Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

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Guidelines Development Process

Table 1. Outline of the Guidelines Development Process

Topic	Comment
Goal of the guidelines	Provide guidance to HIV care practitioners on the optimal use of antiretroviral agents (ARVs) for the treatment of HIV infection in adults and adolescents in the United States.
Panel members	The Panel is composed of approximately 45 voting members who have expertise in HIV care and research, and includes at least one representative from each of the following U.S. Department of Health and Human Services (HHS) agencies: Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), Health Resource and Services Administration (HRSA), and National Institutes of Health (NIH). Approximately two-thirds of the Panel members are non-governmental scientific members. The Panel also includes four to five community members with knowledge in HIV treatment and care. The U.S. government representatives are appointed by their respective agencies; other Panel members are selected after an open announcement to call for nominations. Each member serves on the Panel for a 4 year term with an option for reappointment for an additional term. See the Panel Roster for a list of current Panel members.
Financial disclosure	All members of the Panel submit a written financial disclosure annually, reporting any association with manufacturers of ARV drugs or diagnostics used for management of HIV infections. A list of the latest disclosures is available on the AIDS*info* website (http://aidsinfo.nih.gov/contentfiles/AA_FinancialDisclosures.pdf).
Users of the guidelines	HIV treatment providers
Developer	Panel on Antiretroviral Guidelines for Adults and Adolescents—a working group of the Office of AIDS Research Advisory Council (OARAC)
Funding source	Office of AIDS Research, NIH
Evidence collection	The recommendations in the guidelines are based on studies published in peer reviewed journals. On some occasions, particularly when new information may affect patient safety, unpublished data presented at major conferences or prepared by the FDA and/or manufacturers as warnings to the public may be used as evidence to revise the guidelines.
Recommendation grading	As described in Table 2
Method of synthesizing data	Each section of the guidelines is assigned to a working group of Panel members with expertise in the section's area of interest. The working groups synthesize available data and propose recommendations to the Panel. The Panel discusses all proposals during monthly teleconferences. Recommendations endorsed by the Panel are included in the guidelines.
Other guidelines	These guidelines focus on ART use for HIV-infected adults and adolescents. For more detailed discussion on the use of antiretroviral therapy (ART) for children and pre-pubertal adolescents (SMR Stages I – III), clinicians should refer to the Pediatric Antiretroviral Guidelines. These guidelines also include a brief discussion on the management of women of reproductive age and pregnant women.
Update plan	The Panel meets monthly by teleconference to review data that may warrant modification of the guidelines. Updates may be prompted by new drug approvals (or new indications, dosing formulations, or frequency of dosing), new safety or efficacy data, or other information that may have an impact on the clinical care of patients. In the event of new data of clinical importance, the Panel may post an interim announcement with recommendations on the AIDS*info* website until the guidelines can be updated with the appropriate changes. Updated guidelines are available on the AIDS*info* website (http://www.aidsinfo.nih.gov).
Public comments	A 2-week public comment period follows release of the updated guidelines on the AIDS*info* website. The Panel reviews comments received to determine whether additional revisions to the guidelines are indicated. The public may also submit comments to the Panel at any time at contactus@aidsinfo.nih.gov.

Table 2. Rating Scheme for Recommendations

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement **B:** Moderate recommendation for the statement **C:** Optional recommendation for the statement	**I:** One or more randomized trials with clinical outcomes and/or validated laboratory endpoints **II:** One or more well-designed, non-randomized trials or observational cohort studies with long-term clinical outcomes **III:** Expert opinion

Table 3. Laboratory Testing Schedule for Monitoring HIV-Infected Patients Before and After Initiation of Antiretroviral Therapy[a] (page 1 of 2)

Laboratory Test	Timepoint/Frequency of Testing								
	Entry into Care	ART Initiation[b] or Modification	2 to 8 Weeks After ART Initiation or Modification	Every 3 to 6 Months	Every 6 Months	Every 12 Months	Treatment Failure	Clinically Indicated	If ART Initiation is Delayed[c]
HIV Serology	√ If HIV diagnosis has not been confirmed								
CD4 Count	√	√		√ During first 2 years of ART or if viremia develops while patient on ART or CD4 count <300 cells/mm^3		√ After 2 years on ART with Consistently Suppressed Viral Load: *CD4 Count 300–500 cells/mm^3:* • Every 12 months *CD4 Count >500 cells/mm^3:* • CD4 monitoring is optional	√	√	√ Every 3-6 months
HIV Viral Load	√	√	√[d]	√[e]	√[e]		√	√	Repeat testing is optional
Resistance Testing	√	√[f]					√	√	√[f]
HLA-B*5701 Testing		√ If considering ABC							
Tropism Testing		√ If considering a CCR5 antagonist					√ If considering a CCR5 antagonist or for failure of CCR5 antagonist-based regimen	√	

Table 3. Laboratory Testing Schedule for Monitoring HIV-Infected Patients Before and After Initiation of Antiretroviral Therapy[a] (page 2 of 2)

Laboratory Test	Timepoint/Frequency of Testing								
	Entry into Care	ART Initiation[b] or Modification	2 to 8 Weeks After ART Initiation or Modification	Every 3 to 6 Months	Every 6 Months	Every 12 Months	Treatment Failure	Clinically Indicated	If ART Initiation is Delayed[c]
Hepatitis B Serology[g,h]	√	√ May repeat if patient is nonimmune and not chronically infected with HBV[h]				√ May repeat if patient is nonimmune and not chronically infected with HBV[h]		√	
Hepatitis C Antibody Test (if positive, confirm with HCV RNA test)	√	√ May repeat for at-risk patients if negative result at baseline				√ May repeat for at-risk patients if negative result at baseline		√	
Basic Chemistry[i,j]	√	√	√	√				√	√ Every 6-12 months
ALT, AST, T. bilirubin	√	√	√	√				√	√ Every 6-12 months
CBC with Differential	√	√	√ If on ZDV	√ If on ZDV or if CD4 testing is done	√			√	√ Every 3-6 months
Fasting Lipid Profile[k]	√	√			√ If abnormal at last measurement	√ If normal at last measurement		√	√ If normal at baseline, annually
Fasting Glucose or Hemoglobin A1C	√	√		√ If abnormal at last measurement		√ If normal at last measurement		√	√ If normal at baseline, annually
Urinalysis[j,l]	√	√			√ If on TAF or TDF[l]	√		√	
Pregnancy Test		√ In women with child-bearing potential						√	

[a] This table pertains to laboratory tests done to select an ARV regimen and monitor for treatment responses or ART toxicities. Please refer to the HIV Primary Care guidelines for guidance on other laboratory tests generally recommended for primary health care maintenance of HIV patients.[1]

[b] If ART initiation occurs soon after HIV diagnosis and entry into care, repeat baseline laboratory testing is not necessary.

[c] ART is indicated for all HIV-infected individuals and should be started as soon as possible. However, if ART initiation is delayed, patients should be retained in care, with periodic monitoring as noted above.

[d] If HIV RNA is detectable at 2 to 8 weeks, repeat every 4 to 8 weeks until viral load is suppressed to <200 copies/mL, and thereafter, every 3 to 6 months.

[e] In patients on ART, viral load typically is measured every 3 to 4 months. However, for adherent patients with consistently suppressed viral load and stable immunologic status for more than 2 years, monitoring can be extended to 6-month intervals.

[f] Based on current rates of transmitted drug resistance to different ARV medications, standard genotypic drug-resistance testing in ARV-naive persons should focus on testing for mutations in the reverse transcriptase (RT) and protease (PR) genes. If transmitted integrase strand transfer inhibitor (INSTI) resistance is a concern, providers should also test for resistance mutations to this class of drugs. In ART-naive patients who do not immediately begin ART, repeat testing before initiation of ART is optional if resistance testing was performed at entry into care. In virologically suppressed patients who are switching therapy because of toxicity or for convenience, viral amplification will not be possible; therefore, resistance testing should not be performed. Results from prior resistance testing can be helpful in constructing a new regimen.

[g] If HBsAg is positive, TDF or TAF plus either FTC or 3TC should be used as part of the ARV regimen to treat both HBV and HIV infections. Preliminary data from clinical trials have demonstrated TAF activity against HBV. Final results from ongoing clinical trials will help to define the role of TAF in the treatment of HBV/HIV coinfection.

[h] If HBsAg, HBsAb, and anti-HBc are negative, hepatitis B vaccine series should be administered. Refer to HIV Primary Care and Opportunistic Infections guidelines for more detailed recommendations.[1,2]

[i] Serum Na, K, HCO_3, Cl, BUN, creatinine, glucose (preferably fasting), and creatinine-based estimated glomerular filtration rate. Serum phosphorus should be monitored in patients with chronic kidney disease who are on TAF- or TDF-containing regimens.[3]

[j] Consult the Guidelines for the Management of Chronic Kidney Disease in HIV-Infected Patients: Recommendations of the HIV Medicine Association of the Infectious Diseases Society of America for recommendations on managing patients with renal disease.[3] More frequent monitoring may be indicated for patients with evidence of kidney disease (e.g., proteinuria, decreased glomerular dysfunction) or increased risk of renal insufficiency (e.g., patients with diabetes, hypertension).

[k] Consult the National Lipid Association's recommendations for management of patients with dyslipidemia.[4]

[l] Urine glucose and protein should be assessed before initiating TAF- or TDF- containing regimens, and monitored during treatment with these regimens.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ALT = alanine aminotransferase; ART = antiretroviral therapy; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; Cl = chloride; CrCl = creatinine clearance; EFV = efavirenz; FTC = emtricitabine; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCO_3 = bicarbonate; K = potassium; NA = sodium; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

Table 4. Recommendations on the Indications and Frequency of Viral Load and CD4 Count Monitoring[a]

Clinical Scenario	Viral Load Monitoring	CD4 Count Monitoring
Before initiating ART	At entry into care **(AIII)** If ART initiation is deferred, repeat before initiating ART **(AIII)**. In patients not initiating ART, repeat testing is optional **(CIII)**.	At entry into care **(AI)** If ART is deferred, every 3 to 6 months **(AIII)**.[b]
After initiating ART	Preferably within 2 to 4 weeks (and no later than 8 weeks) after initiation of ART **(AIII)**; thereafter, every 4 to 8 weeks until viral load suppressed **(BIII)**.	3 months after initiation of ART **(AIII)**
After modifying ART because of drug toxicities or for regimen simplification in a patient with viral suppression	4 to 8 weeks after modification of ART to confirm effectiveness of new regimen **(AIII)**.	Monitor according to prior CD4 count and duration on ART, as outlined below.
After modifying ART because of virologic failure	Preferably within 2 to 4 weeks (and no later than 8 weeks) after modification **(AIII)**; thereafter, every 4 to 8 weeks until viral load suppressed **(BIII)**. If viral suppression is not possible, repeat viral load every 3 months or more frequently if indicated **(AIII)**.	Every 3 to 6 months **(AI)**
During the first 2 years of ART	Every 3 to 4 months **(AIII)**	Every 3 to 6 months[a] **(BII)**
After 2 years of ART (VL consistently suppressed, CD4 consistently 300-500 cells/mm^3)	Can extend to every 6 months for patients with consistent viral suppression for ≥2 years **(AIII)**.	Every 12 months **(BII)**
After 2 years of ART (VL consistently suppressed, CD4 consistently >500 cells/mm^3)		Optional **(CIII)**
While on ART with detectable viremia (VL repeatedly >200 copies/mL)	Every 3 months **(AIII)** or more frequently if clinically indicated. (See Virologic Failure and Suboptimal Immunologic Response section)	Every 3 to 6 months **(AIII)**
Change in clinical status (e.g., new HIV clinical symptom or initiation of interferon, chronic systemic corticosteroids, or antineoplastic therapy)	Every 3 months **(AIII)**	Perform CD4 count and repeat as clinically indicated[c] **(AIII)**

[a] Monitoring of lymphocyte subsets other than CD4 (e.g., CD8, CD19) has not proven clinically useful, adds to costs, and is not routinely recommended **(BIII)**.

[b] Some experts may repeat CD4 count every 3 months in patients with low baseline CD4 count (<200–300 cells/mm^3) before ART but every 6 months in those who initiated ART at higher CD4 cell count (e.g., >300 cells/mm^3).

[c] The following are examples of clinically indicated scenarios: changes in a patient's clinical status that may decrease CD4 count and thus prompt initiation of prophylaxis for opportunistic infections (OI), such as new HIV-associated symptoms, or initiation of treatment with medications which are known to reduce CD4 cell count.

Table 5. Recommendations for Using Drug-Resistance Assays (page 1 of 2)

Clinical Setting/Recommendation	Rationale
Drug-resistance assay recommended	
In acute (early) HIV infection: Drug-resistance testing is recommended **(AII)**. A genotypic assay is generally preferred **(AIII)**. Treatment should not be delayed while awaiting results of resistance testing **(AIII)**. If ART is deferred, repeat resistance testing may be considered when therapy is initiated **(CIII)**. A genotypic assay is generally preferred **(AIII)**.	Drug-resistance testing can determine whether drug-resistant virus was transmitted. The initial regimen can be modified once resistance test results are available. Genotypic testing is preferred to phenotypic testing because of lower cost, faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant virus. Repeat testing when ART is initiated may be considered because the patient may have acquired a drug-resistant virus (i.e., superinfection).
In ART-naive patients with chronic HIV infection: Drug-resistance testing is recommended at entry into HIV care to guide selection of initial ART **(AII)**. A genotypic assay is generally preferred **(AIII)**. If an INSTI is considered for an ART-naive patient **and** transmitted INSTI resistance is a concern, providers should supplement standard resistance testing with a specific INSTI genotypic resistance assay **(BIII)**. If therapy is deferred, repeat resistance testing may be considered before initiation of ART (CIII). A genotypic assay is generally preferred **(AIII)**. If use of a CCR5 antagonist is being considered, a co-receptor tropism assay should be performed **(AI)** (see Co-receptor Tropism Assays).	Transmitted HIV with baseline resistance to at least 1 drug is seen in 10% to 17% of patients, and suboptimal virologic responses may be seen in patients with baseline resistant mutations. Some drug-resistance mutations can remain detectable for years in untreated, chronically infected patients. Genotypic assays provide information on resistance to NRTIs, NNRTIs, PIs, and INSTIs. In some circumstances, INSTI-resistance tests need to be ordered separately (clinicians should check with the testing laboratory). Currently, transmitted INSTI resistance is infrequent, but the risk of a patient acquiring INSTI-resistant strains may be greater in certain known exposure settings. Repeat testing before initiation of ART may be considered because the patient may have acquired a drug-resistant virus (i.e., a superinfection). Genotypic testing is preferred to phenotypic testing because of lower cost, faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant virus.
In patients with virologic failure: Drug-resistance testing is recommended in patients on combination ART with HIV RNA levels >1,000 copies/mL **(AI)**. In patients with HIV RNA levels >500 copies/mL but <1,000 copies/mL, testing may not be successful but should still be considered **(BII)**. A standard genotypic resistance assay is generally preferred for patients experiencing virologic failure on their first or second regimens **(AII)**. When virologic failure occurs while a patient is on an INSTI-based regimen, genotypic testing for INSTI resistance should be performed to determine whether to include drugs from this class in subsequent regimens **(AII)**. If use of a CCR5 antagonist is being considered, a co-receptor tropism assay should be performed **(AI)** (see Co-receptor Tropism Assays). Adding phenotypic testing to genotypic testing is generally preferred in patients with known or suspected complex drug-resistance patterns, particularly to PIs **(BIII)**.	Drug-resistance testing can help determine the role of resistance in drug failure and maximize the clinician's ability to select active drugs for the new regimen. Drug-resistance testing should be performed while the patient is taking prescribed ARV drugs or, if not possible, within 4 weeks after discontinuing therapy. Genotypic testing is preferred to phenotypic testing because of lower cost, faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant HIV. Genotypic assays provide information on resistance to NRTI-, NNRTI-, PI-, and INSTI-associated mutations. In some circumstances, INSTI resistance tests need to be ordered separately (clinicians should check with the testing laboratory). Phenotypic testing can provide additional useful information in patients with complex drug resistance mutation patterns, particularly to PIs.

Table 5. Recommendations for Using Drug-Resistance Assays (page 2 of 2)

Clinical Setting/Recommendation	Rationale
In patients with suboptimal suppression of viral load: Drug-resistance testing is recommended in patients with suboptimal viral load suppression after initiation of ART **(AII)**.	Testing can determine the role of resistance and thus help the clinician identify the number of active drugs available for a new regimen.
In HIV-infected pregnant women: Genotypic resistance testing is recommended for all pregnant women before initiation of ART **(AIII)** and for those entering pregnancy with detectable HIV RNA levels while on therapy **(AI)**.	The goal of ART in HIV-infected pregnant women is to achieve maximal viral suppression for treatment of maternal HIV infection and for prevention of perinatal transmission of HIV. Genotypic resistance testing will assist the clinician in selecting the optimal regimen for the patient. However, treatment should not be delayed while awaiting results of resistance testing. The initial regimen can be modified once resistance test results are available.
Drug-resistance assay not usually recommended	
After therapy is discontinued: Drug-resistance testing is not usually recommended more than 4 weeks after ARV drugs are discontinued **(BIII)**.	Drug-resistance mutations may become minor species in the absence of selective drug pressure, and available assays may not detect minor drug-resistant species. If testing is performed in this setting, the detection of drug resistance may be of value; however, the absence of resistance does not rule out the presence of minor drug-resistant species.
In patients with low HIV RNA levels: Drug-resistance testing is not usually recommended in patients with a plasma viral load <500 copies/mL **(AIII)**.	Resistance assays cannot be consistently performed given low HIV RNA levels.

Key to Acronyms: ART = antiretroviral therapy; ARV = antiretroviral; INSTI = integrase strand transfer inhibitors; NNRTI = non-nucleoside reverse-transcriptase inhibitors; NRTI = nucleoside reverse-transcriptase inhibitors; PI = protease inhibitor

Table 6. Recommended, Alternative, and Other Antiretroviral Regimen Options for Treatment-Naive Patients

Selection of a regimen should be individualized based on virologic efficacy, potential adverse effects, pill burden, dosing frequency, drug-drug interaction potential, comorbid conditions, cost, and resistance test results. Some regimens listed in this table may not be appropriate for patients with renal impairment. See Appendix B, Table 7, and the product prescribing information for recommendations on ARV dose modification in the setting of renal impairment. Drug classes and regimens within each class are arranged first by evidence rating and when ratings are equal, in alphabetical order.

Recommended Regimen Options Recommended regimens are those with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use.
INSTI plus 2-NRTI Regimen: • DTG/ABC/3TC[a] **(AI)—if HLA-B*5701 negative** • DTG plus either TDF/FTC[a] **(AI)** or TAF/FTC[b] **(AII)** • EVG/c/TAF/FTC **(AI)** or EVG/c/TDF/FTC **(AI)** • RAL plus either TDF/FTC[a] **(AI)** or TAF/FTC[b] **(AII)** Boosted PI plus 2 NRTIs: • DRV/r plus either TDF/FTC[a] **(AI)** or TAF/FTC[b] **(AII)**
Alternative Regimen Options Alternative regimens are effective and tolerable, but have potential disadvantages when compared with the Recommended regimens, have limitations for use in certain patient populations, or have less supporting data from randomized clinical trials. **However, an Alternative regimen may be the preferred regimen for some patients.**
NNRTI plus 2 NRTIs: • EFV/TDF/FTC[a] **(BI)** • EFV plus TAF/FTC[b] **(BII)** • RPV/TDF/FTC[a] **(BI)** or RPV/TAF/FTC[b] **(BII)—if HIV RNA <100,000 copies/mL and CD4 >200 cells/mm^3** Boosted PI plus 2 NRTIs: • (ATV/c or ATV/r) plus either TDF/FTC[a] **(BI)** or TAF/FTC[b] **(BII)** • DRV/c **(BIII)** or DRV/r **(BII)** plus ABC/3TC[a]—if HLA-B*5701 negative • DRV/c plus either TDF/FTC[a] **(BII)** or TAF/FTC[b] **(BII)**

Table 6. Recommended, Alternative, and Other Antiretroviral Regimen Options for Treatment-Naive Patients (page 2 of 2)

Other Regimen Options
When compared with Recommended and Alternative regimens, Other regimens may have reduced virologic activity, limited supporting data from large comparative clinical trials, or other factors such as greater toxicities, higher pill burden, drug interaction potential, or limitations for use in certain patient populations.
If HIV RNA <100,000 copies/mL and HLA-B*5701 Negative: • ATV/c **(CIII)** or ATV/r **(CI)** plus ABC/3TC • EFV plus ABC/3TC[a] **(CI)** • RAL plus ABC/3TC[a] **(CII)** Other Regimens to Consider when TAF, TDF, or ABC Cannot be Used: • DRV/r plus RAL (BID) **(CI)—if HIV RNA <100,000 copies/mL and CD4 >200 cells/mm^3** • LPV/r plus 3TC[a] (BID) **(CI)**

[a] 3TC may be substituted for FTC, or vice versa, if a non-fixed dose NRTI combination is desired.

[b] The evidence supporting this regimen is based on relative bioavailability data coupled with data from randomized, controlled switch trials demonstrating the safety and efficacy of TAF-containing regimens.

Note: The following are available as coformulated products: ABC/3TC, ATV/c, DRV/c, DTG/ABC/3TC, EFV/TDF/FTC, EVG/c/TAF/FTC, EVG/c/TDF/FTC, LPV/r, RPV/TAF/FTC, RPV/TDF/FTC, TAF/FTC, and TDF/FTC.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; CD4 = CD4 T lymphocyte; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; RAL = raltegravir; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Table 7. Antiretroviral Regimen Considerations as Initial Therapy based on Specific Clinical Scenarios (page 1 of 4)

This table is designed to guide clinicians in choosing an initial ARV regimen according to various patient and regimen characteristics and specific clinical scenarios. When more than one scenario applies to a patient, clinicians should review considerations for each relevant scenario and use their clinical judgment to select the most appropriate regimen. This table is intended to guide the initial choice of regimen. However, if a patient is doing well on a particular regimen, it is not necessary to switch to another regimen based on the scenarios outlined in this table. Please see Table 8 for additional information regarding the advantages and disadvantages of particular ARV medications.

Patient or Regimen Characteristics	Clinical Scenario	Consideration(s)	Rationale/Comments
Pre-ART Characteristics	CD4 count <200 cells/ mm^3	**Do Not Use the Following Regimens:** • RPV-based regimens • DRV/r plus RAL	Higher rate of virologic failure observed in those with low pretreatment CD4 cell count.
	HIV RNA >100,000 copies/mL	**Do Not Use the Following Regimens:** • RPV-based regimens • ABC/3TC with EFV or ATV/r • DRV/r plus RAL	Higher rates of virologic failure observed in those with high pretreatment HIV RNA.
	HLA-B*5701 positive	**Do not use ABC-containing regimen.**	Abacavir hypersensitivity, a potentially fatal reaction, is highly associated with positivity for the HLA-B*5701 allele.
	Must treat before HIV drug resistance results available	**Avoid NNRTI-based regimens.** Recommended ART Regimens: • DRV/r plus TAF/FTC or TDF/FTC • DTG plus TAF/FTC or TDF/FTC	Transmitted mutations conferring NNRTI resistance are more likely than mutations associated with PI or INSTI resistance. Resistance to DRV/r and DTG emerges slowly; transmitted resistance to DRV is rare and transmitted resistance to DTG has not been reported to date.

Table 7. Antiretroviral Regimen Considerations as Initial Therapy based on Specific Clinical Scenarios (page 2 of 4)

Patient or Regimen Characteristics	Clinical Scenario	Consideration(s)	Rationale/Comments
ART-Specific Characteristics	One pill once daily regimen is desired	ART Options Include: • DTG/ABC/3TC • EFV/TDF/FTC • EVG/c/TAF/FTC • EVG/c/TDF/FTC • RPV/TAF/FTC • RPV/TDF/FTC	Do not use RPV-based regimens if HIV RNA >100,000 copies/mL and CD4 count <200/mm^3 Do not use a regimen including ABC if HLA-B*5701 positive See Appendix B, Table 7 for recommendations on ARV dose modification in the setting of renal impairment.
	Food effects	Regimens that Can be Taken Without Regard to Food: • RAL- or DTG-based regimens	Oral bioavailability of these regimens is not significantly affected by food.
		Regimens that Should be Taken with Food: • ATV/r or ATV/c-based regimens • DRV/r or DRV/c-based regimens • EVG/c/TAF/FTC • EVG/c/TDF/FTC • RPV-based regimens	Food improves absorption of these listed regimens. RPV-containing regimens should be taken with at least 390 calories of food.
		Regimens that Should be Taken on an Empty Stomach: • EFV-based regimens	Food increases EFV absorption and may increase CNS side effects.
Presence of Other Conditions	Chronic kidney disease (defined as eGFR <60 mL/min)	**Avoid TDF.** Use ABC or TAF. ABC may be used if HLA-B*5701 negative. If HIV RNA >100,000 copies/mL, do not use ABC/3TC plus (EFV or ATV/r). TAF may be used if eGFR >30 mL/min Other Options When ABC or TAF Cannot be Used (See Text for Discussion): • LPV/r plus 3TC; *or* • RAL plus DRV/r (if CD4 count >200 cells/mm^3, HIV RNA <100,000 copies/mL)	TDF has been associated with proximal renal tubulopathy. Higher rates of renal dysfunction reported in patients using TDF in conjunction with RTV-containing regimens. TAF has less impact on renal function and lower rates of proteinuria than TDF. ABC has not been associated with renal dysfunction. See Appendix B, Table 7 for recommendations on ARV dose modification in patients with renal insufficiency.
	Liver disease with cirrhosis	Some ARVs are contraindicated or may require dosage modification in patients with Child-Pugh class B or C disease.	Refer to Appendix B, Table 7 for specific dosing recommendations. Patients with cirrhosis should be carefully evaluated by an expert in advanced liver disease.
	Osteoporosis	**Avoid TDF.** Use ABC or TAF. ABC may be used if HLA-B*5701 negative. If HIV RNA >100,000 copies/mL, do not use ABC/3TC plus (EFV or ATV/r).	TDF is associated with decreases in bone mineral density along with renal tubulopathy, urine phosphate wasting and resultant osteomalacia. TAF and ABC are associated with smaller declines in bone mineral density than TDF.

Table 7. Antiretroviral Regimen Considerations as Initial Therapy based on Specific Clinical Scenarios (page 3 of 4)

Patient or Regimen Characteristics	Clinical Scenario	Consideration(s)	Rationale/Comments
Presence of Other Conditions, continued	Psychiatric illnesses	**Consider avoiding EFV- and RPV-based regimens.**	EFV and RPV can exacerbate psychiatric symptoms and may be associated with suicidality.
	HIV-associated dementia (HAD)	**Avoid EFV-based regimens if possible.** Favor DRV-based or DTG-based regimens.	EFV-related neuropsychiatric effects may confound assessment of ART's beneficial effects on improvement of HAD-related symptoms. Theoretical CNS penetration advantage
	Narcotic replacement therapy required	**If patient is receiving methadone, consider avoiding EFV-based regimens.** If EFV is used, an increase in methadone dose may be necessary.	EFV reduces methadone concentrations and may lead to withdrawal symptoms.
	High cardiac risk	**Consider avoiding ABC- and LPV/r -based regimens.**	Increased cardiovascular risk in some studies
	Hyperlipidemia	The Following ARV Drugs have been Associated with Dyslipidemia: • PI/r or PI/c • EFV • EVG/c	DTG and RAL have fewer lipid effects. TDF has been associated with more favorable lipid effects than ABC or TAF.
	Pregnancy	Refer to the Perinatal Guidelines.	
Presence of Coinfections	HBV infection	Use TDF or TAF, with FTC or 3TC, whenever possible. If TDF and TAF are Contraindicated: • For treatment of HBV, use FTC or 3TC with entecavir and a suppressive ART regimen (see HBV/HIV Coinfection).	TDF, TAF, FTC, and 3TC are active against both HIV and HBV. 3TC- or FTC-associated HBV mutations can emerge rapidly when these drugs are used without another drug active against HBV.
	HCV treatment required	Refer to recommendations in HCV/HIV Coinfection.	
	Treating TB disease with rifamycins	TAF is not recommended with any rifamycin-containing regimen. If Rifampin is Used: • EFV can be used without dosage adjustment • If RAL is used, increase RAL dose to 800 mg BID. • Use DTG at 50 mg BID dose only in patients without selected INSTI mutations (refer to product label). If using a PI-based regimen, rifabutin should be used in place of rifampin in the TB regimen.	• Rifamycins may significantly reduce TAF exposure. • Rifampin is a strong inducer of CYP3A4 and UGT1A1 enzymes, causing significant decrease in concentrations of PI, INSTI, and RPV. • Rifampin has a less significant effect on EFV concentration than on other NNRTIs, PIs, and INSTIs. • Rifabutin is a less potent inducer and is a good option for patients receiving non-EFV-based regimens. Refer to Tables 19a, b, d and e for dosing recommendations for rifamycins used with different ARV agents.

Table 7. Antiretroviral Regimen Considerations as Initial Therapy based on Specific Clinical Scenarios (page 4 of 4)

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ATV/r = atazanavir/ritonavir; ARV = antiretroviral; c = cobicistat; CKD = chronic kidney disease; CrCl = creatinine clearance; DRV/r = darunavir/ritonavir; DTG = dolutegravir; eGFR = estimated glomerular filtration rate; EFV = efavirenz; EVG = elvitegravir; FDA = Food and Drug Administration; FTC = emtricitabine; HBV = hepatitis B virus; HCV = hepatitis C virus; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PI/r = ritonavir-boosted protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 1 of 3)

Note: All drugs within an ARV class are listed in alphabetical order.

ARV Class	ARV Agent(s)	Advantage(s)	Disadvantage(s)
Dual-NRTI	ABC/3TC	• Coformulated with DTG	• May cause life-threatening hypersensitivity reaction in patients positive for the HLA-B*5701 allele. As a result, HLA-B*5701 testing is required before use. • In the ACTG 5202 study, patients with baseline HIV RNA ≥100,000 copies/mL showed inferior virologic responses when ABC/3TC was given with EFV or ATV/r as opposed to TDF/FTC. This difference was not seen when ABC/3TC was used in combination with DTG. • ABC use has been associated with cardiovascular disease and cardiac events in some, but not all, observational studies.
	TAF/FTC	• Coformulated with EVG/c or RPV • Active against HBV • Smaller decline in renal function, less proteinuria, and smaller reductions in BMD than after initiation of TDF/FTC • Safe in patients with eGFR ≥30 mL/min	• Fasting lipid levels, including LDL and HDL cholesterol and triglycerides, increased more in the TAF group than in the TDF group. Total cholesterol to HDL ratio was unchanged.
	TDF/FTC	• Coformulated with EFV, EVG/c, and RPV as STRs • Active against HBV; recommended dual-NRTI for HIV/HBV coinfected patients • Better virologic responses than with ABC/3TC in patients with baseline viral load ≥100,000 copies/mL when combined with ATV/r or EFV • Associated with more favorable lipid effects than ABC or TAF	• Renal toxicity, including proximal tubulopathy and acute or chronic renal insufficiency • Osteomalacia has been reported as a consequence of proximal tubulopathy. • Decreases BMD more than other NRTI combinations
INSTI	DTG	• Once-daily dosing • Higher barrier to resistance than EVG or RAL • Coformulated with ABC and 3TC • No food requirement • No CYP3A4 interactions	• Oral absorption of DTG can be reduced by simultaneous administration with products containing polyvalent cations (eg, Al, Ca, or Mg-containing antacids or supplements, or multivitamin tablets with minerals). See dosing recommendations in Table 19d. • Inhibits renal tubular secretion of Cr and can increase serum Cr without affecting glomerular function • UGT substrate; potential for drug interactions (see Table 19d) • Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions)
	EVG/c	• Coformulated with TDF/FTC or TAF/FTC • Once-daily dosing • Compared with ATV/r, causes smaller increases in total and LDL cholesterol	• EVG/c/TDF/FTC is only recommended for patients with baseline CrCl ≥70 mL/min; this regimen should be discontinued if CrCl decreases to <50 mL/min. • COBI is a potent CYP3A4 inhibitor, which can result in significant interactions with CYP3A substrates. • Oral absorption of EVG can be reduced by simultaneous administration with products containing polyvalent cations (eg, Al, Ca, or Mg-containing antacids or supplements, or multivitamin tablets with minerals). See dosing recommendations in Table 19d. • COBI inhibits active tubular secretion of Cr and can increase serum Cr, without affecting renal glomerular function. • May have lower genetic barrier to resistance than boosted PI- or DTG-based regimens • Food requirement • Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions)

Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 2 of 3)

ARV Class	ARV Agent(s)	Advantage(s)	Disadvantage(s)
INSTI, cont'd	**RAL**	• Compared to other INSTIs, has longest post-marketing experience • No food requirement • No CYP3A4 interactions	• Twice-daily dosing • May have lower genetic barrier to resistance than boosted PI- or DTG-based regimens • Increases in creatine kinase, myopathy, and rhabdomyolysis have been reported. • Rare cases of severe hypersensitivity reactions (including SJS and TEN) have been reported. • Oral absorption of RAL can be reduced by simultaneous administration with products containing polyvalent cations (eg, Al, Ca, or Mg-containing antacids or supplements, or multivitamin tablets with minerals). See dosing recommendations in Table 19d. • UGT substrate; potential for drug interactions (see Table 19d) • Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions)
NNRTIs	**EFV**	• Once-daily dosing • Coformulated with TDF/FTC • Long-term clinical experience • EFV-based regimens (except for EFV plus ABC/3TC) have well documented efficacy in patients with high HIV RNA.	• Transmitted resistance more common than with PIs and INSTIs • Short-and long-term neuropsychiatric (CNS) side effects, including depression and, in some studies, suicidality • Teratogenic in nonhuman primates; avoid use in women who are trying to conceive or who are sexually active and not using contraception • Dyslipidemia • Greater risk of resistance at the time of treatment failure than with PIs • Skin rash • Potential for CYP450 drug interactions (see Tables 18, 19b, and 20a) • Should be taken on an empty stomach (food increases drug absorption and CNS toxicities)

	RPV	• Once-daily dosing
		• Coformulated with TDF/FTC and TAF/FTC
		• RPV/TDF/FTC and RPV/TAF/FTC have smaller pill size than other coformulated ARV drugs
		• Compared with EFV:
		  • Fewer discontinuations for CNS adverse effects
		  • Fewer lipid effects
		  • Fewer rashes
			• Not recommended in patients with pre-ART HIV RNA >100,000 copies/mL or CD4 count <200 cells/mm^3 because of higher rate of virologic failure in these patients
			• Transmitted resistance more common than with PIs and INSTIs
			• More NNRTI-, TDF-, and 3TC-associated mutations at virologic failure than with regimen containing EFV and two NRTIs
			• Potential for CYP450 drug interactions (see Tables 18, 19b, and 20a)
			• Meal requirement (>390 kcal)
			• Requires acid for adequate absorption
			  • Contraindicated with PPIs
			  • Use with H2 antagonists or antacids with caution (see Table 19a for detailed dosing information).
			• Use caution when coadministering with a drug known to increase the risk of Torsades de Pointes.
			• Depression and suicidality

PIs	**ATV/c or ATV/r**	• Once-daily dosing • Higher genetic barrier to resistance than NNRTIs, EVG, and RAL • PI resistance at the time of treatment failure uncommon with PK-enhanced PIs • ATV/c and ATV/r have similar virologic activity and toxicity profiles	• Commonly causes indirect hyperbilirubinemia, which may manifest as scleral icterus or jaundice • Food requirement • Absorption depends on food and low gastric pH (see Table 19a for interactions with H2 antagonists, antacids, and PPIs) • Nephrolithiasis, cholelithiasis, nephrotoxicity • GI adverse effects • CYP3A4 inhibitors and substrates: potential for drug interactions (see Tables 18 and 19a)

Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 3 of 3)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
PIs, cont'd	**ATV/c** (Specific considerations)	• Coformulated tablet	• COBI inhibits active tubular secretion of Cr and can increase serum Cr, without affecting renal glomerular function. • Coadministration with TDF is not recommended in patients with CrCl <70 mL/min • Less long-term clinical experience than for ATV/r • COBI is a potent CYP3A4 inhibitor, which can result in significant interactions with CYP3A substrates.
	DRV/c or DRV/r	• Once-daily dosing • Higher genetic barrier to resistance than NNRTIs, EVG, and RAL • PI resistance at the time of treatment failure uncommon with PK-enhanced PIs	• Skin rash • Food requirement • GI adverse effects • CYP3A4 inhibitors and substrates: potential for drug interactions (see Tables 18 and 19a)
	DRV/c-specific considerations	• Coformulated tablet	• Less long-term clinical experience than for DRV/r • COBI inhibits active tubular secretion of Cr and can increase serum Cr, without affecting renal glomerular function. • Coadministration with TDF is not recommended in patients with CrCl <70 mL/min • Approval primarily based on PK data comparable to that for DRV/r rather than on trials comparing the efficacy of DRV/c and DRV/r • COBI is a potent CYP3A4 inhibitor, which can result in significant interactions with CYP3A substrates.
	LPV/r	• Only RTV-coformulated PI • No food requirement • Once or twice daily dosing	• Requires 200 mg per day of RTV • Possible higher risk of MI associated with cumulative use of LPV/r • PR and QT interval prolongation have been reported. Use with caution in patients at risk of cardiac conduction abnormalities or in patients receiving other drugs with similar effect • Possible nephrotoxicity • CYP3A4 inhibitors and substrates: potential for drug interactions (see Tables 18 and 19a)

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; Al = aluminum; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BMD = bone mineral density; Ca = calcium; $CaCO_3$ = calcium carbonate; CD4 = CD4 T lymphocyte; CNS = central nervous system; c or COBI= cobicistat; Cr = creatinine; CrCl = creatinine clearance; CYP = cytochrome P450; DRV darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; GI = gastrointestinal; HBV = hepatitis B virus; HDL = high-density lipoprotein; HSR = hypersensitivity reaction; INSTI = integrase strand transfer inhibitor; LDL = low-density lipoprotein; LPV/r = lopinavir/ritonavir; Mg = magnesium; MI = myocardial infarction; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PPI = proton pump inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SJS = Stevens-Johnson syndrome; STRs = single-tablet regimens; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TEN = toxic epidermal necrosis

Table 9. Antiretroviral Components or Regimens Not Recommended as Initial Therapy (page 1 of 2)

ARV Drugs or Components	Reasons for Not Recommending as Initial Therapy
NRTIs	
ABC/3TC/ZDV (Co-Formulated) As triple-NRTI combination regimen	• Inferior virologic efficacy
ABC/3TC/ZDV plus TDF As quadruple-NRTI combination regimen	• Inferior virologic efficacy
d4T plus 3TC	• Significant toxicities including lipoatrophy, peripheral neuropathy, and hyperlactatemia, including symptomatic and life-threatening lactic acidosis, hepatic steatosis, and pancreatitis
ddI plus 3TC (or FTC)	• Inferior virologic efficacy • Limited clinical trial experience in ART-naive patients • ddI toxicities such as pancreatitis, peripheral neuropathy
ddI plus TDF	• High rate of early virologic failure • Rapid selection of resistance mutations • Potential for immunologic nonresponse/CD4 cell decline • Increased ddI drug exposure and toxicities
ZDV/3TC	• Greater toxicities (including bone marrow suppression, GI toxicities, skeletal muscle myopathy, cardiomyopathy, and mitochondrial toxicities such as lipoatrophy, lactic acidosis, and hepatic steatosis) than recommended NRTIs.
NNRTIs	
DLV	• Inferior virologic efficacy • Inconvenient (three times daily) dosing
ETR	• Insufficient data in ART-naive patients
NVP	• Associated with serious and potentially fatal toxicity (hepatic events, severe rash, including SJS and TEN) • When compared to EFV, NVP did not meet noninferiority criteria
PIs	
ATV (Unboosted)	• Less potent than boosted ATV
DRV (Unboosted)	• Use without RTV or COBI has not been studied
FPV (Unboosted) or **FPV/r**	• Virologic failure with unboosted FPV-based regimen may result in selection of mutations that confer resistance to FPV and DRV. • Less clinical trial data for FPV/r than for other PI/r
IDV (Unboosted)	• Inconvenient dosing (three times daily with meal restrictions) • Fluid requirement • IDV toxicities such as nephrolithiasis, crystalluria
IDV/r	• Fluid requirement • IDV toxicities such as nephrolithiasis, crystalluria
LPV/r plus 2 NRTI	• Higher pill burden than other PI-based regimens • Higher ritonavir dose than other PI-based regimens • GI intolerance

Table 9. Antiretroviral Components or Regimens Not Recommended as Initial Therapy (page 2 of 2)

ARV Drugs or Components	Reasons for Not Recommending as Initial Therapy
NFV	• Inferior virologic efficacy • Diarrhea
RTV as sole PI	• High pill burden • GI intolerance • Metabolic toxicity
SQV (**Unboosted**)	• Inadequate bioavailability • Inferior virologic efficacy
SQV/r	• High pill burden • Can cause QT and PR prolongation; requires pretreatment and follow-up ECG
TPV/r	• Inferior virologic efficacy • Higher rate of adverse events than other RTV-boosted PIs • Higher dose of RTV required for boosting than other RTV-boosted PIs
CCR5 Anagonist	
MVC	• Requires testing for CCR5 tropism before initiation of therapy • No virologic benefit when compared with other recommended regimens • Requires twice-daily dosing

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; CD4 = CD4 T lymphocyte; COBI= cobicistat; d4T = stavudine; ddI = didanosine; DLV = delavirdine; DRV = darunavir; EFV = efavirenz; ETR = etravirine; FPV = fosamprenavir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; GI = gastrointestinal; IDV = indinavir; IDV/r = indinavir/ritonavir; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PI/r = ritonavir-boosted protease inhibitor; RTV = ritonavir; SJS = Stevens Johnson Syndrome; SQV = saquinavir; SQV/r = saquinavir/ritonavir; TDF = tenofovir disoproxil fumarate; TEN = toxic epidermal necrolysis; TPV = tipranavir; TPV/r = tipranavir/ritonavir; ZDV = zidovudine

Table 10. Antiretroviral Regimens or Components That Should Not Be Offered At Any Time (page 1 of 2)

	Rationale	Exception
Antiretroviral Regimens Not Recommended		
Monotherapy with NRTI (AII)	• Rapid development of resistance • Inferior ARV activity when compared with combination of three or more ARV agents	• No exception
Dual-NRTI regimens (AI)	• Rapid development of resistance • Inferior ARV activity when compared with combination of three or more ARV agents	• No exception
Triple-NRTI regimens (AI) except for ABC/ZDV/3TC (BI) or possibly TDF + ZDV/3TC (BII)	• High rate of early virologic nonresponse seen when triple-NRTI combinations, including ABC/TDF/3TC and TDF/ddI/3TC, were used as initial regimen in ART-naive patients. • Other triple-NRTI regimens have not been evaluated.	• ABC/ZDV/3TC **(BI)** and possibly TDF + ZDV/3TC **(BII)** in patients in whom other combinations are not desirable
Antiretroviral Components Not Recommended as Part of an Antiretroviral Regimen		
ATV + IDV (AIII)	• Potential additive hyperbilirubinemia	• No exception
ddI + d4T (AII)	• High incidence of toxicities: peripheral neuropathy, pancreatitis, and hyperlactatemia • Reports of serious, even fatal, cases of lactic acidosis with hepatic steatosis with or without pancreatitis in pregnant women	• No exception
ddI + TDF (AII)	• Increased ddI concentrations and serious ddI-associated toxicities • Potential for immunologic nonresponse and/or CD4 cell count decline • High rate of early virologic failure • Rapid selection of resistance mutations at failure	• Clinicians caring for patients who are clinically stable on regimens containing TDF + ddI should consider altering the NRTIs to avoid this combination.
2-NNRTI combination (AI)	• When EFV combined with NVP, higher incidence of clinical adverse events seen when compared with either EFV- or NVP-based regimen. • Both EFV and NVP may induce metabolism and may lead to reductions in ETR exposure; thus, they should not be used in combination with ETR.	• No exception
EFV in first trimester of pregnancy or in women with significant childbearing potential (AIII)	• Teratogenic in nonhuman primates	• When no other ARV options are available and potential benefits outweigh the risks **(BIII)**
FTC + 3TC (AIII)	• Similar resistance profiles • No potential benefit	• No exception
ETR + unboosted PI (AII)	• ETR may induce metabolism of these PIs; appropriate doses not yet established	• No exception
ETR + RTV-boosted ATV or FPV (AII)	• ETR may alter the concentrations of these PIs; appropriate doses not yet established	• No exception
ETR + RTV-boosted TPV (AII)	• ETR concentration may be significantly reduced by RTV-boosted TPV	• No exception

Table 10. Antiretroviral Regimens or Components That Should Not Be Offered At Any Time (page 2 of 2)

	Rationale	Exception
NVP in ARV-naive women with CD4 count >250 cells/mm^3 or men with CD4 count >400 cells/mm^3 (BI)	• High incidence of symptomatic hepatotoxicity	• If no other ARV option available; if used, patient should be closely monitored
d4T + ZDV (AII)	• Antagonistic effect on HIV-1	• No exception
Unboosted DRV, SQV, or TPV (AII)	• Inadequate bioavailability	• No exception

Acronyms: 3TC = lamivudine, ABC = abacavir, ATV = atazanavir, d4T = stavudine, ddI = didanosine, DRV = darunavir, EFV = efavirenz, ETR = etravirine, FPV = fosamprenavir, FTC = emitricitabine, IDV = indinavir, NVP = nevirapine, RTV = ritonavir, SQV = saquinavir, TDF = tenofovir, TPV = tipranavir, ZDV = zidovudine

Table 11. Identifying, Diagnosing, and Managing Acute and Recent HIV-1 Infection

Suspicion of Acute HIV-1 Infection:

- Acute HIV-1 infection should be considered in individuals with signs or symptoms described below and recent (within 2 to 6 weeks) high risk of exposure to HIV-1.[a]
- Signs, symptoms, or laboratory findings of acute HIV-1 infection may include but are not limited to one or more of the following: fever, lymphadenopathy, skin rash, myalgia, arthralgia, headache, diarrhea, oral ulcers, leucopenia, thrombocytopenia, transaminase elevation.
- High-risk exposures include sexual contact with an HIV-1-infected person or a person at risk of HIV-1 infection, sharing of injection drug use paraphernalia, or any exposure in which an individual's mucous membranes or breaks in the skin come in contact with bodily fluid potentially infected with HIV.
- **Differential diagnosis:** The differential diagnosis of patients presenting with HIV-1 infection may include but is not limited to viral illnesses such as Epstein-Barr virus (EBV) and non-EBV (e.g., cytomegalovirus) infectious mononucleosis syndromes, influenza, viral hepatitis, streptococcal infection, or syphilis.

Evaluation/Diagnosis of Acute HIV-1 Infection:

- Acute HIV-1 infection is defined as detectable HIV-1 RNA or p24 antigen (the antigen used in currently available HIV antigen/antibody [Ag/Ab] combination assays) in the setting of a negative or indeterminate HIV-1 antibody test result.
- A reactive HIV antibody test result or Ag/Ab combination test result must be followed by supplemental confirmatory testing.
- A negative or indeterminate HIV-1 antibody test result in a person with a reactive Ag/Ab test result or in whom acute HIV-1 infection is suspected requires plasma HIV-1 RNA testing to diagnose acute HIV-1 infection.
- A positive result on a quantitative or qualitative plasma HIV-1 RNA test in the setting of a negative or indeterminate antibody test result indicates that acute HIV-1 infection is highly likely.

ART After Diagnosis of Early HIV-1 Infection:

- ART is recommended for all HIV-infected individuals **(AI)**, and should be offered to all patients with early HIV-1 infection.
- All pregnant women with early HIV-1 infection should begin ART as soon as possible for their health and to prevent perinatal transmission of HIV-1.
- Genotypic drug resistance testing should be performed before initiation of ART to guide the selection of the regimen **(AII)**.
- If ART is initiated before drug resistance test results are available, a pharmacologically boosted PI-based regimen is recommended because resistance to PIs emerges slowly and clinically significant transmitted resistance to PIs is uncommon. DRV/r plus TDF/FTC is a recommended regimen in this setting **(AIII)**. For similar reasons, DTG plus TDF/FTC is a reasonable option although the data regarding transmission of INSTI-resistant HIV and the efficacy of this regimen in early HIV infection are limited **(AIII)**.
- When results of drug resistance testing are available, the treatment regimen can be modified if warranted **(AII)**. In patients without transmitted drug-resistant virus, ART should be initiated with one of the combination regimens that is recommended for patients with chronic HIV-1 infection (see What to Start) **(AIII)**.
- Once initiated, the goal of ART should be sustained plasma virologic suppression; ART should be continued indefinitely **(AIII)**.

[a] In some settings, behaviors that increase the risk of HIV-1 infection may not be recognized or perceived as risky by the health care provider or the patient or both. Thus, even in the absence of reported high-risk behaviors, symptoms and signs consistent with acute retroviral syndrome should motivate practitioners to consider a diagnosis of acute HIV-1 infection.

Key to Acronyms: ART = antiretroviral therapy; ARV = antiretroviral; DRV/r = darunavir/ritonavir; DTG = dolutegravir; INSTI = integrase strand transfer inhibitor; PI = protease inhibitor; TDF/FTC = tenofovir disoproxil fumerate/emtricitabine

Table 12. Concomitant Use of Selected HIV Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of Hepatitis C in HIV-Infected Adults (page 1 of 3)

The recommendations in this table for concomitant use of selected HIV drugs with FDA-approved HCV direct-acting antiviral (DAA) drugs are based on available pharmacokinetics interaction data or predictions based on the known metabolic pathway of the agents. In some cases, there are not enough data to make any recommendations, and these instances are indicated in the table. In all cases where HIV and HCV drugs are used concomitantly, patients should be closely monitored for HIV and HCV virologic efficacy and potential toxicities. As the field of HCV therapy is rapidly evolving, readers should also refer to the latest drug product labels and HCV guidelines (www.hcvguidelines.org/) for updated information.

Selected HIV Drugs	HCV DAA Drugs					
	NS5A Inhibitor	NS5B Inhibitor	Coformulated NS5A/NS5B Inhibitor	Coformulated NS5A Inhibitor/ NS3A/4A Protease Inhibitor	Coformulated NS5A/NS3A/4A Protease Inhibitor plus NS5B Inhibitor	NS3A/4A Protease Inhibitor[a]
	Daclatasvir	Sofosbuvir	Ledipasvir/ Sofosbuvir	Elbasvir/ Grazoprevir	Ombitasvir/ Paritaprevir/ Ritonavir plus Dasabuvir[b]	Simeprevir
Nucleoside Reverse Transcriptase Inhibitors						
3TC	✓	✓	✓	✓	✓	✓
ABC	✓	✓	✓	✓	✓	✓
FTC	✓	✓	✓	✓	✓	✓
TDF	✓	✓	✓ Monitor for TDF toxicity.	✓	✓	✓
TAF	✓	✓	✓	✓	✓	✓
HIV Protease Inhibitors						
ATV (unboosted)	✓	✓	✓	×	✓ Reduce ATV dose to 300 mg and take in the morning at same time as ombitasvir/ paritaprevir/ritonavir plus dasabuvir. If RTV cannot be used, choose an alternative HCV regimen.	×

Table 12. Concomitant Use of Selected HIV Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of Hepatitis C in HIV-Infected Adults (page 2 of 3)

Selected HIV Drugs	HCV DAA Drugs					
	NS5A Inhibitor	NS5B Inhibitor	Coformulated NS5A/NS5B Inhibitor	Coformulated NS5A Inhibitor/ NS3A/4A Protease Inhibitor	Coformulated NS5A/NS3A/4A Protease Inhibitor plus NS5B Inhibitor	NS3A/4A Protease Inhibitor[a]
	Daclatasvir	Sofosbuvir	Ledipasvir/ Sofosbuvir	Elbasvir/ Grazoprevir	Ombitasvir/ Paritaprevir/ Ritonavir plus Dasabuvir	Simeprevir
HIV Protease Inhibitors, continued						
ATV/r or ATV/c	✓ ↓ DCV dose to 30 mg/day	✓	✓ If PI/r (or ATV/c, DRV/c) is used with TDF, ↑TDF concentrations are expected. If coadministration necessary, monitor for TDF-associated toxicities (see footnote[c]).	×	✓ Take ATV 300 mg in the morning at same time as ombitasvir/ paritaprevir/r plus dasubuvir; discontinue RTV or COBI in HIV regimen until HCV therapy completed.	×
DRV/r or DRV/c	✓	✓		×	×	×
FPV or FPV/r	✓	✓		×	×	×
LPV/r	✓	✓		×	×	×
SQV/r	✓ ↓ DCV dose to 30 mg/day			×	×	×
TPV/r	?	×	×	×	×	×
Non-Nucleoside Reverse Transcriptase Inhibitors						
EFV	✓ ↑ DCV dose to 90 mg/day	✓	✓ If used with TDF, monitor for TDF toxicity.	×	×	×
ETR	↑ DCV dose to 90 mg/day	✓		×	×	×
NVP	↑ DCV dose to 90 mg/day	✓		×	×	×
RPV	✓	✓		✓	×	✓

Table 12. Concomitant Use of Selected HIV Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of Hepatitis C in HIV-Infected Adults (page 3 of 3)

Selected HIV Drugs	HCV DAA Drugs					
	NS5A Inhibitor	NS5B Inhibitor	Coformulated NS5A/NS5B Inhibitor	Coformulated NS5A Inhibitor/ NS3A/4A Protease Inhibitor	Coformulated NS5A/NS3A/4A Protease Inhibitor plus NS5B Inhibitor	NS3A/4A Protease Inhibitor[a]
	Daclatasvir	Sofosbuvir	Ledipasvir/ Sofosbuvir	Elbasvir/ Grazoprevir	Ombitasvir/ Paritaprevir/ Ritonavir plus Dasabuvir	Simeprevir
Integrase Strand Transfer Inhibitors						
DTG	✓	✓	✓ If used with TDF, monitor for TDF toxicity.	✓	✓	✓
EVG/c/TDF/FTC	✓ ↓ DCV dose to 30 mg/day	✓	×	×	×	×
EVG/c/TAF/FTC	✓ ↓ DCV dose to 30 mg/day	✓	×	×	×	×
EVG (plus PI/r without COBI)	✓ ↓ DCV dose to 30 mg/day for all PI/r, except TPV/r — do not coadminister	Refer to Recommendations for individual ritonavir-boosted PI.				
RAL	✓	✓	✓	✓	✓	✓
CCR5 Antagonist						
MVC	✓	✓	✓	?	×	✓

[a] Since boceprevir is no longer recommended for HCV treatment and telaprevir is no longer available in the United States, these products have been removed from this table.

[b] Dasabuvir must be prescribed with ombitasvir/paritaprevir/ritonavir.

[c] Consider alternative HCV or ARV therapy to avoid increases in TDF exposure. If coadministration is necessary, monitor for TDF-associated adverse reactions.

Key to Symbols: ✓ = ARV agents that can be used concomitantly

× = ARV agents not recommended

? = data limited or not available on PK interactions with ARV drug

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ATV/r = atazanavir/ritonavir; ATV/c = atazanavir/cobicistat; c or COBI = cobicistat; DAA = direct-acting antiviral agents; DCV = daclatasvir; DRV/r = darunavir/ritonavir; DRV/c = darunavir/cobicistat; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; HCV = hepatitis C virus; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI/r = ritonavir-boosted protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQV/r = saquinavir/ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumerate; TPV/r = tipranavir/ritonavir; ZDV = zidovudine

Table 13. Strategies to Improve Adherence to Antiretroviral Therapy and Retention in Care
(page 1 of 3)

Strategies	Examples
Use a multidisciplinary team approach. Provide an accessible, trustworthy health care team.	• Nonjudgmental providers, nurses, social workers, pharmacists, and medication managers
Strengthen early linkage to care and retention in care.	• Encourage healthcare team participation in linkage to and retention in care.
Assess patient readiness to start ART.	
Evaluate patient's knowledge about HIV disease, prevention and treatment and, on the basis of the assessment, provide HIV-related information.	• Considering the patient's current knowledge base, provide information about HIV, including the natural history of the disease, HIV viral load and CD4 count and expected clinical outcomes according to these parameters, and therapeutic and prevention consequences of non-adherence.
Identify facilitators, potential barriers to adherence, and necessary medication management skills before starting ART medication.	• Assess patient's cognitive competence and impairment. • Assess behavioral and psychosocial challenges including depression, mental illnesses, levels of social support, high levels of alcohol consumption and active substance use, non-disclosure of HIV serostatus and stigma. • Identify and address language and literacy barriers. • Assess beliefs, perceptions, and expectations about taking ART (e.g., impact on health, side effects, disclosure issues, consequences of non-adherence). • Ask about medication taking skills and foreseeable challenges with adherence (e.g., past difficulty keeping appointments, adverse effects from previous medications, issues managing other chronic medications, need for medication reminders and organizers). • Assess structural issues including unstable housing, lack of income, unpredictable daily schedule, lack of prescription drug coverage, lack of continuous access to medications.
Provide needed resources.	• Provide or refer for mental health and/or substance abuse treatment. • Provide resources to obtain prescription drug coverage, stable housing, social support, and income and food security.

Table 13. Strategies to Improve Adherence to Antiretroviral Therapy and Retention in Care
(page 2 of 3)

Strategies	Examples
Involve the patient in ARV regimen selection.	• Review regimen potency, potential side effects, dosing frequency, pill burden, storage requirements, food requirements, and consequences of nonadherence. • Assess daily activities and tailor regimen to predictable and routine daily events. • Consider preferential use of PI/r-based ART if poor adherence is predicted. • Consider use of fixed-dose combination formulation. • Assess if cost/co-payment for drugs can affect access to medications and adherence.
Assess adherence at every clinic visit.	• Monitor viral load as a strong biologic measure of adherence. • Use a simple behavioral rating scale. • Employ a structured format that normalizes or assumes less-than-perfect adherence and minimizes socially desirable or "white coat adherence" responses. • Ensure that other members of the health care team also assess adherence.
Use positive reinforcement to foster adherence success.	• Inform patients of low or non-detectable levels of HIV viral load and increases in CD4 cell counts. • When needed, consider providing incentives and rewards for achieving high levels of adherence and treatment success.
Identify the type of and reasons for nonadherence.	• Failure to fill the prescription(s) • Failure to understand dosing instructions • Complexity of regimen (e.g., pill burden, size, dosing schedule, food requirements) • Pill aversion • Pill fatigue • Adverse effects • Inadequate understanding of drug resistance and its relationship to adherence • Cost-related issues • Depression, drug and alcohol use, homelessness, poverty • Stigma • Non-disclosure • Other potential barriers
Select from among available effective treatment adherence interventions.	• See http://www.cdc.gov/hiv/topics/research/prs/ma-good-evidence-interventions.htm. • Use adherence-related tools to complement education and counseling interventions (e.g., pill boxes, dose planners, reminder devices). • Use community resources to support adherence (e.g., visiting nurses, community workers, family, peer advocates). • Use patient prescription assistance programs. • Use motivational interviews.

Table 13. Strategies to Improve Adherence to Antiretroviral Therapy and Retention in Care
(page 3 of 3)

Strategies	Examples
Systematically monitor retention in care.	• Record and follow up on missed visits.
On the basis of any problems identified through systematic monitoring, consider options to enhance retention in care given resources available.	• Provide outreach for those patients who drop out of care. • Use peer or paraprofessional treatment navigators. • Employ incentives to encourage clinic attendance or recognize positive clinical outcomes resulting from good adherence. • Arrange for directly observed therapy (if feasible).

Key to Acronyms: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; PI = protease inhibitor; PI/r = ritonavir-boosted protease inhibitor

Table 14. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 1 of 5)

N/A indicates either that there are no reported cases for the particular side effect or that data for the specific ARV drug class are not available. See Appendix B for additional information listed by drug.

Adverse Effect	NRTIs	NNRTIs	PIs	INSTI	EI
Bleeding Events	N/A	N/A	Spontaneous bleeding, hematuria in hemophilia. **TPV:** Intracranial hemorrhage associated with CNS lesions, trauma, alcohol abuse, hypertension, coagulopathy, anticoagulant or antiplatelet agents, vitamin E	N/A	N/A
Bone Density Effects	**TDF:** Associated with greater loss of BMD than other NRTIs; osteomalacia may be associated with renal tubulopathy and urine phosphate wasting **TAF:** Smaller declines in BMD than with TDF.	Decreases in BMD observed after the initiation of any ART regimen.			N/A
Bone Marrow Suppression	**ZDV:** Anemia, neutropenia	N/A	N/A	N/A	N/A
Cardiovascular Disease	**ABC and ddI:** Associated with an increased risk of MI in some cohort studies. Absolute risk greatest in patients with traditional CVD risk factors.	**RPV:** QTc prolongation	Associated with MI and stroke in some cohorts. **SQV/r, ATV/r, and LPV/r:** PR prolongation (risks include pre-existing heart disease, other medications). **SQV/r:** QT prolongation. Obtain ECG before administering SQV.	N/A	N/A
Cholelithiasis	N/A	N/A	**ATV:** Cholelithiasis and kidney stones may present concurrently. Median onset is 42 months.	N/A	N/A
Diabetes Mellitus/ Insulin Resistance	ZDV, d4T, and ddI	N/A	Reported for some (IDV, LPV/r), but not all PIs	N/A	N/A

Table 14. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 2 of 5)

Adverse Effect	NRTIs	NNRTIs	PIs	INSTI	EI
Dyslipidemia	**d4T > ZDV > ABC:** ↑TG and LDL **TAF > TDF:** ↑TG, ↑LDL, ↑HDL (no change in TC:HDL ratio)	**EFV:** ↑TG, ↑LDL, ↑HDL	**All RTV- or COBI-boosted PIs:** ↑TG, ↑LDL, ↑HDL **LPV/r = FPV/r and LPV/r > DRV/r and ATV/r:** ↑TG	**EVG/c:** ↑TG, ↑LDL, ↑HDL	N/A
Gastrointestinal Effects	**ddI and ZDV > other NRTIs:** Nausea and vomiting **ddI:** Pancreatitis	N/A	GI intolerance (eg, diarrhea, nausea, vomiting) **Common with LPV/r and more frequent than with DRV/r and ATV/r:** Diarrhea	**EVG/c:** Nausea and diarrhea	N/A
Hepatic Effects	Reported with most NRTIs. **ZDV, d4T, or ddI:** Steatosis most common **ddI:** Prolonged exposure linked to noncirrhotic portal hypertension, esophageal varices. **When TAF, TDF, 3TC, and FTC are withdrawn or when HBV resistance develops:** HIV/HBV-coinfected patients may develop severe hepatic flares.	NVP > other NNRTIs **NVP:** Severe hepatotoxicity associated with skin rash or hypersensitivity. Two-week NVP dose escalation may reduce risk. Risk is greater for women with pre-NVP CD4 count >250 cells/mm^3 and men with pre-NVP CD4 count >400 cells/mm^3. NVP should **never** be used for postexposure prophylaxis, or in patients with hepatic insufficiency (Child-Pugh B or C).	**All PIs:** Drug-induced hepatitis and hepatic decompensation have been reported; greatest frequency with TPV/r. **IDV, ATV:** Jaundice due to indirect hyperbilirubinemia **TPV/r: Contraindicated** in patients with hepatic insufficiency (Child-Pugh B or C)	N/A	**MVC:** Hepatotoxicity with or without rash or HSRs reported

Table 14. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 3 of 5)

Adverse Effect	NRTIs	NNRTIs	PIs	INSTI	EI
Hypersensitivity Reaction Excluding rash alone or Stevens-Johnson syndrome	**ABC: Contraindicated** if HLA-B*5701 positive. Median onset 9 days; 90% of reactions occur within first 6 weeks of treatment. HSR symptoms (in order of descending frequency): fever, rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal pain, dyspnea, arthralgia, and respiratory symptoms. Symptoms worsen with continuation of ABC. Patients, regardless of HLA-B*5701 status, should not be rechallenged with ABC if HSR is suspected.	**NVP:** Hypersensitivity syndrome of hepatotoxicity and rash that may be accompanied by fever, general malaise, fatigue, myalgias, arthralgias, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia, renal dysfunction, granulocytopenia, or lymphadenopathy. Risk is greater for ARV-naive women with pre-NVP CD4 count >250 cells/mm^3 and men with pre-NVP CD4 count >400 cells/mm^3. Overall, risk is higher for women than men. Two-week dose escalation of NVP reduces risk.	N/A	**RAL:** HSR reported when RAL given in combination with other drugs known to cause HSR. All ARVs should be stopped if HSR occurs. **DTG:** Reported in <1% of patients in clinical development program	**MVC:** Reported as part of a syndrome related to hepatotoxicity
Lactic Acidosis	**Reported with NRTIs, especially d4T, ZDV, and ddI:** Insidious onset with GI prodrome, weight loss, and fatigue. May rapidly progress with tachycardia, tachypnea, jaundice, weakness, mental status changes, pancreatitis, and organ failure. Mortality high if serum lactate >10 mmol/L. Women and obese patients at increased risk.	N/A	N/A	N/A	N/A

Table 14. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 4 of 5)

Adverse Effect	NRTIs	NNRTIs	PIs	INSTI	EI
Lipodystrophy	**Lipoatrophy:** d4T > ZDV. May be more likely when NRTIs combined with EFV than with an RTV-boosted PI.	Lipohypertophy: Trunk fat increase observed with EFV-, PI-, and RAL-containing regimens; however, causal relationship has not been established.			N/A
Myopathy/ Elevated Creatine Phosphokinase	**ZDV:** Myopathy	N/A	N/A	**RAL:** ↑CPK, weakness and rhabdomyolysis	N/A
Nervous System/ Psychiatric Effects	**d4T > ddI and ddC:** Peripheral neuropathy: (can be irreversible). **d4T:** Associated with rapidly progressive, ascending neuromuscular weakness resembling Guillain-Barré syndrome (rare).	**EFV:** Somnolence, insomnia, abnormal dreams, dizziness, impaired concentration, depression, psychosis, and suicidal ideation. Symptoms usually subside or diminish after 2 to 4 weeks. Bedtime dosing may reduce symptoms. Risks include psychiatric illness, concomitant use of agents with neuropsychiatric effects, and increased EFV concentrations because of genetic factors or increased absorption with food. An association between EFV and suicidal ideation, suicide, and attempted suicide (especially among younger patients and those with history of mental illness or substance abuse) was found in a retrospective analysis of comparative trials. **RPV:** Depression, suicidality, sleep disturbances	N/A	**All INSTIs:** Insomnia, depression, and suicidality have been infrequently reported with INSTI use, primarily in patients with pre-existing psychiatric conditions.	N/A
Rash	**FTC:** Hyperpigmentation	All NNRTIs	ATV, DRV, FPV, LPV/r, TPV	RAL, EVG	MVC

Table 14. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 5 of 5)

Adverse Effect	NRTIs	NNRTIs	PIs	INSTI	EI
Renal Effects/ Urolithiasis	**TDF:** ↑SCr, proteinuria, hypophosphatemia, urinary phosphate wasting, glycosuria, hypokalemia, non-anion gap metabolic acidosis. Concurrent use of TDF with COBI or RTV-containing regimens appears to increase risk. **TAF:** Less impact on renal biomarkers and lower rates of proteinuria than TDF.	N/A	**ATV and LPV/r:** Increased risk of chronic kidney disease in a large cohort study. **IDV:** ↑SCr, pyuria, renal atrophy or hydronephrosis **IDV, ATV:** Stone, crystal formation; adequate hydration may reduce risk.	**COBI and DTG:** Inhibits Cr secretion without reducing renal glomerular function.	N/A
Stevens-Johnson Syndrome/Toxic Epidermal Necrosis	**ddI, ZDV:** Reported cases	NVP > DLV, EFV, ETR, RPV	**FPV, DRV, IDV, LPV/r, ATV:** Reported cases	RAL	N/A

Key to Abbreviations: 3TC = lamivudine; ABC = abacavir; ART= antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/r = atazanavir/ritonavir; BMD = bone mineral density; CD4 = CD4 T lymphocyte; CNS = central nervous system; COBI = cobicistat; CPK = creatine phosphokinase; Cr = creatinine; CrCl = creatinine clearance; CVD = cardiovascular disease; d4T = stavudine; ddC = zalcitabine; ddI = didanosine; DLV = delavirdine; DRV = darunavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; ECG = electrocardiogram; EFV = efavirenz; EI = entry inhibitor; ETR = etravirine; EVG = elvitegravir; FPV = fosamprenavir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; GI = gastrointestinal; HBV = hepatitis B virus; HDL = high-density lipoprotein; HSR = hypersensitivity reaction; IDV = indinavir; INSTI = integrase strand transfer inhibitor; LDL = low-density lipoprotein; LPV/r = lopinavir/ritonavir; MI = myocardial infarction; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SCr = serum creatinine; SQV = saquinavir; SQV/r = saquinavir/ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TG = triglyceride; TPV = tipranavir; TPV/r = tipranavir/ritonavir; ZDV = zidovudine

Table 15. Antiretroviral Therapy-Associated Adverse Events That Can Be Managed with Substitution of Alternative Antiretroviral Agent (page 1 of 2)

Adverse Event	ARV Agent(s) or Drug Class		Comments
	Switch from	Switch to	
Bone Density Effects	TDF[a]	ABC[b] or TAF NRTI-sparing regimens or regimens using only 3TC or FTC as NRTI may be considered if appropriate.	Declines in BMD have been observed upon initiation of most ART regimens. Switching from TDF to alternative ARV agents has been shown to increase bone density, but the clinical significance of this increase remains uncertain. TAF is associated with smaller declines in BMD than TDF, and with improvement in BMD upon switching from TDF. The long-term impact of TAF on patients with osteopenia or osteoporosis is unknown; close clinical monitoring is recommended in this setting.
Bone Marrow Suppression	ZDV	TDF, TAF, or ABC[b]	ZDV has been associated with neutropenia and macrocytic anemia.
Central Nervous System, Neuropsychiatric Side Effects Dizziness, suicidal ideation, abnormal dreams, depression	EFV, RPV	ETR or a PI/c or PI/r INSTIs may be considered (see Comments column).	In most patients, EFV-related CNS effects subside within 4 weeks after initiation of the drug. Persistent or intolerable effects should prompt substitution of EFV. INSTIs are associated with insomnia. Depression and suicidality have been infrequently reported with INSTI use, primarily in patients with pre-existing psychiatric conditions.
Dyslipidemia Hypertriglyceridemia (with or without elevated LDL level)	RTV- or COBI-boosted regimens; EFV; EVG/c	RAL, DTG, RPV	Elevated TG and LDL levels are more common with LPV/r and FPV/r than with other RTV-boosted PIs. Improvements in TG and LDL levels have been observed with switch from LPV/r to ATV or ATV/r.[c]
Gastrointestinal Effects Nausea, diarrhea	LPV/r	ATV/c, ATV/r, DRV/c, DRV/r, RAL, DTG, EVG/c	GI intolerance is common with boosted PIs and is linked to the total dose of RTV. More GI toxicity is seen with LPV/r than with ATV/r or DRV/r. GI effects are often transient, and do not warrant substitution unless persistent and intolerable.
	Other RTV- or COBI-boosted regimens	RAL, DTG, NNRTIs	In a trial of treatment-naive patients, rates of diarrhea and nausea were similar for EVG/c/TDF/FTC and ATV/r plus TDF/FTC.
Hypersensitivity Reaction	ABC	TDF or TAF	Never rechallenge with ABC following a suspected HSR, regardless of the patient's HLA-B*5701 status.
	NVP, EFV, ETR, RPV	Non-NNRTI ART	Risk of HSR with NVP is higher for women and those with high CD4 cell counts.
	DTG, RAL MVC	Non-INSTI ART Suitable alternative ART	Reactions to NVP, ETR, RAL, DTG and MVC may be accompanied by elevated liver transaminases.
Insulin Resistance	LPV/r, FPV/r	INSTI, RPV	Results of switch studies have been inconsistent. Studies in HIV-negative patients suggest a direct causal effect of LPV/r (and IDV) on insulin resistance. However, traditional risk factors may be stronger risk factors for insulin resistance than use of any PI.
Jaundice and Icterus	ATV, ATV/c, ATV/r	DRV/c, DRV/r, INSTI, or NNRTI	Increases in unconjugated bilirubin are common with ATV and generally do not require modification of therapy unless resultant symptoms are distressing to the patient.

Table 15. Antiretroviral Therapy-Associated Adverse Events That Can Be Managed with Substitution of Alternative Antiretroviral Agent (page 2 of 2)

Adverse Event	ARV Agent(s) or Drug Class		Comments
	Switch from	Switch to	
Lipoatrophy Subcutaneous fat wasting of limbs, face, buttocks	d4T, ZDV	TDF, TAF, or ABC[b]	Peripheral lipoatrophy is a legacy of prior thymidine analog (d4T and ZDV) use. Switching from these ARVs prevents worsening lipoatrophy, but fat recovery is typically slow (may take years) and incomplete.
Lipohypertrophy	Accumulation of visceral, truncal, dorso-cervical, and breast fat has been observed during ART, particularly during use of older PI-based regimens (eg, IDV), but whether ART directly causes fat accumulation remains unclear. There is no clinical evidence that switching to another first line regimen will reverse weight or visceral fat gain.		
Rash	NNRTIs (especially NVP and EFV)	PI- or INSTI-based regimen	Mild rashes developing after initiation of NNRTIs other than NVP rarely require treatment switch. When serious rash develops due to any NNRTI, switch to another drug class.
	DRV/c, DRV/r	ATV/c, ATV/r, or another drug class (eg, INSTI)	Mild rashes following DRV/r use may resolve with close follow-up only. For more severe reactions, change to an alternative boosted PI or an agent from another drug class.
Renal Effects Including proximal renal tubulopathy, elevated creatinine	TDF[a]	ABC[b] or TAF (for patients with CrCl >30mL/min) or NRTI-sparing regimens, or regimens using only 3TC or FTC as NRTI may be considered if appropriate.	TDF may cause tubulopathy. Switching from TDF to TAF is associated with improvement in proteinuria and renal biomarkers. The long-term impact of TAF on patients with pre-existing renal disease, including overt proximal tubulopathy, is unknown, and close clinical monitoring is recommended in this setting.
	ATV/c, ATV/r, LPV/r	DTG, RAL, or NNRTI	COBI and DTG, and to a lesser extent RPV, can increase SCr through inhibition of creatinine secretion. This effect does not affect glomerular filtration. However, assess for renal dysfunction if SCr increases by >0.4 mg/dL.
Stones Nephrolithiasis and cholelithiasis	ATV, ATV/c, ATV/r	DRV/c, DRV/r, INSTI, or NNRTI	Assuming that ATV is believed to be causing the stones.

[a] In patients with chronic active HBV infection, another agent active against HBV should be substituted for TDF.

[b] ABC should be used only in patients known to be HLA-B*5701 negative.

[c] TDF reduces ATV levels; therefore, unboosted ATV should not be co-administered with TDF. Long-term data for unboosted ATV are unavailable.

Key to Abbreviations: ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BMD = bone mineral density; CNS = central nervous system; COBI or c = cobicistat; d4T = stavudine; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; GI = gastrointestinal; HBV = hepatitis B virus; HSR = hypersensitivity reaction; IDV = indinavir; INSTI = integrase strand transfer inhibitor; LDL = low-density lipoprotein; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PI/c = protease inhibitor/cobicistat; PI/r = protease inhibitor/ritonavir; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SCr = serum creatinine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TG = triglycerides; ZDV = zidovudine

Table 16. Monthly Average Wholesale Price[b] of Commonly Used[c] Antiretroviral Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 1 of 4)

ARV Drug (Generic and Brand Names)	Strength Formulation	Dosing	Tablets, Capsules, or mLs per Month[a]	AWP[b] (Monthly)
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)				
Abacavir				
• Generic	300 mg tablet	2 tablets daily	60 tablets	$602.66
• Ziagen	300 mg tablet	2 tablets daily	60 tablets	$670.37
• Ziagen	20 mg/mL solution	30 mL daily	900 mL	$660.86
Emtricitabine				
• Emtriva	200 mg capsules	1 capsule daily	30 capsules	$643.82
• Emtriva	10 mg/mL solution	24 mL daily	680 mL (28-day supply)	$643.82
Lamivudine				
• Generic	300 mg tablet	1 tablet daily	30 tablets	$283.89
• Epivir	300 mg tablet	1 tablet daily	30 tablets	$498.89
• Epivir	10 mg/mL solution	30 mL daily	900 mL	$498.90
Tenofovir Disoproxil Fumarate				
• Viread	300 mg tablet	1 tablet daily	30 tablets	$1,197.32
Zidovudine				
• Generic	300 mg tablet	1 tablet twice daily	60 tablets	$54.00–$360.97
NRTI Combination Products				
Abacavir/Lamivudine				
• Epzicom	600/300 mg tablets	1 tablet daily	30 tablets	$1,550.05
Tenofovir Alafenamide /Emtricitabine				
• Descovy	25/200 mg tablet	1 tablet daily	30 tablets	$1,759,73
Tenofovir Disoproxil Fumarate/Emtricitabine				
• Truvada	300/200 mg tablet	1 tablet daily	30 tablets	$1,759.73

Table 16. Monthly Average Wholesale Price[b] of Commonly Used[c] Antiretroviral Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 2 of 4)

ARV Drug (Generic and Brand Names)	Strength Formulation	Dosing	Tablets, Capsules, or mLs per Month[a]	AWP[b] (Monthly)
Zidovudine/Lamivudine				
• Generic	300/150 mg tablet	1 tablet twice daily	60 tablets	$877.85
• Combivir	300/150 mg tablet	1 tablet twice daily	60 tablets	$1,081.70
Abacavir Sulfate/Zidovudine/ Lamivudine				
• Generic	300/300/150 mg tablet	1 tablet twice daily	60 tablets	$1,738.46
• Trizivir	300/300/150 mg tablet	1 tablet twice daily	60 tablets	$1,931.64
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)				
Efavirenz				
• Sustiva	600 mg tablet	1 tablet daily	30 tablets	$1,010.13
Etravirine				
• Intelence	200 mg tablet	1 tablet twice daily	60 tablets	$1,308.06
Nevirapine				
• Generic	200 mg tablet	1 tablet twice daily	60 tablets	$648.19
• Viramune	200 mg tablet	1 tablet twice daily	60 tablets	$912.86
• Viramune XR	400 mg tablet	1 tablet daily	30 tablets	$846.66
Rilpivirine				
• Edurant	25 mg tablet	1 tablet daily	30 tablets	$1,075.15
Protease Inhibitors (PIs)				
Atazanavir				
• Reyataz	200 mg capsule	2 capsules daily	60 capsules	$1,656.52
• Reyataz	300 mg capsule[d]	1 capsule daily	30 capsules	$1,640.86
Atazanavir/Cobicistat				
• Evotaz	300/150 mg tablet	1 tablet daily	30 tablets	$1,817.51
Darunavir				
• Prezista	600 mg tablet[e]	1 tablet twice daily	60 tablets	$1,629.06
• Prezista	800 mg tablet[d]	1 tablet daily	30 tablets	$1,629.06
• Prezista	100 mg/mL suspension[e]	8 mL daily 6 mL twice daily	240 mL 360 mL	$1,086.05 $1,629.07
Darunavir/Cobicistat				
• Prezcobix	800/150 mg tablet	1 tablet daily	30 tablets	$1,862.12
Lopinavir/Ritonavir				
• Kaletra	200/50 mg tablet	2 tablets twice daily or 4 tablets once daily	120 tablets	$1,106.29
• Kaletra	80/20 mg per mL solution	5 mL twice daily	300 mL	$1,037.14
Tipranavir				
• Aptivus	250 mg capsule[e]	2 capsules twice daily	120 capsules	$1,685.59

Table 16. Monthly Average Wholesale Price[b] of Commonly Used[c] Antiretroviral Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 3 of 4)

ARV Drug (Generic and Brand Names)	Strength Formulation	Dosing	Tablets, Capsules, or mLs per Month[a]	AWP[b] (Monthly)
Integrase Strand Transfer Inhibitors (INSTIs)				
Dolutegravir • Tivicay	50 mg tablet	1 tablet once daily	30 tablets	$1,707.26
• Tivicay	50 mg tablet	1 tablet twice daily	60 tablets	$3,414.52
Elvitegravir • Vitekta	85 mg tablet	1 tablet daily	30 tablets	$1,445.34
• Vitekta	150 mg tablet	1 tablet daily	30 tablets	$1,445.34
Raltegravir • Isentress	400 mg tablet	1 tablet twice daily	60 tablets	$1,545.07
Fusion Inhibitor				
Enfuviritide • Fuzeon	90 mg injection kit	1 injection twice daily	60 doses (1 kit)	$4,097.78
CCR5 Antagonist				
Maraviroc • Selzentry	150 mg tablet	1 tablet twice daily	60 tablets	$1,296.77
• Selzentry	300 mg tablet	1 tablet twice daily	60 tablets	$1,296.77
• Selzentry	300 mg tablet	2 tablets twice daily	120 tablets	$2,593.54
Co-Formulated Combination Products as Single Tablet Regimens				
Dolutegravir/Abacavir/Lamivudine • Triumeq	50/600/300 mg tablet	1 tablet daily	30 tablets	$2,889.22
Efavirenz/Tenofovir Disoproxil Fumarate/Emtricitabine • Atripla	600/300/200 mg tablet	1 tablet daily	30 tablets	$2,869.86
Elvitegravir/Cobicistat/Tenofovir Alafenamide/Emtricitabine • Genvoya	150/150/10/200 mg tablet	1 tablet daily	30 tablets	$3,093.19
Elvitegravir/Cobicistat/Tenofovir Disoproxil Fumarate/ Emtricitabine • Stribild	150/150/300/200 mg tablet	1 tablet daily	30 tablets	$3,244.76
Rilpivirine/Tenofovir Alafenamide/Emtricitabine • Odefsey	25/25/200 mg tablet	1 tablet daily	30 tablets	$2,815.04
Rilpivirine/Tenofovir Disoproxil Fumarate/Emtricitabine • Complera	25/300/200 mg tablet	1 tablet daily	30 tablets	$2,815.04
Pharmacokinetic Enhancers (Boosters)				
Cobicistat • Tybost	150 mg tablet	1 tablet daily	30 tablets	$230.90
Ritonavir: Total daily dose depends on the dose of the concomitant PI (100 mg once or twice daily, or 200 mg twice daily) • Norvir	100 mg tablet	1 tablet once daily	30 tablets	$308.60
	80 mg/mL solution	100 mg daily	37.5 mL (of a 240 mL bottle)	$270.04

Table 16. Monthly Average Wholesale Price[b] of Commonly Used[c] Antiretroviral Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 4 of 4)

ARV Drug (Generic and Brand Names)	Strength Formulation	Dosing	Tablets, Capsules, or mLs per Month[a]	AWP[b] (Monthly)

[a] Represents 30 days or as specified.

[b] AWP = average wholesale price. Note that the AWP may not represent the pharmacy acquisition price or the price paid by consumers.

Source: http://micromedexsolutions.com. Accessed April 2016.

[c] The following less commonly used ARV drugs are not included in this table: delavirdine, didanosine, fosamprenavir, indinavir, nelfinavir, saquinavir, and stavudine.

[d] Should be used in combination with ritonavir or cobicistat. Please refer to Appendix B, Table 3 for ritonavir doses.

[e] Should be used in combination with ritonavir. Please refer to Appendix B, Table 3 for ritonavir doses.

Key to Abbreviations: ARV = antiretroviral; EC = enteric coated; XR = extended release

Table 17. Mechanisms of Antiretroviral-Associated Drug Interactions (page 1 of 2)

Pharmacokinetic interactions may occur during absorption, metabolism, or elimination of the ARV and/or the interacting drugs. This table does not include a comprehensive list of all possible mechanisms of interactions for individual ARV drugs (eg, transporters); however, the table lists the most common mechanisms of known interactions and focuses on absorption and CYP- and UGT1A1-mediated interactions.

Note: Ellipses (…) indicate that there are no clinically relevant interactions by these mechanisms.

ARV Drugs by Drug Class	Mechanisms That May Affect or Be Affected by Oral Absorption of ARV Drugs			Enzymes That Metabolize or Are Induced or Inhibited by ARV Drugs				Other Mechanisms of Drug Interactions
	Increasing Gastric pH	Cationic Chelation	P-glycoprotein	CYP Substrate	CYP Inhibitor	CYP Inducer	UGT1A1	
Integrase Strand Transfer Inhibitors (INSTIs)								
Dolutegravir (DTG)	…	Concentration decreased by products containing polyvalent cations (eg, Ca, Mg, Al, Fe, Zn)	Substrate	3A4 (small contribution)	…	…	Substrate	Inhibitor of renal transporters OCT2 and MATE
Elvitegravir (EVG)	…		…	3A4	…	2C9	Substrate	…
Raltegravir (RAL)	…		…	…	…	…	Substrate	…
Pharmacokinetic (PK) Enhancers (Boosters)								
Cobicistat (COBI)	…	…	Inhibitor	3A4	3A4, 2D6	…	…	…
Ritonavir (RTV)	…	…	Substrate, inhibitor	3A4, 2D6	3A4, 2D6 (lesser extent)	1A2, 2C8, 2C9, 2C19	Inducer	…
Protease Inhibitors (PIs) **Note:** When PIs are coadministered with PK enhancers (boosters), the pharmacologic properties of both agents should be considered when assessing potential drug interactions.								
Atazanavir (ATV)	Concentration decreased	…	Substrate, inducer, inhibitor	3A4	3A4, 2C8 (weak)	…	Inhibitor	OATP inhibitor
Darunavir (DRV)	…	…	Substrate	3A4	3A4	2C9	…	OATP inhibitor

Table 17. Mechanisms of Antiretroviral-Associated Drug Interactions (page 2 of 2)

ARV Drugs by Drug Class	Mechanisms That May Affect or be Affected by Oral Absorption of ARV Drugs			Enzymes That Metabolize or are Induced or Inhibited by ARV Drugs				Other Mechanisms of Drug Interactions
	Increasing Gastric pH	Cationic Chelation	P-glycoprotein	CYP Substrate	CYP Inhibitor	CYP Inducer	UGT1A1	
Protease Inhibitors (PIs), continued **Note:** When PIs are coadministered with PK enhancers (boosters), the pharmacologic properties of both agents should be considered when assessing potential drug interactions.								
Fosamprenavir (FPV)	Concentration decreased by H2 antagonist	…	Substrate, inhibitor	3A4	3A4	3A4 (weak)	…	…
Lopinavir (LPV)	…	…	Substrate	3A4	3A4	…	…	OATP inhibitor
Saquinavir (SQV)	…	…	Substrate, inhibitor	3A4	3A4	…	…	OATP inhibitor
Tipranavir (TPV)	…	…	Substrate, inducer	3A4	2D6	3A4, 1A2, 2C19	…	OATP inhibitor
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)								
Efavirenz (EFV)	…	…	…	2B6 (primary), 2A6, 3A4	2C9, 2C19, 3A4	3A4, 2B6	…	…
Etravirine (ETR)	…	…	Inducer	3A4, 2C9, 2C19	2C9, 2C19	3A4	…	…
Nevirapine (NVP)	…	…	…	3A4, 2B6	…	3A4, 2B6	…	…
Rilpivirine (RPV)	Concentration decreased	…	…	3A4	…	…	…	…
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)								
Abacavir (ABC)	…	…	…	…	…	…	Substrate	Alcohol dehydrogenase substrate
Emtricitabine (FTC)	…	…	…	…	…	…	…	…
Lamivudine (3TC)	…	…	…	…	…	…	…	…
Tenofovir alafenamide (TAF)	…	…	Substrate	…	…	…	…	OATP substrate
Tenofovir disoproxil fumarate (TDF)	…	…	Substrate	…	…	…	…	Competition of active renal tubular secretion
Zidovudine (ZDV)	…	…	…	…	…	…	…	Glucuronidation
CCR5 Antagonist								
Maraviroc (MVC)	…	…	Substrate	3A4	…	…	…	…
Fusion Inhibitor								
Enfuvirtide (T20)	…	…	…	…	…	…	…	…

Key to Abbreviations: Al = aluminium; ARV = antiretroviral; Ca = calcium; CYP = cytochrome P; Fe = iron; MATE = multidrug and toxin extrusion transporter; Mg = magnesium; OATP = organic anion-transporting polypeptide; OCT2 = organic cation transporter 2; UGT1A1 = uridine diphosphate glucuronosyltransferase; Zn = zinc

Table 18. Drugs That Should Not Be Used With Selected Antiretroviral Agents Due to Proven or Predicted Pharmacokinetic Interactions (Last updated July 14, 2016; last reviewed July 14, 2016) (page 1 of 2)

This table only lists drugs that should not be coadministered at any dose, regardless of RTV or COBI boosting (unless stated otherwise). See Tables 19 and 20 for more detailed pharmacokinetic (PK) interaction data.

ARV Agents[a,b]	Cardiac Agents	Lipid-Lowering Agents	Anti-infective Agents	Antiepileptic Agents	Neurologic Agents	Herbs	HCV Agents[c]	Other Agents
ATV +/– RTV or COBI	Dronedarone Eplerenone Ivabradine Ranolazine	Lovastatin Simvastatin	Rifampin Rifapentine	**ATV/c only:** Carbamazepine Phenobarbital Phenytoin	Lurasidone Midazolam[e] Pimozide Triazolam	St. John's wort	Elbasvir/ Grazoprevir Simeprevir	Alfuzosin Cisapride[f] Ergot derivatives Flibanserin Irinotecan Salmeterol Sildenafil for PAH
DRV/c or DRV/r	Dronedarone Eplerenone Ivabradine Ranolazine	Lovastatin Simvastatin	Rifampin Rifapentine	**DRV/c only:** Carbamazepine Phenobarbital Phenytoin	Lurasidone Midazolam[e] Pimozide Triazolam	St. John's wort	Dasabuvir Elbasvir/ Grazoprevir Ombitasvir Paritaprevir Simeprevir	Alfuzosin Cisapride[e] Ergot derivatives Flibanserin Salmeterol Sildenafil for PAH
FPV +/– RTV	Dronedarone Eplerenone Flecainide Ivabradine Propafenone Ranolazine	Lovastatin Simvastatin	Rifampin Rifapentine	None	Lurasidone Midazolam[e] Pimozide Triazolam	St. John's wort	Dasabuvir Ombitasvir Paritaprevir Simeprevir	Alfuzosin Cisapride[e] Ergot derivatives Flibanserin Salmeterol Sildenafil for PAH
LPV/r	Dronedarone Eplerenone Ivabradine Ranolazine	Lovastatin Simvastatin	Rifampin[f] Rifapentine	None	Lurasidone Midazolam[e] Pimozide Triazolam	St. John's wort	Dasabuvir Elbasvir/ Grazoprevir Ombitasvir Paritaprevir Simeprevir	Alfuzosin Cisapride[e] Ergot derivatives Flibanserin Salmeterol Sildenafil for PAH
SQV/r	Amiodarone Disopyramide Dofetilide Dronedarone Eplerenone Flecainide Ivabradine Lidocaine Propafenone Quinidine Ranolazine	Lovastatin Simvastatin	Clarithromycin Dapsone Erythromycin Pentamidine (parenteral) Rifampin[f] Rifapentine Quinine	None	Clozapine Haloperidol Lurasidone Midazolam[e] Phenothiazines[g] Pimozide Trazodone Triazolam Ziprasidone	ments St. John's wort Garlic supple-	Dasabuvir Elbasvir/ Grazoprevir Ombitasvir Paritaprevir Simeprevir	Alfuzosin Cisapride[f] Ergot derivatives Flibanserin Tacrolimus Salmeterol Sildenafil for PAH
TPV/r	Amiodarone Dronedarone Eplerenone Flecainide Ivabradine Propafenone Quinidine Ranolazine	Lovastatin Simvastatin	Rifampin Rifapentine	None	Lurasidone Midazolam[d] Pimozide Triazolam	St. John's wort	Dasabuvir Elbasvir/ Grazoprevir Ledipasvir Ombitasvir Paritaprevir Simeprevir Sofosbuvir	Alfuzosin Cisapride[e] Ergot derivatives Flibanserin Salmeterol Sildenafil for PAH
EFV	None	None	None	None	None	St. John's wort	Dasabuvir Elbasvir/ Grazoprevir Ombitasvir Paritaprevir Simeprevir	None

Table 18. Drugs That Should Not Be Used With Selected Antiretroviral Agents Due to Proven or Predicted Pharmacokinetic Interactions (Last updated July 14, 2016; last reviewed July 14, 2016) (page 2 of 2)

This table only lists drugs that should not be coadministered at any dose, regardless of RTV or COBI boosting (unless stated otherwise). See Tables 19 and 20 for more detailed pharmacokinetic (PK) interaction data.

ARV Agents[a,b]	Cardiac Agents	Lipid-Lowering Agents	Anti-infective Agents	Antiepileptic Agents	Neurologic Agents	Herbs	HCV Agents[c]	Other Agents
ETR	None	None	Rifampin Rifapentine	Carbamazepine Phenobarbital Phenytoin	None	St John's wort	Dasabuvir Elbasvir/ Grazoprevir Ombitasvir Paritaprevir Simeprevir	Clopidogrel
NVP	None	None	Rifapentine	None	None	St. John's wort	Dasabuvir Elbasvir/ Grazoprevir Ombitasvir Paritaprevir Simeprevir	Ketoconazole
RPV	None	None	Rifampin Rifapentine	Carbamazepine Oxcarbazepine Phenobarbital Phenytoin	None	St. John's wort	Dasabuvir Ombitasvir Paritaprevir	Proton pump inhibitors
MVC	None	None	Rifapentine	None	None	St. John's wort	Dasabuvir Ombitasvir Paritaprevir	None
DTG	Dofetilide	None	Rifapentine	None	None	St. John's wort	None	None
EVG/c **For EVG + PI/r, refer to agents listed for the selected PI**	Eplerenone Ivabradine Ranolazine	Lovastatin Simvastatin	Rifampin Rifapentine	Carbamazepine Phenobarbital Phenytoin	Lurasidone Pimozide Midazolam[d] Triazolam	St. John's wort	Dasabuvir Elbasvir/ Grazoprevir Ledipasvir Ombitasvir Paritaprevir Simeprevir	Alfuzosin Cisapride[e] Ergot derivatives Flibanserin Salmeterol Sildenafil for PAH
RAL	None	None	None	None	None	None	None	None
TAF	None	None	Rifabutin Rifampin Rifapentine	None	None	St. John's wort	None	None

[a] DLV, IDV, NFV, RTV (as sole PI), T-20, and NRTIs other than TAF are not included in this table. Refer to the appropriate FDA package insert for information regarding DLV-, IDV-, NFV-, and RTV (as sole PI)-related drug interactions.

[b] Certain listed drugs are contraindicated on the basis of theoretical considerations. Thus, drugs with narrow therapeutic indices and suspected metabolic involvement with CYP 3A, 2D6, or unknown pathways are included in this table. Actual interactions may or may not occur in patients.

[c] HCV agents listed include only those that are commercially available at the publication of these guidelines.

[d] Use of oral midazolam is contraindicated. Single-dose parenteral midazolam can be used with caution and can be given in a monitored situation for procedural sedation.

[e] The manufacturer of cisapride has a limited-access protocol for patients who meet specific clinical eligibility criteria.

[f] In healthy volunteer studies, a high rate of Grade 4 serum transaminase elevation was seen when a higher dose of RTV was added to LPV/r or SQV or when double-dose LPV/r was used with rifampin to compensate for rifampin's induction effect; therefore, these dosing strategies should not be used when alternatives exist.

[g] Phenothiazines include chlorpromazine, fluphenazine, mesoridazine, perphenazine, prochlorperazine, promethazine, and thioridazine.

Suggested alternatives to:

- **Lovastatin, simvastatin:** Fluvastatin, pitavastatin, and pravastatin (except for pravastatin with DRV/r) have the least potential for drug-drug interactions (see Table 19a). Use atorvastatin and rosuvastatin with caution; start with the lowest possible dose and titrate based on tolerance and lipid-lowering efficacy.
- **Rifampin:** Rifabutin (with dosage adjustment, see Tables 19a and 19b)

• **Midazolam, triazolam:** Temazepam, lorazepam, oxazepam

• **Sildenafil for PAH:** Selexipag

Key to Acronyms: ARV = antiretroviral; ATV = atazanavir; COBI = cobicistat; CYP = cytochrome P; DLV = delavirdine; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDA = Food and Drug Administration; FPV = fosamprenavir; FTC = emtricitabine; HCV = hepatitis C virus; IDV = indinavir; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NFV = nelfinavir; NRTI = nucleos(t)ide reverse transcriptase inhibitor; NVP = nevirapine; PAH = pulmonary arterial hypertension; PI = protease inhibitor; PI/r = ritonavir-boosted protease inhibitor; PK = pharmacokinetic; RPV = rilpivirine; RTV = ritonavir; SQV = saquinavir; SQV/r = saquinavir/ritonavir; TB = tuberculosis; T-20 = enfuvirtide; TAF = tenofovir alafenamide; TPV/r = tipranavir/ritonavir

Table 19a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 1 of 15)

This table provides known or predicted information regarding PK interactions between PIs and non-ARV drugs. When information is available, interactions for specific PK-boosted (with either RTV or COBI) and unboosted PIs are listed separately. The term "All PIs" refers to both unboosted PIs and PIs boosted with either RTV or COBI. For interactions between ARV agents and for dosing recommendations, refer to Tables 19c, 20a, and 20b.

Note: NFV and IDV are **not** included in this table. Please refer to the FDA product labels for NFV and IDV for information regarding drug interactions with these PIs.

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers			
Antacids	ATV, ATV/c, ATV/r	When given simultaneously, ↓ ATV expected	Give ATV at least 2 hours before or 1 to 2 hours after antacids or buffered medications.
	FPV	APV AUC ↓ 18%; ↔ in APV C_{min}	Give FPV simultaneously with (or at least 2 hours before or 1 hour after) antacids.
	TPV/r	TPV AUC ↓ 27%	Give TPV at least 2 hours before or 1 hour after antacids.
H2 Receptor Antagonists	ATV (unboosted)	↓ ATV	H2 receptor antagonist single dose should not exceed a dose equivalent to famotidine 20 mg and the total daily dose should not exceed a dose equivalent to famotidine 20 mg BID in ART-naive patients. Give ATV at least 2 hours before and at least 10 hours after the H2 receptor antagonist.
	ATV/c, ATV/r	↓ ATV	H2 receptor antagonist dose should not exceed a dose equivalent to famotidine 40 mg BID in ART-naive patients or 20 mg BID in ART-experienced patients. Give ATV 300 mg plus COBI 150 mg or RTV 100 mg simultaneously with and/or ≥10 hours after the dose of H2 receptor antagonist. If using TDF and H2 receptor antagonist in ART-experienced patients, use ATV 400 mg plus COBI 150 mg or RTV 100 mg.
	DRV/c, DRV/r, LPV/r	No significant effect shown or expected	No dosage adjustment necessary.
	FPV (unboosted)	APV AUC ↓ 30%; no significant change in APV C_{min}	If concomitant use is necessary, give FPV at least 2 hours before H2 receptor antagonist. Consider boosting FPV with RTV.

Table 19a. Drug Interactions between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 2 of 15)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
PPIs	ATV (unboosted)	↓ ATV	**PPIs are not recommended in patients receiving unboosted ATV.** In these patients, consider alternative acid-reducing agents, RTV or COBI boosting, or alternative PIs.
	ATV/c, ATV/r	↓ ATV	PPIs should not exceed a dose equivalent to omeprazole 20 mg daily in PI-naive patients. PPIs should be administered at least 12 hours before ATV/c or ATV/r. **PPIs are not recommended in PI-experienced patients.**
	DRV/c	No significant effect expected	No dosage adjustment necessary.
	DRV/r	omeprazole AUC ↓ 42%	No dosage adjustment necessary.
	FPV, FPV/r, LPV/r	No significant effect	No dosage adjustment necessary.
	SQV/r	SQV AUC ↑ 82%	Monitor for SQV toxicities.
	TPV/r	↓ omeprazole	May need to increase omeprazole dose.
Anticoagulants and Antiplatelets			
Apixaban	All PIs	↑ apixaban expected	**Avoid concomitant use.**
Dabigatran	All RTV-boosted PIs, ATV/c, DRV/c	↑ dabigatran possible	No dosage adjustment if CrCl >50 mL/min. **Avoid coadministration if CrCl <50 mL/min.**
Edoxaban	All PIs	↑ edoxaban	Avoid concomitant use.
Rivaroxaban	All PIs	↑ rivaroxaban	**Avoid concomitant use.**
Ticagrelor	All PIs	↑ ticagrelor expected	**Avoid concomitant use.**
Vorapaxar	All PIs	↑ vorapaxar expected	**Avoid concomitant use.**
Warfarin	PI/r	↓ warfarin possible	Monitor INR closely when stopping or starting PI/r and adjust warfarin dose accordingly.
	ATV/c, DRV/c	No data	Monitor INR closely when stopping or starting PI/c and adjust warfarin dose accordingly. If switching between RTV and COBI, the effect of COBI on warfarin is not expected to be equivalent to RTV's effect on warfarin.
Anticonvulsants			
Carbamazepine	ATV, FPV (unboosted)	May ↓ PI levels substantially	**Do not coadminister.** Consider alternative anticonvulsant or ATV/r, ATV/c, or FPV/r.
	ATV/c, DRV/c	↓ cobicistat expected ↓ PI levels expected	**Contraindicated. Do not coadminister.**
	ATV/r, FPV/r, LPV/r, SQV/r, TPV/r	↑ carbamazepine possible TPV/r ↑ carbamazepine AUC 26% May ↓ PI levels substantially	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. **Do not coadminister with LPV/r or FPV/r once daily.**
	DRV/r	carbamazepine AUC ↑ 45% DRV: no significant change	Monitor anticonvulsant level and adjust dose accordingly.

Table 19a. Drug Interactions between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 3 of 15)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticonvulsants, continued			
Ethosuximide	All PIs	↑ ethosuximide possible	Clinically monitor for ethosuxamide toxicities.
Lamotrigine	ATV (unboosted)	lamotrigine: no effect	No dose adjustment necessary.
	ATV/r	lamotrigine AUC ↓ 32%	A dose increase of lamotrigine may be needed; consider monitoring lamotrigine concentration or consider alternative anticonvulsant.
	LPV/r	lamotrigine AUC ↓ 50% LPV: no significant change	
	PI/r (other than ATV/r or LPV/r)	↓ lamotrigine possible	
	ATV/c, DRV/c	No data	Monitor lamotrigine concentration or consider alternative anticonvulsant.
Phenobarbital	ATV/c DRV/c	↓ cobicistat expected ↓ PI levels expected	**Contraindicated. Do not coadminister.**
	All unboosted PI or PI/r	May ↓ PI levels substantially	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. **Do not coadminister with LPV/r or FPV/r once daily, or unboosted ATV or FPV.**
Phenytoin	ATV, FPV (unboosted)	May ↓ PI levels substantially	**Do not coadminister.** Consider alternative anticonvulsant or either ATV/r or FPV/r.
	ATV/r, DRV/r, SQV/r, TPV/r	↓ phenytoin possible ↓ PI possible	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response.
	ATV/c, DRV/c	↓ cobicistat expected ↓ PI levels expected	**Contraindicated. Do not coadminister.**
	FPV/r	phenytoin AUC ↓ 22% APV AUC ↑ 20%	Monitor phenytoin level and adjust dose accordingly. No change in FPV/r dose recommended.
	LPV/r	phenytoin AUC ↓ 31% LPV/r AUC ↓ 33%	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. **Do not coadminister with LPV/r once daily.**
Valproic Acid	LPV/r	↓ or ↔ VPA possible LPV AUC ↑ 75%	Monitor VPA levels and virologic response. Monitor for LPV-related toxicities.

Table 19a. Drug Interactions between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 4 of 15)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antidepressants, Anxiolytics, and Antipsychotics (Also see Sedative/Hypnotics section below.)			
Bupropion	LPV/r	bupropion AUC ↓ 57%	Titrate bupropion dose based on clinical response.
	TPV/r	bupropion AUC ↓ 46%	
Buspirone	All PIs	↑ buspirone expected	Use a low dose of buspirone with caution and titrate buspirone dose based on clinical response.
Fluvoxamine	All PIs	↑ or ↓ PI possible	Consider alternative therapeutic agent.
Other Selective Serotonin Reuptake Inhibitors (SSRIs) (eg, citalopram, escitalopram, fluoxetine, paroxetine, sertraline)	RTV	escitalopram ↔	Titrate SSRI dose based on clinical response.
	DRV/r	paroxetine AUC ↓ 39% sertraline AUC ↓ 49%	
	FPV/r	paroxetine AUC ↓ 55%	
	ATV/r, LPV/r, SQV/r, TPV/r	No data	
	ATV/c, DRV/c	Effects unknown	Titrate SSRI dose using the lowest available initial or maintenance dose.
Quetiapine	All PIs	↑ quetiapine expected	Starting quetiapine in a patient receiving a PI: • Start quetiapine at the lowest dose and titrate up as needed. Monitor for quetiapine effectiveness and adverse effects. Starting a PI in a patient receiving a stable dose of quetiapine: • Reduce quetiapine dose to 1/6 of the original dose. Closely monitor for quetiapine effectiveness and adverse effects.
Other Antipsychotics (eg, perphenazine, risperidone, thioridazine)	ATV/c DRV/c, All PI/r	↑ antipsychotic possible	Titrate antipsychotic dose using the lowest initial dose, or adjust maintenance dose accordingly. Monitor for toxicities.
Trazodone	All PIs except SQV/r	RTV 200 mg BID (for 2 days) ↑ trazodone AUC 240%	Use lowest dose of trazodone and monitor for CNS and cardiovascular adverse effects.
	SQV/r	↑ trazodone expected	**Contraindicated. Do not coadminister.**
Tricyclic Antidepressants Amitriptyline, Desipramine, Doxepin, Imipramine, Nortriptyline	All PI/r, ATV/c, DRV/c	↑ TCA expected	Use lowest possible TCA dose and titrate based on clinical assessment and/or drug levels.

Table 19a. Drug Interactions between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 5 of 15)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antifungals			
Fluconazole	ATV/c, ATV/r	No significant effect observed or expected	No dosage adjustment necessary.
	SQV/r	No data with RTV boosting	No dosage adjustment necessary.
	TPV/r	TPV AUC ↑ 50%	Fluconazole >200 mg daily is not recommended. If high-dose fluconazole is indicated, consider alternative ARV.
Isavuconazole	LPV/r	Isavuconazole AUC ↑ 96% LPV AUC ↓ 27%	If coadministered, consider monitoring isavuconazole concentrations and assessing virologic response.
	All PIs except LPV/r	↑ isavuconazole possible ↑ or ↓ PI possible	If coadministered, consider monitoring isavuconazole concentrations. Monitor for PI toxicity and virologic response.
Itraconazole	All PIs	↑ itraconazole possible ↑ PI possible	Consider monitoring itraconazole level to guide dosage adjustments. Doses >200 mg/day are not recommended with PI/r, ATV/c, or DRV/c unless dosing is guided by itraconazole levels.
Posaconazole	ATV/c	↑ ATV possible	Monitor for adverse effects of ATV.
	ATV/r	ATV AUC ↑ 146%	
	ATV	ATV AUC ↑ 268%	
	FPV	With FPV 700 mg BID (without RTV): posaconazole AUC ↓ 23%, APV AUC similar to that with FPV 1400 mg BID With FPV 1400 mg BID: ↑ APV expected	If coadministered, monitor posaconazole concentrations.
	DRV/c, DRV/r, FPV/r, LPV/r, SQV/r, TPV/r	↑ PI possible ↑ posaconazole possible	If coadministered, consider monitoring posaconazole concentrations. Monitor for PI adverse effects.
Voriconazole	ATV, FPV (unboosted)	↑ voriconazole possible ↑ PI possible	Monitor for toxicities.
	All PI/r	RTV 400 mg BID ↓ voriconazole AUC 82% RTV 100 mg BID ↓ voriconazole AUC 39%	**Do not coadminister voriconazole and RTV or COBI unless benefit outweighs risk.** If coadministered, consider monitoring voriconazole concentration and adjust dose accordingly
	ATV/c, DRV/c	Effects unknown	
Antimalarials			
Artemether/ Lumefantrine	DRV/r	artemether AUC ↓ 16% DHA[a] AUC ↓ 18% lumefantrine AUC ↑ 2.5-fold	Clinical significance unknown. If used, monitor closely for antimalarial efficacy and lumefantrine toxicity.
	DRV/c	↑ lumefantrine expected Effect on artemether unknown	
	LPV/r	artemether AUC ↓ 40% DHA AUC ↓ 17% lumefantrine AUC ↑ 470%	

Table 19a. Drug Interactions between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 6 of 15)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antimalarials, continued			
Artesunate/ Mefloquine	LPV/r	dihydroartemisinin AUC ↓ 49% mefloquine AUC ↓ 28% LPV ↔	Clinical significance unknown. If used, monitor closely for antimalarial efficacy.
Atovaquone/ Proguanil	ATV/r, LPV/r	ATV/r ↓ atovaquone AUC 46% and ↓ proguanil AUC 41% LPV/r ↓ atovaquone AUC 74% and ↓ proguanil AUC 38%	No dosage recommendation. Consider alternative drug for malaria prophylaxis, if possible.
Mefloquine	RTV	With RTV 200 mg BID: RTV AUC ↓ 31%, C_{min} ↓ 43%; ↔ mefloquine	Use with caution. Effect on exposure of RTV-boosted PIs is unknown.
Antimycobacterials (for treatment of *Mycobacterium tuberculosis* and non-tuberculosis mycobacterial infections)			
Bedaquiline	All PI/r, ATV/c, DRV/c	With LPV/r: bedaquiline AUC ↑ 1.9 fold With other PI/r, ATV/c, or DRV/c: ↑ bedaquiline possible	Clinical significance unknown. Use with caution if benefit outweighs the risk and monitor for QTc prolongation and liver function tests.
Clarithromycin	ATV (unboosted)	clarithromycin AUC ↑ 94%	May cause QTc prolongation. Reduce clarithromycin dose by 50%. Consider alternative therapy (eg, azithromycin).
	All PI/r, ATV/c, DRV/c	↑ clarithromycin expected	Consider alternative macrolide (eg, azithromycin)
		DRV/r ↑ clarithromycin AUC 57% FPV/r ↑ clarithromycin possible LPV/r ↑ clarithromycin expected RTV 500 mg BID ↑ clarithromycin 77% SQV unboosted ↑ clarithromycin 45% TPV/r ↑ clarithromycin 19% clarithromycin ↑ unboosted SQV 177% clarithromycin ↑ TPV 66%	Monitor for clarithromycin-related toxicities or consider alternative macrolide (eg, azithromycin). Reduce clarithromycin dose by 50% in patients with CrCl 30–60 mL/min. Reduce clarithromycin dose by 75% in patients with CrCl <30 mL/min.
	FPV	APV AUC ↑ 18%	No dosage adjustment necessary.
Rifabutin	ATV (unboosted)	↑ rifabutin AUC expected	Rifabutin 150 mg daily or 300 mg three times a week
	FPV (unboosted)	No data	Consider alternative ARV.
	ATV/c, DRV/c	↑ rifabutin expected	Rifabutin 150 mg once daily or 300 mg three times a week. Monitor for antimycobacterial activity and consider therapeutic drug monitoring. PK data reported in this table are results from healthy volunteer studies. Lower rifabutin exposure has been reported in HIV-infected patients than in the healthy study participants.
	ATV/r	Compared with rifabutin (300 mg once daily) alone, rifabutin (150 mg once daily) with ATV/r, rifabutin AUC ↑ 110% and metabolite AUC ↑ 2101%	
	DRV/r	Compared with rifabutin (300 mg once daily) alone, rifabutin (150 mg every other day) with DRV/r, rifabutin AUC ↔ and metabolite AUC ↑ 881%	

Table 19a. Drug Interactions between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 7 of 15)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antimycobacterials (for treatment of *Mycobacterium tuberculosis* and non-tuberculosis mycobacterial infections), continued			
Rifabutin, continued	FPV/r	Compared with rifabutin (300 mg once daily) alone, rifabutin (150 mg every other day) with FPV/r, rifabutin and metabolite AUC ↑ 64%.	Rifabutin 150 mg once daily or 300 mg three times a week. Monitor for antimycobacterial activity and consider therapeutic drug monitoring. PK data reported in this table are results from healthy volunteer studies. Lower rifabutin exposure has been reported in HIV-infected patients than in the healthy study participants.
	LPV/r	Compared with rifabutin (300 mg daily) alone, rifabutin (150 mg once daily) with LPV/r, rifabutin and metabolite AUC ↑ 473%.	
	SQV/r	↑ rifabutin with unboosted SQV	
	TPV/r	rifabutin and metabolite AUC ↑ 333%	
Rifampin	All PIs	↓ PI concentration by >75%	**Do not coadminister rifampin and PIs.** Additional RTV does not overcome this interaction and may increase hepatotoxicity. Additional COBI is not recommended. Consider rifabutin if a rifamycin is indicated.
Rifapentine	All PIs	↓ PI expected	**Do not coadminister.**
Antipneumocystis and Antitoxoplasmosis Drug			
Atovaquone	ATV/r	Atovaquone ↔	No dosage adjustment necessary.
Cardiac Medications			
Amiodarone	SQV/r, TPV/r	↑ both amiodarone and PI possible	**Do not coadminister.**
	All PIs (except SQV/r, TPV/r)	↑ both amiodarone and PI possible	Use with caution. Monitor for amiodarone toxicity and consider ECG and amiodarone drug level monitoring.
Antiarrhythmics (eg, dofetilide, dronedarone, flecainide, lidocaine, propafenone, quinidine)	SQV/r	↑ antiarrhythmic possible	**Do not coadminister.**
	All PIs	↑ antiarrhythmic possible	Use with caution. **Refer to Table 18 for contraindicated combinations.**
Beta-blockers (eg, metoprolol, timolol)	All PIs	↑ beta-blockers possible	May need to decrease beta-blocker dose; adjust dose based on clinical response. Consider using beta-blockers that are not metabolized by CYP450 enzymes (eg, atenolol, labetalol, nadolol, sotalol).
Bosentan	All PIs	LPV/r ↑ bosentan 48-fold (day 4) and 5-fold (day 10) ↓ ATV expected	**Do not coadminister bosentan and unboosted ATV.** In Patients on a PI (Other than Unboosted ATV) >10 Days: • Start bosentan at 62.5 mg once daily or every other day. In Patients on Bosentan who Require a PI (Other than Unboosted ATV): • Stop bosentan ≥36 hours before PI initiation and 10 days after PI initiation restart bosentan at 62.5 mg once daily or every other day. When switching between COBI and RTV: • Maintain same bosentan dose.

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Cardiac Medications, continued			
Calcium Channel Blockers (CCBs) (except diltiazem)	All PIs	↑ dihydropyridine possible ↑ verapamil possible	Use with caution. Titrate CCB dose and monitor closely. ECG monitoring is recommended when CCB used with ATV and SQV.
Digoxin	PI/r, ATV/c, or DRV/c	RTV (200 mg BID) ↑ digoxin AUC 29% and ↑ half-life 43% SQV/r ↑ digoxin AUC 49% DRV/r ↑ digoxin AUC 36% COBI ↑ digoxin C_{max} 41%, AUC ↔	Use with caution. Monitor digoxin levels. Digoxin dose may need to be decreased. Titrate initial digoxin dose.
Diltiazem	ATV/c, ATV/r, ATV	Unboosted ATV ↑ diltiazem AUC 125% Greater ↑ likely with ATV/c or ATV/r	Decrease diltiazem dose by 50%. ECG monitoring is recommended.
	DRV/c, DRV/r, FPV/r, FPV, LPV/r, SQV/r, TPV/r	↑ diltiazem possible	Use with caution. Adjust diltiazem according to clinical response and toxicities.
Eplerenone	All PIs	↑ eplerenone expected	**Contraindicated. Do not coadminister.**
Ivabradine	All PIs	↑ ivabradine expected	**Contraindicated. Do not coadminister.**
Cortocosteroids			
Beclomethasone Inhaled	DRV/r	RTV 100 mg BID ↑ 17-BMP AUC 2-fold and ↑ C_{max} 1.6-fold (DRV 600 mg + RTV 100 mg) BID ↓ 17-BMP AUC 11% and ↓ C_{max} 19%	No dosage adjustment necessary. Significant interaction between beclomethasone (inhaled or intranasal) and other PI/r, ATV/c, or DRV/c is not expected.
Budesonide Systemic	All PIs	↓ PI levels possible ↑ glucocorticoids	Coadministration can result in adrenal insufficiency and Cushing's syndrome. **Do not coadminister unless potential benefits of systemic budesonide outweigh the risks of systemic corticosteroid adverse effects.**
Budesonide, Fluticasone, Mometasone Inhaled or Intranasal	All PI/r, ATV/c, DRV/c	↑ glucocorticoids possible RTV 100 mg BID ↑ fluticasone AUC 350-fold and ↑ C_{max} 25-fold	Coadministration can result in adrenal insufficiency and Cushing's syndrome. **Do not coadminister unless potential benefits of inhaled or intranasal corticosteroid outweigh the risks of systemic corticosteroid adverse effects.** Consider alternative corticosteroid (eg, beclomethasone).
Dexamethasone Systemic	All PIs	↓ PI levels possible	Use systemic dexamethasone with caution. Consider alternative corticosteroid for long-term use.
Prednisone	LPV/r	↑ prednisolone AUC 31%	Use with caution. Coadministration can result in adrenal insufficiency and Cushing's syndrome. **Do not coadminister unless potential benefits of prednisone outweigh the risks of systemic corticosteroid adverse effects.**
	All PIs	↑ prednisolone possible	
Methyl-prednisolone, Prednisolone, Triamcinolone (local injections, including intra-articular, epidural, intra-orbital)	All PI/r, ATV/c, DRV/c	↑ glucocorticoids expected	**Do not coadminister.** Coadministration can result in adrenal insufficiency and Cushing's syndrome.

Table 19a. Drug Interactions between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 9 of 15)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hepatitis C Direct-Acting Antiviral Agents			
Daclatasvir	ATV/c or ATV/r SQV/r	↑ daclatasvir	Decrease daclatasvir dose to 30 mg once daily.
	DRV/c DRV/r LPV/r ATV (unboosted) FPV/r or FPV (unboosted)	↔ daclatasvir	No dose adjustment necessary.
	TPV/r	No data	No dosing recommendations at this time.
Dasabuvir + Paritaprevir/ Ombitasvir/RTV	ATV	ATV ↔	ATV 300 mg alone, **without COBI or additional RTV**, should be given in the morning with dasabuvir + paritaprevir/ ombitasvir/RTV.
	DRV	DRV C_{min} ↓ 43% to 48%	**Do not coadminister.**
	LPV/r	paritaprevir AUC ↑ 117%	**Do not coadminister.**
	ATV/c, DRV/c, FPV, SQV, TPV	No data	**Do not coadminister.**
Elbasvir/ grazoprevir	ATV/r	elbasvir AUC ↑ 4.8 fold grazoprevir AUC ↑ 10.6 fold ATV ↔ by elbasvir ATV AUC ↑ 43% by grazoprevir	**Contraindicated. Do not coadminister.** May increase the risk of ALT elevations due to a significant increase in grazoprevir plasma concentrations caused by OATP1B1/3 inhibition
	DRV/r	elbasvir AUC ↑ 66% grazoprevir AUC ↑ 7.5 fold DRV ↔	
	LPV/r	elbasvir AUC ↑ 3.7 fold grazoprevir AUC ↑ 12.9 fold LPV ↔	
	ATV, ATV/c, DRV/c, SQV/r, TPV/r	↑ grazoprevir expected	
	FPV/r FPV (unboosted)	No data	No dosing recommendations at this time.

Table 19a. Drug Interactions between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 10 of 15)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hepatitis C Direct-Acting Antiviral Agents, continued			
Ledipasvir/ Sofosbuvir	ATV/r	ATV AUC ↑ 33% ledipasvir AUC ↑ 113% sofosbuvir: no significant effect	No dosage adjustment necessary. Coadministration of ledipasvir/sofosbuvir with TDF and a PI/r results in increased exposure to TDF. The safety of the increased TDF exposure has not been established. Consider alternative HCV or ARV drugs to avoid increased TDF toxicities. If coadministration is necessary, monitor for TDF-associated adverse reactions.
	DRV/r	DRV: no significant effect expected ledipasvir/sofosbuvir: no significant effect	
	ATV/c, DRV/c, FPV, FPV/r, LPV/r, SQV/r	No significant effect expected	
	TPV/r	↓ ledipasvir and sofosbuvir expected	**Do not coadminister.**
Simeprevir	All PIs	Compared with simeprevir 150 mg alone, simeprevir 50 mg plus DRV/r 800/100 mg daily, simeprevir AUC ↑ 159% RTV 100 mg BID ↑ simeprevir AUC 618%	**Do not coadminister.**
Sofosbuvir	TPV/r	↓ sofosbuvir expected	**Do not coadminister.**
Herbal Products			
St. John's Wort	All PIs	↓ PI expected	**Do not coadminister.**
Hormonal Contraceptives			
Hormonal Contraceptives (oral)	ATV (unboosted)	ethinyl estradiol AUC ↑ 48% norethindrone AUC ↑ 110%	Prescribe oral contraceptive that contains no more than 30 mcg of ethinyl estradiol or recommend alternative contraceptive method. Oral contraceptives containing less than 25 mcg of ethinyl estradiol or progestins other than norethindrone or norgestimate have not been studied.[c]
	ATV/r	ethinyl estradiol AUC ↓ 19% and C_{min} ↓ 37% norgestimate ↑ 85% norethindrone AUC ↑ 51% and C_{min} ↑ 67%	Oral contraceptive should contain at least 35 mcg of ethinyl estradiol.[b] Oral contraceptives containing progestins other than norethindrone or norgestimate have not been studied.
	ATV/c, DRV/c	Effects unknown	Consider alternative or additional contraceptive method or alternative ARV drug.
	DRV/r, FPV/r, LPV/r, SQV/r, TPV/r	ethinyl estradiol AUC ↓ 37% to 48% norethindrone AUC ↓ 14% to 34% With TPV/r: norethindrone AUC ↔	Consider alternative or additional contraceptive method or alternative ARV drug.
	FPV	With APV: ↑ ethinyl estradiol ↑ norethindrone C_{min} APV C_{min} ↓ 20%	Oral contraceptive should contain no more than 30 mcg of ethinyl estradiol.[c] Oral contraceptives containing progestins other than norethindrone have not been studied.

Table 19a. Drug Interactions between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 11 of 15)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hormonal Contraceptives, continued			
Depot medroxy-progesterone acetate (MPA) injectable	LPV/r	MPA AUC ↑46%; C_{min} no significant change	Use standard dose.
Etonogestrel-releasing subdermal implant	LPV/r	etonogestrel AUC ↑ 52% and C_{min} ↑ 34%	Use standard dose.
	All other PIs	No data	Consider alternative or additional contraceptive method or alternative ARV drug.
Transdermal ethinyl estradiol/ norelgestromin	LPV/r	LPV ↔ ethinyl estradiol AUC ↓ 45%, norelgestromin AUC ↑ 83%	Use standard dose.
	All other PIs	No data	Consider alternative or additional contraceptive method or alternative ARV drug.
HMG-CoA Reductase Inhibitors			
Atorvastatin	ATV, ATV/c, ATV/r, DRV/c	↑ atorvastatin possible	Titrate atorvastatin dose carefully and use lowest dose necessary.
	DRV/r FPV, FPV/r, SQV/r	DRV/r plus atorvastatin 10 mg similar to atorvastatin 40 mg administered alone FPV +/– RTV ↑ atorvastatin AUC 130% to 153% SQV/r ↑ atorvastatin AUC 79%	Titrate atorvastatin dose carefully and use the lowest necessary dose. Do not exceed 20 mg atorvastatin daily.
	LPV/r	LPV/r ↑ atorvastatin AUC 488%	Use with caution and use the lowest atorvastatin dose necessary.
	TPV/r	↑ atorvastatin AUC 836%	**Do not coadminister.**
Lovastatin	All PIs	Significant ↑ lovastatin expected	**Contraindicated. Do not coadminister.**
Pitavastatin	All PIs	ATV ↑ pitavastatin AUC 31%, C_{max} ↑ 60% ATV: no significant effect DRV/r: no significant effect LPV/r ↓ pitavastatin AUC 20% LPV: no significant effect	No dose adjustment necessary.
Pravastatin	ATV/c, ATV/r	No data	Use lowest starting dose of pravastatin and monitor for efficacy and adverse effects.
	DRV/c, DRV/r	With DRV/r, pravastatin AUC • ↑ 81% following single dose of pravastatin • ↑ 23% at steady state	Use lowest possible starting dose of pravastatin with careful monitoring.
	LPV/r	pravastatin AUC ↑ 33%	No dose adjustment necessary.
	SQV/r	pravastatin AUC ↓ 47% to 50%	No dose adjustment necessary.

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
HMG-CoA Reductase Inhibitors, continued			
Rosuvastatin	ATV/c, DRV/c	↑ rosuvastatin possible	Titrate rosuvastatin dose carefully and use the lowest necessary dose while monitoring for toxicities.
	ATV/r, LPV/r	ATV/r ↑ rosuvastatin AUC 3-fold and C_{max} ↑7-fold LPV/r ↑ rosuvastatin AUC 108% and C_{max} ↑ 366%	Titrate rosuvastatin dose carefully and use the lowest necessary dose. Do not exceed 10 mg rosuvastatin daily.
	DRV/r	rosuvastatin AUC ↑ 48% and C_{max} ↑ 139%	Titrate rosuvastatin dose carefully and use the lowest necessary dose while monitoring for toxicities.
	FPV +/- RTV	No significant effect on rosuvastatin	No dosage adjustment necessary.
	SQV/r	No data available	Titrate rosuvastatin dose carefully and use the lowest necessary dose while monitoring for toxicities.
	TPV/r	rosuvastatin AUC ↑ 26% and C_{max} ↑ 123%	No dosage adjustment necessary.
Simvastatin	All PIs	Significant ↑ simvastatin level: SQV/r 400 mg/400 mg BID ↑ simvastatin AUC 3059%	Contraindicated. Do not coadminister.
Immunosuppressants			
Cyclosporine, Everolimus, Sirolimus, Tacrolimus	All PIs	↑ immunosuppressant expected	Initiate with an adjusted dose of immunosuppressant to account for potential increased concentrations of the immunosuppressant and monitor for toxicities. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with specialist as necessary.
Narcotics and Treatment for Opioid Dependence			
Buprenorphine sublingual/ buccal/implant	ATV (unboosted)	buprenorphine AUC ↑ 93% norbuprenorphine[d] AUC ↑ 76% ↓ ATV possible	**Do not coadminister buprenorphine with unboosted ATV.**
	ATV/r	buprenorphine AUC ↑ 66% norbuprenorphine[d] AUC ↑ 105%	Monitor for sedation and other signs or symptoms of overmedication. Buprenorphine dose reduction may be necessary. It may be necessary to remove implant and treat with a formulation that permits dose adjustments.
	ATV/c, DRV/c	Effects unknown	Titrate buprenorphine dose using the lowest initial dose. Dose adjustment of buprenorphine may be needed. It may be necessary to remove implant and treat with a formulation that permits dose adjustments. Clinical monitoring is recommended.
	DRV/r	buprenorphine: no significant effect norbuprenorphine[d] AUC ↑ 46% and C_{min} ↑ 71%	No dosage adjustment necessary. Clinical monitoring is recommended. When transferring buprenorphine from transmucosal to implantation, monitor to ensure buprenorphine effect is adequate and not excessive.
	FPV/r	buprenorphine: no significant effect norbuprenorphine[d] AUC ↓ 15%	
	LPV/r	No significant effect	
	TPV/r	buprenorphine: no significant effect norbuprenorphine[d] AUC, C_{max}, and C_{min} ↓ 80% TPV C_{min} ↓ 19% to 40%	Consider monitoring TPV level. When transferring buprenorphine from transmucosal to implantation, monitor to ensure buprenorphine effect is adequate and not excessive.

Table 19a. Drug Interactions between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 13 of 15)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Narcotics and Treatment for Opioid Dependence, continued			
Fentanyl	All PIs	↑ fentanyl possible	Clinical monitoring is recommended, including for potentially fatal respiratory depression.
Methadone	ATV (unboosted)	No significant effect	No dosage adjustment necessary.
	ATV/c, DRV/c	Effects unknown	Titrate methadone dose using the lowest feasible initial dose. Dose adjustment of methadone may be needed. Clinical monitoring is recommended.
	FPV (unboosted)	No data with unboosted FPV APV ↓ R-methadone[e] C_{min} 21%, AUC no significant change	Monitor and titrate methadone as clinically indicated. The interaction with FPV is presumed to be similar to that with APV.
	All PI/r	ATV/r, DRV/r, and FPV/r ↓ R-methadone[e] AUC 16% to 18% LPV/r ↓ methadone AUC 26% to 53% SQV/r 1000/100 mg BID ↓ R-methadone[e] AUC 19% TPV/r ↓ R-methadone[e] AUC 48%	Opioid withdrawal unlikely but may occur. Dosage adjustment of methadone is not usually required, but monitor for opioid withdrawal and increase methadone dose as clinically indicated.
Oxycodone	LPV/r	oxycodone AUC ↑ 2.6-fold	Monitor for opioid-related adverse effects. Oxycodone dose reduction may be necessary.
Tramadol	ATV/c, DRV/c	↑ tramadol possible	Tramadol dose reduction may be necessary. Monitor for tramadol toxicities and clinical response.
Phosphodiesterase Type 5 (PDE5) Inhibitors			
Avanafil	All PIs except unboosted ATV and FPV	RTV (600 mg BID for 5 days) ↑ avanafil AUC 13-fold, C_{max} 2.4-fold	**Coadministration is not recommended.**
	ATV, FPV (unboosted)	No data	Avanafil dose should not exceed 50 mg once every 24 hours.
Sildenafil	All PIs	DRV/r plus sildenafil 25 mg similar to sildenafil 100 mg alone RTV 500 mg BID ↑ sildenafil AUC 1,000% SQV unboosted ↑ sildenafil AUC 210%	For Treatment of Erectile Dysfunction: • Start with sildenafil 25 mg every 48 hours and monitor for adverse effects of sildenafil. For Treatment of PAH: • **Contraindicated. Do not coadminister.**

Table 19a. Drug Interactions between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 14 of 15)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Phosphodiesterase Type 5 (PDE5) Inhibitors, continued			
Tadalafil	All PIs	RTV 200 mg BID ↑ tadalafil AUC 124% TPV/r (1st dose) ↑ tadalafil AUC 133% TPV/r steady state: no significant effect	For Treatment of Erectile Dysfunction: • Start with tadalafil 5-mg dose and do not exceed a single dose of 10 mg every 72 hours. Monitor for adverse effects of tadalafil. For Treatment of PAH *In patients on a PI >7 days:* • Start with tadalafil 20 mg once daily and increase to 40 mg once daily based on tolerability. *In patients on tadalafil who require a PI:* • Stop tadalafil ≥24 hours before PI initiation. Seven days after PI initiation, restart tadalafil at 20 mg once daily and increase to 40 mg once daily based on tolerability. *In patients switching between COBI and RTV:* • Maintain tadalafil dose. For Treatment of Benign Prostatic Hyperplasia: Maximum recommended daily dose is 2.5 mg per day.
Vardenafil	All PIs	RTV 600 mg BID ↑ vardenafil AUC 49-fold	Start with vardenafil 2.5 mg every 72 hours and monitor for adverse effects of vardenafil.
Sedative/Hypnotics			
Alprazolam, Clonazepam, Diazepam	All PIs	↑ benzodiazepine possible RTV (200 mg BID for 2 days) ↑ alprazolam half-life 222% and AUC 248%	Consider alternative benzodiazepines such as lorazepam, oxazepam, or temazepam.
Lorazepam, Oxazepam, Temazepam	All PIs	No data	These benzodiazepines are metabolized via non-CYP450 pathways; thus, there is less interaction potential than with other benzodiazepines.
Midazolam	All PIs	↑ midazolam expected SQV/r ↑ midazolam (oral) AUC 1144% and C_{max} 327%	**Do not coadminister oral midazolam and PIs.** Parenteral midazolam can be used with caution when given as a single dose in a monitored situation for procedural sedation.
Suvorexant	All PIs	↑ suvorexant expected	**Coadministration is not recommended.**
Triazolam	All PIs	↑ triazolam expected RTV (200 mg BID) ↑ triazolam half-life 1200% and AUC 2000%	**Do not coadminister.**
Zolpidem	PI/r or ATV/c or DRV/c	↑ zolpidem possible	Initiate zolpidem at a low dose. Dose reduction may be necessary.

Table 19a. Drug Interactions between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 15 of 15)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Miscellaneous Drugs			
Colchicine	All PIs	RTV 100 mg BID ↑ colchicine AUC 296%, C_{max} 184% With all PIs with or without COBI or RTV: significant ↑ colchicine expected	For Treatment of Gout Flares: • Colchicine 0.6 mg x 1 dose, followed by 0.3 mg 1 hour later. Do not repeat dose for at least 3 days. *With FPV without RTV:* • 1.2 mg x 1 dose and no repeat dose for at least 3 days For Prophylaxis of Gout Flares: • Colchicine 0.3 mg once daily or every other day *With FPV without RTV:* • Colchicine 0.3 mg BID or 0.6 mg once daily or 0.3 mg once daily For Treatment of Familial Mediterranean Fever: • Do not exceed colchicine 0.6 mg once daily or 0.3 mg BID. *With FPV without RTV:* • Do not exceed 1.2 mg once daily or 0.6 mg BID. **Do not coadminister in patients with hepatic or renal impairment.**
Flibanserin	All PIs	↑ flibanserin expected	**Contraindicated. Do not coadminister.**
Salmeterol	All PIs	↑ salmeterol possible	**Do not coadminister** because of potential increased risk of salmeterol-associated cardiovascular events.

[a] DHA is an active metabolite of artemether.

[b] The following products contain at least 35 mcg of ethinyl estradiol combined with norethindrone or norgestimate (generic formulation may also be available): Brevicon; Femcon Fe; Modicon; Norinyl 1/35; Ortho-Cyclen; Ortho-Novum 1/35, 7/7/7; Ortho Tri-Cyclen; Ovcon 35; Tri-Norinyl.

[c] The following products contain no more than 30 mcg of ethinyl estradiol combined with norethindrone or norgestimate (generic formulation may also be available): Lo Minastrin Fe; Lo Loestrin Fe; Loestrin 1/20, 1.5/30; Loestrin Fe 1/20, 1.5/30; Loestrin 24 Fe; Minastrin 24 Fe; Ortho Tri-Cyclen Lo.

[d] Norbuprenorphine is an active metabolite of buprenorphine.

[e] R-methadone is the active form of methadone.

Key to Symbols: ↑ = increase, ↓ = decrease, ↔ = no change

Key to Acronyms: 17-BMP = beclomethasone 17-monopropionate; APV = amprenavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; AUC = area under the curve; BID = twice daily; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; CNS = central nervous system; COBI = cobicistat; CrCl = creatinine clearance; CYP = cytochrome P; DHA = dihydroartemisinin; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; ECG = electrocardiogram; FPV = fosamprenavir; FPV/r = fosamprenavir/ritonavir; HCV = hepatitis C virus; INR = international normalized ratio; LPV = lopinavir; LPV/r = ritonavir-boosted lopinavir; MPA = medroxyprogesterone acetate; PAH = pulmonary arterial hypertension; PDE5 = phosphodiesterase type 5; PI = protease inhibitor; PI/c = protease inhibitor/cobicistat; PI/r = protease inhibitorritonavir; PK = pharmacokinetic; PPI = proton pump inhibitor; QTc = QT corrected for heart rate; RAL = raltegravir; RTV = ritonavir; SQV = saquinavir; SQV/r = ritonavir-boosted saquinavir; TCA = tricyclic antidepressant; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; TPV/r = tipranavir/ritonavir; VPA = valproic acid

Note: FPV is a prodrug of APV.

Table 19b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 1 of 7)

This table provides information relating to PK interactions between NNRTIs and non-ARV drugs. For interactions between ARV agents and for dosing recommendations, refer to Tables 19c, 20a and 20b.

Note: DLV is **not** included in this table. Please refer to the DLV FDA package insert for information regarding drug interactions.

Concomitant Drug Class/Name	NNRTI[a]	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers			
Antacids	RPV	↓ RPV expected when given simultaneously	Give antacids at least 2 hours before or at least 4 hours after RPV.
H2-Receptor Antagonists	RPV	↓ RPV	Give H2-receptor antagonists at least 12 hours before or at least 4 hours after RPV.
PPIs	RPV	With omeprazole 20 mg daily: • RPV AUC ↓ 40%, C_{min} ↓ 33%	**Contraindicated. Do not coadminister.**
Anticoagulants/Antiplatelets			
Warfarin	EFV, NVP	↑ or ↓ warfarin possible	Monitor INR and adjust warfarin dose accordingly.
	ETR	↑ warfarin possible	Monitor INR and adjust warfarin dose accordingly.
Clopidogrel	ETR	↓ activation of clopidogrel possible	ETR may prevent metabolism of clopidogrel (inactive) to its active metabolite. Avoid coadministration, if possible.
Anticonvulsants			
Carbamazepine Phenobarbital Phenytoin	EFV	Carbamazepine plus EFV: • Carbamazepine AUC ↓ 27% • EFV AUC ↓ 36% Phenytoin plus EFV: • ↓ EFV • ↓ phenytoin possible	Monitor anticonvulsant and EFV levels or, if possible, use alternative anticonvulsant to those listed.
	ETR	↓ anticonvulsant and ETR possible	**Do not coadminister.** Consider alternative anticonvulsant.
	NVP	↓ anticonvulsant and NVP possible	Monitor anticonvulsant and NVP levels and virologic responses or consider alternative anticonvulsant.
	RPV	↓ RPV possible	**Contraindicated. Do not coadminister.** Consider alternative anticonvulsant.
Oxcarbazepine	RPV	↓ RPV possible	**Contraindicated. Do not coadminister.** Consider alternative anticonvulsant.
Antidepressants			
Bupropion	EFV	Bupropion AUC ↓ 55%	Titrate bupropion dose based on clinical response.
Paroxetine	EFV, ETR	No significant effect	No dosage adjustment necessary.
Sertraline	EFV	Sertraline AUC ↓ 39%	Titrate sertraline dose based on clinical response.

Table 19b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 2 of 7)

Concomitant Drug Class/Name	NNRTI[a]	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antifungals			
Fluconazole	EFV	No significant effect	No dosage adjustment necessary.
	ETR	ETR AUC ↑ 86%	No dosage adjustment necessary. Use with caution.
	NVP	NVP AUC ↑ 110%	Increased risk of hepatotoxicity possible with this combination. Monitor NVP toxicity or use alternative ARV agent.
	RPV	↑ RPV possible	No dosage adjustment necessary. Clinically monitor for breakthrough fungal infection.
Isavuconazole	EFV, ETR, NVP	↓ isavuconazole possible	Dose adjustments for isavuconazole may be necessary. Consider monitoring isavuconazole level and antifungal response.
	RPV	↓ isavuconazole possible (likely to a lesser extent than with other NNRTIs) ↑ RPV possible	No dosage adjustment necessary. Clinically monitor for breakthrough fungal infection.
Itraconazole	EFV	Itraconazole and OH-itraconazole AUC, C_{max}, and C_{min} ↓ 35% to 44%	Failure to achieve therapeutic itraconazole concentrations has been reported. Avoid this combination if possible. If coadministered, closely monitor itraconazole concentration and adjust dose accordingly.
	ETR	↓ itraconazole possible ↑ ETR possible	Dose adjustments for itraconazole may be necessary. Monitor itraconazole level and antifungal response.
	NVP	↓ itraconazole possible ↑ NVP possible	Avoid combination if possible. If coadministered, monitor itraconazole concentration and adjust dose accordingly.
	RPV	↓ itraconazole possible ↑ RPV possible	No dosage adjustment necessary. Clinically monitor for breakthrough fungal infection.
Posaconazole	EFV	Posaconazole AUC ↓ 50% ↔ EFV	Avoid concomitant use unless the benefit outweighs the risk. If coadministered, monitor posaconazole concentration and adjust dose accordingly.
	ETR	↑ ETR possible	No dosage adjustment necessary.
	RPV	↓ posaconazole possible ↑ RPV possible	No dosage adjustment necessary. Clinically monitor for breakthrough fungal infection.
Voriconazole	EFV	Voriconazole AUC ↓ 77% EFV AUC ↑ 44%	**Contraindicated at standard doses.** Dose adjustment: • Voriconazole 400 mg BID, EFV 300 mg daily
	ETR	Voriconazole AUC ↑ 14% ETR AUC ↑ 36%	No dosage adjustment necessary; use with caution. Consider monitoring voriconazole level.
	NVP	↓ voriconazole possible ↑ NVP possible	Monitor for toxicity and antifungal response and/or voriconazole level.
	RPV	↓ voriconazole possible ↑ RPV possible	No dosage adjustment necessary. Clinically monitor for breakthrough fungal infection.

Table 19b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 3 of 7)

Concomitant Drug Class/Name	NNRTI[a]	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antimalarials			
Artemether/ Lumefantrine	EFV	Artemether AUC ↓ 79% DHA AUC ↓ 75% Lumefantrine AUC ↓ 56%	Consider alternative ARV or antimalarial drug. If used in combination, monitor closely for antimalarial efficacy and malaria recurrence.
	ETR	Artemether AUC ↓ 38% DHA AUC ↓ 15% Lumefantrine AUC ↓ 13% ETR AUC ↑ 10%	Clinical significance of the reduced antimalarial drug concentrations unknown. If used in combination with ETR, monitor closely for antimalarial efficacy.
	NVP	Artemether AUC ↓ 67% to 72% DHA: • Study results are conflicting. AUC ↓ 37% in one study, no difference in another. Lumefantrine: • Study results are conflicting. Lumefantrine AUC ↓ 25% to 58% in 2 studies but ↑ 56% in another.	Clinical significance unknown. If used, monitor closely for antimalarial efficacy and lumefantrine toxicity.
Atovaquone/ Proguanil	EFV	Atovaquone AUC ↓ 75% Proguanil AUC ↓ 43%	No dosage recommendation. Consider alternative drug for malaria prophylaxis, if possible.
Antimycobacterials			
Bedaquiline	EFV	↓ bedaquiline possible	Not recommended.
	NVP	↔ bedaquiline AUC	No dosage adjustment necessary.
Clarithromycin	EFV	Clarithromycin AUC ↓ 39%	Monitor for effectiveness or consider alternative agent, such as azithromycin, for MAC prophylaxis and treatment.
	ETR	Clarithromycin AUC ↓ 39% ETR AUC ↑ 42%	Consider alternative agent, such as azithromycin, for MAC prophylaxis and treatment.
	NVP	Clarithromycin AUC ↓ 31%	Monitor for effectiveness or use alternative agent, such as azithromycin, for MAC prophylaxis and treatment.
	RPV	↔ clarithromycin expected ↑ RPV possible	Consider alternative macrolide, such as azithromycin, for MAC prophylaxis and treatment.
Rifabutin	EFV	Rifabutin ↓ 38%	Dose: • Rifabutin 450–600 mg/day; or • Rifabutin 600 mg 3 times/week **if** EFV is not coadministered with a PI.
	ETR	Rifabutin and metabolite AUC ↓ 17% ETR AUC ↓ 37%	**If ETR is used with an RTV-boosted PI, rifabutin should not be coadministered.** Dose: • Rifabutin 300 mg once daily **if** ETR is not coadministered with a PI/r.
	NVP	Rifabutin AUC ↑ 17% and metabolite AUC ↑ 24% NVP C_{min} ↓ 16%	No dosage adjustment necessary. Use with caution.
	RPV	Rifabutin plus RPV 50 mg once daily compared to RPV 25 mg once daily alone: ↔ RPV AUC, C_{min}	Increase RPV dose to 50 mg once daily.

Table 19b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 4 of 7)

Concomitant Drug Class/Name	NNRTI[a]	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antimycobacterials, continued			
Rifampin	EFV	EFV AUC ↓ 26%	Maintain EFV dose at 600 mg once daily and monitor for virologic response. Consider therapeutic drug monitoring.
	ETR	Significant ↓ ETR possible	**Do not coadminister.**
	NVP	NVP ↓ 20% to 58%	**Do not coadminister.**
	RPV	RPV AUC ↓ 80%	**Contraindicated. Do not coadminister.**
Rifapentine	EFV	↔ EFV concentrations	No dosage adjustment necessary.
	ETR, NVP, RPV	↓ NNRTI possible	**Do not coadminister.**
Antipneumocystis and Antitoxoplasmosis Drugs			
Atovaquone	EFV	Atovaquone AUC ↓ 44% to 47%	Consider alternative agent for PCP or toxoplasmosis treatment or use alternative ARV drug. If used in combination, monitor therapeutic efficacy of atovaquone.
Benzodiazepines			
Alprazolam	EFV, ETR, NVP, RPV	No data	Monitor for therapeutic effectiveness of alprazolam.
Diazepam	ETR	↑ diazepam possible	Decreased dose of diazepam may be necessary.
Lorazepam	EFV	Lorazepam C_{max} ↑ 16%, AUC ↔	No dosage adjustment necessary.
Midazolam	EFV	Significant ↑ midazolam expected	**Do not coadminister with oral midazolam.** Parenteral midazolam can be used with caution as a single dose and can be given in a monitored situation for procedural sedation.
Triazolam	EFV	Significant ↑ triazolam expected	**Do not coadminister.**
Cardiac Medications			
Dihydropyridine CCBs	EFV, NVP	↓ CCBs possible	Titrate CCB dose based on clinical response.
Diltiazem Verapamil	EFV	Diltiazem AUC ↓ 69% ↓ verapamil possible	Titrate diltiazem or verapamil dose based on clinical response.
	NVP	↓ diltiazem or verapamil possible	
Corticosteroids			
Dexamethasone	EFV, ETR, NVP	↓ EFV, ETR, NVP possible	Consider alternative corticosteroid for long-term use. If dexamethasone is used with NNRTI, monitor virologic response.
	RPV	Significant ↓ RPV possible	**Contraindicated with more than a single dose of dexamethasone.**
Hepatitis C Direct-Acting Antiviral Agents			
Daclatasvir	EFV, ETR, NVP	Daclatasvir C_{min} ↓ 17%, following daclatasvir 120 mg once daily + EFV 600 mg daily	Daclatasvir 90 mg once daily.
	RPV	No data	No dosage adjustment necessary.

Table 19b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 5 of 7)

Concomitant Drug Class/Name	NNRTI[a]	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hepatitis C Direct-Acting Antiviral Agents, continued			
Dasabuvir plus Paritaprevir/ Ombitasivir/RTV	EFV	No data	**Contraindicated. Do not coadminister.**
	ETR, NVP	↓ DAAs possible	**Do not coadminister.**
	RPV	RPV AUC ↑ 150% to 225%	**Do not coadminister because of potential for QT interval prolongation with higher concentrations of RPV.**
Elbasvir/Grazoprevir	EFV	Elbasvir AUC ↓ 54% Grazoprevir AUC ↓83% EFV ↔ by grazoprevir EFV ↔ AUC by elbasvir	**Contraindicated**.
	ETR, NVP	↓ elbasvir, grazoprevir expected	**Do not coadminister.**
	RPV	Elbasvir, grazoprevir and RPV ↔	No dosage adjustment necessary.
Ledipasvir/ Sofosbuvir	EFV	Ledipasvir AUC, C_{min}, C_{max} – all ↓ 34% Sofosbuvir: no significant effect	No dosage adjustment necessary.
	ETR, NVP, RPV	No significant effect expected	
Simeprevir	EFV	Simeprevir AUC ↓ 71%, C_{min} ↓ 91% ↔ EFV	**Coadministration is not recommended.**
	ETR, NVP	↓ simeprevir expected	**Coadministration is not recommended.**
	RPV	↔ simeprevir and RPV	No dosage adjustment necessary.
Herbal Products			
St. John's Wort	EFV, ETR, NVP, RPV	↓ NNRTI	**Do not coadminister.**
Hormonal Contraceptives			
Hormonal Contraceptives	EFV	Ethinyl estradiol ↔ Levonorgestrel (oral) AUC ↓ 64% Norelgestromin AUC ↓ 64% Etonogestrel (implant) AUC ↓ 63% Levonorgestrel (implant) AUC ↓ 48%	Use alternative or additional contraceptive methods. Norelgestromin and levonorgestrel are active metabolites of norgestimate. Unintended pregnancies were observed in women who used EFV and levonorgestrel implant concomitantly.
	ETR	Ethinyl estradiol AUC ↑ 22% Norethindrone: no significant effect	No dosage adjustment necessary.
	NVP	Ethinyl estradiol AUC ↓ 29%, C_{min} ↓ 58% Norethindrone AUC ↓ 18% Etonogestrel (metabolite of oral desogestrel) ↓ 22%	Consider alternative or additional contraceptive methods.
		DMPA: no significant change	No dosage adjustment necessary.
		Levonorgestrel implant: AUC ↑ 30%	No dosage adjustment necessary.
	RPV	Ethinyl estradiol: no significant change Norethindrone: no significant change	No dosage adjustment necessary.

Table 19b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 6 of 7)

Concomitant Drug Class/Name	NNRTI[a]	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Levonorgestrel For emergency contraception	EFV	Levonorgestrel AUC ↓ 58%	Effectiveness of emergency postcoital contraception may be diminished.
HMG-CoA Reductase Inhibitors			
Atorvastatin	EFV, ETR	Atorvastatin AUC ↓ 32% to 43%	Adjust atorvastatin according to lipid responses, not to exceed the maximum recommended dose.
	RPV	Atorvastatin AUC ↔ Atorvastatin metabolites ↑	No dosage adjustment necessary.
Fluvastatin	ETR	↑ fluvastatin possible	Dose adjustments for fluvastatin may be necessary.
Lovastatin **Simvastatin**	EFV	Simvastatin AUC ↓ 68%	Adjust simvastatin dose according to lipid responses, not to exceed the maximum recommended dose. If EFV is used with a PI/r, simvastatin and lovastatin should be avoided.
	ETR, NVP	↓ lovastatin possible ↓ simvastatin possible	Adjust lovastatin or simvastatin dose according to lipid responses, not to exceed the maximum recommended dose. If ETR or NVP is used with a PI/r, simvastatin and lovastatin should be avoided.
Pitavastatin	EFV	Pitavastatin AUC ↓ 11%, C_{max} ↑ 20%	No dosage adjustment necessary.
	ETR, NVP, RPV	No data	No significant effect expected. No dosage adjustment necessary.
Pravastatin **Rosuvastatin**	EFV	Pravastatin AUC ↓ 44% Rosuvastatin: no data	Adjust statin dose according to lipid responses, not to exceed the maximum recommended dose.
	ETR	No significant effect expected	No dosage adjustment necessary.
Immunosuppressants			
Cyclosporine **Sirolimus** **Tacrolimus**	EFV, ETR, NVP	↓ immunosuppressant possible	Increase in immunosuppressant dose may be necessary. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with specialist as necessary.
Narcotics/Treatments for Opioid Dependence			
Buprenorphine sublingual/buccal	EFV	Buprenorphine AUC ↓ 50% Norbuprenorphine[b] AUC ↓ 71%	No dosage adjustment recommended; monitor for withdrawal symptoms.
	ETR	Buprenorphine AUC ↓ 25%	No dosage adjustment necessary.
	NVP	No significant effect	No dosage adjustment necessary.
Buprenorphine implant	EFV, ETR, NVP	No data	Clinical monitoring is recommended if NNRTI is initiated after insertion of buprenorphine implant.
Methadone	EFV	Methadone AUC ↓ 52%	Opioid withdrawal common; increased methadone dose often necessary.
	ETR	No significant effect	No dosage adjustment necessary.
	NVP	Methadone AUC ↓ 37% to 51% NVP: no significant effect	Opioid withdrawal common; increased methadone dose often necessary.
	RPV	R-methadone[c] AUC ↓ 16%	No dosage adjustment necessary, but monitor for withdrawal symptoms.

Table 19b. Drug Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 7 of 7)

Concomitant Drug Class/Name	NNRTI[a]	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
PDE5 Inhibitors			
Avanafil	EFV, ETR, NVP, RPV	No data	**Coadministration is not recommended.**
Sildenafil	ETR	Sildenafil AUC ↓ 57%	May need to increase sildenafil dose based on clinical effect.
	RPV	↔ sildenafil	No dosage adjustment necessary.
Tadalafil	ETR	↓ tadalafil possible	May need to increase tadalafil dose based on clinical effect.
Vardenafil	ETR	↓ vardenafil possible	May need to increase vardenafil dose based on clinical effect.

[a] Approved dose for RPV is 25 mg once daily. Most PK interaction studies were performed using 75 to 150 mg per dose.

[b] Norbuprenorphine is an active metabolite of buprenorphine.

[c] R-methadone is the active form of methadone.

Key to Symbols: ↑ = increase, ↓ = decrease, ↔ = no change

Key to Acronyms: ARV = antiretroviral; AUC = area under the curve; BID = twice daily; CCB = calcium channel blockers; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; DAAs = direct-acting antivirals; DHA = dihydroartemisinin; DLV = delavirdine; DMPA = depot medroxyprogesterone acetate; EFV = efavirenz; ETR = etravirine; FDA = Food and Drug Administration; HMG-CoA = hydroxy-methylglutaryl-coenzyme A; INR = international normalized ratio; MAC = *Mycobacterium avium* complex; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; OH-itraconazole = active metabolite of itraconazole; PCP = *Pneumocystis jiroveci* pneumonia; PDE5 = phosphodiesterase type 5; PI = protease inhibitor; PK = pharmacokinetic; PPI = proton pump inhibitor; RPV = rilpivirine; RTV = ritonavir

Table 19c. Drug Interactions Between Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Including Antiretroviral Agents) (Last updated July 14, 2016; last reviewed July 14, 2016) (page 1 of 3)

Concomitant Drug Class/Name	NRTI	Effect on NRTI and/or Concomitant Drug Concentrations	Dosage Recommendations and Clinical Comments
Non-ARV Antivirals			
Adefovir	TDF	No data	**Do not coadminister.** Serum concentrations of TDF and/or other renally eliminated drugs may be increased.
Ganciclovir **Valganciclovir**	TDF	No data	Serum concentrations of these drugs and/or TDF may be increased. Monitor for dose-related toxicities.
	ZDV	No significant effect	Potential increase in hematologic toxicities
Ledipasvir/ Sofosbuvir	TAF	No significant effect	No dose adjustment
	TDF	• Ledipasvir ↑ TDF AUC 40% to 98% when TDF given with RPV and EFV • Further ↑ TDF possible if TDF given with PIs	No dose adjustment necessary. Monitor for TDF toxicity. The safety of increased TDF exposure when ledipasvir/sofosbuvir is coadministered with TDF and a PI/r, ATV/c, or DRV/c has not been established. Consider alternative HCV or ARV drugs to avoid increased TDF toxicities. If coadministration is necessary, monitor for TDF-associated adverse reactions. Coadministration of ledipasvir/sofosbuvir with EVG/c/TDF/FTC **is not recommended**.
Ribavirin	ddI	↑ intracellular ddI	**Contraindicated. Do not coadminister.** Fatal hepatic failure and other ddI-related toxicities have been reported with coadministration.
	ZDV	Ribavirin inhibits phosphorylation of ZDV.	Avoid coadministration if possible, or closely monitor HIV virologic response and possible hematologic toxicities.
INSTIs			
DTG	TAF	TAF AUC ↔	No dosage adjustment
	TDF	• TDF AUC ↑ 12% and C_{min} ↑ 19% • DTG ↔	No dosage adjustment
RAL	TDF	RAL AUC ↑ 49%	No dosage adjustment
Narcotics/Treatment for Opioid Dependence			
Buprenorphine	3TC, ddI, TDF, TAF, ZDV	No significant effect	No dosage adjustment
Methadone	ABC	Methadone clearance ↑ 22%	No dosage adjustment
	d4T	d4T AUC ↓ 23%	No dosage adjustment
	ZDV	ZDV AUC ↑ 29% to 43%	Monitor for ZDV-related adverse effects.
NNRTIs			
RPV	ddI	RPV, ddI ↔ when RPV taken 2 hours after ddI	Administer RPV with food 4 hours before or 2 hours after ddI.

Table 19c. Drug Interactions Between Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Including Antiretroviral Agents) (Last updated July 14, 2016; last reviewed July 14, 2016) (page 2 of 3)

Concomitant Drug Class/Name	NRTI	Effect on NRTI and/or Concomitant Drug Concentrations	Dosage Recommendations and Clinical Comments
NRTIs			
ddI	d4T	No significant PK interaction	**Do not coadminister.** Additive toxicities of peripheral neuropathy, lactic acidosis, and pancreatitis seen with this combination.
	TDF	ddI-EC AUC and C_{max} ↑ 48% to 60%	**Avoid coadministration.**
Other			
Allopurinol	ddI	ddI AUC ↑ 113% In patients with renal impairment: • ddI AUC ↑ 312%	**Contraindicated.** Potential for increased ddI-associated toxicities.
Atovaquone	ZDV	ZDV AUC ↑ 31%	Monitor for ZDV-related adverse effects.
Anticonvulsants Carbamazepine, Oxcarbazepine, Phenobarbital, Phenytoin	TAF	↓ TAF possible	Consider alternative anticonvulsant.
Antimycobacterial Rifabutin, Rifampin, Rifapentine	TAF	↓ TAF possible	Coadministration is not recommended.
Herbal Products St. John's wort	TAF	↓ TAF possible	Coadministration is not recommended.
PIs			
ATV +/- RTV or COBI	ddI	With ddI-EC plus ATV (with food): • ddI AUC ↓ 34% • ATV no change	Administer ATV with food 2 hours before or 1 hour after ddI.
	TAF	TAF 10 mg with ATV/r: TAF AUC ↑ 91%	No dosage adjustment (use TAF 25mg).
	TDF	With ATV (unboosted): • ATV AUC ↓ 25% and C_{min} ↓ 23% to 40% (higher C_{min} with RTV than without RTV) • TDF AUC ↑ 24% to 37%	**Avoid concomitant use without RTV or COBI.** Dose: • ATV 300 mg daily plus (RTV 100 mg or COBI 150 mg) daily when coadministered with TDF 300 mg daily. • If using TDF and H2 receptor antagonist in ART-experienced patients, use ATV 400 mg daily plus (RTV 100 mg or COBI 150 mg) daily. Monitor for TDF-associated toxicity.
	ZDV	With ATV (unboosted): • ZDV C_{min} ↓ 30% and AUC ↔	Clinical significance unknown.

Table 19c. Drug Interactions Between Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Including Antiretroviral Agents) (Last updated July 14, 2016; last reviewed July 14, 2016) (page 3 of 3)

Concomitant Drug Class/Name	NRTI	Effect on NRTI and/or Concomitant Drug Concentrations	Dosage Recommendations and Clinical Comments
DRV/c	TAF	TAF 25 mg with DRV/c: TAF AUC ↔	No dosage adjustment
	TDF	Increased TDF possible	Monitor for TDF-associated toxicity.
DRV/r	TAF	TAF 10 mg with DRV/r: TAF AUC ↔	No dosage adjustment
	TDF	TDF AUC ↑ 22% and C_{min} ↑ 37%	Clinical significance unknown. Monitor for TDF toxicity.
LPV/r	TAF	TAF 10 mg with DRV/r: • TAF AUC ↑ 47%	No dosage adjustment
	TDF	• LPV/r AUC ↓ 15% • TDF AUC ↑ 34%	Clinical significance unknown. Monitor for TDF toxicity.
TPV/r	ABC	ABC AUC ↓ 35% to 44%	Appropriate doses for this combination have not been established.
	ddI	ddI-EC AUC ↔ and C_{min} ↓ 34% TPV/r ↔	Separate doses by at least 2 hours.
	TAF	↓ TAF expected	Coadministration **is not recommended**.
	TDF	• TDF AUC ↔ • TPV/r AUC ↓ 9% to 18% and C_{min} ↓ 12% to 21%	No dosage adjustment necessary.
	ZDV	• ZDV AUC ↓ 35% • TPV/r AUC ↓ 31% to 43%	Appropriate doses for this combination have not been established.

Key to Symbols: ↑ = increase, ↓ = decrease, ↔ = no change

Key to Abbreviations: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; AUC = area under the curve; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; COBI = cobicistat; d4T = stavudine; ddI = didanosine; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = douletegravir; EC = enteric coated; EFV = efavirenz; EVG/c/TDF/FTC = elvitegravir/cobicistat/tenofovir disoproxil fumarate/emtricitabine; HCV = hepatitis C virus; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PI/r = ritonavir-boosted protease inhibitor; PK = pharmacokinetic; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TPV/r = tipranavir/ritonavir; ZDV = zidovudine

Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 1 of 11)

This table provides information on known or predicted pharamacokinetic interactions between INSTIs (DTG, EVG, or RAL) and non-ARV drugs. EVG is always coadministered with either COBI or RTV. In this table, the drug interactions with EVG/c products and those with EVG plus PI/r are presented separately. When EVG is given with a PI/r, clinicians should refer to Table 19a for recommendations on the management of drug interactions of concomitant medications and the specific PI/r used with EVG.

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers			
Aluminium, Magnesium +/- Calcium-Containing Antacids Please refer to the Miscellaneous Drugs section of this table for recommendations on use with other polyvalent cation products (eg, iron, calcium supplements, multivitamins).	DTG	DTG AUC ↓ 74% if given simultaneously with antacid; DTG AUC ↓ 26% if given 2 hours before antacid	Give DTG at least 2 hours before or at least 6 hours after antacids containing polyvalent cations.
	EVG/c EVG plus PI/r	EVG AUC ↓ 40% to 50% if given simultaneously with antacid EVG AUC ↓ 15% to 20% if given 2 hours before or after antacid; ↔ with 4-hour interval	Separate EVG/c/TDF/FTC and antacid administration by more than 2 hours.
	RAL	Al-Mg Hydroxide Antacid: • RAL C_{min} ↓ 54% to 63% $CaCO_3$ Antacid: • RAL C_{min} ↓ 32%	**Do not coadminister RAL and Al-Mg hydroxide antacids.** Use alternative acid reducing agent. No dosing separation necessary when coadministering RAL and $CaCO_3$ antacids.
H2-Receptor Antagonists	EVG/c	No significant effect	No dosage adjustment necessary.
	EVG plus PI/r	↔ EVG	No dosage adjustment necessary for EVG. Refer to Table 19a for information on PI/r interactions.
PPIs	DTG	No significant effect	No dosage adjustment necessary.
	EVG/c	No significant effect	No dosage adjustment necessary.
	EVG plus PI/r	↔ EVG	No dosage adjustment necessary for EVG. Refer to Table 19a for information on PI/r interactions.
	RAL	RAL AUC ↑ 212% and C_{min} ↑ 46%	No dosage adjustment necessary.
Anticoagulants and Antiplatelets			
Apixaban	EVG/c EVG plus PI/r	↑ apixaban expected	**Avoid concomitant use.**
Dabigatran	EVG/c EVG plus PI/r	↑ dabigatran possible	No dosage adjustment for dabigatran if CrCl >50 mL/min. **Avoid coadministration if CrCl <50 mL/min.**
Edoxaban	EVG/c EVG plus PI/r	↑ edoxaban expected	**Avoid concomitant use.**
Rivaroxaban	EVG/c EVG plus PI/r	↑ rivaroxaban expected	**Avoid concomitant use.**

Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 2 of 11)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticoagulants and Antiplatelets, continued			
Ticagrelor	EVG/c EVG plus PI/r	↑ ticagrelor expected	**Avoid concomitant use.**
Vorapaxar	EVG/c EVG plus PI/r	↑ vorapaxar expected	**Avoid concomitant use.**
Warfarin	EVG/c EVG plus PI/r	Warfarin levels may be affected	Monitor INR and adjust warfarin dose accordingly.
Anticonvulsants			
Carbamazepine **Phenobarbital** **Phenytoin**	DTG	↓ DTG possible	Consider alternative anticonvulsant.
	EVG/c	carbamazepine AUC ↑ 43% EVG AUC ↓ 69% and C_{min} ↓ >99% ↓ COBI expected	**Contraindicated. Do not coadminister.**
	EVG plus PI/r	↓ EVG	Consider alternative anticonvulsant.
Ethosuximide	EVG/c EVG plus PI/r	↑ ethosuximide possible	Clinically monitor for ethosuxamide toxicities.
Oxcarbazepine	DTG EVG/c EVG plus PI/r	↓ INSTI possible	Consider alternative anticonvulsant.
Antidepressants/Anxiolytics/Antipsychotics Also see Sedative/Hypnotics section below.			
Bupropion	EVG/c	↑ or ↓ bupropion possible	Titrate bupropion dose based on clinical response.
	EVG plus PI/r	↓ bupropion possible	Titrate bupropion dose based on clinical response.
Buspirone	EVG/c EVG plus PI/r	↑ buspirone possible	Initiate buspirone at a low dose. Dose reduction may be necessary.
Fluvoxamine	EVG/c EVG plus PI/r	↑ or ↓ EVG possible	Consider alternative antidepressant or ARV.
Quetiapine	EVG/c EVG plus PI/r	↑ quetiapine AUC expected.	Initiation of quetiapine in a patient receiving EVG/c: • Start quetiapine at the lowest dose and titrate up as needed. Monitor for quetiapine efficacy and adverse effects. Initiation of EVG/c in a patient receiving a stable dose of quetiapine: • Reduce quetiapine dose to 1/6 of the original dose, and closely monitor for quetiapine efficacy and adverse effects.

Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 3 of 11)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antidepressants/Anxiolytics/Antipsychotics, continued Also see Sedative/Hypnotics section below.			
SSRIs Citalopram Escitalopram Fluoxetine Paroxetine Sertraline	EVG/c	↑ SSRI possible	Initiate with lowest dose of SSRI and titrate dose carefully based on antidepressant response.
	EVG plus PI/r	↑ or ↓ SSRI possible	Titrate SSRI dose based on clinical response.
	RAL	↔ RAL ↔ citalopram	No dosage adjustment necessary.
TCAs Amitriptyline Desipramine Doxepin Imipramine Nortriptyline	EVG/c	Desipramine AUC ↑ 65%	Initiate with lowest dose of TCA and titrate dose carefully.
	EVG plus PI/r	↑ TCA expected	Initiate with lowest dose of TCA and titrate dose carefully based on antidepressant response and/or drug levels.
Trazodone	EVG/c EVG plus PI/r	↑ trazodone possible	Initiate with lowest dose of trazodone and titrate dose carefully.
Antifungals			
Isavuconazole	EVG/c	↑ isavuconazole expected ↑ EVG and COBI possible	If coadministered, consider monitoring isavuconazole concentrations and assess virologic response.
	EVG plus PI/r	Changes in isavuconazole and EVG possible	Refer to Table 19a for PI recommendations.
Itraconazole	EVG/c	↑ itraconazole expected ↑ EVG and COBI possible	Consider monitoring itraconazole level to guide dosage adjustments. High itraconazole doses (>200 mg/day) are not recommended unless dose is guided by itraconazole levels.
	EVG plus PI/r	↑ EVG possible	Refer to Table 19a for PI recommendations.
Posaconazole	EVG/c	↑ EVG and COBI possible ↑ posaconazole possible	If coadministered, monitor posaconazole concentrations.
	EVG plus PI/r	↑ EVG possible	Refer to Table 19a for PI recommendations.
Voriconazole	EVG/c	↑ voriconazole expected ↑ EVG and COBI possible	Risk/benefit ratio should be assessed to justify use of voriconazole. If administered, consider monitoring voriconazole level. Adjust dose accordingly.
	EVG plus PI/r	Changes in voriconazole and EVG possible	Refer to Table 19a for PI recommendations.

Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 4 of 11)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antimycobacterials			
Clarithromycin	EVG/c	↑ clarithromycin possible ↑ COBI possible	CrCl 50–60 mL/min: • Reduce clarithromycin dose by 50%. CrCl <50 mL/min: • EVG/c is not recommended.
Rifabutin	DTG	Rifabutin (300 mg once daily): • DTG AUC ↔ and C_{min} ↓ 30%	No dosage adjustment necessary.
	EVG/c	Rifabutin 150 mg every other day with EVG/c once daily compared to Rifabutin 300 mg once daily alone: ↔ rifabutin AUC 25-O-desacetyl-rifabutin AUC ↑ 625% EVG AUC ↓ 21%, C_{min} ↓ 67%	**Do not coadminister.**
	EVG plus PI/r	↔ EVG ↔ rifabutin AUC 25-O-desacetyl-rifabutin AUC ↑ 951%	Refer to Table 19a for dosing recommendations for rifabutin with PI.
	RAL	RAL AUC ↑ 19% and C_{min} ↓ 20%	No dosage adjustment necessary.
Rifampin	DTG	Rifampin with DTG 50 mg BID compared to DTG 50 mg BID alone: DTG AUC ↓ 54%, C_{min} ↓ 72% Rifampin with DTG 50 mg BID compared to DTG 50 mg once daily alone: DTG AUC ↑ 33%, C_{min} ↑ 22%	Dose: DTG 50 mg BID (instead of 50 mg once daily) for patients without suspected or documented INSTI mutation. **Alternative to rifampin should be used in patients with certain suspected or documented INSTI-associated resistance substitutions. Consider using rifabutin.**
	EVG/c EVG plus PI/r	Significant ↓ EVG and COBI expected	**Do not coadminister.**
	RAL	RAL 400 mg: • RAL AUC ↓ 40%, C_{min} ↓ 61% Compared with RAL 400 mg BID alone, Rifampin with RAL 800 mg BID: • RAL AUC ↑ 27%, C_{min} ↓ 53%	Dose: • RAL 800 mg BID Monitor closely for virologic response or consider using rifabutin as an alternative rifamycin.
Rifapentine	DTG	Significant ↓ DTG expected	**Do not coadminister.**
	EVG/c EVG plus PI/r	Significant ↓ EVG and COBI expected	**Do not coadminister.**
	RAL	Rifapentine 600 mg once daily: RAL C_{min} ↓ 41% Rifapentine 900 mg once weekly: RAL AUC ↑ 71%, C_{min} ↓ 12%	**Do not coadminister with once-daily rifapentine.** For once-weekly rifapentine, use standard doses.

Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 5 of 11)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Cardiac Medications			
Antiarrhythmics Amiodarone Bepridil Digoxin Disopyramide Dronedarone Flecainide Systemic lidocaine Mexilitine Propafenone Quinidine	EVG/c	↑ antiarrhythmics possible digoxin C_{max} ↑ 41% and AUC no significant change	Use antiarrhythmics with caution. Therapeutic drug monitoring, if available, is recommended for antiarrhythmics.
	EVG plus PI/r	↑ antiarrhythmics possible	Refer to Table 18 and 19a for use of antiarrhythmics and PI/r.
Bosentan	EVG/c	↑ bosentan possible	In patients on EVG/c ≥10 days: • Start bosentan at 62.5 mg once daily or every other day based on individual tolerability. In patients on bosentan who require EVG/c: • Stop bosentan ≥36 hours before EVG/c initiation. At least 10 days after initiation of EVG/c, resume bosentan at 62.5 mg once daily or every other day based on individual tolerability.
	EVG plus PI/r	↑ bosentan possible	Refer to Table 19a for recommendations on bosentan dosing when used with PI/r.
Beta-blockers (eg, metoprolol, timolol)	EVG/c EVG plus PI/r	↑ beta-blockers possible	Beta-blocker dose may need to be decreased; adjust dose based on clinical response. Consider using beta-blockers that are not metabolized by CYP450 enzymes (eg, atenolol, labetalol, nadolol, sotalol).
CCBs	EVG/c EVG plus PI/r	↑ CCBs possible	Coadminister with caution. Titrate CCB dose and monitor for CCB efficacy and toxicities. Refer to Table 19a for diltiazem plus ATV/r and SQV/r recommendations.
Dofetilide	DTG	↑ dofetilide expected	**Do not coadminister.**
Eplerenone	EVG/c EVG plus PI/r	↑ eplerenone expected	**Contraindicated. Do not coadminister.**
Ivabradine	EVG/c EVG plus PI/r	↑ ivabradine expected	**Contraindicated. Do not coadminister.**

Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 6 of 11)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Corticosteroids			
Dexamethasone (systemic)	EVG/c	↓ EVG and COBI possible	Use systemic dexamethasone with caution. Monitor virologic response to ART. Consider alternative corticosteroid.
	EVG plus PI/r	↓ EVG possible	
Fluticasone Inhaled/Intranasal	EVG/c EVG plus PI/r	↑ fluticasone possible	Coadministration may result in adrenal insufficiency and Cushing's syndrome. Consider alternative therapy (eg, beclomethasone), particularly for long-term use.
Methylprednisolone **Prednisolone** **Triamcinolone** Local injections, including intra-articular, epidural, intra-orbital	EVG/c EVG plus PI/r	↑ glucocorticoids expected	Coadministration may result in adrenal insufficiency and Cushing's syndrome. **Do not coadminister.**
Hepatitis C Direct Acting Antivirals			
Daclatasvir	DTG	↔ Daclatasvir	No dosage adjustment necessary.
	EVG/c	↑ Daclatasvir	Decrease daclastavir dose to 30 mg once daily.
	EVG plus PI/r	↑ Daclatasvir expected	Decrease daclastavir dose to 30 mg once daily, regardless of which PI/r is used, except for TPV/r. Do not coadminister EVG plus TPV/r with daclastavir.
	RAL	No data	No dosage adjustment necessary.
Dasabuvir plus Ombitasvir/Paritaprevir/r	DTG	No data	No dosing recommendations at this time.
	EVG plus PI/r EVG/c	No data	**Do not coadminister.**
	RAL	RAL AUC ↑ 134%	No dosage adjustment necessary.
Elbasvir/Grazoprevir	DTG	↔ Elbasvir ↔ Grazoprevir ↔ DTG	No dosage adjustment necessary.
	EVG plus PI/r		Refer to Table 19a for PI dosing recommendations.
	EVG/c	↑ elbasvir, grazoprevir expected	**Coadministration is not recommended.**
	RAL	↔ Elbasvir ↔ Grazoprevir RAL ↔ with elbasvir RAL AUC ↑ 43% with grazoprevir	No dosage adjustment necessary.
Ledipasvir/Sofosbuvir	EVG/c	↑ TDF and ↑ ledipasvir expected	**Do not coadminister.**
	EVG/c	↔ EVG/c/TAF/FTC expected	No dosage adjustment necessary.
	EVG plus PI/r	↔ EVG expected	Refer to Table 19a for PI dosing recommendations.
	DTG RAL	↔ DTG or RAL	No dosage adjustment necessary.

Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 7 of 11)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hepatitis C Direct Acting Antivirals, continued			
Simeprevir	DTG	↔ DTG expected	No dosage adjustment necessary.
	EVG/c	↑ simeprevir expected	**Coadministration is not recommended.**
	EVG plus PI/r	↔ EVG expected	**Coadministration is not recommended.**
	RAL	No significant effect	No dosage adjustment necessary.
Sofosbuvir	All INSTIs	No significant effect expected	No dosage adjustment necessary.
Herbal Products			
St. John's Wort	DTG	↓ DTG possible	**Do not coadminister.**
	EVG/c EVG plus PI/r	↓ EVG and COBI possible	**Do not coadminister.**
Hormonal Contraceptives			
Hormonal Contraceptives	RAL	No clinically significant effect	No dosage adjustment necessary.
Norgestimate/Ethinyl Estradiol	DTG	No significant effect	No dosage adjustment necessary.
	EVG/c	Norgestimate AUC, C_{max}, and C_{min} ↑ >2-fold Ethinyl estradiol AUC ↓ 25% and C_{min} ↓ 44%	The effects of increases in progestin (norgestimate) are not fully known and can include insulin resistance, dyslipidemia, acne, and venous thrombosis. Weigh the risks and benefits of the drug, and consider alternative contraceptive method.
	EVG plus PI/r	⇔ EVG	Refer to Table 19a for recommendations when used with PI/r.
HMG-CoA Reductase Inhibitors			
Atorvastatin	EVG/c	↑ atorvastatin possible	Titrate statin dose slowly and use the lowest dose possible.
	EVG plus PI/r	⇔ EVG expected	Refer to Table 19a for dosing recommendations when used with PI/r.
Lovastatin	EVG/c EVG plus PI/r	Significant ↑ lovastatin expected	**Contraindicated. Do not coadminister.**
Pitavastatin **Pravastatin**	EVG/c	No data	No dosage recommendation
	EVG plus PI/r	⇔ EVG expected	Refer to Table 19a for dosing recommendations when used with PI/r.
Rosuvastatin	EVG/c	Rosuvastatin AUC ↑ 38% and C_{max} ↑ 89%	Titrate statin dose slowly and use the lowest dose possible.
	EVG plus PI/r	⇔ EVG expected	Refer to Table 19a for dosing recommendations when used with PI/r.
Simvastatin	EVG/c EVG plus PI/r	Significant ↑ simvastatin expected	**Contraindicated. Do not coadminister.**

Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 8 of 11)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Immunosuppressants			
Cyclosporine **Everolimus** **Sirolimus** **Tacrolimus**	EVG/c EVG plus PI/r	↑ immunosuppressant possible	Initiate with an adjusted immunosuppressant dose to account for potential increased concentration and monitor for toxicities. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with specialist as necessary.
Narcotics/Treatment for Opioid Dependence			
Buprenorphine Sublingual/Buccal/Implant	EVG/c	Buprenorphine AUC ↑ 35%, C_{max} ↑ 12%, and C_{min} ↑ 66% Norbuprenorphine AUC ↑ 42%, C_{max} ↑ 24%, and C_{min} ↑ 57%	No dosage adjustment necessary. Clinical monitoring is recommended. When transferring buprenorphine from transmucosal to implantation, monitor to ensure buprenorphine effect is adequate and not excessive.
	EVG plus PI/r	↔ EVG expected	Refer to Table 19a for dosing recommendations when used with PI/r.
	RAL	No significant effect observed (sublingual) or expected (implant)	No dosage adjustment necessary.
Methadone	DTG	No significant effect	No dosage adjustment necessary.
	EVG/c	No significant effect	No dosage adjustment necessary.
	EVG plus PI/r	↓ methadone	Opioid withdrawal unlikely but may occur. Dosage adjustment of methadone is not usually required. Monitor for opioid withdrawal and increase methadone dose as clinically indicated.
	RAL	No significant effect	No dosage adjustment necessary.
Neuroleptics			
Perphenazine **Risperidone** **Thioridazine**	EVG/c	↑ neuroleptic possible	Initiate neuroleptic at a low dose. Decrease in neuroleptic dose may be necessary.
PDE5 Inhibitors			
Avanafil	EVG/c EVG plus PI/r	No data	**Coadministration is not recommended.**
Sildenafil	EVG/c EVG plus PI/r	↑ sildenafil expected	For treatment of erectile dysfunction: • Start with sildenafil 25 mg every 48 hours and monitor for adverse effects of sildenafil. For treatment of PAH: • **Contraindicated**

Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 9 of 11)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
PDE5 Inhibitors, continued			
Tadalafil	EVG/c EVG plus PI/r	↑ tadalafil expected	For treatment of erectile dysfunction: • Start with tadalafil 5-mg dose and do not exceed a single dose of 10 mg every 72 hours. Monitor for adverse effects of tadalafil. For treatment of PAH *In patients on EVG/c >7 days:* • Start with tadalafil 20 mg once daily and increase to 40 mg once daily based on tolerability. *In patients on tadalafil who require EVG/c:* • Stop tadalafil ≥24 hours before EVG/c initiation. Seven days after EVG/c initiation, restart tadalafil at 20 mg once daily, and increase to 40 mg once daily based on tolerability.
Vardenafil	EVG/c EVG plus PI/r	↑ vardenafil expected	Start with vardenafil 2.5 mg every 72 hours and monitor for adverse effects of vardenafil.
Sedative/Hypnotics			
Clonazepam **Clorazepate** **Diazepam** **Estazolam** **Flurazepam**	EVG/c EVG plus PI/r	↑ benzodiazepines possible	Dose reduction of benzodiazepine may be necessary. Initiate with low dose and clinically monitor. Consider alternative benzodiazepines to diazepam, such as lorazepam, oxazepam, or temazepam.
Midazolam **Triazolam**	DTG	With DTG 25 mg: midazolam AUC ↔	No dosage adjustment necessary.
	EVG/c EVG plus PI/r	↑ midazolam expected ↑ triazolam expected	**Do not coadminister triazolam or oral midazolam and EVG/c or (EVG plus PI).** Parenteral midazolam can be used with caution in a closely monitored setting. Consider dose reduction, especially if more than one dose is administered.
Suvorexant	EVG/c EVG plus PI/r	↑ suvorexant expected	**Coadministration is not recommended.**
Zolpidem	EVG/c EVG plus PI/r	↑ zolpidem expected	Initiate zolpidem at a low dose. Dose reduction may be necessary.

Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 10 of 11)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Miscellaneous Drugs			
Colchicine	EVG/c EVG plus PI/r	↑ colchicine expected	**Do not coadminister in patients with hepatic or renal impairment.** For treatment of gout flares: • Colchicine 0.6 mg for 1 dose, followed by 0.3 mg 1 hour later. Do not repeat dose for at least 3 days. For prophylaxis of gout flares: • If original dose was colchicine 0.6 mg BID, decrease to colchicine 0.3 mg once daily. If regimen was 0.6 mg once daily, decrease to 0.3 mg every other day. For treatment of familial Mediterranean fever: • Do not exceed colchicine 0.6 mg once daily or 0.3 mg BID.
Flibanserin	EVG/c EVG plus PI/r	↑ flibanserin expected	**Contraindicated. Do not coadminister.**
Metformin	DTG	DTG 50 mg once daily plus metformin 500 mg BID: Metformin AUC ↑ 79%, C_{max} ↑ 66% DTG 50 mg BID plus metformin 500 mg BID: Metformin AUC ↑ 2.4 fold, C_{max} ↑ 2 fold	Limit metformin dose to no more than 1,000 mg per day. When starting/stopping DTG in patient on metformin, dose adjustment of metformin may be necessary to maintain optimal glycemic control and/or minimize GI symptoms.
Polyvalent Cation Supplements Mg, Al, Fe, Ca, Zn, including multivitamins with minerals **Note:** Please refer to the Acid Reducers section in this table for recommendations on use with Al-, Mg-, and Ca-containing antacids.	All INSTIs	↓ INSTI possible DTG ↔ when administered with Ca or Fe supplement simultaneously with food	If coadministration is necessary, give INSTI at least 2 hours before or at least 6 hours after supplements containing polyvalent cations, including but not limited to the following products: cation-containing laxatives; Fe, Ca, or Mg supplements; and sucralfate. Monitor for virologic efficacy. DTG and supplements containing Ca or Fe can be taken simultaneously with food. Many oral multivitamins also contain varying amounts of polyvalent cations; the extent and significance of chelation is unknown.
Salmeterol	EVG/c EVG plus PI/r	↑ salmeterol possible	**Do not coadminister** due to potential increased risk of salmeterol-associated cardiovascular events.

Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 11 of 11)

Key to Acronyms: Al = aluminum; ART = antiretroviral therapy; ARV = antiretroviral; ATV/r = atazanavir/ritonavir; AUC = area under the curve; BID = twice daily; Ca = calcium; CaCO3 = calcium carbonate; CCB = calcium channel blocker; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; c or COBI = cobicistat; CrCl = creatinine clearance; CYP = cytochrome P; DTG = dolutegravir; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; Fe = iron; GI = gastrointestinal; INR= international normalized ratio; INSTI = integrase strand transfer inhibitor; Mg = magnesium; PAH = pulmonary arterial hypertension; PI = protease inhibitor; PI/r = ritonavir-boosted protease inhibitor; PPI = proton pump inhibitor; RAL = raltegravir; SQV/r = saquanavir/ritonavir; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; Zn = zinc

Table 19e. Drug Interactions between CCR5 Antagonist (Maraviroc) and Other Drugs (Including Antiretroviral Agents) (Last updated July 14, 2016; last reviewed July 14, 2016) (page 1 of 3)

Concomitant Drug Class/Name	CCR5 Antagonist	Effect on CCR5 Antagonist and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticonvulsants			
Carbamazepine, Phenobarbital, Phenytoin	MVC	↓ MVC possible	If used without a strong CYP3A inhibitor, use MVC 600 mg BID or an alternative antiepileptic agent.
Antifungals			
Isavuconazole	MVC	↑ MVC possible	Consider dose reduction to MVC 150 mg BID.
Itraconazole	MVC	↑ MVC possible	Dose: • MVC 150 mg BID
Posaconazole	MVC	↑ MVC possible	Dose: • MVC 150 mg BID
Voriconazole	MVC	↑ MVC possible	Consider dose reduction to MVC 150 mg BID.
Antimycobacterials			
Clarithromycin	MVC	↑ MVC possible	Dose: • MVC 150 mg BID
Rifabutin	MVC	↓ MVC possible	If used without a strong CYP3A inducer or inhibitor, use MVC 300 mg BID. If used with a strong CYP3A inhibitor, use MVC 150 mg BID.
Rifampin	MVC	MVC AUC ↓ 64%	**Coadministration is not recommended.** If coadministration is necessary, use MVC 600 mg BID. If coadministered with a strong CYP3A inhibitor, use MVC 300 mg BID.
Rifapentine	MVC	↓ MVC expected	**Do not coadminister.**
Hepatitis C Direct Acting Antivirals			
Daclatasvir	MVC	↔ MVC expected ↔ Daclatasvir expected	**No dose adjustment for daclatasvir. MVC dose 300 mg BID.**
Dasabuvir + Ombitasvir/ Paritaprevir/RTV	MVC	↑ MVC expected	**Do not coadminister.**
Elbasvir/ Grazoprevir	MVC	No data	No dosing recommendations at this time
Ledipasvir/ Sofosbuvir	MVC	↔ MVC expected ↔ Daclatasvir expected	Dose: • MVC 300 mg BID
Simeprevir	MVC	↔ MVC expected	Dose: • MVC 300 mg BID
Sofosbuvir	MVC	↔ MVC expected	Dose: • MVC 300 mg BID

Table 19e. Drug Interactions Between CCR5 Antagonist (Maraviroc) and Other Drugs (Including Antiretroviral Agents) (Last updated July 14, 2016; last reviewed July 14, 2016) (page 2 of 3)

Concomitant Drug Class/Name	CCR5 Antagonist	Effect on CCR5 Antagonist and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Herbal Products			
St. John's Wort	MVC	↓ MVC possible	**Coadministration is not recommended.**
Hormonal Contraceptives			
Hormonal Contraceptives	MVC	No significant effect on ethinyl estradiol or levonorgestrel	Safe to use in combination
ARV Drugs			
INSTIs			
EVG/c	MVC	↑ MVC possible	**Do not coadminister.**
EVG + PI/r	MVC	No data	Refer to PIs listed below for dosing recommendations when MVC is used with a PI/r.
RAL	MVC	MVC AUC ↓ 21% RAL AUC ↓ 37%	Dose: • Standard
NNRTIs			
EFV	MVC	MVC AUC ↓ 45%	Dose: • MVC 600 mg BID
ETR	MVC	MVC AUC ↓ 53%	Dose: • MVC 600 mg BID in the absence of a potent CYP3A inhibitor
NVP	MVC	MVC AUC ↔	Without HIV PI: • MVC 300 mg BID With HIV PI (except TPV/r): • MVC 150 mg BID
PIs			
ATV +/- RTV or COBI	MVC	With Unboosted ATV: • MVC AUC ↑ 257% With (ATV 300 mg Plus RTV 100 mg) Once Daily: • MVC AUC ↑ 388%	Dose: • MVC 150 mg BID
DRV/r or DRV/c	MVC	With (DRV 600 mg Plus RTV 100 mg) BID: • MVC AUC ↑ 305% With (DRV 600 mg Plus RTV 100 mg) BID and ETR: • MVC AUC ↑ 210%	Dose: • MVC 150 mg BID
FPV +/- RTV	MVC	With (FPV 700 mg Plus RTV 100 mg) BID and MVC 300 mg BID: • MVC AUC ↑ 149%, C_{min} ↑ 374% With (FPV 1400 mg Plus RTV 200 mg) Once Daily and MVC 300 mg Once Daily: • MVC AUC ↑ 126%, C_{min} ↑ 80%	Dose: • MVC 150 mg BID
LPV/r	MVC	MVC AUC ↑ 295% With LPV/r and EFV: • MVC AUC ↑ 153%	Dose: • MVC 150 mg BID

Table 19e. Drug Interactions Between CCR5 Antagonist (Maraviroc) and Other Drugs (Including Antiretroviral Agents) (Last updated July 14, 2016; last reviewed July 14, 2016) (page 3 of 3)

Concomitant Drug Class/Name	CCR5 Antagonist	Effect on CCR5 Antagonist and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
PIs, continued			
RTV	MVC	With RTV 100 mg BID: • MVC AUC ↑ 161%	Dose: • MVC 150 mg BID
SQV/r	MVC	With (SQV 1000 mg Plus RTV 100 mg) BID: • MVC AUC ↑ 877% With (SQV 1000 mg Plus RTV 100 mg) BID and EFV: • MVC AUC ↑ 400%	Dose: • MVC 150 mg BID
TPV/r	MVC	With (TPV 500 mg Plus RTV 200 mg) BID: • MVC AUC ↔	Dose: • MVC 300 mg BID

Note: FPV is a prodrug of APV.

Key to Symbols: ↑ = increase, ↓ = decrease, ↔ = no change

Key to Acronyms: ARV = antiretroviral; ATV = atazanavir; ATV/r = atazanavir/ritonavir; AUC = area under the curve; BID = twice daily; COBI = cobicistat; CYP = cytochrome P; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; FPV = fosamprenavir; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; RAL = raltegravir; RTV = ritonavir; SQV/r = saquinavir/ritonavir; TDF = tenofovir disoproxil fumarate; TPV/r = tipranavir/ritonavir

Table 20a. Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors and Protease Inhibitors[a] (Last updated April 8, 2015; last reviewed April 8, 2015) (Page 1 of 3)

Note: DLV, IDV, and NFV are **not** included in this table. Refer to the DLV, IDV, and NFV Food and Drug Administration package inserts for information regarding drug interactions.

PIs		NNRTIs			
		EFV	**ETR**	**NVP**	**RPV[a]**
ATV Unboosted	**PK Data**	EFV: no significant change ATV AUC ↓ 74%	ETR AUC ↑ 50% and C_{min} ↑ 58% ATV AUC ↓ 17% and C_{min} ↓ 47%	↓ ATV possible	↑ RPV possible
	Dose	**Do not coadminister.**	**Do not coadminister.**	**Do not coadminister.**	Standard doses
ATV/c	**PK Data**	↓ ATV ↓ COBI	↓ ATV ↓ COBI	↓ COBI	↑ RPV possible ↔ ATV expected
	Dose	EFV standard dose In ART-Naive Patients: • ATV 400 mg plus COBI 150 mg Once Daily **Do not coadminister in ART-experienced patients.**	**Do not coadminister.**	**Do not coadminister.**	Standard doses
ATV/r	**PK Data**	(ATV 300 mg plus RTV 100 mg) Once Daily: • ATV concentrations are similar to those with unboosted ATV without EFV.	(ATV 300 mg plus RTV 100 mg) Once Daily: • ETR AUC and C_{min} both ↑ ~30% • ATV AUC ↔ and C_{min} ↓ 18%	(ATV 300 mg plus RTV 100 mg) Once Daily: • ATV AUC ↓ 42% and C_{min} ↓ 72% • NVP AUC ↑ 25%	↑ RPV possible
	Dose	EFV standard dose In ART-Naive Patients: • (ATV 400 mg plus RTV 100 mg) Once Daily **Do not coadminister in ART-experienced patients.**	ETR standard dose (ATV 300 mg plus RTV 100 mg) Once Daily	**Do not coadminister.**	Standard doses
DRV/c	**PK Data**	↓ DRV possible ↓ COBI possible	Effect on DRV unknown ↓ COBI possible	Effect on DRV unknown ↓ COBI possible	↔ DRV expected ↑ RPV possible
	Dose	**Do not coadminister.**	**Do not coadminister.**	**Do not coadminister.**	Standard doses

Table 20a. Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors, and Protease Inhibitors[a] (Last updated April 8, 2015; last reviewed April 8, 2015) (Page 2 of 3)

PIs		NNRTIs			
		EFV	ETR	NVP	RPV[a]
DRV/r	PK Data	With (DRV 300 mg plus RTV 100 mg) BID: • EFV AUC ↑ 21% • DRV AUC ↓ 13% and C_{min} ↓ 31%	ETR 100 mg BID with (DRV 600 mg plus RTV 100 mg) BID: • ETR AUC ↓ 37% and C_{min} ↓ 49% • DRV: no significant change	With (DRV 400 mg plus RTV 100 mg) BID: • NVP AUC ↑ 27% and C_{min} ↑ 47% • DRV AUC ↑ 24%[b]	RPV 150 mg Once Daily with (DRV 800 mg plus RTV 100 mg) Once Daily: • RPV AUC ↑ 130% and C_{min} ↑ 178% • DRV: no significant change
	Dose	Clinical significance unknown. Use standard doses and monitor patient closely. Consider monitoring drug levels.	Standard doses Safety and efficacy of this combination, despite reduced ETR concentration, have been established in a clinical trial.	Standard doses	Standard doses
FPV +/- RTV	PK Data	With (FPV 1400 mg plus RTV 200 mg) Once Daily: • APV C_{min} ↓ 36%	With (FPV 700 mg plus RTV 100 mg) BID: • APV AUC ↑ 69% and C_{min} ↑ 77%	With Unboosted FPV 1400 mg BID: • NVP AUC ↑ 29% • APV AUC ↓ 33% With (FPV 700 mg plus RTV 100 mg) BID: • NVP C_{min} ↑ 22%	With Boosted and Unboosted FPV: • ↑ RPV possible
	Dose	(FPV 1400 mg plus RTV 300 mg) Once Daily **or** (FPV 700 mg plus RTV 100 mg) BID EFV standard dose	**Do not coadminister with FPV +/− RTV.**	(FPV 700 mg plus RTV 100 mg) BID NVP standard dose	Standard doses
LPV/r	PK Data	With LPV/r Tablets 500/125 mg[c] BID: • LPV concentration similar to that with LPV/r 400/100 mg BID without EFV	With LPV/r Tablets: • ETR AUC ↓ 35% (comparable to the decrease with DRV/r) • LPV AUC ↓ 13%	With LPV/r Capsules: • LPV AUC ↓ 27% and C_{min} ↓ 51%	RPV 150 mg Once Daily with LPV/r Capsules: • RPV AUC ↑ 52% and C_{min} ↑ 74% • LPV no significant change
	Dose	LPV/r tablets 500/125 mg[c] BID; LPV/r oral solution 533/133 mg BID EFV standard dose	Standard doses	LPV/r tablets 500/125 mgc BID; LPV/r oral solution 533/133 mg BID NVP standard dose	Standard doses

Table 20a. Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors, and Protease Inhibitors[a] (Last updated April 8, 2015; last reviewed April 8, 2015) (Page 3 of 3)

PIs		NNRTIs			
		EFV	ETR	NVP	RPV[a]
SQV Always use with RTV	**PK Data**	With SQV 1200 mg TID: • EFV AUC ↓ 12% • SQV AUC ↓ 62%	With (SQV 1000 mg plus RTV 100 mg) BID: • ETR AUC ↓ 33% and C_{min} ↓ 29% • SQV AUC ↔ ↓ ETR levels similar to reduction with DRV/r	With SQV 600 mg TID: • NVP: no significant change • SQV AUC ↓ 24%	↑ RPV possible
	Dose	(SQV 1000 mg plus RTV 100 mg) BID	(SQV 1000 mg plus RTV 100 mg) BID	Dose with SQV/r not established	Standard doses
TPV Always use with RTV	**PK Data**	With (TPV 500 mg plus RTV 100 mg) BID: • EFV no significant change • TPV AUC ↓ 31% and C_{min} ↓ 42% With (TPV 750 mg plus RTV 200 mg) BID: • EFV: no significant change • TPV: no significant change	With (TPV 500 mg plus RTV 200 mg) BID: • ETR AUC ↓ 76% and C_{min} ↓ 82% • TPV AUC ↑ 18% and C_{min} ↑ 24%	With (TPV 250 mg plus RTV 200 mg) BID or with (TPV 750 mg plus RTV 100 mg) BID: • NVP: no significant change • TPV: no data	↑ RPV possible
	Dose	Standard doses	**Do not coadminister.**	Standard doses	Standard doses

[a] Approved dose for RPV is 25 mg once daily. Most PK studies were performed using 75 mg to 150 mg RPV per dose.

[b] Based on between-study comparison.

[c] Use a combination of two LPV/r 200 mg/50 mg tablets plus one LPV/r 100 mg/25 mg tablet to make a total dose of LPV/r 500 mg/125 mg.

Key to Symbols: ↑ = increase, ↓ = decrease, ↔ = no change

Key to Acronyms: APV = amprenavir; ART = antiretroviral therapy; ATV = atazanavir; ATV/c = atazanavir/cobicistat; AUC = area under the curve; BID = twice daily; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; CYP = cytochrome P; DLV = delavirdine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; EFV = efavirenz; ETR = etravirine; FDA = Food and Drug Administration; FPV = fosamprenavir; IDV = indinavir; LPV = lopinavir; LPV/r = lopinavir/ritonavir; NFV = nelfinavir; NVP = nevirapine; PK = pharmacokinetic; RPV = rilpivirine; RTV = ritonavir; SQV = saquinavir; SQV/r = saquinavir/ritonavir; TID = three times a day; TPV = tipranavir

Table 20b. Interactions between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (page 1 of 4)

ARV Drugs by Drug Class		INSTIs			
		DTG	EVG/c	EVG (when used with PI/r)	RAL
NNRTIs					
EFV	**PK Data**	With DTG 50 mg once daily: • DTG AUC ↓ 57% and C_{min} ↓ 75%	↑ or ↓ EVG, COBI, EFV possible	↓ EVG expected	RAL: • AUC ↓ 36%
	Dose	In patients without INSTI resistance: • DTG 50 mg BID In patients with certain INSTI-associated resistance[a] or clinically suspected INSTI resistance: • **Consider alternative combination.**	**Do not coadminister.**	**Do not coadminister.**	Standard doses
ETR	**PK Data**	ETR 200 mg BID plus DTG 50 mg once daily: • DTG AUC ↓ 71% and C_{min} ↓ 88% ETR 200 mg BID with (DRV 600 mg plus RTV 100 mg) BID and DTG 50 mg once daily: • DTG AUC ↓ 25% and C_{min} ↓ 37% ETR 200 mg BID with (LPV 400 mg plus RTV 100 mg) BID and DTG 50 mg once daily: • DTG AUC ↑ 11% and C_{min} ↑ 28%	↑ or ↓ EVG, COBI, ETR possible	No significant interaction between EVG/r and ETR	• ETR C_{min} ↓ 17% • RAL C_{min} ↓ 34%
	Dose	**Do not coadminister ETR and DTG without concurrently administering ATV/r, DRV/r, or LPV/r.** In patients without INSTI resistance: • DTG 50 mg once daily with ETR (concurrently with ATV/r, DRV/r, or LPV/r) In patients with certain INSTI-associated resistance[a] or clinically suspected INSTI resistance: • DTG 50 mg BID with ETR (concurrently with ATV/r, DRV/r, or LPV/r)	**Do not coadminister.**	May coadminister EVG with ETR plus (ATV/r, DRV/r, or LPV/r) EVG: • Standard dose depending on the concomitant PI (see below)	Standard doses

Table 20b. Interactions between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (page 2 of 4)

ARV Drugs by Drug Class		INSTIs			
		DTG	EVG/c	EVG (when used with PI/r)	RAL
NNRTIs, continued					
NVP	**PK Data**	With DTG 50 mg once daily: DTG AUC ↓ 19% and C_{min} ↓ 34%	↑ or ↓ EVG, COBI, NVP possible	↓ EVG possible	No data
	Dose	Standard doses	**Do not coadminister.**	**Do not coadminister.**	Standard doses
RPV	**PK Data**	With DTG 50 mg once daily: • DTG AUC ↔ and C_{min} ↑ 22% • RPV AUC ↔ and C_{min} ↑ 21%	↑ or ↓ EVG, COBI, RPV possible	↑ RPV expected	• RPV ↔ • RAL C_{min} ↑ 27%
	Dose	Standard doses	**Do not coadminister.**	EVG: • Standard dose depending on the concomitant PI (see below) RPV: • Standard dose	Standard doses
PIs					
ATV/c	**PK Data**	No data	ATV/c plus EVG/c: • No data	No data	No data
	Dose	Standard doses	**Do not coadminister.**	**Do not coadminister.**	Standard doses
ATV +/- RTV	**PK Data**	Unboosted ATV plus DTG 30 mg once daily: • DTG AUC ↑ 91% and C_{min} ↑ 180% (ATV 300 mg plus RTV 100 mg) once daily plus DTG 30 mg once daily: • DTG AUC ↑ 62% and C_{min} ↑ 121%	↑ or ↓ EVG, COBI, ATV possible	EVG 85 mg with (ATV 300 mg plus RTV 100 mg) once daily: • EVG AUC ↔ and C_{min} ↑ 38% • ATV AUC and C_{min} ↔	With unboosted ATV: • RAL AUC ↑ 72% With (ATV 300 mg plus RTV 100 mg) once daily: • RAL AUC ↑ 41%
	Dose	Standard doses	**Do not coadminister.**	• EVG 85 mg once daily • (ATV 300 mg plus RTV 100 mg) once daily	Standard doses
DRV/c	**PK Data**	No data	DRV/c plus EVG/c: • ↓ EVG possible	No data	No data
	Dose	Standard doses	**Do not coadminister.**	**Do not coadminister.**	Standard doses

Table 20b. Interactions between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (page 3 of 4)

ARV Drugs by Drug Class		INSTIs			
		DTG	EVG/c	EVG (when used with PI/r)	RAL
PIs, continued					
DRV/r	**PK Data**	(DRV 600 mg plus RTV 100 mg) BID with DTG 30 mg once daily: • DTG AUC ↓ 22% and C_{min} ↓ 38%	↑ or ↓ EVG, COBI, DRV possible	EVG 125 mg once daily with (DRV 600 mg plus RTV 100 mg) BID: • EVG AUC and C_{min} ↔ • DRV AUC and C_{min} ↔	With (DRV 600 mg plus RTV 100 mg) BID: • RAL AUC ↓ 29% and C_{min} ↑ 38%
	Dose	Standard doses: • Once or twice daily dosing of DRV/r	**Do not coadminister.**	• EVG 150 mg once daily • (DRV 600 mg plus RTV 100 mg) BID	Standard doses
FPV +/- RTV	**PK Data**	With (FPV 700 mg plus RTV 100 mg) BID and DTG 50 mg once daily: • DTG AUC ↓ 35% and C_{min} ↓ 49%	↑ or ↓ EVG, COBI, FPV possible	No significant interaction with FPV and EVG	FPV: No significant effect
	Dose	In patients without INSTI resistance: • DTG 50 mg BID In patients with certain INSTI-associated resistance[a] or clinically suspected INSTI resistance: • **Consider alternative combination.**	**Do not coadminister.**	• EVG 150 mg once daily • (FPV 700 mg plus RTV 100 mg) BID	Standard doses
LPV/r	**PK Data**	With (LPV 400 mg plus RTV 100 mg) BID and DTG 30 mg once daily: • DTG: no significant effect	↑ or ↓ EVG, COBI, LPV possible RTV and COBI have similar effects on CYP3A.	EVG 125 mg once daily with (LPV 400 mg plus RTV 100 mg) BID: • EVG AUC ↑ 75% and C_{min} ↑ 138% • LPV AUC and C_{min} ↔	• ↓ RAL • ↔ LPV/r
	Dose	Standard doses: • Once or twice daily dosing of LPV/r	**Do not coadminister.**	• EVG 85 mg once daily • (LPV 400 mg plus RTV 100 mg) BID	Standard doses
SQV/r	**PK Data**	No data	↑ or ↓ EVG, COBI, SQV possible RTV and COBI have similar effects on CYP3A.	No data	No data
	Dose	Standard doses	**Do not coadminister.**	No dosage recommendation	Standard doses

Table 20b. Interactions between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (page 4 of 4)

ARV Drugs by Drug Class		INSTIs			
		DTG	EVG/c	EVG (when used with PI/r)	RAL
PIs, continued					
TPV/r	**PK Data**	With (TPV 500 mg plus RTV 200 mg) BID and DTG 50 mg once daily: • DTG AUC ↓ 59% and C_{min} ↓ 76%	↑ or ↓ EVG, COBI, TPV possible RTV and COBI have similar effects on CYP3A.	EVG 200 mg once daily with (TPV 500 mg plus RTV 200 mg) BID: • EVG AUC and C_{min} ↔ • TPV AUC and C_{min} ↔	With (TPV 500 mg plus RTV 200 mg) BID: • RAL AUC ↓ 24%
	Dose	In patients without INSTI resistance: • DTG 50 mg BID In patients with certain INSTI-associated resistancea or clinically suspected INSTI resistance: • **Consider alternative combination.**	**Do not coadminister.**	• EVG 150 mg once daily • (TPV 500 mg plus RTV 200 mg) BID	Standard doses

[a] Refer to dolutegravir product labeling for details.

Key to Symbols: ↑ = increase; ↓ = decrease; ↔ = no change

Key to Abbreviations: ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; AUC = area under the curve; BID = twice daily; C_{min} = minimum plasma concentration; COBI, c = cobicistat; CYP = cytochrome P; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; EVG/c/TDF/FTC = elvitegravir/cobicistat/tenofovir disoproxil fumarate/emtricitabine; EVG/r = elvitegravir/ritonavir; FPV = fosamprenavir; INSTI = integrase strand transfer inhibitor; LPV = lopinavir; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PI/r = ritonavir-boosted protease inhibitor; PK = pharmacokinetic; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQV = saquinavir; SQV/r = saquinavir/ritonavir; TPV = tipranavir; TPV/r = tipranavir/ritonavir

Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (page 1 of 6)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination	Serum/ Intracellular Half-Lives	Adverse Events[b]
Abacavir (ABC) *Ziagen* **Note:** Generic available in tablet formulation **Also available as a component of fixed-dose combinations (by trade name and abbreviation):**	Ziagen: • 300 mg tablet • 20 mg/mL oral solution	Ziagen: • 300 mg BID, *or* • 600 mg once daily • Take without regard to meals	Metabolized by alcohol dehydrogenase and glucuronyl transferase Renal excretion of metabolites: 82% Dosage adjustment for ABC is recommended in patients with hepatic insufficiency (see Appendix B, Table 7).	1.5 hours/ 12–26 hours	• HSRs: Patients who test positive for HLA-B*5701 are at highest risk. HLA screening should be done before initiation of ABC. • For patients with history of HSR, re-challenge is not recommended. • Symptoms of HSR may include fever, rash, nausea, vomiting, diarrhea, abdominal pain, malaise, fatigue, or respiratory symptoms such as sore throat, cough, or shortness of breath. • Some cohort studies suggest increased risk of MI with recent or current use of ABC, but this risk is not substantiated in other studies.
Trizivir (ABC/ZDV/3TC) **Note:** Generic available	Trizivir: • (ABC 300 mg plus ZDV 300 mg plus 3TC 150 mg) tablet	Trizivir: • 1 tablet BID			
Epzicom (ABC/3TC)	Epzicom: • (ABC 600 mg plus 3TC 300 mg) tablet	Epzicom: • 1 tablet once daily			
Triumeq (ABC/3TC/DTG)	Triumeq: • (ABC 600 mg plus 3TC 300 mg plus DTG 50 mg) tablet	Triumeq: • 1 tablet once daily			
Didanosine (ddI) *Videx* *Videx EC* **Note:** Generic available; dose same as Videx or Videx EC	Videx EC: • 125, 200, 250, and 400 mg capsules Videx: • 10 mg/mL oral solution	Body Weight ≥60 kg: • 400 mg once daily *With TDF:* • 250 mg once daily Body Weight <60 kg: • 250 mg once daily *With TDF:* • 200 mg once daily Take 1/2 hour before or 2 hours after a meal. **Note:** Preferred dosing with oral solution is BID (total daily dose divided into 2 doses).	Renal excretion: 50% Dosage adjustment in patients with renal insufficiency is recommended (see Appendix B, Table 7).	1.5 hours/ >20 hours	• Pancreatitis • Peripheral neuropathy • Retinal changes, optic neuritis • Lactic acidosis with hepatic steatosis with or without pancreatitis (rare but potentially life-threatening toxicity) • Nausea, vomiting • Potential association with non-cirrhotic portal hypertension; in some cases, patients presented with esophageal varices • One cohort study suggested increased risk of MI with recent or current use of ddI, but this risk is not substantiated in other studies. • Insulin resistance/diabetes mellitus

Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (page 2 of 6)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination	Serum/ Intracellular Half-Lives	Adverse Events[b]
Emtricitabine (FTC) *Emtriva* **Also available as a component of fixed-dose combinations (by trade name and abbreviation):**	Emtriva: • 200 mg hard gelatin capsule • 10 mg/mL oral solution	Emtriva: *Capsule:* • 200 mg once daily *Oral Solution:* • 240 mg (24 mL) once daily Take without regard to meals.	Renal excretion: 86% Dosage adjustment in patients with renal insufficiency is recommended (see Appendix B, Table 7).	10 hours/ >20 hours	• Minimal toxicity • Hyperpigmentation/skin discoloration • Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue FTC.
Atripla (FTC/EFV/TDF)	Atripla: • (FTC 200 mg plus EFV 600 mg plus TDF 300 mg) tablet	Atripla: • 1 tablet at or before bedtime • Take on an empty stomach to reduce side effects.			
Complera (FTC/RPV/TDF)	Complera: • (FTC 200 mg plus RPV 25 mg plus TDF 300 mg) tablet	Complera: • 1 tablet once daily with a meal			
Descovy (FTC/TAF)	Descovy: • (FTC 200 mg plus TAF 25 mg) tablet	Descovy: • 1 tablet once daily			
Genvoya (FTC/EVG/c/TAF)	Genvoya: • (FTC 200 mg plus EVG 150 mg plus COBI 150 mg plus TAF 10 mg) tablet	Genvoya: • 1 tablet once daily with food			
Odefsey (FTC/RPV/TAF)	Odefsey: • (FTC 200 mg plus RPV 25 mg plus TAF 25 mg) tablet	Odefsey: • 1 tablet once daily with a meal			
Stribild (FTC/EVG/c/TDF)	Stribild: • (FTC 200 mg plus EVG 150 mg plus COBI 150 mg plus TDF 300 mg) tablet	Stribild: • 1 tablet once daily with food			
Truvada (FTC/TDF)	Truvada: • (FTC 200 mg plus TDF 300 mg) tablet	Truvada: • 1 tablet once daily			

Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (page 3 of 6)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination	Serum/ Intracellular Half-Lives	Adverse Events[b]
Lamivudine (3TC) *Epivir* **Note:** Generic available **Also available as a component of fixed-dose combinations (by trade name and abbreviation):**	Epivir: • 150 and 300 mg tablets • 10 mg/mL oral solution	Epivir: • 150 mg BID, *or* • 300 mg once daily • Take without regard to meals.	Renal excretion: 70% Dosage adjustment in patients with renal insufficiency is recommended (see Appendix B, Table 7).	5–7 hours/ 18–22 hours	• Minimal toxicity • Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue 3TC.
Combivir (3TC/ZDV) **Note:** Generic available	Combivir: • (3TC 150 mg plus ZDV 300 mg) tablet	Combivir: • 1 tablet BID			
Epzicom (3TC/ABC)	Epzicom: • (3TC 300 mg plus ABC 600 mg) tablet	Epzicom: • 1 tablet once daily			
Trizivir (3TC/ZDV/ABC) **Note:** Generic available	Trizivir: • (3TC 150 mg plus ZDV 300 mg plus ABC 300 mg) tablet	Trizivir: • 1 tablet BID			
Triumeq (3TC/ABC/DTG)	Triumeq: • (3TC 300 mg plus ABC 600 mg plus DTG 50 mg) tablet	Triumeq: • 1 tablet once daily			
Stavudine (d4T) *Zerit* **Note:** Generic available	Zerit: • 15, 20, 30, and 40 mg capsules • 1 mg/mL oral solution	Body Weight ≥60 kg: • 40 mg BID Body Weight <60 kg: • 30 mg BID Take without regard to meals. **Note:** WHO recommends 30 mg BID dosing regardless of body weight.	Renal excretion: 50% Dosage adjustment in patients with renal insufficiency is recommended (see Appendix B, Table 7).	1 hour/7.5 hours	• Peripheral neuropathy • Lipoatrophy • Pancreatitis • Lactic acidosis/severe hepatomegaly with hepatic steatosis (rare but potentially life-threatening toxicity) • Hyperlipidemia • Insulin resistance/diabetes mellitus • Rapidly progressive ascending neuromuscular weakness (rare)

Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (page 4 of 6)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination	Serum/ Intracellular Half-Lives	Adverse Events[b]
Tenofovir Alafenamide (TAF) **Only available as a component of fixed-dose combinations (by trade name and abbreviation):**	See fixed-dose combinations below.	See fixed-dose combinations below.	Metabolized by cathepsin A; P-glycoprotein substrate Not recommended in patients with CrCl < 30 mL/min (see Appendix B, Table 7).	0.5 hours/150–180 hours	• Renal insufficiency, Fanconi syndrome, proximal renal tubulopathy; less likely than from TDF • Osteomalacia, decrease in bone mineral density; lesser effect than from TDF • Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue TAF. • Diarrhea, nausea, headache
Descovy (TAF/FTC)	Descovy: • (FTC 200 mg plus TAF 25 mg) tablet	Descovy: • 1 tablet once daily			
Genvoya (TAF/EVG/c/FTC)	Genvoya: • (TAF 10 mg plus EVG 150 mg plus COBI 150 mg plus FTC 200 mg) tablet	Genvoya: • 1 tablet once daily with food			
Odefsey (TAF/RPV/FTC)	Odefsey: • (TAF 25 mg plus RPV 25 mg plus FTC 200 mg) tablet	Odefsey: • 1 tablet once daily with a meal			

Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (page 5 of 6)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination	Serum/ Intracellular Half-Lives	Adverse Events[b]
Tenofovir Disoproxil Fumarate (TDF) *Viread* **Also available as a component of fixed-dose combinations (by trade name and abbreviation):**	Viread: • 150, 200, 250, and 300 mg tablets • 40 mg/g oral powder	Viread: • 300 mg once daily, *or* • 7.5 level scoops once daily (dosing scoop dispensed with each prescription; 1 level scoop contains 1 g of oral powder). • Take without regard to meals. Mix oral powder with 2–4 ounces of a soft food that does not require chewing (e.g., applesauce, yogurt). **Do not mix oral powder with liquid.**	Renal excretion is primary route of elimination. Dosage adjustment in patients with renal insufficiency is recommended (see Appendix B, Table 7).	17 hours/ >60 hours	• Renal insufficiency, Fanconi syndrome, proximal renal tubulopathy • Osteomalacia, decrease in bone mineral density • Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue TDF. • Asthenia, headache, diarrhea, nausea, vomiting, and flatulence
Atripla (TDF/EFV/FTC)	Atripla: • (TDF 300 mg plus EFV 600 mg plus FTC 200 mg) tablet	Atripla: • 1 tablet at or before bedtime • Take on an empty stomach to reduce side effects.			
Complera (TDF/RPV/FTC)	Complera: • (TDF 300 mg plus RPV 25 mg plus FTC 200 mg) tablet	Complera: • 1 tablet once daily • Take with a meal.			
Stribild (TDF/EVG/c/FTC)	Stribild: • (TDF 300 mg plus EVG 150 mg plus COBI 150 mg plus FTC 200 mg) tablet	Stribild: • 1 tablet once daily • Take with food.			
Truvada (TDF/FTC)	Truvada: • (TDF 300 mg plus FTC 200 mg) tablet	Truvada: • 1 tablet once daily • Take without regard to meals.			

Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (page 6 of 6)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination	Serum/ Intracellular Half-Lives	Adverse Events[b]
Zidovudine (ZDV) *Retrovir* **Note:** Generic available **Also available as a component of fixed-dose combinations (by trade name and abbreviation):**	Retrovir: • 100 mg capsule • 300 mg tablet (only available as generic) • 10 mg/mL intravenous solution • 10 mg/mL oral solution	Retrovir: • 300 mg BID, *or* • 200 mg TID • Take without regard to meals.	Metabolized to GAZT Renal excretion of GAZT Dosage adjustment in patients with renal insufficiency is recommended (see Appendix B, Table 7).	1.1 hours/ 7 hours	• Bone marrow suppression: macrocytic anemia or neutropenia • Nausea, vomiting, headache, insomnia, asthenia • Nail pigmentation • Lactic acidosis/severe hepatomegaly with hepatic steatosis (rare but potentially life-threatening toxicity) • Hyperlipidemia • Insulin resistance/diabetes mellitus • Lipoatrophy • Myopathy
Combivir (ZDV/3TC) **Note:** Generic available	Combivir: • (ZDV 300 mg plus 3TC 150 mg) tablet	Combivir: • 1 tablet BID • Take without regard to meals.			
Trizivir (ZDV/3TC/ABC) **Note:** Generic available	Trizivir: • (ZDV 300 mg plus 3TC 150 mg plus ABC 300 mg) tablet	Trizivir: • 1 tablet BID • Take without regard to meals.			

[a] For dosage adjustment in renal or hepatic insufficiency, see Appendix B, Table 7.

[b] Also see Table 14.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; BID = twice daily; c, COBI = cobicistat; CrCl = creatinine clearance; d4T = stavudine; ddI = didanosine; DTG = dolutegravir; EC = enteric coated; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; GAZT = azidothymidine glucuronide; HBV = hepatitis B virus; HLA = human leukocyte antigen; HSR = hypersensitivity reaction; MI = myocardial infarction; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TID = three times a day; WHO = World Health Organization; ZDV = zidovudine

Appendix B, Table 2. Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (page 1 of 2)

Note: Delavirdine (DLV) is not included in this table. Please refer to the DLV Food and Drug Administration package insert for related information.

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum Half-Life	Adverse Events[b]
Efavirenz (EFV) *Sustiva* **Also available as a component of fixed-dose combination (by trade name and abbreviation):**	Sustiva: • 50 and 200 mg capsules • 600 mg tablet	Sustiva: • 600 mg once daily, at or before bedtime • Take on an empty stomach to reduce side effects.	Metabolized by CYPs 2B6 (primary), 3A4, and 2A6 CYP3A4 mixed inducer/inhibitor (more an inducer than an inhibitor) CYP2C9 and 2C19 inhibitor; 2B6 inducer	40–55 hours	• Rash[c] • Neuropsychiatric symptoms[d] • Increased transaminase levels • Hyperlipidemia • False-positive results with some cannabinoid and benzodiazepine screening assays reported. • Teratogenic in non-human primates and potentially teratogenic during the first trimester of pregnancy in humans
Atripla (EFV/TDF/FTC)	Atripla: • (EFV 600 mg plus TDF 300 mg plus FTC 200 mg) tablet	Atripla: • 1 tablet once daily, at or before bedtime			
Etravirine (ETR) *Intelence*	• 25, 100, and 200 mg tablets	• 200 mg BID • Take following a meal.	CYP3A4, 2C9, and 2C19 substrate 3A4 inducer; 2C9 and 2C19 inhibitor	41 hours	• Rash, including Stevens-Johnson syndrome[c] • HSRs, characterized by rash, constitutional findings, and sometimes organ dysfunction (including hepatic failure) have been reported. • Nausea

Nevirapine (NVP) *Viramune or Viramine XR*
Generic available for 200 mg tablets and oral suspension
	• 200 mg tablet
	• 400 mg XR tablet
	• 50 mg/5 mL oral suspension
		• 200 mg once daily for 14 days (lead-in period); thereafter, 200 mg BID, or 400 mg (Viramune XR tablet) once daily
		• Take without regard to meals.
		• Repeat lead-in period if therapy is discontinued for >7 days.
		• In patients who develop mild-to-moderate rash without constitutional symptoms, continue lead-in period until rash resolves but not longer than 28 days total.
			CYP450 substrate, inducer of 3A4 and 2B6; 80% excreted in urine (glucuronidated metabolites, <5% unchanged); 10% in feces	25–30 hours	• Rash, including Stevens-Johnson syndrome[c]
					• Symptomatic hepatitis, including fatal hepatic necrosis, has been reported:
					  • Rash reported in approximately 50% of cases.
					  • Occurs at significantly higher frequency in ARV-naive female patients with pre-NVP CD4 counts >250 cells/mm^3 and in ARV-naive male patients with pre-NVP CD4 counts >400 cells/mm^3. NVP should not be initiated in these patients unless the benefit clearly outweighs the risk.

Appendix B, Table 2. Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (page 2 of 2)

Note: Delavirdine (DLV) is not included in this table. Please refer to the DLV Food and Drug Administration package insert for related information.

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum/ Half-Life	Adverse Events[b]
Rilpivirine (RPV) *Edurant* **Also available as a component of fixed-dose combinations (by trade name and abbreviation):**	Edurant: • 25 mg tablet	Edurant: • 25 mg once daily • Take with a meal.	CYP3A4 substrate	50 hours	• Rash[c] • Depression, insomnia, headache • Hepatotoxicity
Complera (RPV/TDF/FTC)	Complera: • (RPV 25 mg plus TDF 300 mg plus FTC 200 mg) tablet	Complera: • 1 tablet once daily • Take with a meal.			
Odefsey (RPV/TAF/FTC)	Odefsey: • (RPV 25 mg plus TAF 25 mg plus FTC 200 mg) tablet	Odefsey: • 1 tablet once daily • Take with a meal.			

[a] For dosage adjustment in renal or hepatic insufficiency, see Appendix B, Table 7.

[b] Also see Table 14.

[c] Rare cases of Stevens-Johnson syndrome have been reported with most NNRTIs; the highest incidence of rash was seen with NVP.

[d] Adverse events can include dizziness, somnolence, insomnia, abnormal dreams, depression, suicidality (suicide, suicide attempt or ideation), confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, and euphoria. Approximately 50% of patients receiving EFV may experience any of these symptoms. Symptoms usually subside spontaneously after 2 to 4 weeks but may necessitate discontinuation of EFV in a small percentage of patients.

Key to Abbreviations: ARV = antiretroviral; BID = twice daily; CD4 = CD4 T lymphocyte; CYP = cytochrome P; DLV = delavirdine; EFV = efavirenz; ETR = etravirine; FDA = Food and Drug Administration; FTC = emtricitabine; HSR = hypersensitivity reaction; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; XR = extended release

Appendix B, Table 3. Characteristics of Protease Inhibitors (Last updated April 8, 2015; last reviewed April 8, 2015) (page 1 of 4)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum Half-Life	Storage	Adverse Events[b]
Atazanavir (ATV) *Reyataz* **Also available as a component of fixed-dose combination (by trade name and abbreviation):**	Reyataz: • 100, 150, 200, and 300 mg capsules • 50 mg single packet oral powder	In ARV-Naive Patients: • (ATV 300 mg plus RTV 100 mg) once daily; *or* • ATV 400 mg once daily With TDF or in ARV-Experienced Patients: • (ATV 300 mg plus RTV 100 mg) once daily With EFV in ARV-Naive Patients: • (ATV 400 mg plus RTV 100 mg) once daily Take with food. For recommendations on dosing with H2 antagonists and PPIs, refer to Table 19a.	CYP3A4 inhibitor and substrate; weak CYP2C8 inhibitor; UGT1A1 inhibitor Dosage adjustment in patients with hepatic insufficiency is recommended (see Appendix B, Table 7).	7 hours	Room temperature (up to 25° C or 77° F)	• Indirect hyperbilirubinemia • PR interval prolongation: First degree symptomatic AV block reported. Use with caution in patients with underlying conduction defects or on concomitant medications that can cause PR prolongation. • Hyperglycemia • Fat maldistribution • Cholelithiasis • Nephrolithiasis • Renal insufficiency • Serum transaminase elevations • Hyperlipidemia (especially with RTV boosting) • Skin rash • Increase in serum creatinine (with COBI)
Evotaz (ATV/c)	Evotaz: • (ATV 300 mg plus COBI 150 mg) tablet	Evotaz: • 1 tablet once daily • Take with food. With TDF: • **Not recommended** for patients with baseline CrCl <70 mL/min (see Appendix B, Table 7 for the equation for calculating CrCl).	ATV: as above COBI: substrate of CYP3A, CYP2D6 (minor); CYP3A inhibitor			
Darunavir (DRV) *Prezista* **Also available as a component of fixed-dose combination (by trade name and abbreviation):**	• 75, 150, 600, and 800 mg tablets • 100 mg/mL oral suspension	In ARV-Naive Patients or ARV-Experienced Patients with No DRV Mutations: • (DRV 800 mg plus RTV 100 mg) once daily In ARV-Experienced Patients with One or More DRV Resistance Mutations: • (DRV 600 mg plus RTV 100 mg) BID Unboosted DRV **is not recommended**. Take with food.	CYP3A4 inhibitor and substrate CYP2C9 inducer	15 hours (when combined with RTV)	Room temperature (up to 25° C or 77° F)	• Skin rash (10%): DRV has a sulfonamide moiety; Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and erythrema multiforme have been reported. • Hepatotoxicity • Diarrhea, nausea • Headache • Hyperlipidemia • Serum transaminase elevation • Hyperglycemia • Fat maldistribution • Increase in serum creatinine (with COBI)
Prezcobix (DRV/c)	Prezcobix: • (DRV 800 mg plus COBI 150 mg) tablet	Prezcobix: • 1 tablet once daily • Take with food. **Not recommended** for patients with one or more DRV resistance-associated mutations. With TDF: • **Not recommended** for patients with baseline CrCl <70 mL/min (see Appendix B, Table 7 for the equation for calculating CrCl).	DRV: As above COBI: substrate of CYP3A, CYP2D6 (minor); CYP3A inhibitor			

Appendix B, Table 3. Characteristics of Protease Inhibitors (Last updated April 8, 2015; last reviewed April 8, 2015) (page 2 of 4)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum Half-Life	Storage	Adverse Events[b]
Fosamprenavir (FPV) *Lexiva* (a prodrug of APV)	• 700 mg tablet • 50 mg/mL oral suspension	In ARV-Naive Patients: • FPV 1400 mg BID, *or* • (FPV 1400 mg plus RTV 100–200 mg) once daily, *or* • (FPV 700 mg plus RTV 100 mg) BID In PI-Experienced Patients (**Once-Daily Dosing Not Recommended**): • (FPV 700 mg plus RTV 100 mg) BID With EFV: • (FPV 700 mg plus RTV 100 mg) BID, *or* • (FPV 1400 mg plus RTV 300 mg) once daily *Tablet:* • Without RTV tablet: Take without regard to meals. • With RTV tablet: Take with meals. *Oral Suspension:* • Take without food.	APV is a CYP3A4 substrate, inhibitor, and inducer. Dosage adjustment in patients with hepatic insufficiency is recommended (see Appendix B, Table 7).	7.7 hours (APV)	Room temperature (up to 25º C or 77º F)	• Skin rash (12% to 19%): FPV has a sulfonamide moiety. • Diarrhea, nausea, vomiting • Headache • Hyperlipidemia • Serum transaminase elevation • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia • Nephrolithiasis
Indinavir (IDV) *Crixivan*	• 100, 200, and 400 mg capsules	• 800 mg every 8 hours • Take 1 hour before or 2 hours after meals; may take with skim milk or a low-fat meal. With RTV: • (IDV 800 mg plus RTV 100–200 mg) BID • Take without regard to meals.	CYP3A4 inhibitor and substrate Dosage adjustment in patients with hepatic insufficiency is recommended (see Appendix B, Table 7).	1.5–2 hours	Room temperature (15º to 30º C or 59º to 86º F) Protect from moisture.	• Nephrolithiasis • GI intolerance, nausea • Hepatitis • Indirect hyperbilirubinemia • Hyperlipidemia • Headache, asthenia, blurred vision, dizziness, rash, metallic taste, thrombocytopenia, alopecia, and hemolytic anemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia

Appendix B, Table 3. Characteristics of Protease Inhibitors (Last updated April 8, 2015; last reviewed April 8, 2015) (page 3 of 4)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum Half-Life	Storage	Adverse Events[b]
Lopinavir/ Ritonavir (LPV/r) *Kaletra*	Tablets: • (LPV 200 mg plus RTV 50 mg), *or* • (LPV 100 mg plus RTV 25 mg) Oral Solution: • Each 5 mL contains (LPV 400 mg plus RTV 100 mg). • Oral solution contains 42% alcohol.	• (LPV 400 mg plus RTV 100 mg) BID, *or* • (LPV 800 mg plus RTV 200 mg) once daily Once-daily dosing is not recommended for patients with ≥3 LPV-associated mutations, pregnant women, or patients receiving EFV, NVP, FPV, NFV, carbamazepine, phenytoin, or phenobarbital. With EFV or NVP (PI-Naive or PI-Experienced Patients): • LPV/r 500 mg/125 mg tablets BID (use a combination of 2 LPV/r 200 mg/50 mg tablets plus 1 LPV/r 100 mg/25 mg tablet to make a total dose of LPV/r 500 mg/125 mg), *or* • LPV/r 533 mg/133 mg oral solution BID *Tablet:* • Take without regard to meals. *Oral Solution:* • Take with food.	CYP3A4 inhibitor and substrate	5–6 hours	Oral tablet is stable at room temperature. Oral solution is stable at 2° to 8° C (36° to 46° F) until date on label and is stable for up to 2 months when stored at room temperature (up to 25° C or 77° F).	• GI intolerance, nausea, vomiting, diarrhea • Pancreatitis • Asthenia • Hyperlipidemia (especially hypertriglyceridemia) • Serum transaminase elevation • Hyperglycemia • Insulin resistance/diabetes mellitus • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia • PR interval prolongation • QT interval prolongation and torsades de pointes have been reported; however, causality could not be established.
Nelfinavir (NFV) *Viracept*	• 250 and 625 mg tablets • 50 mg/g oral powder	• 1250 mg BID, *or* • 750 mg TID Dissolve tablets in a small amount of water, mix admixture well, and consume immediately. Take with food.	CYP2C19 and 3A4 substrate—metabolized to active M8 metabolite; CYP3A4 inhibitor	3.5–5 hours	Room temperature (15° to 30° C or 59° to 86° F)	• Diarrhea • Hyperlipidemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia • Serum transaminase elevation
Ritonavir (RTV) *Norvir* **Also available as a component of fixed-dose combination (see Lopinavir/ Ritonavir)**	• 100 mg tablet • 100 mg soft gel capsule • 80 mg/mL oral solution Oral solution contains 43% alcohol.	As Pharmacokinetic Booster (or Enhancer) for Other PIs: • 100–400 mg per day in 1 or 2 divided doses (refer to other PIs for specific dosing recommendations). *Tablet:* • Take with food. *Capsule and Oral Solution:* • To improve tolerability, take with food if possible.	CYP3A4 >2D6 substrate; potent 3A4, 2D6 inhibitor; Inducer of CYPs 1A2, 2C8, 2C9, and 2C19 and UGT1A1	3–5 hours	Tablets do not require refrigeration. Refrigerate capsules. Capsules can be left at room temperature (up to 25° C or 77° F) for up to 30 days. **Oral solution should not be refrigerated.**	• GI intolerance, nausea, vomiting, diarrhea • Paresthesia (circumoral and extremities) • Hyperlipidemia (especially hypertriglyceridemia) • Hepatitis • Asthenia • Taste perversion • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia

Appendix B, Table 3. Characteristics of Protease Inhibitors (Last updated April 8, 2015; last reviewed April 8, 2015) (page 4 of 4)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum Half-Life	Storage	Adverse Events[b]
Saquinavir (SQV) *Invirase*	• 500 mg tablet • 200 mg capsule	• (SQV 1000 mg plus RTV 100 mg) BID • Unboosted SQV **is not recommended**. • Take with meals or within 2 hours after a meal.	CYP3A4 substrate	1–2 hours	Room temperature (15º to 30º C or 59º to 86º F)	• GI intolerance, nausea, and diarrhea • Headache • Serum transaminase elevation • Hyperlipidemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia • PR interval prolongation • QT interval prolongation, torsades de pointes have been reported. Patients with pre-SQV QT interval >450 msec should not receive SQV.
Tipranavir (TPV) *Aptivus*	• 250 mg capsule • 100 mg/mL oral solution	• (TPV 500 mg plus RTV 200 mg) BID Unboosted TPV **is not recommended**. With RTV Tablets: • Take with meals. With RTV Capsules or Solution: • Take without regard to meals.	CYP P450 3A4 inducer and substrate CYP2D6 inhibitor; CYP3A4, 1A2, and 2C19 inducer Net effect when combined with RTV (CYP3A4, 2D6 inhibitor)	6 hours after single dose of TPV/r	Refrigerate capsules. Capsules can be stored at room temperature (25º C or 77º F) for up to 60 days. **Oral solution should not be refrigerated or frozen** and should be used within 60 days after bottle is opened.	• Hepatotoxicity: Clinical hepatitis (including hepatic decompensation and hepatitis-associated fatalities) has been reported; monitor patients closely, especially those with underlying liver diseases. • Skin rash (3% to 21%): TPV has a sulfonamide moiety; use with caution in patients with known sulfonamide allergy. • Rare cases of fatal and nonfatal intracranial hemorrhages have been reported. Risks include brain lesion, head trauma, recent neurosurgery, coagulopathy, hypertension, alcoholism, and the use of anti-coagulant or anti-platelet agents (including vitamin E). • Hyperlipidemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia

[a] For dosage adjustment in hepatic insufficiency, see Appendix B, Table 7.

[b] Also see Table 14.

Key to Acronyms: APV = amprenavir; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; AV = atrioventricular; BID = twice daily; COBI = cobicistat; CYP = cytochrome P; DRV = darunavir; DRV/c = darunavir/cobicistat; EFV = efavirenz; FPV = fosamprenavir; GI = gastrointestinal; IDV = indinavir; LPV = lopinavir; LPV/r = lopinavir/ritonavir; msec = millisecond; NFV = nelfinavir; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; PPI = proton pump inhibitor; RTV = ritonavir; SQV = saquinavir; TDF = tenofovir disoproxil fumarate; TID = three times a day; TPV = tipranavir

Appendix B, Table 4. Characteristics of Integrase Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (page 1 of 2)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathways	Serum Half-Life	Adverse Events[b]
Dolutegravir (DTG) *Tivicay* **Also available as a component of fixed-dose combination (by trade name and abbreviation):**	• 50 mg tablet	ARV-Naive or ARV-Experienced, INSTI-Naive Patients: • 50 mg once daily ARV-Naive or ARV-Experienced, INSTI-Naive Patients when Co-Administered with EFV, FPV/r, TPV/r, or Rifampin: • 50 mg BID INSTI-Experienced Patients with Certain INSTI Mutations (See Product Label) or with Clinically Suspected INSTI Resistance: • 50 mg BID Take without regard to meals.	UGT1A1 mediated glucuronidation Minor contribution from CYP3A4	~14 hours	• HSRs, including rash, constitutional symptoms, and organ dysfunction (including liver injury) have been reported. • Insomnia • Headache • Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions)
Triumeq (DTG/ABC/3TC)	Triumeq: • (DTG 50 mg plus ABC 600 mg plus 3TC 300 mg) tablet	Triumeq: • Take 1 tablet daily without regard to meals.			
Elvitegravir (EVG) *Vitekta* **Also available as a component of fixed-dose combinations (by trade name and abbreviation):**	• 85 and 150 mg tablets	With Once Daily ATV/r or BID LPV/r: • 85 mg once daily with food With BID DRV/r, FPV/r, or TPV/r: • 150 mg once daily with food Unboosted EVG **is not recommended**.	CYP3A, UGT1A1/3 substrate	~9 hours	• Nausea • Diarrhea • Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions)
Genvoya (EVG/c/FTC/TAF)	Genvoya: • (EVG 150 mg plus COBI 150 mg plus FTC 200 mg plus TAF 10 mg) tablet	Genvoya: • 1 tablet once daily with food **Not recommended** for patients with CrCl <30 mL/min (see Appendix B, Table 7 for the equation for calculating CrCl). **Not recommended for use with other ARV drugs.**	EVG: As above COBI: CYP3A, CYP2D6 (minor); CYP3A inhibitor	~13 hours	
Stribild (EVG/c/FTC/TDF)	Stribild: • (EVG 150 mg plus COBI 150 mg plus FTC 200 mg plus TDF 300 mg) tablet	Stribild: • 1 tablet once daily with food **Not recommended** for patients with baseline CrCl <70 mL/min (see Appendix B Table 7 for the equation for calculating CrCl). **Not recommended for use with other ARV drugs.**		~13 hours	

Appendix B, Table 4. Characteristics of Integrase Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (page 2 of 2)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathways	Serum Half-Life	Adverse Events[b]
Raltegravir (RAL) *Isentress*	• 400 mg tablet • 25 and 100 mg chewable tablets • 100 mg single packet for oral suspension	• 400 mg BID With Rifampin: • 800 mg BID Take without regard to meals.	UGT1A1-mediated glucuronidation	~9 hours	• Rash, including Stevens-Johnson syndrome, HSR, and toxic epidermal necrolysis • Nausea • Headache • Diarrhea • Pyrexia • CPK elevation, muscle weakness, and rhabdomyolysis • Insomnia • Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions)

[a] For dosage adjustment in hepatic insufficiency, see Appendix B, Table 7.

[b] Also see Table 14.

Key to Abbreviations: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV/r = atazanavir/ritonavir; BID = twice daily; c, COBI = cobicistat; CPK = creatine phosphokinase; CrCl = creatinine clearance; CYP = cytochrome P; DRV/r = darunavir/ritonavir; DTG = dolutegravirEFV = efavirenz; EVG = elvitegravir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; HBV = hepatitis B virus; HSR = hypersensitivity reaction; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; RAL = raltegravir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumerate; TPV/r = tipranavir/ritonavir; UGT = uridine diphosphate gluconyltransferase

Appendix B, Table 5. Characteristics of Fusion Inhibitor (Last updated January 29, 2008; last reviewed April 8, 2015)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendation	Serum Half-Life	Elimination	Storage	Adverse Events[a]
Enfuvirtide (T20) *Fuzeon*	• Injectable; supplied as lyophilized powder • Each vial contains 108 mg of T20; reconstitute with 1.1 mL of sterile water for injection for delivery of approximately 90 mg/1 mL.	• 90 mg (1 mL) subcutaneously BID	3.8 hours	Expected to undergo catabolism to its constituent amino acids, with subsequent recycling of the amino acids in the body pool	Store at room temperature (up to 25° C or 77° F). Re-constituted solution should be refrigerated at 2° to 8° C (36° to 46° F) and used within 24 hours.	• Local injection site reactions (e.g., pain, erythema, induration, nodules and cysts, pruritus, ecchymosis) in almost 100% of patients • Increased incidence of bacterial pneumonia • HSR (<1% of patients): Symptoms may include rash, fever, nausea, vomiting, chills, rigors, hypotension, or elevated serum transaminases. Re-challenge is not recommended.

[a] Also see Table 14.

Key to Abbreviations: BID = twice daily; HSR = hypersensitivity reaction; T20 = enfuvirtide

Appendix B, Table 6. Characteristics of CCR5 Antagonist (Last updated March 27, 2012; last reviewed April 8, 2015)

Generic Name (Abbreviation)/ *Trade Name*	Formulation	Dosing Recommendations[a]	Serum Half-Life	Elimination/ Metabolic Pathway	Adverse Events[b]
Maraviroc (MVC) *Selzentry*	• 150 and 300 mg tablets	• **150 mg BID** when given with drugs that are strong CYP3A inhibitors (with or without CYP3A inducers) including PIs (except TPV/r) • **300 mg BID** when given with NRTIs, T20, TPV/r, NVP, RAL, and other drugs that are not strong CYP3A inhibitors or inducers • **600 mg BID** when given with drugs that are CYP3A inducers, including EFV, ETR, etc. (without a CYP3A inhibitor) • Take without regard to meals.	14–18 hours	CYP3A4 substrate	• Abdominal pain • Cough • Dizziness • Musculoskeletal symptoms • Pyrexia • Rash • Upper respiratory tract infections • Hepatotoxicity, which may be preceded by severe rash or other signs of systemic allergic reactions • Orthostatic hypotension, especially in patients with severe renal insufficiency

[a] For dosage adjustment in hepatic insufficiency, see Appendix B, Table 7.

[b] Also see Table 14.

Key to Abbreviations: BID = twice daily; CYP = cytochrome P; EFV = efavirenz; ETR = etravirine; MVC = maraviroc; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; T20 = enfuvirtide; TPV/r = tipranavir/ritonavir

Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated July 14, 2016; last reviewed July 14, 2016) (page 1 of 6)

See the reference section at the end of this table for creatinine clearance (CrCl) calculation formulas and criteria for Child-Pugh classification.

<table>
<tr><th>ARVs
Generic Name
(Abbreviation)
Trade Name</th><th>Usual Daily Dose[a]</th><th>Dosing in Renal Insufficiency[b]</th><th>Dosing in Hepatic Impairment</th></tr>
<tr><td colspan="4">NRTIs
Stribild should not be initiated in patients with CrCl <70 mL/min. Use of the following fixed-dose combinations is not recommended in patients with CrCl <50 mL/min: Atripla, Combivir, Complera, Epzicom, Stribild, Triumeq, or Trizivir. Use of Truvada is not recommended in patients with CrCl <30 mL/min.</td></tr>
<tr><td>Abacavir
(ABC)
Ziagen</td><td>• 300 mg PO BID</td><td>No dosage adjustment necessary</td><td>Child-Pugh Class A:
• 200 mg PO BID (use oral solution)
Child-Pugh Class B or C:
• Contraindicated</td></tr>
<tr><td>Didanosine EC
(ddI)
Videx EC</td><td>Body Weight ≥60 kg:
• 400 mg PO once daily
Body Weight <60 kg:
• 250 mg PO once daily</td><td><table><tr><th colspan="3">Dose (Once Daily)</th></tr><tr><th>CrCl (mL/min)</th><th>≥60 kg</th><th><60 kg</th></tr><tr><td>30–59</td><td>200 mg</td><td>125 mg</td></tr><tr><td>10–29</td><td>125 mg</td><td>125 mg</td></tr><tr><td><10, HD[c], CAPD</td><td>125 mg</td><td>75 mg oral solution</td></tr></table></td><td>No dosage adjustment necessary</td></tr>
<tr><td>Didanosine Oral Solution
(ddI)
Videx</td><td>Body Weight ≥60 kg:
• 200 mg PO BID, or
• 400 mg PO once daily
Body Weight <60 kg:
• 250 mg PO once daily, or
• 125 mg PO BID</td><td><table><tr><th colspan="3">Dose (Once Daily)</th></tr><tr><th>CrCl (mL/min)</th><th>≥60 kg</th><th><60 kg</th></tr><tr><td>30–59</td><td>200 mg</td><td>150 mg</td></tr><tr><td>10–29</td><td>150 mg</td><td>100 mg</td></tr><tr><td><10, HD[c], CAPD</td><td>100 mg</td><td>75 mg</td></tr></table></td><td>No dosage adjustment necessary</td></tr>
<tr><td>Emtricitabine
(FTC)
Emtriva</td><td>• 200 mg oral capsule once daily, or
• 240 mg (24 mL) oral solution once daily</td><td><table><tr><th colspan="3">Dose</th></tr><tr><th>CrCl (mL/min)</th><th>Capsule</th><th>Solution</th></tr><tr><td>30–49</td><td>200 mg q48h</td><td>120 mg q24h</td></tr><tr><td>15–29</td><td>200 mg q72h</td><td>80 mg q24h</td></tr><tr><td><15 or on HD[c]</td><td>200 mg q96h</td><td>60 mg q24h</td></tr></table></td><td>No dosage recommendation</td></tr>
<tr><td>Lamivudine
(3TC)
Epivir</td><td>• 300 mg PO once daily, or
• 150 mg PO BID</td><td><table><tr><th>CrCl (mL/min)</th><th>Dose</th></tr><tr><td>30–49</td><td>150 mg q24h</td></tr><tr><td>15–29</td><td>1 x 150 mg, then 100 mg q24h</td></tr><tr><td>5–14</td><td>1 x 150 mg, then 50 mg q24h</td></tr><tr><td><5 or on HD[c]</td><td>1 x 50 mg, then 25 mg q24h</td></tr></table></td><td>No dosage adjustment necessary</td></tr>
</table>

Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated July 14, 2016; last reviewed July 14, 2016) (page 2 of 6)

ARVs Generic Name (Abbreviation) *Trade Name*	Usual Daily Dose[a]	Dosing in Renal Insufficiency[b]	Dosing in Hepatic Impairment
NRTIs, continued			
Stavudine (d4T) *Zerit*	Body Weight ≥60 kg: • 40 mg PO BID Body Weight <60 kg: • 30 mg PO BID	**Dose** **CrCl (mL/min)** / **≥60 kg** / **<60 kg** 26–50 / 20 mg q12h / 15 mg q12h 10–25 or on HD[c] / 20 mg q24h / 15 mg q24h	No dosage recommendation
Tenofovir Alafenamide/ Emtricitabine (TAF/FTC) *Descovy*	TAF only available as a component of fixed-dose combinations (i.e., *Descovy*, *Genvoya*, and *Odefsey*) • TAF 10 mg PO daily with EVG/c (*Genvoya*), *or* • TAF 25 mg PO daily in other FDCs	**CrCl (mL/min)** / **Dose** <30 or on HD[c] / Not recommended	Child-Pugh Class A or B: • No dosage adjustment Child-Pugh Class C: • No dosage recommendation
Tenofovir Disoproxil Fumarate (TDF) *Viread*	• 300 mg PO once daily	**CrCl (mL/min)** / **Dose** 30–49 / 300 mg q48h 10–29 / 300 mg twice weekly (every 72–96 hours) <10 and not on HD / No recommendation On HD[c] / 300 mg q7d	No dosage adjustment necessary
Tenofovir Disoproxil Fumarate/ Emtricitabine (TDF/FTC) *Truvada*	• 1 tablet PO once daily	**CrCl (mL/min)** / **Dose** 30–49 / 1 tablet q48h <30 or on HD / Not recommended	No dosage recommendation
Zidovudine (AZT, ZDV) *Retrovir*	• 300 mg PO BID	**CrCl (mL/min)** / **Dose** <15 or on HD[c] / 100 mg TID or 300 mg once daily	No dosage recommendation
NNRTIs			
Delavirdine (DLV) *Rescriptor*	• 400 mg PO TID	No dosage adjustment necessary	No dosage recommendation; use with caution in patients with hepatic impairment.
Efavirenz (EFV) *Sustiva*	• 600 mg PO once daily, at or before bedtime	No dosage adjustment necessary	No dosage recommendation; use with caution in patients with hepatic impairment.
Efavirenz/ Tenofovir Disoproxil Fumarate/ Emtricitabine (EFV/TDF/FTC) *Atripla*	• 1 tablet PO once daily	Not recommended for use in patients with CrCl <50 mL/min. Instead use the individual drugs of the fixed-dose combination and adjust TDF and FTC doses according to CrCl level.	

Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated July 14, 2016; last reviewed July 14, 2016) (page 3 of 6)

ARVs Generic Name (Abbreviation) *Trade Name*	Usual Daily Dose[a]	Dosing in Renal Insufficiency[b]	Dosing in Hepatic Impairment
NNRTIs, continued			
Etravirine (ETR) *Intelence*	• 200 mg PO BID	No dosage adjustment necessary	Child-Pugh Class A or B: • No dosage adjustment Child-Pugh Class C: • No dosage recommendation
Nevirapine (NVP) *Viramune* or *Viramune XR*	• 200 mg PO BID, *or* • 400 mg PO once daily (using Viramune XR formulation)	Patients on HD: • Limited data; no dosage recommendation	Child-Pugh Class A: • No dosage adjustment Child-Pugh Class B or C: • Contraindicated
Rilpivirine (RPV) *Edurant*	• 25 mg PO once daily	No dosage adjustment necessary	Child-Pugh Class A or B: • No dosage adjustment Child-Pugh Class C: • No dosage recommendation
Rilpivirine/Tenofovir Alafenamide/ Emtricitabine (RPV/TAF/FTC) *Odefsey*	• 1 tablet PO once daily	Not recommended for use in patients with CrCl <30 mL/min	Child-Pugh Class A or B: • No dosage adjustment Child-Pugh Class C: • No dosage recommendation
Rilpivirine/Tenofovir Disoproxil Fumarate/ Emtricitabine (RPV/TDF/FTC) *Complera*	• 1 tablet PO once daily	Not recommended for use in patients with CrCl <50 mL/min. Instead use the individual drugs of the fixed-dose combination and adjust TDF and FTC doses according to CrCl level.	Child-Pugh Class A or B: • No dosage adjustment Child-Pugh Class C: • No dosage recommendation
PIs			
Atazanavir (ATV) *Reyataz*	• 400 mg PO once daily, *or* • (ATV 300 mg plus RTV 100 mg) PO once daily	No dosage adjustment for patients with renal dysfunction who do not require HD. ARV-Naive Patients on HD: • (ATV 300 mg plus RTV 100 mg) once daily ARV-Experienced Patients on HD: • ATV or ATV/r not recommended	Child-Pugh Class B: • 300 mg once daily Child-Pugh Class C: • Not recommended RTV boosting **is not recommended** in patients with hepatic impairment.
Atazanavir/ Cobicistat (ATV/c) *Evotaz*	• 1 tablet PO once daily	If Used with TDF: • Not recommended for use in patients with CrCl <70 mL/min	Not recommended in patients with hepatic impairment

Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated July 14, 2016; last reviewed July 14, 2016) (page 4 of 6)

ARVs Generic Name (Abbreviation) *Trade Name*	Usual Daily Dose[a]	Dosing in Renal Insufficiency[b]	Dosing in Hepatic Impairment
PIs, continued			
Darunavir (DRV) *Prezista*	ARV-Naive Patients and ARV-Experienced Patients with No DRV Resistance Mutations: • (DRV 800 mg plus RTV 100 mg) PO once daily ARV-Experienced Patients with at Least One DRV Resistance Mutation: • (DRV 600 mg plus RTV 100 mg) PO BID	No dosage adjustment necessary	Mild-to-Moderate Hepatic Impairment: • No dosage adjustment Severe Hepatic Impairment: • Not recommended
Darunavir/ Cobicistat (DRV/c) *Prezcobix*	• 1 tablet PO once daily (only recommended for patients without DRV-associated resistance mutations)	If Used with TDF: • Not recommended for use in patients with CrCl <70 mL/min	Child-Pugh Class A or B: • No dosage adjustment Child-Pugh Class C: • Not recommended
Fosamprenavir (FPV) *Lexiva*	• 1400 mg PO BID, *or* • (FPV 1400 mg plus RTV 100–200 mg) PO once daily, *or* • (FPV 700 mg plus RTV 100 mg) PO BID	No dosage adjustment necessary	PI-Naive Patients Only *Child-Pugh Score 5–9:* • 700 mg BID *Child-Pugh Score 10–15:* • 350 mg BID PI-Naive or PI-Experienced Patients *Child-Pugh Score 5–6:* • (700 mg BID plus RTV 100 mg) once daily *Child-Pugh Score 7–9:* • (450 mg BID plus RTV 100 mg) once daily *Child-Pugh Score 10–15:* • (300 mg BID plus RTV 100 mg) once daily
Indinavir (IDV) *Crixivan*	• 800 mg PO q8h	No dosage adjustment necessary	Mild-to-Moderate Hepatic Insufficiency Because of Cirrhosis: • 600 mg q8h

Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated July 14, 2016; last reviewed July 14, 2016) (page 5 of 6)

ARVs Generic Name (Abbreviation) *Trade Name*	Usual Daily Dose[a]	Dosing in Renal Insufficiency[b]	Dosing in Hepatic Impairment
PIs, continued			
Lopinavir/Ritonavir (LPV/r) *Kaletra*	• (LPV 400 mg plus RTV 100 mg) PO BID, *or* • (LPV 800 mg plus RTV 200 mg) PO once daily	Avoid once-daily dosing in patients on HD.	No dosage recommendation; use with caution in patients with hepatic impairment.
Nelfinavir (NFV) *Viracept*	• 1250 mg PO BID	No dosage adjustment necessary	Mild Hepatic Impairment: • No dosage adjustment Moderate-to-Severe Hepatic Impairment: • Do not use.
Ritonavir (RTV) *Norvir*	As a PI-Boosting Agent: • 100–400 mg per day	No dosage adjustment necessary	Refer to recommendations for the primary PI.
Saquinavir (SQV) *Invirase*	• (SQV 1000 mg plus RTV 100 mg) PO BID	No dosage adjustment necessary	Mild-to-Moderate Hepatic Impairment: • Use with caution. Severe Hepatic Impairment: • Contraindicated
Tipranavir (TPV) *Aptivus*	• (TPV 500 mg plus RTV 200 mg) PO BID	No dosage adjustment necessary	Child-Pugh Class A: • Use with caution. Child-Pugh Class B or C: • Contraindicated
INSTIs			
Dolutegravir (DTG) *Tivicay*	• 50 mg once daily, *or* • 50 mg BID	No dosage adjustment necessary	Child-Pugh Class A or B: • No dosage adjustment Child-Pugh Class C: • Not recommended
Elvitegravir (EVG) *Vitekta*	• 85 mg or 150 mg[a] once daily	No dosage adjustment necessary	Child-Pugh Class A or B: • No dosage adjustment Child-Pugh Class C: • Not recommended
Elvitegravir/ Cobicistat/Tenofovir Alafenamide/ Emtricitabine (EVG/c/TAF/FTC) *Genvoya*	• 1 tablet once daily	Not recommended for use in patients with CrCl <30 mL/min	Mild-to-Moderate Hepatic Insufficiency: • No dosage adjustment necessary Severe Hepatic Insufficiency: • Not recommended

Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated July 14, 2016; last reviewed July 14, 2016) (page 6 of 6)

ARVs Generic Name (Abbreviation) *Trade Name*	Usual Daily Dose[a]	Dosing in Renal Insufficiency[b]	Dosing in Hepatic Impairment
INSTIs, continued			
Elvitegravir/ Cobicistat/ Tenofovir Disoproxil Fumarate/ Emtricitabine (EVG/c/TDF/FTC) *Stribild*	• 1 tablet once daily	EVG/c/TDF/FTC **should not be initiated** in patients with CrCl <70 mL/min. Discontinue EVG/c/TDF/FTC if CrCl declines to <50 mL/min while patient is on therapy.	Mild-to-Moderate Hepatic Insufficiency: • No dosage adjustment necessary Severe Hepatic Insufficiency: • Not recommended
Raltegravir (RAL) *Isentress*	• 400 mg BID	No dosage adjustment necessary	Mild-to-Moderate Hepatic Insufficiency: • No dosage adjustment necessary Severe Hepatic Insufficiency: • No recommendation
Fusion Inhibitor			
Enfuvirtide (T20) *Fuzeon*	• 90 mg subcutaneous BID	No dosage adjustment necessary	No dosage adjustment necessary
CCR5 Antagonist			
Maraviroc (MVC) *Selzentry*	• The recommended dose differs based on concomitant medications and potential for drug-drug interactions. See Appendix B, Table 6 for detailed dosing information.	CrCl <30 mL/min or on HD *Without Potent CYP3A Inhibitors or Inducers:* • 300 mg BID; reduce to 150 mg BID if postural hypotension occurs *With Potent CYP3A Inducers or Inhibitors:* • Not recommended	No dosage recommendations. Concentrations will likely be increased in patients with hepatic impairment.

[a] Refer to Appendix B, Tables 1–6 for additional dosing information.

[b] Including with chronic ambulatory peritoneal dialysis and hemodialysis.

[c] On dialysis days, take dose after HD session.

Key to Abbreviations: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; AZT = zidovudine; BID = twice daily; c, COBI = cobicistat; CAPD = chronic ambulatory peritoneal dialysis; CrCl = creatinine clearance; CYP = cytochrome P; d4T = stavudine; ddI = didanosine; DLV = delavirdine; DRV = darunavir; DTG = dolutegravir; EC = enteric coated; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; FPV = fosamprenavir; FTC = emtricitabine; HD = hemodialysis; IDV = indinavir; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PO = orally; q(n)d = every (n) days; q(n)h = every (n) hours; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQV = saquinavir; T20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TID = three times daily; TPV = tipranavir; XR = extended release; ZVD = zidovudine

Creatinine Clearance Calculation	
Male: $\frac{(140 - \text{age in years}) \times (\text{weight in kg})}{72 \times (\text{serum creatinine})}$	Female: $\frac{(140 - \text{age in years}) \times (\text{weight in kg}) \times (0.85)}{72 \times (\text{serum creatinine})}$

Child-Pugh Score			
Component	**Points Scored**		
	1	**2**	**3**
Encephalopathy[a]	None	Grade 1–2	Grade 3–4
Ascites	None	Mild or controlled by diuretics	Moderate or refractory despite diuretics
Albumin	>3.5 g/dL	2.8–3.5 g/dL	<2.8 g/dL
Total bilirubin or	<2 mg/dL (<34 µmol/L)	2–3 mg/dL (34 µmol/L to 50 µmol/L)	>3 mg/dL (>50 µmol/L)
Modified total bilirubin[b]	<4 mg/dL	4–7 mg/dL	>7 mg/dL
Prothrombin time (seconds prolonged) or	<4	4–6	>6
International normalized ratio (INR)	<1.7	1.7–2.3	>2.3

[a] Encephalopathy Grades

Grade 1: Mild confusion, anxiety, restlessness, fine tremor, slowed coordination

Grade 2: Drowsiness, disorientation, asterixis

Grade 3: Somnolent but rousable, marked confusion, incomprehensible speech, incontinence, hyperventilation

Grade 4: Coma, decerebrate posturing, flaccidity

[b] Modified total bilirubin used for patients who have Gilbert's syndrome or who are taking indinavir or atazanavir

Child-Pugh Classification	Total Child-Pugh Score[a]
Class A	5–6 points
Class B	7–9 points
Class C	>9 points

[a] Sum of points for each component of the Child-Pugh Score