



# 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*

### Contents

<b>Purpose of this Guideline .....</b>	<b>2</b>
<b>Available ART Regimens .....</b>	<b>3</b>
<i>Available Antiretroviral Agents and Regimens.....</i>	<i>3</i>
<i>Single-Tablet Regimens Versus Multi-Tablet Regimens .....</i>	<i>4</i>
<i>Table 1: Preferred Initial ART Regimens for Nonpregnant Adults.....</i>	<i>5</i>
<i>Table 2: Alternative Initial ART Regimens for Nonpregnant Adults.....</i>	<i>6</i>
<i>Table 3: Other ART Regimens Not Included as Preferred or Alternative for Nonpregnant Adults.....</i>	<i>7</i>
<b>General Principles in Choosing an Initial ART Regimen.....</b>	<b>9</b>
<i>Table 4: Individual ARVs or Combinations to Avoid in Initial Therapy for Nonpregnant Adults .....</i>	<i>10</i>
<b>General Considerations with Initial ART Regimens.....</b>	<b>11</b>
<b>Specific Factors to Consider and Discuss with Patients.....</b>	<b>12</b>
<i>Table 5: Select Drug-Drug Interactions to Discuss before Initiating ART in Treatment-Naive Patients.....</i>	<i>12</i>
<i>Box 1: ARVs That Must Be Taken With and Without Food or on an Empty Stomach.....</i>	<i>13</i>
<i>Table 6: Acceptable Alternative Formulations and Methods of Administration of Antiretroviral Medications .....</i>	<i>14</i>
<b>Special Considerations for Comorbid Conditions.....</b>	<b>15</b>
<b>ART-Initiation Laboratory Testing .....</b>	<b>17</b>
<i>Table 7: Contraindicated ART Regimens Based on Routine Baseline [a] Laboratory Parameters .....</i>	<i>18</i>
<b>ARV Dose Adjustments for Renal and Hepatic Impairment .....</b>	<b>19</b>
<i>Table 8: Recommended Dose Adjustments for Use of Selected Fixed-Dose Combination Antiretroviral Medications in Patients with Hepatic or Renal Impairment.....</i>	<i>19</i>
<b>All Recommendations .....</b>	<b>28</b>
<b>Appendix: Use of Dolutegravir in Individuals of Childbearing Capacity .....</b>	<b>37</b>



# Selecting an Initial ART Regimen

## Purpose of this Guideline

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  $\geq 18$  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](#).

## Available ART Regimens

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

### RECOMMENDATIONS: Available ART Regimens

- 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 should be performed at diagnosis, or at the initial visit if not done previously, for the protease (A2), reverse transcriptase (A2), and integrase (B2) genes. See the [Specific Factors to Consider and Discuss with Patients](#) section of this guideline.
- 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 A, 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/mm<sup>3</sup>.

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 A, et al. 2016b]. In the same study, STR NNRTI-based therapy led to greater rates of suppression than MTR NNRTI therapy [Mills A, 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 CJ, et al. 2013a; Colombo, et al. 2013; Hanna, et al. 2014; Nachega, et al. 2014; Sweet, et al. 2014; Armstrong, et al. 2015; Maggiolo, et al. 2015; Griffith, et al. 2016; Mills A, 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.

<b>Table 1: Preferred Initial ART Regimens for Nonpregnant* Adults</b> (listed alphabetically; for specific details, see <i>Specific Factors to Consider</i> or drug package inserts)		
<b>Regimen</b>	<b>Comments</b>	<b>Rating</b>
<i>Available as a Single-Tablet Formulation</i>		
Abacavir/lamivudine/ dolutegravir* (ABC/3TC/DTG; Trumeq)	<ul style="list-style-type: none"> <li>Initiate <b>only</b> 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.</li> <li>Initiate <b>only</b> in patients with CrCl <math>\geq</math>50 mL/min.</li> <li>Consider underlying risk of coronary heart disease.</li> <li>Documented DTG resistance after initiation in treatment-naive patients is rare.</li> <li>Magnesium- or aluminum-containing antacids may be taken 2 hours before or 6 hours after DTG; calcium-containing antacids or iron supplements may be taken simultaneously if taken with food.</li> </ul>	A1
Tenofovir alafenamide/ emtricitabine/bictegravir (TAF 25 mg/FTC/BIC; Biktarvy)	<ul style="list-style-type: none"> <li>Initiate <b>only</b> in patients with CrCl <math>\geq</math>30 mL/min.</li> <li>Contains 25 mg of TAF, unboosted.</li> <li>Magnesium- or aluminum-containing antacids may be taken 2 hours before or 6 hours after BIC; calcium-containing antacids or iron supplements may be taken simultaneously if taken with food.</li> </ul>	A1
<i>Available as a Multi-Tablet Regimen with Once-Daily Dosing</i>		
Tenofovir alafenamide/ emtricitabine <i>and</i> dolutegravir* (TAF 25 mg/FTC <i>and</i> DTG; Descovy <i>and</i> Tivicay)	<ul style="list-style-type: none"> <li>Initiate <b>only</b> in patients with CrCl <math>\geq</math>30 mL/min.</li> <li>Documented DTG resistance after initiation in treatment-naive patients is rare.</li> <li>Contains 25 mg of TAF, unboosted.</li> <li>Magnesium- or aluminum-containing antacids may be taken 2 hours before or 6 hours after DTG; calcium-containing antacids or iron supplements may be taken simultaneously if taken with food.</li> </ul>	A1
Tenofovir alafenamide/ emtricitabine <i>and</i> raltegravir (TAF 25 mg/FTC <i>and</i> RAL HD; Descovy <i>and</i> Isentress HD)	<ul style="list-style-type: none"> <li>Initiate <b>only</b> in patients with CrCl <math>\geq</math>30 mL/min.</li> <li>To date, no clinical trials have been conducted with TAF and RAL; data are based on bioequivalence pharmacokinetic studies.</li> <li>Contains 25 mg of TAF, unboosted.</li> <li>Administer as TAF/FTC once daily and RAL HD 1200 mg once daily, dosed as two 600 mg HD tablets.</li> <li>Magnesium- or aluminum-containing antacids are contraindicated; co-administration of calcium-containing antacids is not recommended with RAL HD.</li> </ul>	A2
<ul style="list-style-type: none"> <li><b>Additional abbreviations:</b> ART, antiretroviral therapy; CrCl, creatinine clearance.</li> <li><b>ART Regimens for individuals of childbearing potential:</b> 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>.</li> <li><b>Substitutions:</b> 1) In all cases, FTC and 3TC are interchangeable. 2) TAF 10 mg and TAF 25 mg are not interchangeable.</li> <li><b>Dose adjustments:</b> Refer to <a href="#">Table 8: ARV Dose Adjustments for Renal and Hepatic Impairment</a> for adjustment based on renal or hepatic function.</li> </ul> <p>*See <a href="#">Appendix: Use of Dolutegravir in Individuals of Childbearing Capacity</a>.</p>		

**Table 2: Alternative Initial ART Regimens for Nonpregnant\* Adults**

(listed alphabetically; for specific details, see *Specific Factors to Consider* 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"> <li>• Initiate <b>only</b> in patients with CrCl <math>\geq</math>30 mL/min.</li> <li>• Carefully consider drug-drug interactions with COBI [Eron JJ, et al. 2018b].</li> <li>• Contains 10 mg TAF, boosted.</li> </ul>	B2
Tenofovir alafenamide/ emtricitabine/cobicistat/ elvitegravir (TAF 10 mg/FTC/COBI/EVG; Genvoya)	<ul style="list-style-type: none"> <li>• Initiate <b>only</b> in patients with CrCl <math>\geq</math>30 mL/min.</li> <li>• Carefully consider drug-drug interactions with COBI.</li> <li>• Contains 10 mg of TAF, boosted with COBI.</li> <li>• Separate dosing of antacids by 2 hours, either before or after dose of EVG.</li> </ul>	B1
Tenofovir alafenamide/ emtricitabine/rilpivirine (TAF 25 mg/FTC/RPV; Odefsey)	<ul style="list-style-type: none"> <li>• Initiate <b>only</b> in patients confirmed to have a CD4 cell count <math>\geq</math>200 cells/mm<sup>3</sup> and viral load <math>&lt;</math>100,000 copies/mL.</li> <li>• 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.</li> <li>• Initiate <b>only</b> in patients with CrCl <math>\geq</math>30 mL/min.</li> <li>• Use with caution in patients with depression or a history of suicidality.</li> <li>• To date, no clinical trials have been conducted; data are based on bioequivalence pharmacokinetic studies of TAF compared with TDF.</li> <li>• Contraindicated with PPIs.</li> <li>• Use H<sub>2</sub>-blockers with caution and separate dosing by 12 hours.</li> <li>• Must take with food.</li> <li>• Contains 25 mg of TAF, unboosted.</li> </ul>	B3
Tenofovir disoproxil fumarate/ lamivudine/doravirine (TDF/3TC/DOR; Delstrigo)	<ul style="list-style-type: none"> <li>• Initiate <b>only</b> in patients with CrCl <math>\geq</math>50 mL/min.</li> <li>• Contraindicated when co-administered with drugs that are strong cytochrome P450 (CYP)3A enzyme inducers.</li> <li>• Consider bone mineral density.</li> </ul>	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"> <li>• Initiate <b>only</b> in patients confirmed to be negative for HLA-B*5701.</li> <li>• 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.</li> <li>• Consider underlying risk of coronary heart disease.</li> <li>• Contraindicated when co-administered with drugs that are strong cytochrome P450 (CYP)3A enzyme inducers.</li> </ul>	B2
Tenofovir alafenamide/ emtricitabine and doravirine (TAF 25 mg/FTC and DOR; Descovy and Pifeltro)	<ul style="list-style-type: none"> <li>• Initiate <b>only</b> in patients with CrCl <math>\geq</math>30 mL/min.</li> <li>• Contraindicated when co-administered with drugs that are strong CYP3A enzyme inducers.</li> </ul>	B2
Tenofovir disoproxil fumarate/ emtricitabine and dolutegravir* (TDF/FTC and DTG; Truvada and Tivicay)	<ul style="list-style-type: none"> <li>• Initiate <b>only</b> in patients with CrCl <math>\geq</math>50 mL/min.</li> <li>• Documented DTG resistance after initiation in treatment-naive patients is rare.</li> <li>• Consider bone mineral density.</li> <li>• Magnesium- or aluminum-containing antacids may be taken 2 hours before or 6 hours after DTG; calcium-containing antacids or iron supplements may be taken simultaneously if taken with food.</li> </ul>	B1

**Table 2: Alternative Initial ART Regimens for Nonpregnant\* Adults**

(listed alphabetically; for specific details, see *Specific Factors to Consider* 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"> <li>Initiate <b>only</b> in patients with CrCl <math>\geq</math>50 mL/min.</li> <li>Consider bone mineral density.</li> <li>Administer as TDF/FTC once daily and RAL HD 1200 mg once daily, dosed as two 600 mg HD tablets.</li> <li>Magnesium- or aluminum-containing antacids are contraindicated; co-administration of calcium-containing antacids is not recommended with RAL HD.</li> </ul>	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"> <li>Initiate <b>only</b> in patients with CrCl <math>\geq</math>30 mL/min.</li> <li>Administer as ABC/3TC once daily and RAL 400 mg twice daily.</li> <li>Magnesium- or aluminum-containing antacids are contraindicated; calcium-containing antacids are acceptable with RAL.</li> </ul>	B3
<ul style="list-style-type: none"> <li><b>Additional abbreviations:</b> ART, antiretroviral therapy; CrCl, creatinine clearance; PPI, proton-pump inhibitor.</li> <li><b>ART Regimens for individuals of childbearing potential:</b> 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>.</li> <li><b>Substitutions:</b> 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.</li> <li><b>Dose adjustments:</b> Refer to <i>Table 8: ARV Dose Adjustments for Renal and Hepatic Impairment</i> for adjustment based on renal or hepatic function.</li> </ul> <p>*See <i>Use of Dolutegravir in Individuals of Childbearing Capacity</i>, February 2020.</p>		

**Table 3: Other ART Regimens Not Included as Preferred or Alternative for Nonpregnant\* Adults**

(listed alphabetically; for specific details, see *Specific Factors to Consider* 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"> <li>Initiate <b>only</b> in patients with CrCl <math>\geq</math>50 mL/min.</li> <li>Use with caution in patients with depression or a history of suicidality.</li> <li>Consider bone mineral density.</li> </ul>	B1
Tenofovir disoproxil fumarate/ emtricitabine/rilpivirine [a] (TDF/FTC/RPV; Complera)	<ul style="list-style-type: none"> <li>Initiate <b>only</b> in patients confirmed to have a CD4 cell count <math>\geq</math>200 cells/mm<sup>3</sup> <i>and</i> viral load <math>&lt;</math>100,000 copies/mL.</li> <li>Initiate <b>only</b> in patients with CrCl <math>\geq</math>50 mL/min.</li> <li>Use with caution in patients with depression or a history of suicidality.</li> <li>Contraindicated with PPIs.</li> <li>Use H<sub>2</sub>-blockers with caution and separate dosing by 12 hours.</li> <li>Must take with food.</li> <li>Consider bone mineral density.</li> </ul>	B1
<i>Available as a Multi-Tablet Regimen with Once-Daily Dosing</i>		
Abacavir/lamivudine <i>and</i> atazanavir <i>and</i> ritonavir (ABC/3TC <i>and</i> ATV <i>and</i> RTV; Epzicom <i>and</i> Reyataz <i>and</i> Norvir)	<ul style="list-style-type: none"> <li>Initiate <b>only</b> in patients confirmed to be negative for HLA-B*5701 [b].</li> <li>Initiate <b>only</b> in patients with viral load <math>&lt;</math>100,000 copies/mL.</li> <li>Carefully consider drug-drug interactions with RTV.</li> <li>Consider underlying risk of coronary heart disease.</li> <li>In treatment-naïve patients on boosted ATV, H<sub>2</sub>-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.</li> </ul>	C1

**Table 3: Other ART Regimens Not Included as Preferred or Alternative for Nonpregnant\* Adults**  
(listed alphabetically; for specific details, see *Specific Factors to Consider* and/or drug package inserts)

Regimen	Comments	Rating
	<ul style="list-style-type: none"> <li>Use no more than equivalent of 20 mg of omeprazole with ATV, separated by 12 hours.</li> <li>Scleral icterus from benign hyperbilirubinemia may be a concern.</li> </ul>	
Abacavir/lamivudine and darunavir/cobicistat (ABC/3TC and DRV/COBI; Epzicom and Prezcobix)	<ul style="list-style-type: none"> <li>Initiate <b>only</b> in patients confirmed to be negative for HLA-B*5701 [b].</li> <li>Carefully consider drug-drug interactions with COBI.</li> <li>Consider underlying risk of coronary heart disease.</li> </ul>	B3
Abacavir/lamivudine and darunavir and ritonavir (ABC/3TC and DRV and RTV; Epzicom and Prezista and Norvir)	<ul style="list-style-type: none"> <li>Initiate <b>only</b> in patients confirmed to be negative for HLA-B*5701 [b].</li> <li>Carefully consider drug-drug interactions with RTV.</li> <li>Consider underlying risk of coronary heart disease.</li> </ul>	B2
Abacavir/lamivudine and efavirenz (ABC/3TC and EFV; Epzicom and Sustiva)	<ul style="list-style-type: none"> <li>Initiate <b>only</b> in patients confirmed to be negative for HLA-B*5701 [b].</li> <li>Initiate <b>only</b> in patients with viral load &lt;100,000 copies/mL.</li> <li>Use with caution in patients with depression or a history of suicidality.</li> <li>Consider underlying risk of coronary heart disease.</li> </ul>	C1
Tenofovir alafenamide/emtricitabine and efavirenz (TAF 25 mg/FTC and EFV; Descovy and Sustiva)	<ul style="list-style-type: none"> <li>Initiate <b>only</b> in patients with CrCl ≥50 mL/min.</li> <li>Use with caution in patients with depression or a history of suicidality.</li> <li>Contains 25 mg of TAF, unboosted.</li> </ul>	B3
Abacavir/lamivudine and raltegravir (ABC/3TC and RAL HD; Epzicom and Isentress HD)	<ul style="list-style-type: none"> <li>Initiate <b>only</b> in patients confirmed to be negative for HLA-B*5701 [b].</li> <li>Consider underlying risk of coronary heart disease.</li> <li>Administer as ABC/3TC once daily and RAL HD 1200 mg once daily, dosed as two 600 mg HD tablets.</li> <li>Magnesium- or aluminum-containing antacids are contraindicated; co-administration of calcium-containing antacids is not recommended with RAL HD.</li> </ul>	B3
<i>Available as a Multi-Tablet Regimen with Twice-Daily Dosing</i>		
Tenofovir disoproxil fumarate/emtricitabine and raltegravir (TDF/FTC and RAL; Truvada and Isentress)	<ul style="list-style-type: none"> <li>Initiate <b>only</b> in patients with CrCl ≥50 mL/min.</li> <li>Consider bone mineral density.</li> <li>TDF/FTC once daily and RAL 400 mg twice daily.</li> <li>Magnesium- or aluminum-containing antacids are contraindicated; calcium-containing antacids are acceptable with RAL.</li> </ul>	B1
Abacavir/lamivudine and raltegravir (ABC/3TC and RAL; Epzicom and Isentress)	<ul style="list-style-type: none"> <li>Initiate <b>only</b> in patients confirmed to be negative for HLA-B*5701 [b].</li> <li>Consider underlying risk of coronary heart disease.</li> <li>Administer as ABC/3TC once daily and RAL 400 mg twice daily.</li> <li>Magnesium- or aluminum-containing antacids are contraindicated; calcium-containing antacids are acceptable with RAL.</li> </ul>	B1
<ul style="list-style-type: none"> <li><b>Additional abbreviations:</b> ART, antiretroviral therapy; CrCl, creatinine clearance; PPI, proton-pump inhibitor.</li> <li><b>ART Regimens for individuals of childbearing potential:</b> 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>.</li> <li><b>Substitutions:</b> 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.</li> <li><b>Dose adjustments:</b> Refer to <i>Table 8: ARV Dose Adjustments for Renal and Hepatic Impairment</i> for adjustment based on renal or hepatic function.</li> </ul> <p><b>Notes:</b></p> <ol style="list-style-type: none"> <li>When a “rapid-start” or “test-and-treat” initiation of ART occurs before viral load and CD4 count are available, avoid use of RPV.</li> <li>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.</li> </ol>		

# General Principles in Choosing an Initial ART Regimen

**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, With Protocol for Rapid Initiation*). 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/mm<sup>3</sup>, 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/bictegravir (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 A, et al. 2016a; 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-naive 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. 2013b; 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/mm<sup>3</sup>.
- 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-naive 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-naive 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)	<b>Life-threatening rash:</b> Stevens-Johnson syndrome and toxic epidermal necrolysis are possible.
<ul style="list-style-type: none"> <li>• Stavudine (d4T; Zerit)</li> <li>• Didanosine (ddI; Videx)</li> </ul>	<b>Serious toxicities:</b> Potentially fatal lactic acidosis, peripheral neuropathy, pancreatitis, lipoatrophy, 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-naive patients.
<ul style="list-style-type: none"> <li>• Maraviroc (MVC; Selzentry)</li> <li>• NRTI-only regimens, either triple or quadruple</li> </ul>	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"> <li>• Fosamprenavir (FPV; Lexiva)</li> <li>• Indinavir (IDV; Crixivan)</li> <li>• Tipranavir (TPV; Aptivus)</li> <li>• Nelfinavir (NFV; Viracept)</li> </ul>	Either not well studied or limited by dosing and side effects relative to recommended PIs.
<b>Additional abbreviations:</b> ART, antiretroviral therapy; ARV, antiretroviral, FDA, U.S. Food and Drug Administration; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor.	

# General Considerations with Initial ART Regimens

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 A, et al. 2016b]. 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  $\geq 200$  cells/mm<sup>3</sup>, are somewhat arbitrary. For example, most studies including RPV show that its efficacy is diminished when initiated at viral loads  $\geq 100,000$  copies/mL, and 1 study showed that RPV worked even less well than EFV-based therapy at a viral load of  $\geq 500,000$  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/EVG is approved for use at any starting viral load, reports of failure using TDF/FTC/COBI/EVG, 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].

## Specific Factors to Consider and Discuss with Patients

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 <sub>2</sub> -blockers	<ul style="list-style-type: none"> <li>• <b>ATV:</b> In treatment-naive patients on boosted ATV, H<sub>2</sub>-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.</li> <li>• <b>RPV:</b> Use with caution; administer at least 12 hours before or at least 4 hours after RPV.</li> </ul>
<ul style="list-style-type: none"> <li>• Inhaled steroids</li> <li>• Statins</li> </ul>	<ul style="list-style-type: none"> <li>• <b>COBI; RTV:</b> Alternatives or dose adjustments may be needed.</li> <li>• Consult the package inserts for drug-drug interactions between specific statins and ARVs.</li> </ul>
Polyvalent cations [a]	<ul style="list-style-type: none"> <li>• <b>DTG; BIC:</b> Take 2 hours before or 6 hours after DTG; calcium-containing antacids or iron supplements may be taken simultaneously if taken with food.</li> <li>• <b>RAL:</b> Magnesium- or aluminum-containing antacids are contraindicated; calcium-containing antacids are acceptable.</li> <li>• <b>RAL HD:</b> Magnesium- or aluminum-containing antacids are contraindicated; co-administration of calcium-containing antacids is not recommended.</li> <li>• <b>EVG:</b> Separate dosing by 2 hours, either before or after dose of EVG.</li> </ul>
PPIs	<ul style="list-style-type: none"> <li>• <b>ATV:</b> 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.</li> <li>• <b>RPV:</b> Contraindicated.</li> </ul>

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"> <li>• <b>DTG:</b> 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.</li> </ul>
Ethinyl estradiol and norethindrone [b]	<ul style="list-style-type: none"> <li>• <b>EFV; COBI/ATV; COBI/DRV; RTV and DRV:</b> Use alternative or additional (e.g., barrier) contraceptive methods or choose alternative ART regimen.</li> <li>• <b>ATV; RTV and ATV:</b> Use with caution; see manufacturer’s package insert for specific dosing information.</li> </ul>
Factor Xa inhibitors	<p><b>COBI; RTV:</b></p> <ul style="list-style-type: none"> <li>• 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).</li> <li>• Dabigatran: No adjustment needed if CrCl ≥50 mL/min; avoid if CrCl &lt;50 mL/min.</li> <li>• Rivaroxaban: Avoid use.</li> </ul>
Platelet inhibitors	<p><b>COBI; RTV:</b></p> <ul style="list-style-type: none"> <li>• Clopidogrel: Avoid use.</li> <li>• Prasugrel: No adjustment needed.</li> <li>• Ticagrelor: Avoid use.</li> </ul>
<p><b>Abbreviations:</b> 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><b>Notes:</b></p> <p>a. Aluminum, calcium, magnesium, or iron in some antacids or vitamin preparations.</p> <p>b. 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.</p>	

**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		
Take With or Without Food	Take With Food	Take on Empty Stomach
<ul style="list-style-type: none"> <li>• 3TC</li> <li>• ABC</li> <li>• DOR</li> <li>• DTG</li> <li>• FTC</li> <li>• RAL</li> <li>• TAF</li> <li>• TDF</li> <li>• TAF/FTC/BIC</li> <li>• TAF/FTC/DOR</li> </ul>	<ul style="list-style-type: none"> <li>• ATV/COBI</li> <li>• ATV and RTV</li> <li>• DRV/COBI</li> <li>• DRV and RTV</li> <li>• EVG</li> <li>• RPV</li> <li>• TAF/FTC/COBI/EVG</li> <li>• TAF/FTC/COBI/DRV</li> </ul>	<ul style="list-style-type: none"> <li>• EFV</li> </ul>
<p><b>Drug name abbreviation key:</b> 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.

<b>Table 6: Acceptable Alternative Formulations and Methods of Administration of Antiretroviral Medications</b>		
<b>Drug</b>	<b>Available as Liquid, Powder, or Chewable Tablet?</b>	<b>Can Tablet be Split/Crushed/Dissolved?</b>
<i>Single-Tablet Formulations</i>		
Abacavir/lamivudine/dolutegravir (ABC/3TC/DTG; Trimeq)	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; Prezobix)	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
Dolutegravir (DTG; Tivicay)	No	Acceptable to crush
Efavirenz (EFV; Sustiva)	No	No

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?
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 and Promote Sexual Health*).

## Special Considerations for Comorbid Conditions

**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 [Libre 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, With Protocol for Rapid Initiation](#)).

**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 [Goicoechea, 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. 2012a; 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 AM, et al. 2013; Arribas, et al. 2014; Cazanave, 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).

# ART-Initiation Laboratory Testing

## → 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/mm<sup>3</sup> 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, reverse transcriptase, and integrase 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].

Transmitted integrase resistance was identified in 0.7% of genotypic resistance tests obtained within 3 months of HIV diagnosis from 2013 to 2017 in New York State [Wang, et al. 2019]. Similarly, 0.8% of baseline genotypic resistance tests across 23 CDC U.S. jurisdictions reported INSTI resistance, which had a higher prevalence (1.6%) in metropolitan areas (population  $>50,000$  to 500,000) [McClung, et al. 2019]. Although INSTI resistance overall remains rare, most experts believe that transmission of INSTI resistance will increase over time given that this class of ARVs has become the preferred first line therapy for treatment initiation (including rapid ART initiation) in all major guidelines.

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 a second generation INSTI (dolutegravir [DTG] or bictegravir [BIC]), or 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.

**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"> <li>• ABC/3TC and COBI/ATV (Epzicom and Evotaz)</li> <li>• ABC/3TC and EFV (Epzicom and Sustiva)</li> <li>• ABC/3TC and RTV and ATV (Epzicom and Norvir and Reyataz)</li> <li>• TAF/FTC/RPV (Odefsey)</li> <li>• TDF/FTC/RPV (Complera)</li> </ul>
CD4 $< 200$ cells/mm <sup>3</sup>	<ul style="list-style-type: none"> <li>• TAF/FTC/RPV (Odefsey)</li> <li>• TDF/FTC/RPV (Complera)</li> </ul>
CrCl $< 50$ mL/min	<ul style="list-style-type: none"> <li>• ABC/3TC (Epzicom)</li> <li>• ABC/3TC/DTG (Triumeq)</li> <li>• TDF/3TC/DOR (Delstrigo)</li> <li>• TDF/FTC/EFV (Atripla)</li> <li>• TDF/FTC/RPV (Complera)</li> </ul>
CrCl $< 30$ mL/min	<ul style="list-style-type: none"> <li>• TAF/FTC (Descovy)</li> <li>• TAF/FTC/BIC (Biktarvy)</li> <li>• TAF/FTC/COBI/DRV (Symtuza)</li> <li>• TAF/FTC/COBI/EVG (Genvoya) [b]</li> <li>• TAF/FTC/RPV (Odefsey)</li> <li>• TDF/FTC (Truvada)</li> </ul>
<p><b>Abbreviations:</b> 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><b>Notes:</b></p> <p>a. For renal adjustment of fixed-dose combinations and single-tablet regimens while on therapy, see <a href="#">Table 8: ARV Dose Adjustments for Renal and Hepatic Impairment</a>.</p> <p>b. Unless CrCl <math>&lt; 15</math> mL/min and on chronic hemodialysis.</p>	

# ARV Dose Adjustments for Renal and Hepatic Impairment

Lead authors Nicole Bradley PharmD, BCPS, BCIDP; Yuman Lee, PharmD, BCIDP, AAHIVP, John M. Conry, PharmD, AAHIVP, FNAP; with the Medical Care Criteria Committee, May 2020

**Table 8: Recommended Dose Adjustments for Use of Selected Fixed-Dose Combination Antiretroviral Medications in Patients with Hepatic or Renal Impairment**

Fixed-Dose Combination	Hepatic Impairment Dose Adjustment [a]	Recommended Dose Adjustments for Renal Impairment		
		Recommended Dose Adjustment [a]	Individual Components of FDC and Recommended Dose Adjustment [a]	Clinical Comments
<i>Integrase Strand Transfer Inhibitors (INSTIs)</i>				
Abacavir/dolutegravir/lamivudine (ABC/DTG/3TC; Triumeq)  <a href="#">See package insert</a>	<b>Child-Pugh A, B, C:</b> Do not use.	<b>CrCl &lt;50 mL/min:</b> Use of FDC is not recommended.	<b>ABC:</b> No renal dose adjustment is needed. <b>DTG:</b> No renal dose adjustment is needed. <b>3TC:</b> <b>CrCl 30 to 49 mL/min:</b> 150 mg once daily. <b>CrCl 15 to 29 mL/min:</b> 150 mg first dose then 100 mg once daily. <b>CrCl 5 to 14 mL/min:</b> 150 mg first dose then 50 mg once daily. <b>CrCl &lt;5 mL/min:</b> 50 mg first dose then 25 mg once daily.	<b>CrCl &gt;30 mL/min:</b> Limited data to support use of FDC; 21 patients with CrCl >30 mL/min received full dose 3TC with minimal increases in AUC. No elevations in lactate or other ADRs reported [Fischetti, et al. 2018]. <b>CrCl &lt;30 mL/min, without HD:</b> Renal adjustment should be based on individual components; 13 patients with CrCl <30 mL/min not on HD received 100 mg to 150 mg of 3TC with minimal increases in AUC. No elevations in lactate or other ADRs reported [Fischetti, et al. 2018]. <b>CrCl &lt;30 mL/min, with HD:</b> Limited data to support use of FDC. Case series evaluating safety and efficacy of FDC in 9 patients with end-stage renal disease on HD reported viral suppression achieved in all 9 patients. No change in immune function. FDC generally well tolerated; one patient complained of nausea, which resolved without drug discontinuation [Michienzi, et al. 2019]. <b>Note:</b> DTG serum concentrations appear to be reduced in uninfected healthy controls with eGFR <30 mL/min/m <sup>2</sup> compared to those with normal kidney function. This may increase the risk of therapeutic failure among patients with HIV drug resistance to

**Table 8: Recommended Dose Adjustments for Use of Selected Fixed-Dose Combination Antiretroviral Medications in Patients with Hepatic or Renal Impairment**

Fixed-Dose Combination	Hepatic Impairment Dose Adjustment [a]	Recommended Dose Adjustments for Renal Impairment		
		Recommended Dose Adjustment [a]	Individual Components of FDC and Recommended Dose Adjustment [a]	Clinical Comments
				INSTIs. <a href="#">[Tivicay Package insert]</a> .
Bictegravir/emtricitabine/tenofovir alafenamide [b] (BIC/FTC/TAF; Biktarvy)  <a href="#">See package insert</a>	<b>Child-Pugh A, B:</b> No dose adjustment is needed. <b>Child-Pugh C:</b> Do not use	<b>CrCl &lt;30 mL/min:</b> Use of FDC is not recommended.	<b>BIC:</b> No renal adjustment is needed. <b>FTC:</b> <b>CrCl 30 to 49 mL/min:</b> 200 mg every 48 hours. <b>CrCl 15 to 29 mL/min:</b> 200 mg every 72 hours. <b>CrCl &lt;15 mL/min:</b> 200 mg every 96 hours. <b>TAF:</b> <b>CrCl &lt;15 mL/min, without HD:</b> Use is not recommended. <b>CrCl &lt;15 mL/min, with HD:</b> No renal dose adjustment is needed.	<b>CrCl &lt;30 mL/min:</b> No data to support use of FDC. Renal dose adjustment should be based on individual components. <b>CrCl 15 to 29 mL/min:</b> No BIC dose adjustment is needed. In a study of 10 patients with CrCl 15 to 29 mL/min compared to 8 patients with normal renal function who received a single dose of BIC 75 mg, severe renal impairment did not produce clinically relevant changes in BIC exposure [Zhang, et al. 2017].
Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF; Stribild)  <a href="#">See package insert</a>	<b>Child-Pugh A, B:</b> No dose adjustment is needed. <b>Child-Pugh C:</b> No data; do not use.	<b>CrCl &lt;70 mL/min:</b> Do not initiate therapy. <b>Drop in CrCl to &lt;50 mL/min during treatment:</b> Discontinue therapy.	<b>EVG:</b> No renal dose adjustment is needed. <b>EVG/COBI:</b> No renal dose adjustment is needed. <b>FTC:</b> <b>CrCl 30 to 49 mL/min:</b> 200mg every 48 hours. <b>CrCl 15 to 29 mL/min:</b> 200 mg every 72 hours. <b>CrCl &lt;15 mL/min:</b> 200mg every 96 hours. <b>TDF:</b> <b>CrCl 30 to 49 mL/min:</b> 300 mg every 48 hours. <b>CrCl 10 to 29 mL/min:</b> 300 mg every 72 to 96 hours. <b>CrCl &lt;10 mL/min, without HD:</b> No data available. <b>CrCl &lt;10 mL/min, with HD:</b> 300 mg every 7 days.	<b>CrCl &lt;30 mL/min:</b> No data to support use of FDC. Renal dose adjustment should be based on individual components. <b>EVG/COBI:</b> Dose adjustment not warranted. In 12 patients with eGFR <30 mL/min (not on HD) and 12 controls with normal renal function given 7 days of EVG/COBI, lower EVG AUC, C <sub>max</sub> , and C <sub>min</sub> values and higher COBI AUC, C <sub>max</sub> , and C <sub>min</sub> values were observed in severe renal impairment, but values were not considered clinically relevant [German, et al. 2012b].
Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide [b] (EVG/COBI/FTC/TAF; Genvoya)	<b>Child-Pugh A, B:</b> No dose adjustment is needed. <b>Child-Pugh C:</b> Do not use	<b>CrCl &lt;30mL/min:</b> Use of FDC is not recommended.	<b>EVG:</b> No renal dose adjustment is needed. <b>EVG/COBI:</b> No renal dose adjustment is needed. <b>FTC:</b> <b>CrCl 30 to 49 mL/min:</b> 200 mg every 48 hours. <b>CrCl 15 to 29 mL/min:</b> 200 mg every 72 hours. <b>CrCl &lt;15 mL/min:</b> 200 mg every 96 hours.	<b>CrCl &lt;30 mL/min, without HD:</b> No data to support use of FDC. Renal adjustment should be based on individual components. <b>CrCl &lt;15 mL/min, with HD:</b> In a study of 55 patients on FDC for up to 96 weeks, 18 (33%) had grade 3 or higher ADR during treatment, and 3 patients

**Table 8: Recommended Dose Adjustments for Use of Selected Fixed-Dose Combination Antiretroviral Medications in Patients with Hepatic or Renal Impairment**

Fixed-Dose Combination	Hepatic Impairment Dose Adjustment [a]	Recommended Dose Adjustments for Renal Impairment		
		Recommended Dose Adjustment [a]	Individual Components of FDC and Recommended Dose Adjustment [a]	Clinical Comments
<a href="#">See package insert</a>			<b>TAF:</b> <b>CrCl &lt;15 mL/min, without HD:</b> Use is not recommended. <b>CrCl &lt;15 mL/min, with HD:</b> No renal dose adjustment is needed. <b>ESRD, with HD:</b> One tablet once daily; administer after HD on HD days.	discontinued treatment due to adverse effects. The authors concluded that, at 48 weeks, the FDC regimen was well tolerated in patients on HD [Eron JJ, Jr., et al. 2018a].
Dolutegravir/lamivudine (DTG/3TC; Dovato)  <a href="#">See package insert</a>	<b>Child-Pugh A, B:</b> No dose adjustment is needed. <b>Child-Pugh C:</b> Do not use.	<b>CrCl &lt;50 mL/min:</b> Use of FDC is not recommended.	<b>DTG:</b> No renal dose adjustment is needed. <b>3TC:</b> <b>CrCl 30 to 49 mL/min:</b> 150 mg once daily. <b>CrCl 15 to 29 mL/min:</b> 150 mg first dose, then 100 mg once daily. <b>CrCl 5 to 14 mL/min:</b> 150 mg first dose, then 50 mg once daily. <b>CrCl &lt;5 mL/min:</b> 50 mg first dose, then 25 mg once daily.	<b>CrCl &lt;50mL/min:</b> No data to support use of FDC. Renal dose adjustment should be based on individual components.
Dolutegravir/rilpivirine (DTG/RPV; Juluca)  <a href="#">See package insert</a>	<b>Child-Pugh A, B:</b> No dose adjustment is needed. <b>Child-Pugh C:</b> No data; do not use.	<b>CrCl &lt;30 mL/min or ESRD:</b> No dose adjustment is needed; increased monitoring is recommended.	—	—
<i>Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTIs)</i>				
Emtricitabine/rilpivirine/tenofovir alafenamide/FTC/RPV/TAF; Odefsey) [b]	<b>Child-Pugh A, B:</b> No dose adjustment is needed. <b>Child-Pugh C:</b>	<b>CrCl &lt;30 mL/min:</b> Use of FDC is not recommended.	<b>FTC:</b> <b>CrCl 30 to 49 mL/min:</b> 200 mg every 48 hours. <b>CrCl 15 to 29 mL/min:</b> 200 mg every 72 hours. <b>CrCl &lt;15 mL/min:</b> 200 mg every 96 hours.	<b>CrCl &lt;30 mL/min, without HD:</b> No data to support use of FDC. Renal dose adjustment should be based on individual components. <b>CrCl &lt;30 mL/min, with HD:</b> One FDC tablet once daily.

**Table 8: Recommended Dose Adjustments for Use of Selected Fixed-Dose Combination Antiretroviral Medications in Patients with Hepatic or Renal Impairment**

Fixed-Dose Combination	Hepatic Impairment Dose Adjustment [a]	Recommended Dose Adjustments for Renal Impairment		
		Recommended Dose Adjustment [a]	Individual Components of FDC and Recommended Dose Adjustment [a]	Clinical Comments
<a href="#">See package insert</a>	No data.		<p><b>RPV:</b> No renal dose adjustment needed.</p> <p><b>TAF:</b></p> <p><b>CrCl &lt;15 mL/min, without HD:</b> Use is not recommended.</p> <p><b>CrCl &lt;15 mL/min, with HD:</b> No renal dose adjustment is needed.</p>	<p>On HD days, administer after dialysis [AIDSinfo 2019].</p> <p>Dose recommended based on data using FTC/TAF as part of FDC with EVG/COBI in patients on HD: In a study of 55 patients on EVG/COBI/FTC/TAF for up to 96 weeks, 18 (33%) had grade 3 or higher ADRs during treatment, and 3 patients discontinued treatment due to adverse effects. The authors concluded that at 48 weeks, the FDC regimen was well tolerated in patients on HD [Eron JJ, Jr., et al. 2018a].</p>
<p>Doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF; Delstrigo)</p> <p><a href="#">See package insert</a></p>	<p><b>Child-Pugh A, B:</b> No dose adjustment is needed.</p> <p><b>Child-Pugh C:</b> No data.</p>	<p><b>CrCl &lt;50 mL/min:</b> Use of FDC is not recommended.</p>	<p><b>DOR:</b> No renal dose adjustment is needed.</p> <p><b>3TC:</b></p> <p><b>CrCl 30 to 49 mL/min:</b> 150 mg once daily.</p> <p><b>CrCl 15 to 29 mL/min:</b> 150 mg first dose, then 100 mg once daily.</p> <p><b>CrCl 5 to 14 mL/min:</b> 150 mg first dose, then 50 mg once daily.</p> <p><b>CrCl &lt;5 mL/min:</b> 50 mg first dose, then 25 mg once daily.</p> <p><b>TDF:</b></p> <p><b>CrCl 30 to 49 mL/min:</b> 300 mg every 48 hours.</p> <p><b>CrCl 10 to 29 mL/min:</b> 300 mg every 72 to 96 hours.</p> <p><b>CrCl &lt;10 mL/min, without HD:</b> No data available.</p> <p><b>CrCl &lt;10 mL/min, with HD:</b> 300 mg every 7 days.</p>	<p><b>CrCl &lt; 50 mL/min:</b> No data to support use of FDC. Renal dose adjustment should be based on individual components.</p>
<p>Efavirenz/lamivudine/tenofovir disoproxil fumarate (EFV/3TC/TDF; Symfi Lo)</p>	<p><b>Child-Pugh A:</b> No dose adjustment is needed.</p>	<p><b>CrCl &lt;50 mL/min:</b> Use of FDC is not recommended.</p>	<p><b>EFV:</b> No renal dose adjustment is needed.</p> <p><b>3TC:</b></p> <p><b>CrCl 30 to 49 mL/min:</b> 150 mg once daily.</p> <p><b>CrCl 15 to 29 mL/min:</b> 150mg first dose, then 100 mg</p>	<p><b>CrCl &lt;50 mL/min:</b> No data to support use of FDC. Renal dose adjustment should be based on individual components.</p>

**Table 8: Recommended Dose Adjustments for Use of Selected Fixed-Dose Combination Antiretroviral Medications in Patients with Hepatic or Renal Impairment**

Fixed-Dose Combination	Hepatic Impairment Dose Adjustment [a]	Recommended Dose Adjustments for Renal Impairment		
		Recommended Dose Adjustment [a]	Individual Components of FDC and Recommended Dose Adjustment [a]	Clinical Comments
<a href="#">See package insert</a>	<b>Child-Pugh B, C:</b> No data; do not use.		<p>once daily.</p> <p><b>CrCl 5 to 14 mL/min:</b> 150 mg first dose, then 50 mg once daily.</p> <p><b>TDF:</b></p> <p><b>CrCl 30 to 49 mL/min:</b> 300 mg every 48 hours.</p> <p><b>CrCl 10 to 29 mL/min:</b> 300 mg every 72 to 96 hours.</p> <p><b>CrCl &lt;10 mL/min, without HD:</b> No data available.</p> <p><b>CrCl &lt;10 mL/min, with HD:</b> 300 mg every 7 days.</p>	
<p>Efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/FTC//TDF; Atripla)</p> <p><a href="#">See package insert</a></p>	<p><b>Child-Pugh A:</b> No adjustment is needed.</p> <p><b>Child-Pugh B, C:</b> No data; do not use.</p>	<b>CrCl &lt;50 mL/min:</b> Use of FDC is not recommended.	<p>EFV: No renal dose adjustment is needed.</p> <p><b>FTC:</b></p> <p><b>CrCl 30 to 49 mL/min:</b> 200 mg every 48 hours.</p> <p><b>CrCl 15 to 29 mL/min:</b> 200 mg every 72 hours.</p> <p><b>CrCl &lt;15 mL/min:</b> 200 mg every 96 hours.</p> <p><b>TDF:</b></p> <p><b>CrCl 30 to 49 mL/min:</b> 300 mg every 48 hours.</p> <p><b>CrCl 10 to 29 mL/min:</b> 300 mg every 72 to 96 hours.</p> <p><b>CrCl &lt;10 mL/min, without HD:</b> No data available.</p> <p><b>CrCl &lt;10 mL/min, with HD:</b> 300 mg every 7 days.</p>	<b>CrCl &lt;50 mL/min:</b> No data to support use of FDC. Renal dose adjustment should be based on individual components.
<i>Protease Inhibitors (PIs)</i>				
<p>Darunavir/cobicistat/emtricitabine/tenofovir alafenamide (DRV/COBI/FTC/TAF; Symtuza) [b]</p> <p><a href="#">See package insert</a></p>	<p><b>Child-Pugh A, B:</b> No adjustment is needed.</p> <p><b>Child-Pugh C:</b> Do not use.</p>	<b>CrCl &lt;30 mL/min:</b> Use of FDC is not recommended.	<p><b>DRV; DRV/COBI:</b> No renal dose adjustment required unless being combined with TDF. Renal dose adjustment for CrCl &lt;70 mL/min is recommended when combined with TDF.</p> <p><b>FTC:</b></p> <p><b>CrCl 30 to 49 mL/min:</b> 200 mg every 48 hours.</p> <p><b>CrCl 15 to 29 mL/min:</b> 200 mg every 72 hours.</p> <p><b>CrCl &lt;15 mL/min:</b> 200 mg every 96 hours.</p> <p><b>TAF:</b></p>	<p><b>CrCl &lt;30 mL/min, without HD:</b> No data to support use of FDC. Renal adjustment should be based on individual components.</p> <p><b>CrCl &lt;30mL/min, with HD:</b> One FDC tablet once daily. On HD days, administer after dialysis [AIDSinfo 2019]. Dose recommended based on data using FTC/TAF as part of FDC with EVG/COBI in patients on HD: In a study of 55 patients on EVG/COBI/FTC/TAF for up to 96 weeks, 18 (33%) had grade 3 or higher ADRs</p>

**Table 8: Recommended Dose Adjustments for Use of Selected Fixed-Dose Combination Antiretroviral Medications in Patients with Hepatic or Renal Impairment**

Fixed-Dose Combination	Hepatic Impairment Dose Adjustment [a]	Recommended Dose Adjustments for Renal Impairment		
		Recommended Dose Adjustment [a]	Individual Components of FDC and Recommended Dose Adjustment [a]	Clinical Comments
			<p><b>CrCl &lt;15 mL/min, without HD:</b> Use is not recommended.</p> <p><b>CrCl &lt;15 mL/min, with HD:</b> No renal dose adjustment is needed.</p>	during treatment, and 3 patients discontinued treatment due to adverse effects. The authors concluded that at 48 weeks, the FDC regimen was well tolerated in patients on HD [Eron JJ, Jr., et al. 2018a].
<i>Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)</i>				
<p>Emtricitabine/tenofovir alafenamide (FTC/TAF; Descovy)</p> <p><a href="#">See package insert</a></p>	<p><b>Child-Pugh A, B:</b> No dose adjustment is needed.</p> <p><b>Child-Pugh C:</b> No data.</p>	<p><b>CrCl &lt;30 mL/min:</b> Use of FDC is not recommended.</p>	<p><b>FTC:</b></p> <p><b>CrCl 30 to 49 mL/min:</b> 200 mg every 48 hours.</p> <p><b>CrCl 15 to 29 mL/min:</b> 200 mg every 72 hours.</p> <p><b>CrCl &lt;15 mL/min:</b> 200 mg every 96 hours.</p> <p><b>TAF:</b></p> <p><b>CrCl &lt;15 mL/min, without HD:</b> Use is not recommended.</p> <p><b>CrCl &lt;15 mL/min, with HD:</b> No renal dose adjustment is needed.</p>	<p><b>CrCl &lt;30 mL/min, without HD:</b> No data to support use of FDC. Renal adjustment should be based on individual components.</p> <p><b>CrCl &lt;30 mL/min, with HD:</b> One FDC once daily. On HD days, administer after HD [AIDSinfo 2019].</p> <p>Dose recommended based on data using FTC/TAF as part of FDC with EVG/COBI in patients on HD: In a study of 55 patients on EVG/COBI/FTC/TAF for up to 96 weeks, 18 (33%) had grade 3 or higher ADRs during treatment, and 3 patients discontinued treatment due to adverse effects. The authors concluded that at 48 weeks, the FDC regimen was well tolerated in patients on HD [Eron JJ, Jr., et al. 2018a].</p>
<p>Emtricitabine/tenofovir disoproxil fumarate (FTC/TDF; Truvada)</p> <p><a href="#">See package insert</a></p>	No dose adjustment is needed.	<p><b>CrCl 30 to 49 mL/min:</b> FTC 200 mg/TDF 300 mg every 48 hours.</p> <p><b>CrCl &lt;30 mL/min:</b> Use of FDC is not recommended.</p>	<p><b>FTC:</b></p> <p><b>CrCl 30 to 49 mL/min:</b> 200 mg every 48 hours.</p> <p><b>CrCl 15 to 29 mL/min:</b> 200 mg every 72 hours.</p> <p><b>CrCl &lt;15 mL/min:</b> 200 mg every 96 hours.</p> <p><b>TDF:</b></p> <p><b>CrCl 30 to 49 mL/min:</b> 300 mg every 48 hours.</p> <p><b>CrCl 10 to 29 mL/min:</b> 300 mg every 72 to 96 hours.</p> <p><b>CrCl &lt;10 mL/min, without HD:</b> No data available.</p>	<p><b>CrCl &lt;30 mL/min:</b> No data to support use of FDC. Renal dose adjustment should be based on individual components.</p>

**Table 8: Recommended Dose Adjustments for Use of Selected Fixed-Dose Combination Antiretroviral Medications in Patients with Hepatic or Renal Impairment**

Fixed-Dose Combination	Hepatic Impairment Dose Adjustment [a]	Recommended Dose Adjustments for Renal Impairment		
		Recommended Dose Adjustment [a]	Individual Components of FDC and Recommended Dose Adjustment [a]	Clinical Comments
			<b>CrCl &lt;10 mL/min, with HD:</b> 300 mg every 7 days	
Abacavir/lamivudine (ABC/3TC; Epzicom)  <a href="#">See package insert</a>	<b>Child-Pugh A, B, C:</b> Do not use.	<b>CrCl &lt;50 mL/min:</b> Use of FDC is not recommended.	<p><b>ABC:</b> No renal dose adjustment is needed.</p> <p><b>3TC:</b></p> <p><b>CrCl 30 to 49 mL/min:</b> 150 mg once daily.</p> <p><b>CrCl 15 to 29 mL/min:</b> 150 mg first dose, then 100 mg once daily.</p> <p><b>CrCl 5 to 14 mL/min:</b> 150 mg first dose, then 50 mg once daily.</p> <p><b>CrCl &lt;5 mL/min:</b> 50 mg first dose, then 25 mg once daily.</p>	<p><b>CrCl &gt;30 mL/min:</b> Limited data to support use of FDC. No elevations in lactate or other ADRs reported in a study of 21 patients with CrCl &gt;30 mL/min who received full dose of 3TC; minimal increases in AUC. [Fischetti, et al. 2018].</p> <p><b>CrCl &lt;30 mL/min, without HD:</b> Renal dose adjustment should be based on individual components. 13 patients with CrCl &lt;30 mL/min received 100-150 mg of 3TC with minimal increases in AUC. No elevations in lactate or other ADRs reported [Fischetti, et al. 2018].</p> <p><b>CrCl &lt;30 mL/min, with HD:</b> Limited data to support use of FDC. A case series evaluating safety and efficacy of Triumeq (ABC/3TC/DTG) as an FDC in 9 patients with ESRD on HD showed viral suppression was achieved in all 9 patients. No change in immune function. FDC was generally well tolerated; one patient complained of nausea, which resolved without drug discontinuation [Michienzi, et al. 2019].</p> <p><b>Note:</b> DTG serum concentrations appear to be reduced in uninfected healthy controls with eGFR &lt;30 mL/min/m<sup>2</sup> compared to those with normal kidney function. This may increase the risk of therapeutic failure among patients with HIV drug resistance to INSTIs. [<a href="#">Tivicay Package insert</a>].</p>

**Table 8: Recommended Dose Adjustments for Use of Selected Fixed-Dose Combination Antiretroviral Medications in Patients with Hepatic or Renal Impairment**

Fixed-Dose Combination	Hepatic Impairment Dose Adjustment [a]	Recommended Dose Adjustments for Renal Impairment		
		Recommended Dose Adjustment [a]	Individual Components of FDC and Recommended Dose Adjustment [a]	Clinical Comments
<p><b>Abbreviations:</b> ADR, adverse drug reaction; AUC, area under the curve; C<sub>max</sub>, maximum plasma concentration; C<sub>min</sub>, minimum plasma concentration; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HD, hemodialysis.</p> <p><b>Notes:</b></p> <p>a. Per package inserts; see links.</p> <p>b. Per package inserts, FTC can be used at standard dose in FDCs that contain FTC/TAF when CrCl is &gt;30 mL/min. FTC as an individual component requires renal dose adjustment when CrCl is &lt;50 mL/min.</p> <p><b>Other ARVs, not included above:</b></p> <p>TDF/FTC/RPV (Complera): <a href="#">See package insert</a> Renal dose adjustment: CrCl &lt;50 mL/min: do not use. Hepatic dose adjustment: Child-Pugh A,B—no adjustment; Child-Pugh C—no data</p> <p>Atazanavir (ATV; Reyataz): <a href="#">See package insert</a> Renal dose adjustment: No adjustment, but use only 300 mg dose with 100 mg RTV; do not use in treatment-experienced patients on HD. Hepatic dose adjustment: Child-Pugh A,B—no adjustment; Child-Pugh C—no data</p> <p>ATV/COBI (Evotaz): <a href="#">See package insert</a> Renal dose adjustment: Do not use in patients with CrCl &lt;70 mL/min taking a TDF-containing regimen; do not use in treatment-experienced patients on HD. Hepatic dose adjustment: No data; not recommended.</p> <p>Raltegravir (RAL; Isentress): <a href="#">See package insert</a> Renal dose adjustment: None Hepatic dose adjustment: 400 mg twice daily-- Child-Pugh A, B—no adjustment; Child-Pugh C—no data. 600 mg once daily: No data; use with caution.</p>				

**DRUG MANUFACTURER PACKAGE INSERTS**

**Atripla:** FDA. Atripla (efavirenz/emtricitabine/tenofovir disoproxil fumarate) tablets, for oral use. 2006. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2015/021937s0371bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021937s0371bl.pdf) [accessed 2020 Mar 5].

**Biktarvy:** FDA. Biktarvy (bictegravir, emtricitabine, and tenofovir alafenamide) tablets, for oral use. 2018 Feb. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/210251s0001bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210251s0001bl.pdf) [accessed 2020 Mar 5].

**Complera:** FDA. Complera (emtricitabine/rilpivirine/tenofovir disoproxil fumarate) tablets, for oral use. 2013 Jan. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/202123s0031bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/202123s0031bl.pdf) [accessed 2020 May 14].

**Descovy:** FDA. Descovy (emtricitabine and tenofovir alafenamide) tablets, for oral use. 2016 Apr. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/208215s0001bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208215s0001bl.pdf) [accessed 2020 Mar 5].

**Delstrigo:** FDA. Delstrigo (doravirine, lamivudine, and tenofovir disoproxil fumarate) tablets, for oral use. 2018 Aug. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/210807s0001bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210807s0001bl.pdf) [accessed 2020 Mar 5].

- Dovato:** FDA. Dovato (dolutegravir and lamivudine) tablets, for oral use. 2019 Apr. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/211994s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211994s000lbl.pdf) [accessed 2020 Mar 5].
- Epzicom:** FDA. Epzicom (abacavir sulfate and lamivudine) tablets for oral use. 2012 Mar. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2012/021652s015lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021652s015lbl.pdf) [accessed 2020 Mar 5].
- Evotaz:** FDA. Evotaz (atazanavir and cobicistat) tablets, for oral use. 2015 Jan. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2015/206353s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206353s000lbl.pdf) [accessed 2020 May 14].
- Genvoya:** FDA. Genvoya (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide) tablets, for oral use. 2015 Nov. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2015/207561s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207561s000lbl.pdf) [accessed 2020 Mar 5].
- ISENTRESS:** FDA. ISENTRESS (raltegravir) tablets for oral use. 2013 June. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/022145s029lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022145s029lbl.pdf) [accessed 2020 May 14].
- Juluca:** FDA. Juluca (dolutegravir and rilpivirine) tablets, for oral use. 2017 Nov. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/210192s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/210192s000lbl.pdf) [accessed 2020 Mar 5].
- Odefsey:** FDA. Odefsey (emtricitabine, rilpivirine, and tenofovir alafenamide) tablets, for oral use. 2016 Mar. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/208351s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208351s000lbl.pdf) [accessed 2020 Mar 5].
- Reyataz:** FDA. Reyataz (atazanavir) capsules, for oral use. 2016 Sept. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/021567s039.206352s004lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021567s039.206352s004lbl.pdf) [accessed 2020 May 14].
- Stribild:** FDA. Stribild (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate) tablets, for oral use. 2016 Sep. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/203100s024lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/203100s024lbl.pdf) [accessed 2020 Mar 5].
- Symfi Lo:** FDA. Symfi lo (efavirenz, lamivudine, and tenofovir disoproxil fumarate) tablets, for oral use. 2018 Feb. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/208255s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208255s000lbl.pdf) [accessed 2020 Mar 5].
- Symtuza:** FDA. Symtuza (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide) tablets, for oral use. 2018 Jul. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/210455s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210455s000lbl.pdf) [accessed 2020 Mar 5].
- Triumeq:** FDA. Triumeq (abacavir, dolutegravir, and lamivudine) tablets, for oral use. 2017 Nov. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/205551s011lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205551s011lbl.pdf) [accessed 2020 Mar 5].
- Truvada:** FDA. Truvada (emtricitabine/tenofovir disoproxil fumarate) tablets, for oral use. 2004. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/021752s047lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021752s047lbl.pdf) [accessed 2020 Mar 5].
- Tivicay:** FDA. Tivicay (dolutegravir) tablets, for oral use. 2013. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/204790lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204790lbl.pdf) [accessed 2020 Apr 13].

# All Recommendations

## ☑ All RECOMMENDATIONS: Selecting an Initial ART Regimen

### Available ART Regimens

- 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 should be performed at diagnosis, or at the initial visit if not done previously, for the protease (A2), reverse transcriptase (A2), and integrase (B2) genes. See the *Specific Factors to Consider and Discuss with Patients* section of this guideline.
- 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-naive 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.

## REFERENCES

- Aberg JA, Gallant JE, Ghanem KG, et al. Primary care guidelines for the management of persons infected with HIV: 2013 update by the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis* 2014;58(1):1-10. [PMID: 24343580] <https://www.ncbi.nlm.nih.gov/pubmed/24343580>
- Adams JL, Byrne D, Pepe R, et al. Virological failure in two patients with HIV-1 RNA viral loads >1,000,000 copies/ml initiated on elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate. *Antivir Ther* 2016;21(2):175-180. [PMID: 26308882] <https://www.ncbi.nlm.nih.gov/pubmed/26308882>
- 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]
- AIDSinfo. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency. 2019 Jul 10.  
<https://aidsinfo.nih.gov/guidelines/htmltables/1/7580> [accessed 2020 Feb 20]
- Armstrong B, Chan DJ, Stewart MJ, et al. Single tablet regimen usage and efficacy in the treatment of HIV infection in Australia. *AIDS Res Treat* 2015;2015:570316. [PMID: 26550490] <https://www.ncbi.nlm.nih.gov/pubmed/26550490>
- Arribas JR, Pialoux G, Gathe J, et al. Simplification to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus continuation of ritonavir-boosted protease inhibitor with emtricitabine and tenofovir in adults with virologically suppressed HIV (STRATEGY-PI): 48 week results of a randomised, open-label, phase 3b, non-inferiority trial. *Lancet Infect Dis* 2014;14(7):581-589. [PMID: 24908551] <https://www.ncbi.nlm.nih.gov/pubmed/24908551>
- Bangalore S, Kamalakkannan G, Parkar S, et al. Fixed-dose combinations improve medication compliance: a meta-analysis. *Am J Med* 2007;120(8):713-719. [PMID: 17679131] <https://www.ncbi.nlm.nih.gov/pubmed/17679131>
- Baril JG, Angel JB, Gill MJ, et al. Dual therapy treatment strategies for the management of patients infected with HIV: A systematic review of current evidence in ARV-naïve or ARV-experienced, virologically suppressed patients. *PLoS One* 2016;11(2):e0148231. [PMID: 26849060] <https://www.ncbi.nlm.nih.gov/pubmed/26849060>
- Bedimo RJ, Drechsler H, Jain M, et al. The RADAR study: week 48 safety and efficacy of Raltegravir combined with boosted DARunavir compared to tenofovir/emtricitabine combined with boosted darunavir in antiretroviral-naïve patients. Impact on bone health. *PLoS One* 2014;9(8):e106221. [PMID: 25170938] <https://www.ncbi.nlm.nih.gov/pubmed/25170938>
- Bedimo RJ, Westfall AO, Drechsler H, et al. Abacavir use and risk of acute myocardial infarction and cerebrovascular events in the highly active antiretroviral therapy era. *Clin Infect Dis* 2011;53(1):84-91. [PMID: 21653308] <https://www.ncbi.nlm.nih.gov/pubmed/21653308>
- Behrens G, Rijnders B, Nelson M, et al. Rilpivirine versus efavirenz with emtricitabine/tenofovir disoproxil fumarate in treatment-naïve HIV-1-infected patients with HIV-1 RNA  $\leq$ 100,000 copies/mL: week 96 pooled ECHO/THRIVE subanalysis. *AIDS Patient Care STDS* 2014;28(4):168-175. [PMID: 24660840] <https://www.ncbi.nlm.nih.gov/pubmed/24660840>
- Bonora S, Calcagno A, Trentalange A, et al. Elvitegravir, cobicistat, emtricitabine and tenofovir alafenamide for the treatment of HIV in adults. *Expert Opin Pharmacother* 2016;17(3):409-419. [PMID: 26642079] <https://www.ncbi.nlm.nih.gov/pubmed/26642079>
- Borroto-Esoda K, Waters JM, Bae AS, et al. Baseline genotype as a predictor of virological failure to emtricitabine or stavudine in combination with didanosine and efavirenz. *AIDS Res Hum Retroviruses* 2007;23(8):988-995. [PMID: 17725415] <https://www.ncbi.nlm.nih.gov/pubmed/17725415>
- Brothers CH, Hernandez JE, Cutrell AG, et al. Risk of myocardial infarction and abacavir therapy: no increased risk across 52 GlaxoSmithKline-sponsored clinical trials in adult subjects. *J Acquir Immune Defic Syndr* 2009;51(1):20-28. [PMID: 19282778] <https://www.ncbi.nlm.nih.gov/pubmed/19282778>
- Cahn P, Andrade-Villanueva J, Arribas JR, et al. Dual therapy with lopinavir and ritonavir plus lamivudine versus triple therapy with lopinavir and ritonavir plus two nucleoside reverse transcriptase inhibitors in antiretroviral-therapy-naïve adults with HIV-1 infection: 48 week results of the randomised, open label, non-inferiority GARDEL trial. *Lancet Infect Dis* 2014;14(7):572-580. [PMID: 24783988] <https://www.ncbi.nlm.nih.gov/pubmed/24783988>
- Cahn P, Kaplan R, Sax PE, et al. Raltegravir 1200 mg once daily versus raltegravir 400 mg twice daily, with tenofovir disoproxil fumarate and emtricitabine, for previously untreated HIV-1 infection: a randomised, double-blind, parallel-group, phase 3, non-inferiority trial. *Lancet HIV* 2017;4(11):e486-e494. [PMID: 28918877] <https://www.ncbi.nlm.nih.gov/pubmed/28918877>
- Cahn P, Madero JS, Arribas JR, et al. Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naïve adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials. *Lancet* 2018. [PMID: 30420123] <https://www.ncbi.nlm.nih.gov/pubmed/30420123>

- Cahn P, Rolan MJ, Figueroa MI, et al. Dolutegravir-lamivudine as initial therapy in HIV-Infected, ARV naïve patients 48 Week Results of the PADDLE trial. International AIDS Conference; 2016 Jul 18-22; Durban, South Africa.  
[http://www.natap.org/2016/IAC/IAC\\_54.htm](http://www.natap.org/2016/IAC/IAC_54.htm)
- Cazanave C, Reigadas S, Mazubert C, et al. Switch to rilpivirine/emtricitabine/tenofovir single-tablet regimen of human immunodeficiency virus-1 RNA-suppressed patients, Agence Nationale de Recherches sur le SIDA et les Hepatites Virales CO3 Aquitaine Cohort, 2012-2014. *Open Forum Infect Dis* 2015;2(1):ofv018. [PMID: 26034768]  
<https://www.ncbi.nlm.nih.gov/pubmed/26034768>
- Choi AI, Vittinghoff E, Deeks SG, et al. Cardiovascular risks associated with abacavir and tenofovir exposure in HIV-infected persons. *Aids* 2011;25(10):1289-1298. [PMID: 21516027] <https://www.ncbi.nlm.nih.gov/pubmed/21516027>
- Clay PG, Nag S, Graham CM, et al. Meta-analysis of studies comparing single and multi-tablet fixed dose combination HIV treatment regimens. *Medicine (Baltimore)* 2015;94(42):e1677. [PMID: 26496277]  
<https://www.ncbi.nlm.nih.gov/pubmed/26496277>
- Cohen C, Wohl D, Arribas JR, et al. Week 48 results from a randomized clinical trial of rilpivirine/emtricitabine/tenofovir disoproxil fumarate vs. efavirenz/emtricitabine/tenofovir disoproxil fumarate in treatment-naïve HIV-1-infected adults. *Aids* 2014;28(7):989-997. [PMID: 24508782] <https://www.ncbi.nlm.nih.gov/pubmed/24508782>
- Cohen CJ, Meyers JL, Davis KL. Association between daily antiretroviral pill burden and treatment adherence, hospitalisation risk, and other healthcare utilisation and costs in a US medicaid population with HIV. *BMJ Open* 2013a;3(8). [PMID: 23906955] <https://www.ncbi.nlm.nih.gov/pubmed/23906955>
- Cohen CJ, Molina JM, Cahn P, et al. Efficacy and safety of rilpivirine (TMC278) versus efavirenz at 48 weeks in treatment-naïve HIV-1-infected patients: pooled results from the phase 3 double-blind randomized ECHO and THRIVE Trials. *J Acquir Immune Defic Syndr* 2012;60(1):33-42. [PMID: 22343174] <https://www.ncbi.nlm.nih.gov/pubmed/22343174>
- Cohen CJ, Molina JM, Cassetti I, et al. Week 96 efficacy and safety of rilpivirine in treatment-naïve, HIV-1 patients in two Phase III randomized trials. *Aids* 2013b;27(6):939-950. [PMID: 23211772]  
<https://www.ncbi.nlm.nih.gov/pubmed/23211772>
- Colombo GL, Di Matteo S, Maggiolo F. Antiretroviral therapy in HIV-infected patients: a proposal to assess the economic value of the single-tablet regimen. *Clinicoecon Outcomes Res* 2013;5:59-68. [PMID: 23430273]  
<https://www.ncbi.nlm.nih.gov/pubmed/23430273>
- Currier J, Averitt Bridge D, Hagins D, et al. Sex-based outcomes of darunavir-ritonavir therapy: a single-group trial. *Ann Intern Med* 2010;153(6):349-357. [PMID: 20855799] <https://www.ncbi.nlm.nih.gov/pubmed/20855799>
- Cuzin L, Pugliese P, Allavena C, et al. Antiretroviral therapy as a risk factor for chronic kidney disease: Results from traditional regression modeling and causal approach in a large observational study. *PLoS One* 2017;12(12):e0187517. [PMID: 29216208] <https://www.ncbi.nlm.nih.gov/pubmed/29216208>
- Danel C, Moh R, Gabillard D, et al. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. *N Engl J Med* 2015;373(9):808-822. [PMID: 26193126] <https://www.ncbi.nlm.nih.gov/pubmed/26193126>
- DeJesus E, Rockstroh JK, Lennox JL, et al. Efficacy of raltegravir versus efavirenz when combined with tenofovir/emtricitabine in treatment-naïve HIV-1-infected patients: week-192 overall and subgroup analyses from STARTMRK. *HIV Clin Trials* 2012;13(4):228-232. [PMID: 22849964] <https://www.ncbi.nlm.nih.gov/pubmed/22849964>
- Ding X, Andraca-Carrera E, Cooper C, et al. No association of abacavir use with myocardial infarction: findings of an FDA meta-analysis. *J Acquir Immune Defic Syndr* 2012;61(4):441-447. [PMID: 22932321]  
<https://www.ncbi.nlm.nih.gov/pubmed/22932321>
- Domingo P, Ribera E. [Data on rilpivirine in treatment-naïve patients. Lessons from ECHO, THRIVE and STaR]. *Enferm Infecc Microbiol Clin* 2013;31 Suppl 2:20-29. [PMID: 24252530] <https://www.ncbi.nlm.nih.gov/pubmed/24252530>
- El-Sadr WM, Lundgren J, Neaton JD, et al. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med* 2006;355(22):2283-2296. [PMID: 17135583] <https://www.ncbi.nlm.nih.gov/pubmed/17135583>
- Eron JJ, Jr., Lelievre JD, Kalayjian R, et al. Safety of elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide in HIV-1-infected adults with end-stage renal disease on chronic haemodialysis: an open-label, single-arm, multicentre, phase 3b trial. *Lancet HIV* 2018a. [PMID: 30555051] <https://www.ncbi.nlm.nih.gov/pubmed/30555051>

- Eron JJ, Orkin C, Gallant J, et al. A week-48 randomized phase-3 trial of darunavir/cobicistat/emtricitabine/tenofovir alafenamide in treatment-naïve HIV-1 patients. *Aids* 2018b;32(11):1431-1442. [PMID: 29683855] <https://www.ncbi.nlm.nih.gov/pubmed/29683855>
- FDA. Tivicay (dolutegravir) tablets for oral use. 2013 Aug. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/204790lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204790lbl.pdf) [accessed 2018 May 2]
- FDA. Descovy (emtricitabine and tenofovir alafenamide) tablets, for oral use. 2016a Apr. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/208215s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208215s000lbl.pdf) [accessed 2018 May 2]
- FDA. Genvoya (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide) tablets, for oral use. 2016b Dec. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/207561s002lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/207561s002lbl.pdf) [accessed 2018 May 2]
- FDA. Odefsey (emtricitabine, rilpivirine, and tenofovir alafenamide) tablets, for oral use. 2016c Mar. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/208351s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208351s000lbl.pdf) [accessed 2018 May 2]
- FDA. Prezcoibix (darunavir and cobicistat) tablets, for oral use. 2016d Mar. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/205395s001lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/205395s001lbl.pdf) [accessed 2018 May 2]
- FDA. Biktarvy (bictegravir, emtricitabine, and tenofovir alafenamide) tablets, for oral use. 2018a Feb. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/210251s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210251s000lbl.pdf) [accessed 2018 May 2]
- FDA. Symtuza (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide) tablets, for oral use. 2018b Jul. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/210455s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210455s000lbl.pdf) [accessed 2018 Oct 30]
- Fischetti B, Shah K, Taft DR, et al. Real-world experience with higher-than-recommended doses of lamivudine in patients with varying degrees of renal impairment. *Open Forum Infect Dis* 2018;5(10):ofy225. [PMID: 30302352] <https://www.ncbi.nlm.nih.gov/pubmed/30302352>
- Fisher M, Moyle GJ, Shahmanesh M, et al. A randomized comparative trial of continued zidovudine/lamivudine or replacement with tenofovir disoproxil fumarate/emtricitabine in efavirenz-treated HIV-1-infected individuals. *J Acquir Immune Defic Syndr* 2009;51(5):562-568. [PMID: 19561519] <https://www.ncbi.nlm.nih.gov/pubmed/19561519>
- Gallant J, Lazzarin A, Mills A, et al. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. *Lancet* 2017;390(10107):2063-2072. [PMID: 28867497] <https://www.ncbi.nlm.nih.gov/pubmed/28867497>
- Gallant JE, Daar ES, Raffi F, et al. Efficacy and safety of tenofovir alafenamide versus tenofovir disoproxil fumarate given as fixed-dose combinations containing emtricitabine as backbones for treatment of HIV-1 infection in virologically suppressed adults: a randomised, double-blind, active-controlled phase 3 trial. *Lancet HIV* 2016;3(4):e158-165. [PMID: 27036991] <https://www.ncbi.nlm.nih.gov/pubmed/27036991>
- Gallant JE, Koenig E, Andrade-Villanueva J, et al. Cobicistat versus ritonavir as a pharmacoenhancer of atazanavir plus emtricitabine/tenofovir disoproxil fumarate in treatment-naïve HIV type 1-infected patients: week 48 results. *J Infect Dis* 2013;208(1):32-39. [PMID: 23532097] <https://www.ncbi.nlm.nih.gov/pubmed/23532097>
- Gardner EM, Sharma S, Peng G, et al. Differential adherence to combination antiretroviral therapy is associated with virological failure with resistance. *Aids* 2008;22(1):75-82. [PMID: 18090394] <https://www.ncbi.nlm.nih.gov/pubmed/18090394>
- German P, Liu HC, Szwarcberg J, et al. Effect of cobicistat on glomerular filtration rate in subjects with normal and impaired renal function. *J Acquir Immune Defic Syndr* 2012a;61(1):32-40. [PMID: 22732469] <https://www.ncbi.nlm.nih.gov/pubmed/22732469>
- German P, Wei X, Mizuno V, et al. Pharmacokinetics of elvitegravir and cobicistat in subjects with severe renal impairment. 13th International Workshop on Clinical Pharmacology of HIV Therapy; 2012b Apr 16-18; Barcelona, Spain. [http://www.natap.org/2012/pharm/Pharm\\_29.htm](http://www.natap.org/2012/pharm/Pharm_29.htm)
- Gervasoni C, Meraviglia P, Landonio S, et al. Low body weight in females is a risk factor for increased tenofovir exposure and drug-related adverse events. *PLoS One* 2013;8(12):e80242. [PMID: 24312465] <https://www.ncbi.nlm.nih.gov/pubmed/24312465>

- Goicoechea M, Liu S, Best B, et al. Greater tenofovir-associated renal function decline with protease inhibitor-based versus nonnucleoside reverse-transcriptase inhibitor-based therapy. *J Infect Dis* 2008;197(1):102-108. [PMID: 18171292] <https://www.ncbi.nlm.nih.gov/pubmed/18171292>
- Griffith D, Farmer C, Rutstein R, et al. Uptake and virologic outcomes of one-pill versus multi-pill antiretroviral therapy among treatment-naïve non-perinatally HIV-infected youth (2006-2014). IDWeek; 2016 Oct 26-30; New Orleans, LA. <https://idsa.confex.com/idsa/2016/webprogram/Paper58740.html>
- Gulick RM, Mellors JW, Havlir D, et al. Treatment with indinavir, zidovudine, and lamivudine in adults with human immunodeficiency virus infection and prior antiretroviral therapy. *N Engl J Med* 1997;337(11):734-739. [PMID: 9287228] <https://www.ncbi.nlm.nih.gov/pubmed/9287228>
- Gulick RM, Mellors JW, Havlir D, et al. 3-year suppression of HIV viremia with indinavir, zidovudine, and lamivudine. *Ann Intern Med* 2000;133(1):35-39. [PMID: 10877738] <https://www.ncbi.nlm.nih.gov/pubmed/10877738>
- Hanna DB, Hessel NA, Golub ET, et al. Increase in single-tablet regimen use and associated improvements in adherence-related outcomes in HIV-infected women. *J Acquir Immune Defic Syndr* 2014;65(5):587-596. [PMID: 24326606] <https://www.ncbi.nlm.nih.gov/pubmed/24326606>
- Hill A, Hughes SL, Gotham D, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate: is there a true difference in efficacy and safety? *J Virus Erad* 2018;4(2):72-79. [PMID: 29682298] <https://www.ncbi.nlm.nih.gov/pubmed/29682298>
- Kakuda TN, Opsomer M, Timmers M, et al. Pharmacokinetics of darunavir in fixed-dose combination with cobicistat compared with coadministration of darunavir and ritonavir as single agents in healthy volunteers. *J Clin Pharmacol* 2014;54(8):949-957. [PMID: 24644095] <https://www.ncbi.nlm.nih.gov/pubmed/24644095>
- Karras A, Lafaurie M, Furco A, et al. Tenofovir-related nephrotoxicity in human immunodeficiency virus-infected patients: three cases of renal failure, Fanconi syndrome, and nephrogenic diabetes insipidus. *Clin Infect Dis* 2003;36(8):1070-1073. [PMID: 12684922] <https://www.ncbi.nlm.nih.gov/pubmed/12684922>
- Koteff J, Borland J, Chen S, et al. A phase 1 study to evaluate the effect of dolutegravir on renal function via measurement of iohexol and para-aminohippurate clearance in healthy subjects. *Br J Clin Pharmacol* 2013;75(4):990-996. [PMID: 22905856] <https://www.ncbi.nlm.nih.gov/pubmed/22905856>
- Kumar S, Rao PS, Earla R, et al. Drug-drug interactions between anti-retroviral therapies and drugs of abuse in HIV systems. *Expert Opin Drug Metab Toxicol* 2015;11(3):343-355. [PMID: 25539046] <https://www.ncbi.nlm.nih.gov/pubmed/25539046>
- Kuritzkes DR, Lalama CM, Ribaldo HJ, et al. Preexisting resistance to nonnucleoside reverse-transcriptase inhibitors predicts virologic failure of an efavirenz-based regimen in treatment-naïve HIV-1-infected subjects. *J Infect Dis* 2008;197(6):867-870. [PMID: 18269317] <https://www.ncbi.nlm.nih.gov/pubmed/18269317>
- Lee FJ, Amin J, Carr A. Efficacy of initial antiretroviral therapy for HIV-1 infection in adults: a systematic review and meta-analysis of 114 studies with up to 144 weeks' follow-up. *PLoS One* 2014;9(5):e97482. [PMID: 24830290] <https://www.ncbi.nlm.nih.gov/pubmed/24830290>
- Lennox JL, Landovitz RJ, Ribaldo HJ, et al. Efficacy and tolerability of 3 nonnucleoside reverse transcriptase inhibitor-sparing antiretroviral regimens for treatment-naïve volunteers infected with HIV-1: a randomized, controlled equivalence trial. *Ann Intern Med* 2014;161(7):461-471. [PMID: 25285539] <https://www.ncbi.nlm.nih.gov/pubmed/25285539>
- Lepist EI, Zhang X, Hao J, et al. Contribution of the organic anion transporter OAT2 to the renal active tubular secretion of creatinine and mechanism for serum creatinine elevations caused by cobicistat. *Kidney Int* 2014;86(2):350-357. [PMID: 24646860] <https://www.ncbi.nlm.nih.gov/pubmed/24646860>
- Llibre JM, Hill A. Abacavir and cardiovascular disease: A critical look at the data. *Antiviral Res* 2016;132:116-121. [PMID: 27260856] <https://www.ncbi.nlm.nih.gov/pubmed/27260856>
- Lundgren JD, Babiker AG, Gordin F, et al. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med* 2015;373(9):795-807. [PMID: 26192873] <https://www.ncbi.nlm.nih.gov/pubmed/26192873>
- Maggiolo F, Colombo GL, Di Matteo S, et al. Cost-effectiveness analysis of antiretroviral therapy in a cohort of HIV-infected patients starting first-line highly active antiretroviral therapy during 6 years of observation. *Patient Relat Outcome Meas* 2015;6:53-60. [PMID: 25733942] <https://www.ncbi.nlm.nih.gov/pubmed/25733942>

- Maggiolo F, Di Filippo E, Valenti D, et al. NRTI sparing therapy in virologically controlled HIV-1 infected subjects: Results of a controlled, randomized trial (Probe). *J Acquir Immune Defic Syndr* 2016;72(1):46-51. [PMID: 26910503] <https://www.ncbi.nlm.nih.gov/pubmed/26910503>
- Mallal S, Phillips E, Carosi G, et al. HLA-B\*5701 screening for hypersensitivity to abacavir. *N Engl J Med* 2008;358(6):568-579. [PMID: 18256392] <https://www.ncbi.nlm.nih.gov/pubmed/18256392>
- Marcus JL, Neugebauer RS, Leyden WA, et al. Use of abacavir and risk of cardiovascular disease among HIV-infected individuals. *J Acquir Immune Defic Syndr* 2016;71(4):413-419. [PMID: 26536316] <https://www.ncbi.nlm.nih.gov/pubmed/26536316>
- 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] <https://www.ncbi.nlm.nih.gov/pubmed/21680580>
- McClung RP, Ocfemia CB, Saduvala N, et al. Integrase and other transmitted HIV drug resistance: 23 US jurisdictions, 2013-2016. CROI; 2019 Mar 4-7; Seattle, WA. <http://www.croiconference.org/sessions/integrase-and-other-transmitted-hiv-drug-resistance-23-us-jurisdictions-2013-2016>
- McComsey GA, Kitch D, Daar ES, et al. Bone mineral density and fractures in antiretroviral-naïve persons randomized to receive abacavir-lamivudine or tenofovir disoproxil fumarate-emtricitabine along with efavirenz or atazanavir-ritonavir: Aids Clinical Trials Group A5224s, a substudy of ACTG A5202. *J Infect Dis* 2011;203(12):1791-1801. [PMID: 21606537] <https://www.ncbi.nlm.nih.gov/pubmed/21606537>
- Michienzi SM, Schriever CA, Badowski ME. Abacavir/lamivudine/dolutegravir single tablet regimen in patients with human immunodeficiency virus and end-stage renal disease on hemodialysis. *Int J STD AIDS* 2019;30(2):181-187. [PMID: 30381029] <https://www.ncbi.nlm.nih.gov/pubmed/30381029>
- Mills A, Arribas JR, Andrade-Villanueva J, et al. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in antiretroviral regimens for virologically suppressed adults with HIV-1 infection: a randomised, active-controlled, multicentre, open-label, phase 3, non-inferiority study. *Lancet Infect Dis* 2016a;16(1):43-52. [PMID: 26538525] <https://www.ncbi.nlm.nih.gov/pubmed/26538525>
- Mills A, Fusco J, Schulman K, et al. The impact of antiretroviral tablet burden and polypharmacy on viral suppression in treatment naïve patients. *Open Forum Infectious Diseases* 2016b;3(suppl\_1):1512-1512. [PMID: 10.1093/ofid/ofw172.1214] <https://www.ncbi.nlm.nih.gov/pubmed/10.1093/ofid/ofw172.1214>
- Mills AM, Cohen C, Dejesus E, et al. Efficacy and safety 48 weeks after switching from efavirenz to rilpivirine using emtricitabine/tenofovir disoproxil fumarate-based single-tablet regimens. *HIV Clin Trials* 2013;14(5):216-223. [PMID: 24144898] <https://www.ncbi.nlm.nih.gov/pubmed/24144898>
- Mocroft A, Lundgren JD, Ross M, et al. Cumulative and current exposure to potentially nephrotoxic antiretrovirals and development of chronic kidney disease in HIV-positive individuals with a normal baseline estimated glomerular filtration rate: a prospective international cohort study. *Lancet HIV* 2016;3(1):e23-32. [PMID: 26762990] <https://www.ncbi.nlm.nih.gov/pubmed/26762990>
- Molina JM, Andrade-Villanueva J, Echevarria J, et al. Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naïve HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study. *Lancet* 2008;372(9639):646-655. [PMID: 18722869] <https://www.ncbi.nlm.nih.gov/pubmed/18722869>
- Molina JM, Clotet B, van Lunzen J, et al. Once-daily dolutegravir is superior to once-daily darunavir/ritonavir in treatment-naïve HIV-1-positive individuals: 96 week results from FLAMINGO. *J Int AIDS Soc* 2014;17(4 Suppl 3):19490. [PMID: 25393999] <https://www.ncbi.nlm.nih.gov/pubmed/25393999>
- Molina JM, Podsadecki TJ, Johnson MA, et al. A lopinavir/ritonavir-based once-daily regimen results in better compliance and is non-inferior to a twice-daily regimen through 96 weeks. *AIDS Res Hum Retroviruses* 2007;23(12):1505-1514. [PMID: 18160008] <https://www.ncbi.nlm.nih.gov/pubmed/18160008>
- Molina JM, Squires K, Sax PE, et al. Doravirine versus ritonavir-boosted darunavir in antiretroviral-naïve adults with HIV-1 (DRIVE-FORWARD): 48-week results of a randomised, double-blind, phase 3, non-inferiority trial. *Lancet HIV* 2018;5(5):e211-e220. [PMID: 29592840] <https://www.ncbi.nlm.nih.gov/pubmed/29592840>

- Nachega JB, Parienti JJ, Uthman OA, et al. Lower pill burden and once-daily antiretroviral treatment regimens for HIV infection: A meta-analysis of randomized controlled trials. *Clin Infect Dis* 2014;58(9):1297-1307. [PMID: 24457345] <https://www.ncbi.nlm.nih.gov/pubmed/24457345>
- Obel N, Farkas DK, Kronborg G, et al. Abacavir and risk of myocardial infarction in HIV-infected patients on highly active antiretroviral therapy: a population-based nationwide cohort study. *HIV Med* 2010;11(2):130-136. [PMID: 19682101] <https://www.ncbi.nlm.nih.gov/pubmed/19682101>
- Orkin C, DeJesus E, Khanlou H, et al. Final 192-week efficacy and safety of once-daily darunavir/ritonavir compared with lopinavir/ritonavir in HIV-1-infected treatment-naive patients in the ARTEMIS trial. *HIV Med* 2013;14(1):49-59. [PMID: 23088336] <https://www.ncbi.nlm.nih.gov/pubmed/23088336>
- Orkin C, Squires KE, Molina JM, et al. Doravirine/lamivudine/tenofovir disoproxil fumarate is non-inferior to efavirenz/emtricitabine/tenofovir disoproxil fumarate in treatment-naive adults with human immunodeficiency virus-1 infection: Week 48 results of the DRIVE-AHEAD Trial. *Clin Infect Dis* 2018. [PMID: 30184165] <https://www.ncbi.nlm.nih.gov/pubmed/30184165>
- Panichsillapakit T, Smith DM, Wertheim JO, et al. Prevalence of transmitted HIV drug resistance among recently infected persons in San Diego, CA 1996-2013. *J Acquir Immune Defic Syndr* 2016;71(2):228-236. [PMID: 26413846] <https://www.ncbi.nlm.nih.gov/pubmed/26413846>
- Perrot S, Aslangul E, Szwebel T, et al. Bone pain due to fractures revealing osteomalacia related to tenofovir-induced proximal renal tubular dysfunction in a human immunodeficiency virus-infected patient. *J Clin Rheumatol* 2009;15(2):72-74. [PMID: 19265350] <https://www.ncbi.nlm.nih.gov/pubmed/19265350>
- Post FA, Moyle GJ, Stellbrink HJ, et al. Randomized comparison of renal effects, efficacy, and safety with once-daily abacavir/lamivudine versus tenofovir/emtricitabine, administered with efavirenz, in antiretroviral-naive, HIV-1-infected adults: 48-week results from the ASSERT study. *J Acquir Immune Defic Syndr* 2010;55(1):49-57. [PMID: 20431394] <https://www.ncbi.nlm.nih.gov/pubmed/20431394>
- Pozniak A, Arribas JR, Gathe J, et al. Switching to tenofovir alafenamide, coformulated with elvitegravir, cobicistat, and emtricitabine, in HIV-infected patients with renal impairment: 48-week results from a single-arm, multicenter, open-label phase 3 study. *J Acquir Immune Defic Syndr* 2016;71(5):530-537. [PMID: 26627107] <https://www.ncbi.nlm.nih.gov/pubmed/26627107>
- Quesada PR, Esteban LL, Garcia JR, et al. Incidence and risk factors for tenofovir-associated renal toxicity in HIV-infected patients. *Int J Clin Pharm* 2015;37(5):865-872. [PMID: 26008219] <https://www.ncbi.nlm.nih.gov/pubmed/26008219>
- Raboud J, Li M, Walmsley S, et al. Once daily dosing improves adherence to antiretroviral therapy. *AIDS Behav* 2011;15(7):1397-1409. [PMID: 20878227] <https://www.ncbi.nlm.nih.gov/pubmed/20878227>
- Raffi F, Babiker AG, Richert L, et al. Ritonavir-boosted darunavir combined with raltegravir or tenofovir-emtricitabine in antiretroviral-naive adults infected with HIV-1: 96 week results from the NEAT001/ANRS143 randomised non-inferiority trial. *Lancet* 2014;384(9958):1942-1951. [PMID: 25103176] <https://www.ncbi.nlm.nih.gov/pubmed/25103176>
- Raffi F, Jaeger H, Quiros-Roldan E, et al. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial. *Lancet Infect Dis* 2013;13(11):927-935. [PMID: 24074642] <https://www.ncbi.nlm.nih.gov/pubmed/24074642>
- Rhee SY, Blanco JL, Jordan MR, et al. Geographic and temporal trends in the molecular epidemiology and genetic mechanisms of transmitted HIV-1 drug resistance: an individual-patient- and sequence-level meta-analysis. *PLoS Med* 2015;12(4):e1001810. [PMID: 25849352] <https://www.ncbi.nlm.nih.gov/pubmed/25849352>
- Ribaud HJ, Benson CA, Zheng Y, et al. No risk of myocardial infarction associated with initial antiretroviral treatment containing abacavir: short and long-term results from ACTG A5001/ALLRT. *Clin Infect Dis* 2011;52(7):929-940. [PMID: 21427402] <https://www.ncbi.nlm.nih.gov/pubmed/21427402>
- Ryom L, Mocroft A, Kirk O, et al. Association between antiretroviral exposure and renal impairment among HIV-positive persons with normal baseline renal function: the D:A:D study. *J Infect Dis* 2013;207(9):1359-1369. [PMID: 23382571] <https://www.ncbi.nlm.nih.gov/pubmed/23382571>

- Saag M, Balu R, Phillips E, et al. High sensitivity of human leukocyte antigen-b\*5701 as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients. *Clin Infect Dis* 2008;46(7):1111-1118. [PMID: 18444831] <https://www.ncbi.nlm.nih.gov/pubmed/18444831>
- Sabin CA, Worm SW, Weber R, et al. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. *Lancet* 2008;371(9622):1417-1426. [PMID: 18387667] <https://www.ncbi.nlm.nih.gov/pubmed/18387667>
- Sax PE, Pozniak A, Montes ML, et al. Coformulated bicitgravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380-1490): a randomised, double-blind, multicentre, phase 3, non-inferiority trial. *Lancet* 2017;390(10107):2073-2082. [PMID: 28867499] <https://www.ncbi.nlm.nih.gov/pubmed/28867499>
- Sax PE, Tierney C, Collier AC, et al. Abacavir/lamivudine versus tenofovir DF/emtricitabine as part of combination regimens for initial treatment of HIV: final results. *J Infect Dis* 2011;204(8):1191-1201. [PMID: 21917892] <https://www.ncbi.nlm.nih.gov/pubmed/21917892>
- Sax PE, Tierney C, Collier AC, et al. Abacavir-lamivudine versus tenofovir-emtricitabine for initial HIV-1 therapy. *N Engl J Med* 2009;361(23):2230-2240. [PMID: 19952143] <https://www.ncbi.nlm.nih.gov/pubmed/19952143>
- Sax PE, Wohl D, Yin MT, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. *Lancet* 2015;385(9987):2606-2615. [PMID: 25890673] <https://www.ncbi.nlm.nih.gov/pubmed/25890673>
- SMART/INSIGHT. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients. *Aids* 2008;22(14):F17-24. [PMID: 18753925] <https://www.ncbi.nlm.nih.gov/pubmed/18753925>
- Smith KY, Garcia F, Kumar P, et al. Assessing darunavir/ritonavir-based therapy in a racially diverse population: 48-week outcomes from GRACE. *J Natl Med Assoc* 2012;104(7-8):366-376. [PMID: 23092052] <https://www.ncbi.nlm.nih.gov/pubmed/23092052>
- Smith KY, Patel P, Fine D, et al. Randomized, double-blind, placebo-matched, multicenter trial of abacavir/lamivudine or tenofovir/emtricitabine with lopinavir/ritonavir for initial HIV treatment. *Aids* 2009;23(12):1547-1556. [PMID: 19542866] <https://www.ncbi.nlm.nih.gov/pubmed/19542866>
- Souza SJ, Luzia LA, Santos SS, et al. Lipid profile of HIV-infected patients in relation to antiretroviral therapy: a review. *Rev Assoc Med Bras (1992)* 2013;59(2):186-198. [PMID: 23582562] <https://www.ncbi.nlm.nih.gov/pubmed/23582562>
- Stekler JD, McKernan J, Milne R, et al. Lack of resistance to integrase inhibitors among antiretroviral-naive subjects with primary HIV-1 infection, 2007-2013. *Antivir Ther* 2015;20(1):77-80. [PMID: 24831260] <https://www.ncbi.nlm.nih.gov/pubmed/24831260>
- Stellbrink HJ, Orkin C, Arribas JR, et al. Comparison of changes in bone density and turnover with abacavir-lamivudine versus tenofovir-emtricitabine in HIV-infected adults: 48-week results from the ASSERT study. *Clin Infect Dis* 2010;51(8):963-972. [PMID: 20828304] <https://www.ncbi.nlm.nih.gov/pubmed/20828304>
- Sweet D, Song J, Zhong Y, et al. Real-world medication persistence with single versus multiple tablet regimens for HIV-1 treatment. *J Int AIDS Soc* 2014;17(4 Suppl 3):19537. [PMID: 25394046] <https://www.ncbi.nlm.nih.gov/pubmed/25394046>
- Taiwo B, Zheng L, Gallien S, et al. Efficacy of a nucleoside-sparing regimen of darunavir/ritonavir plus raltegravir in treatment-naive HIV-1-infected patients (ACTG A5262). *Aids* 2011;25(17):2113-2122. [PMID: 21857490] <https://www.ncbi.nlm.nih.gov/pubmed/21857490>
- Tashima K, Crofoot G, Tomaka FL, et al. Cobicistat-boosted darunavir in HIV-1-infected adults: week 48 results of a Phase IIIb, open-label single-arm trial. *AIDS Res Ther* 2014;11:39. [PMID: 25926858] <https://www.ncbi.nlm.nih.gov/pubmed/25926858>
- Trottier B, Machouf N, Thomas R, et al. Abacavir/lamivudine fixed-dose combination with ritonavir-boosted darunavir: a safe and efficacious regimen for HIV therapy. *HIV Clin Trials* 2012;13(6):335-342. [PMID: 23195671] <https://www.ncbi.nlm.nih.gov/pubmed/23195671>

- van Lunzen J, Antinori A, Cohen CJ, et al. Rilpivirine vs. efavirenz-based single-tablet regimens in treatment-naive adults: week 96 efficacy and safety from a randomized phase 3b study. *Aids* 2016;30(2):251-259. [PMID: 26684822] <https://www.ncbi.nlm.nih.gov/pubmed/26684822>
- Wainberg MA, Mesplede T. Implications for the future of the HIV epidemic if drug resistance against dolutegravir cannot occur in first-line therapy. *J Int AIDS Soc* 2015;18:20824. [PMID: 26642452] <https://www.ncbi.nlm.nih.gov/pubmed/26642452>
- Walmsley S, Baumgarten A, Berenguer J, et al. Brief report: Dolutegravir plus abacavir/lamivudine for the treatment of HIV-1 infection in antiretroviral therapy-naive patients: Week 96 and week 144 results from the SINGLE randomized clinical trial. *J Acquir Immune Defic Syndr* 2015;70(5):515-519. [PMID: 26262777] <https://www.ncbi.nlm.nih.gov/pubmed/26262777>
- Walmsley SL, Antela A, Clumeck N, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. *N Engl J Med* 2013;369(19):1807-1818. [PMID: 24195548] <https://www.ncbi.nlm.nih.gov/pubmed/24195548>
- Wang Z, Collura RV, Rosenthal M, et al. Integrase genotypic testing and drug resistance among new HIV diagnoses in New York. CROI; 2019 Mar 4-7; Seattle, WA. <http://www.croiconference.org/sessions/integrase-genotypic-testing-and-drug-resistance-among-new-hiv-diagnoses-new-york>
- Young B, Vanig T, Dejesus E, et al. A pilot study of abacavir/lamivudine and raltegravir in antiretroviral-naive HIV-1-infected patients: 48-week results of the SHIELD trial. *HIV Clin Trials* 2010;11(5):260-269. [PMID: 21126956] <https://www.ncbi.nlm.nih.gov/pubmed/21126956>
- Zack J, Chu H, Chuck S, et al. Bioequivalence of two co-formulations of emtricitabine/tenofovir alafenamide fixed-dose combinations with 200/10 mg and 200/25 mg. *J Bioequiv Availab* 2016a;8:68-73. [PMID: ]
- Zack J, Chuck S, Chu H, et al. Bioequivalence of the rilpivirine/emtricitabine/tenofovir alafenamide single-tablet regimen. *J Bioequiv Availab* 2016b;8:49-54. [PMID: ]
- Zhang H, Shao Y, Garner W, et al. The effect of hepatic or renal impairment on bicitegravir pharmacokinetics. 18th International Workshop on Clinical Pharmacology of Antiviral Therapy; 2017 Jun 14-17; Chicago, IL. [http://www.natap.org/2017/Pharm/Pharm\\_31.htm](http://www.natap.org/2017/Pharm/Pharm_31.htm)
- Zimmermann AE, Pizzoferrato T, Bedford J, et al. Tenofovir-associated acute and chronic kidney disease: a case of multiple drug interactions. *Clin Infect Dis* 2006;42(2):283-290. [PMID: 16355343] <https://www.ncbi.nlm.nih.gov/pubmed/16355343>

# Appendix: Use of Dolutegravir in Individuals of Childbearing Capacity

Lead author Geoffrey A. Weinberg, MD, with the *Medical Care Criteria Committee*, February 2020

Evidence from multiple studies indicates no difference in rates of total birth defects among infants exposed to antiretroviral (ARV) medications during the first trimester compared with infants exposed later in pregnancy. ARVs are generally considered safe and may be taken by pregnant patients with HIV without increasing the risk of infant birth defects.

**Small risk associated with DTG:** There is, however, a small increased risk of neural tube defects (NTDs) in infants exposed to dolutegravir (DTG) during the periconception period [Zash, et al. 2018; Zash, et al. 2019; Reefhuis, et al. 2020]. NTDs are birth defects, including meningomyelocele and spina bifida, thought to occur very early after conception when the embryonic neural tube is being formed. The neural tube closes by approximately 8 weeks gestational age, which is 8 weeks after the last menstrual period or approximately 6 weeks post-conception. Ingestion of folic acid or folate by a pregnant individual significantly lowers the rate of NTDs; all individuals in the United States who are pregnant or trying to conceive and engaged in prenatal care are routinely administered 400 µg of folic acid daily. The background rate of NTDs in the general population in the United States and in other countries that routinely fortify food with folate or folic acid is low: approximately 0.07% of all births (7/10,000 births) [Reefhuis, et al. 2020].

In a large observational clinical trial conducted in Botswana, a country in which food is not routinely fortified with folate or folic acid, the rate of infant NTDs with maternal DTG-based antiretroviral therapy (ART) use at conception was 0.30% (95% confidence interval [CI], 0.13-0.69). In infants exposed to non-DTG-based ART at conception, the rate was 0.10% (95% CI, 0.06-0.17). The rate in infants born to mothers who did not have HIV was 0.08% (95% CI, 0.06-0.10) [Zash, et al. 2019]. These data suggest that the risk of NTDs with use of DTG-based ART at conception is 3-fold greater than that associated with non-DTG-based ART but that the actual effect size is small—perhaps 2 infants with NTDs for every 1,000 births [Zash, et al. 2019]. This slight increase in NTD rates is lower than that found initially by the same investigators [Zash, et al. 2018], and although statistically significant, contains wide CIs and may require recalculation as more data are collected [Zash, et al. 2018; van De Ven, et al. 2019; Zash, et al. 2019; Reefhuis, et al. 2020]. The effects of DTG on folate metabolism have not been confirmed, but it is notable that very few women in the trial received folate before conception and approximately half received it throughout pregnancy [Zash, et al. 2019].

**Benefits of DTG:** In contrast to this potentially small increase in NTD risk are the known benefits of DTG as a component of ART for all adults, pregnant or not, and many children. DTG is potent, rapidly reduces viral load, has a high barrier to HIV genetic resistance, and is generally well tolerated. Moreover, folate deficiency is uncommon in countries such as the United States, and the apparent added risk of infant NTDs associated with DTG use is small. Thus, both the [U.S. Department of Health and Human Services](#) and the [World Health Organization](#) consider DTG a preferred ARV drug for individuals with HIV in all trimesters of pregnancy and an alternative for those with HIV who are trying to conceive.

**Informed decision-making:** When caring for an individual with HIV who is very early in the first trimester of pregnancy (<8 weeks post-last menstrual period) or trying to conceive, clinicians should provide the above information and engage the patient in joint decision-making regarding choice of ARVs [Redfield, et al. 2019]. If an alternative ART regimen that does not include DTG is the best choice, preferred alternatives to DTG during pregnancy include raltegravir, ritonavir-boosted atazanavir, or ritonavir-boosted darunavir (see the NYSDOH AI guideline [Selecting an Initial ART Regimen > Specific Factors to Consider and Discuss With Patients](#)). No data currently exist to support the use of bictegravir or cobicistat-boosted elvitegravir during pregnancy or the period surrounding conception.

## References

DHHS. Recommendations for the use of antiretroviral drugs in pregnant women with HIV infection and interventions to reduce perinatal HIV transmission in the United States.

2020 <https://aidsinfo.nih.gov/guidelines/html/3/perinatal/224/whats-new-in-the-guidelines> [accessed 22 Jan 2020]

Redfield RR, Modi S, Moore CA, et al. Health care autonomy of women living with HIV. *N Engl J Med* 2019;381(9):798-800. [PMID: 31339674]

- 
- Reefhuis J, FitzHarris LF, Gray KM, et al. Neural tube defects in pregnancies among women with diagnosed HIV infection – 15 jurisdictions, 2013-2017. *MMWR Morb Mortal Wkly Rep* 2020;69(1):1-5. [PMID: 31917782]
- van De Ven NS, Pozniak AL, Levi JA, et al. Analysis of pharmacovigilance databases for dolutegravir safety in pregnancy. *Clin Infect Dis* 2019. [PMID: 31595301]
- Zash R, Holmes L, Diseko M, et al. Neural-tube defects and antiretroviral treatment regimens in Botswana. *N Engl J Med* 2019;381(9):827-840. [PMID: 31329379]
- Zash R, Makhema J, Shapiro RL. Neural-tube defects with dolutegravir treatment from the time of conception. *N Engl J Med* 2018;379(10):979-981. [PMID: 30037297]