 10 mg and TAF 25 mg are not interchangeable. Dose adjustments: Refer to Table 8: ARV Dose Adjustments for Renal and Hepatic Impairment for adjustment based on renal or hepatic function. | | |

| Table 2: Alternative Initial ART Regimens for Nonpregnant* Adults (listed alphabetically; for specific details, see <i>Specific Factors to Consider</i> or drug package inserts) | | |
|--|--|--------|
| Regimen | Comments | Rating |
| <i>Available as a Single-Tablet Formulation</i> | | |
| Tenofovir alafenamide/emtricitabine/cobicistat/darunavir (TAF 10 mg/FTC/COBI/ DRV; Symtuza) | <ul style="list-style-type: none"> Initiate only in patients with CrCl ≥ 30 mL/min. Carefully consider drug-drug interactions with COBI [Eron, et al. 2018]. Contains 10 mg TAF, boosted. | B2 |
| Tenofovir alafenamide/emtricitabine/cobicistat/elvitegravir (TAF 10 mg/FTC/COBI/EVG; Genvoya) | <ul style="list-style-type: none"> Initiate only in patients with CrCl ≥ 30 mL/min. Carefully consider drug-drug interactions with COBI. Contains 10 mg of TAF, boosted with COBI. Separate dosing of antacids by 2 hours, either before or after dose of EVG. | B1 |
| Tenofovir alafenamide/emtricitabine/rilpivirine (TAF 25 mg/FTC/RPV; Odefsey) | <ul style="list-style-type: none"> Initiate only in patients confirmed to have a CD4 cell count ≥ 200 cells/mm³ and viral load $< 100,000$ copies/mL. When a “rapid-start” or “test-and-treat” initiation of ART occurs before a patient’s viral load and CD4 count are available, avoid use of RPV. Initiate only in patients with CrCl ≥ 30 mL/min. Use with caution in patients with depression or a history of suicidality. To date, no clinical trials have been conducted; data are based on bioequivalence pharmacokinetic studies of TAF compared with TDF. Contraindicated with PPIs. Use H₂-blockers with caution and separate dosing by 12 hours. Must take with food. Contains 25 mg of TAF, unboosted. | B3 |
| Tenofovir disoproxil fumarate/lamivudine/ doravirine (TDF/3TC/DOR; Delstrigo) | <ul style="list-style-type: none"> Initiate only in patients with CrCl ≥ 50 mL/min. Contraindicated when co-administered with drugs that are strong cytochrome P450 (CYP)3A enzyme inducers. Consider bone mineral density. | B1 |
| <i>Available as a Multi-Tablet Regimen with Once-Daily Dosing</i> | | |
| Abacavir/lamivudine and doravirine (ABC/3TC and DOR; Epzicom and Pifeltro) [Molina, et al. 2018] | <ul style="list-style-type: none"> Initiate only in patients confirmed to be negative for HLA-B*5701. When a “rapid-start” or “test-and-treat” initiation of ART occurs before baseline laboratory test results are available, avoid use of ABC until a patient’s HLA-B*5701 test is confirmed negative. Consider underlying risk of coronary heart disease. Contraindicated when co-administered with drugs that are strong cytochrome P450 (CYP)3A enzyme inducers. | B2 |
| Tenofovir alafenamide/emtricitabine and doravirine (TAF 25 mg/FTC and DOR; Descovy and Pifeltro) | <ul style="list-style-type: none"> Initiate only in patients with CrCl ≥ 30 mL/min. Contraindicated when co-administered with drugs that are strong CYP3A enzyme inducers. | B2 |
| Tenofovir disoproxil fumarate/emtricitabine and dolutegravir (TDF/FTC and DTG; Truvada and Tivicay) | <ul style="list-style-type: none"> Initiate only in patients with CrCl ≥ 50 mL/min. Documented DTG resistance after initiation in treatment-naive patients is rare. Consider bone mineral density. Take magnesium- or aluminum-containing antacids 2 hours before or 6 hours after DTG; calcium-containing antacids or iron supplements may be taken simultaneously if taken with food. | B1 |

| Table 2: Alternative Initial ART Regimens for Nonpregnant* Adults (listed alphabetically; for specific details, see <i>Specific Factors to Consider</i> or drug package inserts) | | |
|---|---|--------|
| Regimen | Comments | Rating |
| Tenofovir disoproxil fumarate/ emtricitabine <i>and</i> raltegravir (TDF/FTC <i>and</i> RAL HD; Truvada <i>and</i> Isentress HD) | <ul style="list-style-type: none"> Initiate only in patients with CrCl \geq50 mL/min. Consider bone mineral density. Administer as TDF/FTC once daily and RAL HD 1200 mg once daily, dosed as two 600 mg HD tablets. Magnesium- or aluminum-containing antacids are contraindicated; co-administration of calcium-containing antacids is not recommended with RAL HD. | B1 |
| <i>Available as a Multi-Tablet Regimen with Twice-Daily Dosing</i> | | |
| Tenofovir alafenamide/ emtricitabine <i>and</i> raltegravir (TAF 25 mg/FTC <i>and</i> RAL; Descovy <i>and</i> Isentress) | <ul style="list-style-type: none"> Initiate only in patients with CrCl \geq30 mL/min. Administer as ABC/3TC once daily and RAL 400 mg twice daily. Magnesium- or aluminum-containing antacids are contraindicated; calcium-containing antacids are acceptable with RAL. | B3 |
| <ul style="list-style-type: none"> Additional abbreviations: ART, antiretroviral therapy; CrCl, creatinine clearance; PPI, proton-pump inhibitor. ART Regimens for individuals of childbearing potential: Refer to the DHHS guideline: Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. Substitutions: 1) In all cases, FTC and 3TC are interchangeable. 2) TAF 10 mg and TAF 25 mg are not interchangeable. 3) COBI and RTV should not be considered interchangeable because of their drug-interaction profiles. Dose adjustments: Refer to Table 8: ARV Dose Adjustments for Renal and Hepatic Impairment for adjustment based on renal or hepatic function. | | |

| Table 3: Other ART Regimens Not Included as Preferred or Alternative for Nonpregnant* Adults (listed alphabetically; for specific details, see <i>Specific Factors to Consider</i> and/or drug package inserts) | | |
|---|--|--------|
| Regimen | Comments | Rating |
| <i>Available as a Single-Tablet Regimen</i> | | |
| Tenofovir disoproxil fumarate/emtricitabine/efavirenz (TDF/FTC/EFV; Atripla) | <ul style="list-style-type: none"> Initiate only in patients with CrCl \geq50 mL/min. Use with caution in patients with depression or a history of suicidality. Consider bone mineral density. | B1 |
| Tenofovir disoproxil fumarate/emtricitabine/rilpivirine [a] (TDF/FTC/RPV; Complera) | <ul style="list-style-type: none"> Initiate only in patients confirmed to have a CD4 cell count \geq200 cells/mm³ and viral load $<$100,000 copies/mL. Initiate only in patients with CrCl \geq50 mL/min. Use with caution in patients with depression or a history of suicidality. Contraindicated with PPIs. Use H₂-blockers with caution and separate dosing by 12 hours. Must take with food. Consider bone mineral density. | B1 |
| <i>Available as a Multi-Tablet Regimen with Once-Daily Dosing</i> | | |
| Abacavir/lamivudine and atazanavir and ritonavir (ABC/3TC and ATV and RTV; Epzicom and Reyataz and Norvir) | <ul style="list-style-type: none"> Initiate only in patients confirmed to be negative for HLA-B*5701 [b]. Initiate only in patients with viral load $<$100,000 copies/mL. Carefully consider drug-drug interactions with RTV. Consider underlying risk of coronary heart disease. In treatment-naïve patients on boosted ATV, H₂-blockers should be either taken simultaneously with ATV or, if simultaneous dosing is not possible, separated from ATV by 10 hours; prescribe no more than 20 mg of famotidine or equivalent for one dose and no more than 40 mg twice daily of famotidine or equivalent for daily dose. Use no more than equivalent of 20 mg of omeprazole with ATV, separated by 12 hours. Scleral icterus from benign hyperbilirubinemia may be a concern. | C1 |
| Abacavir/lamivudine and darunavir/cobicistat (ABC/3TC and DRV/COBI; Epzicom and Prezcobix) | <ul style="list-style-type: none"> Initiate only in patients confirmed to be negative for HLA-B*5701 [b]. Carefully consider drug-drug interactions with COBI. Consider underlying risk of coronary heart disease. | B3 |
| Abacavir/lamivudine and darunavir and ritonavir (ABC/3TC and DRV and RTV; Epzicom and Prezista and Norvir) | <ul style="list-style-type: none"> Initiate only in patients confirmed to be negative for HLA-B*5701 [b]. Carefully consider drug-drug interactions with RTV. Consider underlying risk of coronary heart disease. | B2 |
| Abacavir/lamivudine and efavirenz (ABC/3TC and EFV; Epzicom and Sustiva) | <ul style="list-style-type: none"> Initiate only in patients confirmed to be negative for HLA-B*5701 [b]. Initiate only in patients with viral load $<$100,000 copies/mL. Use with caution in patients with depression or a history of suicidality. Consider underlying risk of coronary heart disease. | C1 |
| Tenofovir alafenamide/emtricitabine and efavirenz (TAF 25 mg/FTC and EFV; Descovy and Sustiva) | <ul style="list-style-type: none"> Initiate only in patients with CrCl \geq50 mL/min. Use with caution in patients with depression or a history of suicidality. Contains 25 mg of TAF, unboosted. | B3 |

| Table 3: Other ART Regimens Not Included as Preferred or Alternative for Nonpregnant* Adults (listed alphabetically; for specific details, see <i>Specific Factors to Consider</i> and/or drug package inserts) | | |
|---|---|---------------|
| Regimen | Comments | Rating |
| Abacavir/lamivudine <i>and</i> raltegravir (ABC/3TC <i>and</i> RAL HD; Epzicom <i>and</i> Isentress HD) | <ul style="list-style-type: none"> Initiate only in patients confirmed to be negative for HLA-B*5701 [b]. Consider underlying risk of coronary heart disease. Administer as ABC/3TC once daily and RAL HD 1200 mg once daily, dosed as two 600 mg HD tablets. Magnesium- or aluminum-containing antacids are contraindicated; co-administration of calcium-containing antacids is not recommended with RAL HD. | B3 |
| <i>Available as a Multi-Tablet Regimen with Twice-Daily Dosing</i> | | |
| Tenofovir disoproxil fumarate/ emtricitabine <i>and</i> raltegravir (TDF/FTC <i>and</i> RAL; Truvada <i>and</i> Isentress) | <ul style="list-style-type: none"> Initiate only in patients with CrCl \geq50 mL/min. Consider bone mineral density. TDF/FTC once daily and RAL 400 mg twice daily. Magnesium- or aluminum-containing antacids are contraindicated; calcium-containing antacids are acceptable with RAL. | B1 |
| Abacavir/lamivudine <i>and</i> raltegravir (ABC/3TC <i>and</i> RAL; Epzicom <i>and</i> Isentress) | <ul style="list-style-type: none"> Initiate only in patients confirmed to be negative for HLA-B*5701 [b]. Consider underlying risk of coronary heart disease. Administer as ABC/3TC once daily and RAL 400 mg twice daily. Magnesium- or aluminum-containing antacids are contraindicated; calcium-containing antacids are acceptable with RAL. | B1 |
| <ul style="list-style-type: none"> Additional abbreviations: ART, antiretroviral therapy; CrCl, creatinine clearance; PPI, proton-pump inhibitor. ART Regimens for individuals of childbearing potential: Refer to the DHHS guideline: <i>Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States</i>. Substitutions: 1) In all cases, FTC and 3TC are interchangeable. 2) TAF 10 mg and TAF 25 mg are not interchangeable. 3) COBI and ritonavir should not be considered interchangeable because of their drug-interaction profiles. Dose adjustments: Refer to Table 8: ARV Dose Adjustments for Renal and Hepatic Impairment for adjustment based on renal or hepatic function. <p>Notes:</p> <ol style="list-style-type: none"> When a “rapid-start” or “test-and-treat” initiation of ART occurs before viral load and CD4 count are available, avoid use of RPV. When a “rapid-start” or “test-and-treat” initiation of ART occurs before baseline laboratory test results are available, avoid use of ABC until HLA-B*5701 is confirmed negative. | | |

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General Principles in Choosing an Initial ART Regimen

Lead Author: Samuel T. Merrick, MD, with the Medical Care Criteria Committee, updated January 2019

Goals of antiretroviral therapy (ART): The issue of when to start ART was settled with the publication of the START (Strategic Timing of Antiretroviral Treatment) and TEMPRANO (Early Antiretroviral Treatment and/or Early Isoniazid Prophylaxis Against Tuberculosis in HIV-infected Adults) studies early in 2015 [Danel, et al. 2015; Lundgren, et al. 2015]. Treatment is now recommended for all individuals with confirmed HIV regardless of CD4 cell count or viral load (see the NYSDOH guideline *When to Initiate ART*). The goal of ART is complete and durable suppression of plasma viremia while minimizing toxicity and maximizing quality of life. Properly selected ART may never require a change or adjustment once started. Treatment interruptions should be avoided [El-Sadr, et al. 2006].

Since the approval of zidovudine (ZDV) on March 19, 1987, there have been 30 individual agents approved for the treatment of HIV and 1 pharmacokinetic enhancer (or booster), cobicistat (COBI), which is currently used to enhance the pharmacokinetics of elvitegravir (EVG), atazanavir (ATV), or darunavir (DRV). Ritonavir (RTV) at treatment doses is poorly tolerated and is used only at lower doses for pharmacokinetic boosting of PIs. An additional 18 U.S. Food and Drug Administration (FDA)-approved fixed-dose combination tablets (FDCs) are also available. These FDCs include STRs, of which there are 9 currently available that provide a complete and effective treatment regimen for HIV that is combined into 1 pill for use in properly selected individuals. The goal of initial therapy is to start a regimen that suits an individual's lifestyle and is appropriate given existing baseline medical comorbidities.

Three active drugs from at least 2 different classes: Although regimen options for treatment-naïve, nonpregnant individuals are constantly evolving, the same general principles that were established with the first effective and durable therapies are still true today [Gulick, et al. 2000]. Patients should receive 3 active drugs from at least 2 different classes. The backbone of therapy remains 2 nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) paired with 1 of the following: a non-nucleoside reverse transcriptase inhibitor (NNRTI), a boosted protease inhibitor (PI), or a boosted or unboosted integrase strand transfer inhibitor (INSTI). In a large meta-analysis, INSTIs were superior to other drug classes as a third drug [Lee, et al. 2014], and dolutegravir (DTG) may have specific advantages because of the lack, to date, of documented resistance developing in ART-naïve patients who initiate DTG-containing regimens [Wainberg and Mesplede 2015]. Two other classes of approved medications, entry inhibitors and fusion inhibitors, are not recommended for initial therapy (see Table 5, below) but may have a role in treatment-experienced patients with extensive drug resistance (see *All FDA-Approved HIV Medications*, including generic and trade names).

Although dual- or even monotherapy regimens have been and continue to be studied [Taiwo, et al. 2011; Bedimo, et al. 2014; Cahn, et al. 2014; Raffi, et al. 2014; Baril, et al. 2016; Cahn, et al. 2016; Maggiolo, et al. 2016; Cahn, et al. 2018], they cannot be recommended currently as initial therapy until more data are available. Existing studies demonstrate limitations with these regimens in ART-naïve individuals, particularly in patients with viral loads >100,000 copies/mL or CD4 counts <200 cells/mm³, or have not yet demonstrated long-term durability compared with recommended therapy.

Tenofovir alafenamide (TAF), which is a newer pro-drug formulation for tenofovir, was developed as an alternative to tenofovir disoproxil fumarate (TDF) and has been approved as part of 4 single-tablet regimens (STRs) (TAF 10 mg/emtricitabine (FTC)/COBI/EVG, TAF 25 mg/FTC/rilpivirine (RPV), TAF 25 mg/FTC/ bicitgravir (BIC) [FDA 2016b, 2016c, 2018a], TAF 10 mg/FTC/COBI/DRV [FDA 2018b]) and the FDC TAF 25 mg/FTC [FDA 2016a]. Oral administration of TAF results in lower circulating levels of tenofovir in plasma and affects markers of renal toxicity and bone mineral density less adversely [Sax, et al. 2015; Mills, et al. 2016; Pozniak, et al. 2016]. Bioequivalence studies in healthy volunteers show that the TAF 10 mg dose administered with COBI 150 mg is equivalent to the TAF 25 mg dose without COBI [Zack, et al. 2016a; Zack, et al. 2016b]. A switch study showed good maintenance of viral suppression when changing TDF/FTC to TAF 10 mg/FTC if the third drug was a boosted PI, or TAF 25 mg/FTC if the third drug was an unboosted NNRTI or INSTI [Gallant JE, et al. 2016]. **(Note that TAF 10 mg alone and TAF 10 mg/FTC are not currently FDA-approved.)** Until further safety data are available, this Committee has not included TAF 25 mg/FTC in combination with COBI or RTV as recommended regimens and recommends caution when using TAF 25 mg/FTC with regimens that contain either COBI or RTV in the setting of creatinine clearance (CrCl) <50 mL/min.

COBI-boosted DRV was approved based on bioavailability studies [Kakuda, et al. 2014; FDA 2016d] and has demonstrated comparable efficacy to RTV-boosted DRV in a single-arm study [Tashima, et al. 2014]. However, because COBI-boosted DRV compared with RTV-boosted DRV has not yet been studied in randomized clinical trials, it has a lower evidence strength. COBI-boosted ATV showed non-inferiority when compared with RTV-boosted ATV with a TDF/FTC backbone in a randomized double-blind study [Gallant JE, et al. 2013].

All of the currently recommended preferred regimens have similar virologic efficacy when measured by an "on-treatment" metric, but adherence, the potential for drug interactions, and tolerability under real-life conditions may inform the choice of preferred versus alternative versus other regimens.

The following general conclusions can be drawn based on currently available evidence from a number of pivotal studies:

- When abacavir/lamivudine (ABC/3TC) is used as a backbone with efavirenz (EFV) or boosted ATV, time to failure was shorter in the $\geq 100,000$ copies/mL viral load stratum when compared with a backbone of TDF/FTC [Sax, et al. 2009; Post, et al. 2010; Sax, et al. 2011].
- Dolutegravir (DTG) is as efficacious as (i.e., non-inferior to) raltegravir (RAL) [Raffi, et al. 2013] and superior to both RTV-boosted DRV [Molina, et al. 2014] and coformulated TDF/FTC/EFV [Walmsley S, et al. 2015]. DTG was superior at 48 weeks when combined with ABC/3TC as compared to TDF/FTC/EFV [Walmsley SL, et al. 2013].
- RAL, although dosed twice daily, has a favorable tolerability profile and provides durable virologic control [Young, et al. 2010; DeJesus, et al. 2012; Lennox, et al. 2014] and was superior to both RTV-boosted DRV and RTV-boosted ATV based on the cumulative incidence of virologic failure and tolerability [Lennox, et al. 2014].
- In a study of ART-naïve individuals, RAL HD 1200 mg once daily was non-inferior to RAL 400 mg tablets dosed twice daily [Cahn, et al. 2017].
- TAF/FTC/COBI/EVG as an STR was non-inferior to the STR TDF/FTC/COBI/EVG, with fewer adverse effects on kidney function and bone mineral density [Sax, et al. 2015].
- RPV has excellent efficacy relative to EFV when baseline viral load is $< 100,000$ copies/mL and is better tolerated [Cohen CJ, et al. 2012; Cohen CJ, et al. 2013; Behrens, et al. 2014; Cohen C, et al. 2014; van Lunzen, et al. 2016] but should not be initiated in individuals with baseline viral load $> 100,000$ copies/mL or CD4 counts < 200 cells/mm³.
- RTV-boosted DRV once daily is better tolerated and non-inferior to either RTV-boosted ATV or lopinavir (LPV)/RTV [Orkin, et al. 2013; Lennox, et al. 2014], although LPV/RTV shows excellent efficacy when combined with either commonly used NRTI backbone [Smith, et al. 2009] and when compared with RTV-boosted ATV [Molina, et al. 2008]. One open-label study using ABC/3TC as the backbone combined with RTV-boosted DRV showed good safety and efficacy [Trottier, et al. 2012].
- In 2 separate trials of treatment-naïve individuals, TAF/FTC/BIC was non-inferior to both TAF/FTC and DTG [Sax, et al. 2017] and ABC/3TC/DTG [Gallant J, et al. 2017].
- In 2 separate trials of treatment-naïve individuals, TDF/3TC/doravirine (DOR) was non-inferior to TDF/FTC/EFV, or RTV-boosted DRV with either TDF/FTC or ABC/3TC [Molina, et al. 2018; Orkin, et al. 2018].

Table 4: Individual ARVs or Combinations to Avoid in Initial Therapy for Nonpregnant Adults

| ARV | Comments |
|---|---|
| Nevirapine (NVP; Viramune) | Life-threatening rash: Stevens-Johnson syndrome and toxic epidermal necrolysis are possible. |
| <ul style="list-style-type: none"> • Stavudine (d4T; Zerit) • Didanosine (ddI; Videx) | Serious toxicities: Potentially fatal lactic acidosis, peripheral neuropathy, pancreatitis, lipodystrophy, and hepatic steatosis are possible. |
| Delavirdine (DLV; Rescriptor) | Thrice-daily dosing and inferior efficacy. |
| Etravirine (ETR; Intelence) | ETR does not have an FDA indication in ART-naïve patients. |
| <ul style="list-style-type: none"> • Maraviroc (MVC; Selzentry) • NRTI-only regimens, either triple or quadruple | Inferior efficacy and durability. |
| Zidovudine (ZDV; Retrovir) | Not well tolerated because of bone marrow suppression (notably anemia), headache, and myopathies. |
| Unboosted PIs | Inferior efficacy relative to boosted PIs. |
| <ul style="list-style-type: none"> • Fosamprenavir (FPV; Lexiva) • Indinavir (IDV; Crixivan) • Tipranavir (TPV; Aptivus) • Nelfinavir (NFV; Viracept) | Either not well studied or limited by dosing and side effects relative to recommended PIs. |

Additional abbreviations: ART, antiretroviral therapy; ARV, antiretroviral, FDA, U.S. Food and Drug Administration; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor.

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General Considerations with Initial ART Regimens

Lead Author: Samuel T. Merrick, MD, with the Medical Care Criteria Committee, updated January 2019

The recommended antiretroviral therapy (ART) regimens should work well for the majority of patients, but some circumstances may make one regimen more favorable than another for a given individual. In general, an integrase strand transfer inhibitor (INSTI)-based regimen will be the best option for most patients [Lee, et al. 2014; Mills, et al. 2016]. To date, no resistance has been reported in ART-naïve patients treated with dolutegravir (DTG) when used as part of combination therapy, suggesting that this antiretroviral (ARV) may be an excellent choice, particularly given its tolerability and lack of drug-drug interactions [Wainberg and Mesplede 2015]. Regimens containing a boosted protease inhibitor or DTG may be more appropriate when adherence is a concern, given the higher barrier to resistance. For patients with acute symptomatic infection or advanced HIV with an opportunistic infection, some experts would use both DTG and boosted darunavir (DRV) together with the nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) backbone given the possibility of transmitted NRTI resistance until genotypic information is available, at which time the regimen can be adjusted. Consultation with an experienced HIV care provider is recommended when choosing a regimen for patients with extensive comorbidities, impaired renal function, hepatitis B virus or hepatitis C virus coinfection, or very high viral loads.

→ KEY POINT

- INSTI-based regimens are generally the best choice for most individuals because of tolerability and durability.

Early clinical trials in HIV used surrogate markers, such as viral load and CD4 cell count, or clinical end points, such as morbidity and mortality, to demonstrate superiority of new therapies over the “gold standard” treatment of the era. One of the trials that led to the 1996 approval of indinavir (IDV) compared IDV alone versus zidovudine (ZDV) plus lamivudine (3TC) versus ZDV plus 3TC plus IDV in ZDV treatment-experienced patients, given that, at the time, dual NRTI treatment was considered acceptable [Gulick, et al. 1997]. As treatment has evolved and become more effective, the use of clinical end points has become challenging; most trials in the current era of HIV therapy are powered to detect non-inferiority when compared with standard of care. For a variety of reasons, including cost and complexity, it would be impractical to conduct head-to-head comparisons of all available regimens. Some single-tablet regimens and fixed-dose combinations have been approved primarily based on bioequivalence studies when compared with the individual components, such as tenofovir disoproxil fumarate/emtricitabine/efavirenz (TDF/FTC/EFV), abacavir/lamivudine/dolutegravir (ABC/3TC/DTG), tenofovir alafenamide/emtricitabine/rilpivirine (TAF/FTC/RPV), TAF/FTC, and cobicistat/darunavir (COBI/DRV).

Some of the cutoff values used for comparisons, such as viral load <100,000 copies/mL or CD4 count ≥200 cells/mm³, are somewhat arbitrary. For example, most studies including RPV show that its efficacy is diminished when initiated at viral loads ≥100,000 copies/mL, and 1 study showed that RPV worked even less well than EFV-based therapy at a viral load of ≥500,000 copies/mL [Domingo and Ribera 2013].

Some agents have been approved based on non-inferiority to the relatively less well-tolerated TDF/FTC/EFV regimen, which is, nevertheless, a potent and effective regimen for those who tolerate it well. The higher prevalence of NNRTI resistance mutations when transmitted drug resistance occurs has prompted most experts to avoid NNRTI-based regimens if treatment is indicated prior to the availability of genotypic information [Rhee, et al. 2015; Stekler, et al. 2015; Panichsillapakit, et al. 2016]. Although coformulated TAF/FTC/COBI/EFV is approved for use at any starting viral load, reports of failure using TDF/FTC/COBI/EFV, with resistance, have been documented at very high baseline viral loads >1,000,000 copies/mL [Rhee, et al. 2015; Adams, et al. 2016].

A paucity of data is available demonstrating how different ARVs perform based on race and gender, although studies have suggested, for instance, that ritonavir (RTV)-boosted DRV is less well tolerated in women than in men and that black individuals have higher discontinuation rates on RTV-boosted DRV than other populations [Currier, et al. 2010; Smith, et al. 2012].

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Specific Factors to Consider and Discuss with Patients

Lead Author: Samuel T. Merrick, MD, with the Medical Care Criteria Committee, updated January 2019

Before initiating antiretroviral therapy (ART), the following factors are important to consider and discuss with patients.

Age: As individuals with HIV age, they have a higher prevalence of comorbidities than younger patients with HIV and are likely to be on more non-HIV-specific medications, particularly cardiovascular or gastrointestinal agents, posing a higher risk for adverse interactions [Marzolini, et al. 2011]. For individuals older than age 50 years, careful regimen selection, with the use of integrase strand transfer inhibitors (INSTIs) when possible rather than cytochrome P450 inhibitors, such as cobicistat (COBI) or ritonavir (RTV), can help minimize interactions. And use of tenofovir alafenamide (TAF) rather than tenofovir disoproxil fumarate can lower the risk of renal and bone toxicity.

Comorbidities: Assessment for existing cardiovascular risk, renal disease or risk factors for the development of renal disease, hepatic disease, bone health, mental health, and substance use should be performed.

Cost: Single-tablet regimens (STRs) may be favorable because of the lower copays that could be associated with fewer prescriptions. Conversely, the individual components of these regimens may be available generically as separate pills.

Dosing requirements (daily vs twice daily): Most patients express a preference for once-daily dosing, especially those who are not taking other medications or are taking other medications that are dosed once daily. If individuals are already on twice-daily dosing of other medications and report no adherence issues, twice-daily dosing is an acceptable option.

Drug-drug interactions: Some key interactions exist (Table 5, below), such as avoiding use of proton-pump inhibitors (PPIs) with rilpivirine (RPV), which is especially important to discuss with patients, given the availability of over-the-counter PPIs and the possibility that these drugs may be prescribed by someone other than the HIV care provider. To avoid unnecessary regimen changes once started, even patients who are not currently on PPIs should be asked whether they have needed PPIs in the past or may need them in the future.

RTV and COBI have many significant and important interactions, including with cardiac medications. Methadone maintenance requirements may also change with some antiretroviral (ARV) agents. A detailed review of all medications, including over-the-counter medications or supplements, is essential. Using automated drug-drug interaction software embedded in the electronic medical record or consulting an up-to-date database, such as the [Database of Antiretroviral Drug Interactions](#) or the [University of Liverpool HIV Drug Interactions Checker](#), for interactions with currently prescribed medications BEFORE prescribing a regimen, can help avoid serious problems.

| Table 5: Select Drug-Drug Interactions to Discuss before Initiating ART in Treatment-Naive Patients | |
|---|---|
| Drugs | ARV(s): Comments |
| H ₂ -blockers | <ul style="list-style-type: none"> • ATV: In treatment-naive patients on boosted ATV, H₂-blockers should be taken simultaneously with ATV or, if simultaneous dosing is not possible, separated from ATV by 10 hours; prescribe no more than 20 mg of famotidine or equivalent for 1 dose and no more than 40 mg twice daily of famotidine or equivalent for daily dose. • RPV: Use with caution; administer at least 12 hours before or at least 4 hours after RPV. |
| <ul style="list-style-type: none"> • Inhaled steroids • Statins | <ul style="list-style-type: none"> • COBI; RTV: Alternatives or dose adjustments may be needed. • Consult the package inserts for drug-drug interactions between specific statins and ARVs. |
| Polyvalent cations [a] | <ul style="list-style-type: none"> • DTG; BIC: Take 2 hours before or 6 hours after DTG; calcium-containing antacids or iron supplements may be taken simultaneously if taken with food. • RAL: Magnesium- or aluminum-containing antacids are contraindicated; calcium-containing antacids are acceptable. • RAL HD: Magnesium- or aluminum-containing antacids are contraindicated; co-administration of calcium-containing antacids is not recommended. • EVG: Separate dosing by 2 hours, either before or after dose of EVG. |
| PPIs | <ul style="list-style-type: none"> • ATV: Contraindicated with ATV in treatment-experienced patients; in treatment-naive patients, use no more than equivalent of 20 mg of omeprazole with ATV, separated by 12 hours. • RPV: Contraindicated. |

| Table 5: Select Drug-Drug Interactions to Discuss before Initiating ART in Treatment-Naive Patients | |
|---|--|
| Drugs | ARV(s): Comments |
| Metformin | <ul style="list-style-type: none"> • DTG: Metformin levels are significantly raised when co-administered with DTG. If used concomitantly, total daily dose of metformin should not exceed 1,000 mg without clinical evaluation of efficacy and adverse events. |
| Ethinyl estradiol and norethindrone [b] | <ul style="list-style-type: none"> • EFV; COBI/ATV; COBI/DRV; RTV and DRV: Use alternative or additional (e.g., barrier) contraceptive methods or choose alternative ART regimen. • ATV; RTV and ATV: Use with caution; see manufacturer’s package insert for specific dosing information. |
| Factor Xa inhibitors | <ul style="list-style-type: none"> • COBI; RTV: <ul style="list-style-type: none"> - Apixaban: Reduce dose by 50% if patient is on 5 mg twice daily; avoid use if the indicated dose is 2.5 mg twice daily (based on age, weight, creatinine level). - Dabigatran: No adjustment needed if CrCl ≥50 mL/min; avoid if CrCl <50 mL/min. - Rivaroxaban: Avoid use. |
| Platelet inhibitors | <ul style="list-style-type: none"> • COBI; RTV: <ul style="list-style-type: none"> - Clopidogrel: Avoid use. - Prasugrel: No adjustment needed. - Ticagrelor: Avoid use. |
| <p>Abbreviations: ART, antiretroviral therapy; ARV, antiretroviral; ATV, atazanavir; COBI, cobicistat; CrCl, creatinine clearance; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; PPI, proton-pump inhibitor; RAL, raltegravir; RPV, rilpivirine; RTV, ritonavir.</p> <p>Notes:</p> <ol style="list-style-type: none"> Aluminum, calcium, magnesium, or iron in some antacids or vitamin preparations. For emergency contraception, other oral combinations, and patch, ring, or injectable formulations, please refer to package insert for specific ARV for dosing instructions and safety information. | |

Food requirements: Because an individual may have a strong preference for taking medication with or without food, it is important to discuss which pills must be taken on an empty stomach, which must be taken with food, and which can be taken with or without food, as listed in Box 1, below.

| Box 1: ARVs That Must Be Taken With and Without Food or on an Empty Stomach | | |
|---|--|---|
| With or Without Food | With Food | On Empty Stomach |
| <ul style="list-style-type: none"> • 3TC • ABC • DOR • DTG • FTC • RAL • TAF • TDF • TAF/FTC/BIC • TAF/FTC/DOR | <ul style="list-style-type: none"> • ATV/COBI • ATV and RTV • DRV/COBI • DRV and RTV • EVG • RPV • TAF/FTC/COBI/EVG • TAF/FTC/COBI/DRV | <ul style="list-style-type: none"> • EFV |
| <p>Drug name abbreviation key: 3TC, lamivudine; ABC, abacavir; ATV, atazanavir; BIC, bictegravir; COBI, cobicistat; DOR, doravirine; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; EVG, elvitegravir; FTC, emtricitabine; RAL, raltegravir; RPV, rilpivirine; RTV, ritonavir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.</p> | | |

Known side effects and toxicities: Review known and potential side effects in advance.

Number of pills: Some patients feel strongly that the fewer the number of pills, the better. For others, the greatest concern may be the ability to take all pills (regardless of the number) together once daily. Sometimes using individual agents rather than a multi-agent fixed-dose combination or STR may be attractive depending on pill size. In rare cases, individuals who either cannot or will not swallow pills may need liquid formulations or pill crushing. Table 6, below, presents an abbreviated summary of commonly used ARVs and their availability in liquid formulation and/or the acceptability of crushing or dissolving them prior to ingestion. A full list that gives greater detail is available.

| Table 6: Acceptable Alternative Formulations and Methods of Administration of Antiretroviral Medications | | |
|---|---|---|
| Drug | Available as Liquid, Powder, or Chewable Tablet? | Can Tablet be Split/Crushed/Dissolved? |
| <i>Single-Tablet Formulations</i> | | |
| Abacavir/lamivudine/dolutegravir (ABC/3TC/DTG; Trumeq) | No | Probably acceptable to split/crush |
| Tenofovir alafenamide/emtricitabine/ bictegravir (TAF/FTC/BIC; Biktarvy) | No | No data; not recommended |
| Tenofovir alafenamide/emtricitabine/cobicistat/darunavir (TAF/FTC/COBI/DRV; Symtuza) | No | No data; not recommended |
| Tenofovir alafenamide/emtricitabine/elvitegravir/ cobicistat (TAF/FTC/COBI/EVG; Genvoya) | No | No data; not recommended |
| Tenofovir alafenamide/emtricitabine/rilpivirine (TAF/FTC/RPV; Odefsey) | No | No data; not recommended |
| Tenofovir disoproxil fumarate/emtricitabine/doravirine (TDF/3TC/DOR); Delstrigo) | No | No data; not recommended |
| Tenofovir disoproxil fumarate/emtricitabine/efavirenz (TDF/FTC/EFV; Atripla) | No | No data; not recommended |
| Tenofovir disoproxil fumarate/emtricitabine/rilpivirine (TDF/FTC/RPV; Complera) | No | No data; not recommended |
| <i>Fixed-Dose Combinations</i> | | |
| Abacavir/lamivudine (ABC/3TC; Epzicom) | See individual components below | Probably acceptable to split/crush |
| Darunavir/cobicistat (DRV/COBI; Prezcobix) | No | No |
| Tenofovir alafenamide/emtricitabine (TAF/FTC; Descovy) | No | No |
| Tenofovir disoproxil fumarate/emtricitabine (TDF/FTC; Truvada) | See individual components below | Acceptable to crush/dissolve |
| Zidovudine/lamivudine (ZDV/3TC; Combivir) | See individual components below | Probably acceptable to split/crush |
| <i>Individual Drugs</i> | | |
| Abacavir (ABC; Ziagen) | Oral solution (20 mg/mL) | No data |
| Atazanavir (ATV; Reyataz) | Oral dispersible powder (50 mg/packet) | Can open capsule and sprinkle contents |
| Darunavir (DRV; Prezista) | Oral suspension (100 mg/mL) | Probably acceptable to crush |
| Doravirine (DOR; Pifeltro) | No | No data |

| Table 6: Acceptable Alternative Formulations and Methods of Administration of Antiretroviral Medications | | |
|--|--|--|
| Drug | Available as Liquid, Powder, or Chewable Tablet? | Can Tablet be Split/Crushed/Dissolved? |
| Dolutegravir (DTG; Tivicay) | No | Acceptable to crush |
| Efavirenz (EFV; Sustiva) | No | No |
| Elvitegravir (EVG; Vitekta) | No | No data |
| Emtricitabine (FTC; Emtriva) | Oral solution (10 mg/mL) | Acceptable to open and dissolve in water |
| Lamivudine (3TC; Epivir) | Oral solution (10 mg/mL) | Acceptable to crush or split |
| Raltegravir (RAL; Isentress) | Chewable tablet (25 mg, 100 mg); oral powder for suspension (100 mg/packet); neither is bioequivalent to the 400 mg adult dose | Not recommended |
| Raltegravir HD (RAL HD; Isentress HD) | No | No data; not recommended |
| Rilpivirine (RPV; Edurant) | No | No data; not recommended |
| Ritonavir (RTV; Norvir) | Oral solution (80 mg/mL) | No |
| Tenofovir disoproxil fumarate (TDF; Viread) | Oral powder mixed with soft food only (40 mg/1 g) | Acceptable to dissolve in water |

Pill size: Use images or real examples to give patients an idea of pill size BEFORE they fill the prescription (examples of visual guides include those of [AIDSinfo](#) and [HIV i-Base](#)). TAF/emtricitabine (FTC)/bictegravir (BIC) and TAF/FTC/rilpivirine (RPV) are the smallest STRs.

Pregnancy or conception planning: Individuals of childbearing age should receive a pregnancy test and be assessed for use of contraception. When selecting an initial regimen for those who are not using effective contraception, clinicians should consult the U.S. Department of Health and Human Services (DHHS) guideline, *Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*. All patients should be assessed for conception plans; this can be an opportunity to discuss pre-exposure prophylaxis (PrEP) for uninfected partners (see the NYSDOH AI guideline *PrEP to Prevent HIV Acquisition*).

Dolutegravir (DTG) Safety Statement, May 2018

- On May 18, 2018, the FDA and the DHHS Antiretroviral Guidelines Panels issued statements in response to preliminary results from a study that reported increased risk of neural tube defects in babies born to mothers taking DTG-based ARV drug regimens at the time of conception [[AIDSinfo 2018](#); [FDA 2018](#)].
- Until more data become available, **DTG-containing regimens should be avoided in any HIV-exposed individual who is pregnant in the first trimester or could become pregnant and is not using effective contraception**. If there are no alternatives to DTG for individuals child-bearing potential, then clinicians should strongly advise the use of effective contraception and should obtain a pregnancy test before initiating treatment.
- For more information, see: *DHHS Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*

Reference

Marzolini C, Back D, Weber R, et al. Ageing with HIV: medication use and risk for potential drug-drug interactions. *J Antimicrob Chemother* 2011;66(9):2107-2111. [PMID: 21680580]

Special Considerations for Comorbid Conditions

Lead Author: Samuel T. Merrick, MD, with the Medical Care Criteria Committee, updated January 2019

Bone disease: Tenofovir disoproxil fumarate (TDF) causes a decrease in bone mineral density in all patients after initiation of therapy and should be used with caution in patients with preexisting severe osteoporosis [Perrot, et al. 2009; Stellbrink, et al. 2010; McComsey, et al. 2011]. Some experts recommend baseline bone densitometry screening for osteoporosis in postmenopausal women and in men and transgender women older than 50 years who have HIV [Aberg, et al. 2014]. The tenofovir alafenamide (TAF) formulation available currently in tenofovir alafenamide/emtricitabine (TAF/FTC), tenofovir alafenamide/emtricitabine/cobicistat/elvitegravir (TAF/FTC/COBI/EVG), tenofovir alafenamide/emtricitabine/bictegravir (TAF/FTC/BIC), and tenofovir alafenamide/emtricitabine/rilpivirine (TAF/FTC/RPV), is a better alternative with less bone toxicity [Bonora, et al. 2016; Pozniak, et al. 2016].

Cardiovascular risks: Cobicistat (COBI)- or ritonavir (RTV)-containing regimens typically elevate lipids; TDF-containing regimens can have a beneficial effect on lipids [Souza, et al. 2013]. Abacavir (ABC) has been associated with a higher risk of myocardial infarction in some studies [Sabin, et al. 2008; SMART/INSIGHT 2008; Obel, et al. 2010; Choi, et al. 2011; Marcus, et al. 2016], whereas other studies have not confirmed this association [Brothers, et al. 2009; Bedimo, et al. 2011; Ribaud, et al. 2011; Ding, et al. 2012]. Based on the available data, ABC should be used with caution in those with multiple cardiac risk factors or known coronary heart disease; however, the absolute risk of myocardial infarction remains low, and no clear causality has been established. In the appropriate clinical setting, such as a patient with impaired renal function, the use of ABC would be acceptable [Llibre and Hill 2016]. Clinicians should be made aware of the conflicting study data and share this information with patients.

Liver disease: In patients with existing liver disease of any etiology, dose adjustment of ARVs may be required depending on the severity of hepatic impairment (see *Table 8: ARV Dose Adjustments for Renal and Hepatic Impairment*).

Mental health and substance use: Modifiable factors that may influence adherence should be addressed. There are also potential interactions between illicit (e.g. methamphetamine) and licit substances (e.g. methadone) and ART [Kumar, et al. 2015].

→ KEY POINT

- Neither mental health nor substance use disorders are contraindications to initiating therapy. In some special cases, delay of initiation (for as short a time as possible) may be appropriate while addressing adherence issues and/or possible interactions (see the NYSDOH AI guideline *When to Initiate ART*).

Renal function: TDF can cause renal tubular dysfunction, such as acquired Fanconi syndrome [Karras, et al. 2003; Zimmermann, et al. 2006]. The risk of renal impairment has been shown to be elevated in patients with preexisting renal disease, longer treatment duration, low body weight, and when used in conjunction with RTV- or COBI-boosted regimens [Gervasoni, et al. 2013; Mocroft, et al. 2016]. In general, full-dose TDF should be used with caution in patients with baseline creatinine clearance (CrCl) <70 mL/min and should be adjusted or changed to an alternative agent if CrCl decreases to <50 mL/min; TAF is a better choice in these patients. As noted above, TAF 25 mg/FTC should be used with caution in boosted regimens when CrCl is <50 mL/min.

Both RTV-boosted atazanavir (ATV/r) and lopinavir (LPV/r) have also been independently associated with a greater decrease in renal function over time compared with NNRTI-based regimens [Goicochea, et al. 2008; Quesada, et al. 2015]. COBI, and to a lesser extent dolutegravir (DTG), can inhibit the excretion of creatinine, with expected elevations of creatinine at initiation of therapy. However, such increases are not clinically relevant and do not significantly affect glomerular filtration rate [German, et al. 2012; Koteff, et al. 2013; Lepist, et al. 2014].

Although DTG is highly bound to plasma proteins and is unlikely to be removed by dialysis, it has not been studied in this population [FDA 2013]; therefore, raltegravir (RAL) or a boosted protease inhibitor (PI) with renally-adjusted lamivudine (3TC) and either ABC or once-weekly TDF are usually the regimens of choice in this setting.

Additional information on prescribing agents in the setting of reduced renal function is available in *Table 8: ARV Dose Adjustments for Renal and Hepatic Impairment*.

Very high viral loads (>750,000 copies/mL): In some cases, experts will recommend use of both boosted DRV and DTG when the viral load is very high, with possible simplification once viral suppression is achieved. Numerous switch studies have demonstrated the safety of simplifying antiretroviral regimens in virally suppressed individuals with no preexisting resistance [Fisher, et al. 2009; Mills, et al. 2013; Arribas, et al. 2014; Cazavane, et al. 2015]. Consultation with an experienced HIV care provider in these situations is helpful.

→ KEY POINTS

- Both COBI and DTG can cause decreased tubular excretion of creatinine and may cause a slight increase in measured creatinine.
- ABC has been associated with a higher risk of myocardial infarction in some studies, although not in others. No clear causal link has been established.
- Boosted PIs and COBI-boosted EVG are associated with a higher incidence of hyperlipidemia than unboosted integrase strand transfer inhibitors.
- Consultation with an experienced HIV care provider is advised when a patient's baseline viral load is very high (>750,000 copies/mL).

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ART–Initiation Laboratory Testing

Lead Author: Samuel T. Merrick, MD, with the Medical Care Criteria Committee, updated January 2019

→ KEY POINT

- When initiating therapy at the time of diagnosis (“rapid start”) it is not necessary to have the results of baseline laboratory tests immediately available. Labs, as indicated below, should be ordered at the time of initiation of antiretroviral therapy (ART), and any necessary adjustments to therapy should be made as soon as the results are available (such as for renal function or evidence of resistance). Abacavir (ABC)–containing regimens should not be used for rapid start without documentation of negative HLA–B*5701 test results.

Baseline CD4 cell count: Some regimens should not be used when the CD4 count is <200 cells/mm³ because of an increased risk of treatment failure (see Table 7, below). When *Pneumocystis jiroveci* pneumonia prophylaxis is indicated, it may be prudent to defer ART for 7 to 10 days if 2 medications that may cause rash will be started, such as trimethoprim–sulfamethoxazole (TMP–SMX) and efavirenz (EFV).

Baseline HIV genotypic resistance profile: Genotypic resistance testing that includes the protease and reverse transcriptase genes should be obtained at diagnosis (or initial visit if not done previously), but ART initiation should not be delayed pending the results [Borroto–Esoda, et al. 2007; Kuritzkes, et al. 2008]. Consultation with a care provider experienced in ART management is warranted when patients have baseline resistance that requires treatment with a regimen other than the listed preferred or alternative regimens. If treatment is indicated prior to the availability of genotypic resistance testing, non–nucleoside reverse transcriptase inhibitor (NNRTI)–based regimens should be avoided because of the higher prevalence of transmitted resistance in NNRTIs than in protease inhibitors or integrase strand transfer inhibitors [Rhee, et al. 2015; Stekler, et al. 2015; Panichsillapakit, et al. 2016]. In the case of, for example, a patient with symptomatic acute infection or advanced HIV with an opportunistic infection, some experts would include dolutegravir (DTG), boosted darunavir (DRV), or both together with the NRTI backbone, given the possibility of transmitted NRTI resistance, with possible simplification once genotypic information is available. Because of the low prevalence, to date, of transmitted integrase resistance in ART–naive individuals [Garcia–Diaz, et al. 2014; Volpe, et al. 2016], routine integrase resistance testing is not recommended in these patients. However, when integrase resistance is suspected, this test can be ordered as a supplement to protease and reverse transcriptase testing.

Baseline viral load: Some regimens should not be used when the viral load is $\geq 100,000$ copies/mL (see Table 7, below; comments in Table 2: *Alternative Initial ART Regimens for Nonpregnant Adults* and Table 3: *Other ART Regimens Not Included as Preferred or Alternative for Nonpregnant Adults*).

Coinfections: Hepatitis B virus (HBV), hepatitis C virus, and tuberculosis (TB) infection status should be assessed. The ART regimen for individuals with chronic HBV should treat both HIV and HBV when possible (see the NYSDOH AI guideline *HBV–HIV Coinfection*). For those planning *concurrent HCV treatment* or treatment for active TB, drug–drug interactions will play an important role in the selection of a regimen. The *University of Liverpool HEP Drug Interactions Checker* is a useful resource for identifying drug–drug interactions.

Creatinine clearance (CrCl): Some ARVs are contraindicated below a given CrCl level, and some may need adjustments that require the use of individual elements of an FDC or STR rather than the single–tablet version of the drug. See Table 8: *ARV Dose Adjustments for Renal and Hepatic Impairment* for more information.

Hepatic profile: Some antiretroviral drugs require dose adjustment in the presence of impaired liver function; patients with abnormal liver enzyme levels or evidence of decreased synthetic function should be assessed for underlying liver disease. See the *Special Considerations for Comorbid Conditions* section of this guideline and Table 8: *ARV Dose Adjustments for Renal and Hepatic Impairment*.

HLA–B*5701 testing: To avoid potentially serious or life–threatening hypersensitivity reactions, HLA–B*5701 testing is mandatory before initiating ART that includes ABC [Mallal, et al. 2008; Saag, et al. 2008].

Initiation of the regimens listed in Table 7, below, is contraindicated based on the listed baseline laboratory parameters.

| Table 7: Contraindicated ART Regimens Based on Routine Baseline [a] Laboratory Parameters | |
|---|---|
| Lab Parameter | Contraindicated ART Regimens |
| Viral load $\geq 100,000$ copies/mL | <ul style="list-style-type: none"> • ABC/3TC and COBI/ATV (Epzicom and Evotaz) • ABC/3TC and EFV (Epzicom and Sustiva) • ABC/3TC and RTV and ATV (Epzicom and Norvir and Reyataz) • TAF/FTC/RPV (Odefsey) • TDF/FTC/RPV (Complera) |
| CD4 < 200 cells/mm ³ | <ul style="list-style-type: none"> • TAF/FTC/RPV (Odefsey) • TDF/FTC/RPV (Complera) |
| CrCl < 50 mL/min | <ul style="list-style-type: none"> • ABC/3TC (Epzicom) • ABC/3TC/DTG (Triumeq) • TDF/3TC/DOR (Delstrigo) • TDF/FTC/EFV (Atripla) • TDF/FTC/RPV (Complera) |
| CrCl < 30 mL/min | <ul style="list-style-type: none"> • TAF/FTC (Descovy) • TAF/FTC/BIC (Biktarvy) • TAF/FTC/COBI/DRV (Symtuza) • TAF/FTC/COBI/EVG (Genvoya) [b] • TAF/FTC/RPV (Odefsey) • TDF/FTC (Truvada) |
| <p>Abbreviations: 3TC, lamivudine; ABC, abacavir; ATV, atazanavir; BIC, bictegravir; COBI, cobicistat; CrCl, creatinine clearance; DOR, doravirine; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; EVG, elvitegravir; FTC, emtricitabine; RAL, raltegravir; RPV, rilpivirine; RIT, ritonavir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.</p> <p>Notes:</p> <p>a. For renal adjustment of fixed-dose combinations and single-tablet regimens while on therapy, see Table 8: ARV Dose Adjustments for Renal and Hepatic Impairment.</p> <p>b. Unless CrCl < 15 mL/min and on chronic hemodialysis.</p> | |

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ARV Dose Adjustments for Renal and Hepatic Impairment

Lead Author: Samuel T. Merrick, MD, with the Medical Care Criteria Committee, updated January 2019

| Table 8: ARV Dose Adjustments for Renal and Hepatic Impairment [information below is from drug package inserts, which should be consulted for more information] | | |
|---|--|--|
| Formulation and Usual Adult Dose* | Renal Insufficiency | Hepatic Impairment |
| <i>Single-Tablet Regimens</i> | | |
| Abacavir/lamivudine/ dolutegravir (ABC/3TC/DTG; Triumeq) • 1 pill once daily | • CrCl <50 mL/min: do not use | • Child-Pugh A, B, C: do not use |
| Tenofovir alafenamide/ emtricitabine/ bictegravir (TAF/FTC/BIC; Biktarvy) • 1 pill once daily | • CrCl <30 mL/min: do not use | • Child-Pugh A, B: no adjustment • Child-Pugh C: do not use |
| Tenofovir alafenamide/ emtricitabine/ cobicistat/ darunavir (TAF/FTC/COBI/DRV; Symtuza) • 1 pill once daily | • CrCl <30 mL/min: do not use | • Child-Pugh A, B: no adjustment • Child-Pugh C: do not use |
| Tenofovir alafenamide/ emtricitabine/ cobicistat/ elvitegravir (TAF/FTC/COBI/EVG; Genvoya) • 1 pill once daily | • CrCl 15 mL/min to <30 mL/min: do not use • CrCl <15 mL/min: do not use unless on chronic hemodialysis | • Child-Pugh A, B: no adjustment • Child-Pugh C: do not use |
| Tenofovir alafenamide/emtricitabine/ rilpivirine (TAF/FTC/RPV; Odefsey) • 1 pill once daily | • CrCl <30 mL/min: do not use | • Child-Pugh A, B: no adjustment • Child-Pugh C: no data |
| Tenofovir disoproxil fumarate/ emtricitabine/doravirine (TDF/FTC/DOR; Delstrigo) • 1 pill once daily | • CrCl <50 mL/min: do not use | • Child-Pugh A, B: no adjustment • Child-Pugh C: no data |
| Tenofovir disoproxil fumarate/ emtricitabine/efavirenz (TDF/FTC/EFV; Atripla) • 1 pill once each night | • CrCl <50 mL/min: do not use | • Child-Pugh A: no adjustment • Child-Pugh B, C: no data |
| Tenofovir disoproxil fumarate/ emtricitabine/rilpivirine (TDF/FTC/RPV; Complera) • 1 pill once daily | • CrCl <50 mL/min: do not use | • Child-Pugh A, B: no adjustment • Child-Pugh C: no data |
| <i>Fixed-Dose Combinations</i> | | |
| Abacavir/lamivudine (ABC/3TC; Epzicom)* • 1 pill once daily | • CrCl <50 mL/min: do not use | • Child-Pugh A, B, C: do not use |
| Tenofovir alafenamide/ emtricitabine (TAF/FTC; Descovy) • 1 pill once daily | • CrCl <30 mL/min: do not use | • Child-Pugh A, B: no adjustment • Child-Pugh C: no data |

| Table 8: ARV Dose Adjustments for Renal and Hepatic Impairment [information below is from drug package inserts, which should be consulted for more information] | | |
|---|--|---|
| Formulation and Usual Adult Dose* | Renal Insufficiency | Hepatic Impairment |
| Tenofovir disoproxil fumarate/ emtricitabine (TDF/FTC Truvada) <ul style="list-style-type: none"> • 1 pill once daily | <ul style="list-style-type: none"> • CrCl 30 to 49 mL/min: 1 pill every 48 hrs. • CrCl <30 mL/min: do not use | <ul style="list-style-type: none"> • No adjustment |
| <i>Individual Drug Components</i> | | |
| Abacavir (ABC; Ziagen)* <ul style="list-style-type: none"> • 300 mg twice daily or 600 mg once daily | <ul style="list-style-type: none"> • No adjustment | <ul style="list-style-type: none"> • Child-Pugh A: 200 mg twice daily as solution • Child-Pugh B, C: do not use |
| Atazanavir (ATV; Reyataz)* <ul style="list-style-type: none"> • 300 mg daily with RTV 100 mg once daily or 400 mg once daily | <ul style="list-style-type: none"> • No adjustment, but use only 300 mg dose with 100 mg RTV • Treatment-experienced patients on dialysis: do not use | <ul style="list-style-type: none"> • Child-Pugh A, B: no adjustment • Child-Pugh C: no data |
| Atazanavir/cobicistat (ATV/COBI; Evotaz) <ul style="list-style-type: none"> • 1 pill once daily | <ul style="list-style-type: none"> • CrCl <70 mL/min with TDF-containing regimen: do not use • Treatment-experienced patients on dialysis: do not use | <ul style="list-style-type: none"> • No data; not recommended |
| Darunavir (DRV; Prezista) <ul style="list-style-type: none"> • Treatment naive: 800 mg daily with ritonavir 100 mg once daily • Treatment experienced or ≥1 mutation associated with DRV resistance: 600 mg twice daily with ritonavir 100 mg twice daily | <ul style="list-style-type: none"> • No adjustment | <ul style="list-style-type: none"> • Child-Pugh A, B: no adjustment • Child-Pugh C: no data |
| Darunavir/cobicistat (DRV/COBI; Prezcobix) <ul style="list-style-type: none"> • Treatment naive: 1 pill once daily • Treatment experienced or ≥1 mutation associated with DRV resistance: do not use | <ul style="list-style-type: none"> • CrCl <70 mL/min with TDF-containing regimen: do not use • No data on dose adjustments | <ul style="list-style-type: none"> • Child-Pugh A, B: no adjustment • Child-Pugh C: no data |
| Dolutegravir (DTG; Tivicay) <ul style="list-style-type: none"> • Treatment naive or no DTG resistance mutations: 50 mg once daily • Known INSTI mutations or given with CYP3A inducers (e.g., EFV, LPV/RTV): 50 mg twice daily [Moltó, et al. 2016] | <ul style="list-style-type: none"> • No adjustment, but limited data with CrCl ≤30 mL/min | <ul style="list-style-type: none"> • Child-Pugh A, B: no adjustment • Child-Pugh C: no data |
| Doravirine (DOR, Pifeltro) <ul style="list-style-type: none"> • 100 mg once daily | <ul style="list-style-type: none"> • No adjustment, but not studied in dialysis | <ul style="list-style-type: none"> • Child-Pugh A, B: no adjustment • Child-Pugh C: no data |
| Efavirenz (EFV; Sustiva)* <ul style="list-style-type: none"> • 600 mg daily or at night | <ul style="list-style-type: none"> • No adjustment | <ul style="list-style-type: none"> • No data; use with caution |
| Elvitegravir (EVG; Vitekta) <ul style="list-style-type: none"> • Not commonly used as single agent, see package insert for dosing with boosted PIs | <ul style="list-style-type: none"> • No adjustment | <ul style="list-style-type: none"> • Child-Pugh A, B: no adjustment • Child-Pugh C: no data |

| Table 8: ARV Dose Adjustments for Renal and Hepatic Impairment [information below is from drug package inserts, which should be consulted for more information] | | |
|--|--|---|
| Formulation and Usual Adult Dose* | Renal Insufficiency | Hepatic Impairment |
| Emtricitabine (FTC; Emtriva) • 200 mg once daily or 240 mg once daily of suspension | <ul style="list-style-type: none"> • CrCl 30 to 49 mL/min: 200 mg every 48 hrs. • CrCl 15 to 29 mL/min: 200 mg every 72 hrs. • CrCl <15 mL/min: 200 mg every 96 hrs. or solution 120/80/60 every 24 hrs. | <ul style="list-style-type: none"> • No adjustment |
| Lamivudine (3TC; Epivir)* • 150 mg twice daily or 300 mg once daily | <ul style="list-style-type: none"> • CrCl >50 mL/min: 150 mg twice daily or 300 mg once daily • CrCl 30 to 49 mL/min: 150 mg once daily • CrCl 15 to 29 mL/min: 150 mg first dose then 100 mg once daily • CrCl 5 to 14 mL/min: 150 mg first dose then 50 mg once daily • CrCl <5 mL/min: HD 50 mg first dose then 25 mg once daily | <ul style="list-style-type: none"> • No adjustment |
| Raltegravir (RAL; Isentress) • 400 mg twice daily | <ul style="list-style-type: none"> • No adjustment | <ul style="list-style-type: none"> • Child-Pugh A, B: no adjustment • Child-Pugh C: no data |
| Raltegravir (RAL; Isentress) • 600 mg 2 pills once daily | <ul style="list-style-type: none"> • No adjustment | <ul style="list-style-type: none"> • No data; use with caution |
| Rilpivirine (RPV; Edurant) • 25 mg once daily | <ul style="list-style-type: none"> • No adjustment | <ul style="list-style-type: none"> • Child-Pugh A, B: no adjustment • Child-Pugh C: no data |
| Tenofovir disoproxil fumarate (TDF; Viread)* • 300 mg once daily | <ul style="list-style-type: none"> • CrCl 30 to 49 mL/min: 300 mg every 48 hrs. • CrCl 10 to 29 mL/min: 300 mg every 72 to 96 hrs. • Dialysis: 300 mg every 7 days | <ul style="list-style-type: none"> • No adjustment |
| <p>Additional abbreviations: ARV antiretroviral; CrCl, creatinine clearance; INSTI, integrase strand transfer inhibitor; PI, protease inhibitor.</p> <p>*Generic formulations are available for ATV, RTV, ABC, 3TC, TDF, EFV, ABC/3TC, TDF/3TC (Cimduo), TDF/3TC/EFV (Symfi) and can be used when cost or availability are considerations; however, higher pill counts can adversely affect adherence as discussed above, and in some cases may actually lead to higher copays.</p> | | |

Reference

Moltó J, Graterol F, Miranda C, et al. Minimal Removal of Dolutegravir by Hemodialysis in HIV-Infected Patients. CROI; 2016 Feb 22-25; Boston, MA. <http://www.croiconference.org/sessions/minimal-removal-dolutegravir-hemodialysis-hiv-infected-patients>

All Recommendations

Lead Author: Samuel T. Merrick, MD, with the Medical Care Criteria Committee, updated January 2019

Dolutegravir (DTG) Safety Statement, May 2018

- On May 18, 2018, the FDA and the DHHS Antiretroviral Guidelines Panels issued statements in response to preliminary results from a study that reported increased risk of neural tube defects in babies born to mothers taking DTG-based ARV drug regimens at the time of conception [AIDSinfo 2018; FDA 2018].
- Until more data become available, DTG-containing regimens should be avoided in any HIV-exposed individual who is pregnant in the first trimester or could become pregnant and is not using effective contraception. If there are no alternatives to DTG for individuals of child-bearing potential, then clinicians should strongly advise the use of effective contraception and should obtain a pregnancy test before initiating treatment.
- For more information, see: *DHHS Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*

☑ ALL RECOMMENDATIONS: SELECTING AN INITIAL ART REGIMEN

- Clinicians should involve their patients when deciding which ART regimen is most likely to result in adherence. (A3)
 - Clinicians should perform the following when initiating ART:
 - Assessment for comorbidities and chronic co-administered medications that may affect the choice of regimen for initial therapy. (A3)
 - Genotypic resistance testing for the protease and reverse transcriptase genes at diagnosis or at the initial visit if not done previously. (A2) See the *Specific Factors to Consider and Discuss with Patients* section of this guideline.
 - Baseline testing is currently not recommended for either integrase resistance (unless transmitted integrase strand transfer inhibitor [INSTI] resistance is suspected) or tropism. (A3)
 - For individuals who have delayed initiation of ART and have engaged in high-risk behaviors associated with acquisition of HIV superinfection, genotypic resistance testing should be repeated before choosing the ART regimen. (B3)
 - Clinicians should consult with a care provider experienced in ART management when:
 - Baseline resistance indicates the need for treatment with a regimen other than the listed preferred or alternative regimens. (A3)
 - Selecting a regimen for individuals with extensive comorbidities and/or comedications, impaired renal function, hepatitis B virus or hepatitis C virus coinfection, or active opportunistic infections. (B3)
 - Clinicians should ask individuals about their reproductive plans and discuss the use of contraception. (A3)
 - Refer to the DHHS guideline when choosing an initial regimen for individuals of childbearing potential: *Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*.
 - For ART-naïve individuals, clinicians should select an initial ART regimen that is preferred; see *Table 1: Preferred Initial ART Regimens for Nonpregnant Adults*. (A1)
 - A single-tablet regimen or regimen with once-daily dosing is preferred unless contraindicated by resistance, drug-drug interactions, intolerance, allergy, or access. (A2)
 - In general, a preferred regimen should be selected (see *Table 1: Preferred Initial ART Regimens for Nonpregnant Adults*), although there may be times when an alternative regimen may be a better choice for an individual patient (*Table 2: Alternative Initial ART Regimens for Nonpregnant Adults*).
 - Clinicians should not prescribe two-drug regimens as initial therapy. (A2)
 - Clinicians or clinic staff should follow up, by telephone or other methods, within 2 weeks after treatment initiation to assess tolerance and adherence. Adherence should be reinforced at regular intervals. (A3)
 - Clinicians should obtain a viral load test within 4 weeks after ART initiation to assess initial response to therapy (A3); see the NYSDOH AI guideline *Virologic and Immunologic Monitoring* for more information.
- See the following tables:**
- Table 1: Preferred Initial ART Regimens for Nonpregnant Adults
 - Table 2: Alternative Initial ART Regimens for Nonpregnant Adults
 - Table 3: Other ART Regimens Not Included as Preferred or Alternative for Nonpregnant Adults
 - Table 4: Individual ARVs or Combinations to Avoid in Initial Therapy for Nonpregnant Adults
 - Table 5: Select Drug-Drug Interactions to Discuss before Initiating ART in Treatment-Naïve Patients
 - Table 6: Acceptable Alternative Formulations and Methods of Administration of Antiretroviral Medications
 - Table 7: Contraindicated ART Regimens Based on Routine Baseline Laboratory Parameters
 - Table 8: ARV Dose Adjustments for Renal and Hepatic Impairment