Table 15. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy (page 1 of 5)

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

Adverse Effect	Drug Class				
	NRTIs	NNRTIs	PIs	INSTIs	EIs
Bleeding Events	N/A	N/A	Spontaneous bleeding, hematuria in hemophilia TPV: Intracranial hemorrhage is associated with CNS lesions, trauma, alcohol abuse, hypertension, coagulopathy, anticoagulant or antiplatelet agents, and the use of vitamin E supplements.	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: Associated with smaller declines in BMD than those seen 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
Cardiac Conduction Effects	N/A	RPV, EFV: QTc prolongation	SQV/r, ATV/r, and LPV/r: PR prolongation. Risk factors include pre-existing heart disease and the use of other medications. SQV/r: QT prolongation. Obtain ECG before administering SQV.	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.	N/A	DRV, FPV, IDV, and LPV/r: Associated with cardiovascular events in some cohorts	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

Table 15. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy (page 2 of 5)

Adverse Effect	Drug Class				
	NRTIs	NNRTIs	PIs	INSTIs	EIs
Diabetes Mellitus and Insulin Resistance	ZDV, d4T, and ddI	N/A	Reported for some (IDV, LPV/r), but not all, PIs.	N/A	N/A
Dyslipidemia	d4T > ZDV > ABC: ↑ TG and LDL TAF: ↑ TG, ↑ LDL, ↑ HDL (no change in TC:HDL ratio) TDF has been associated with lower lipid levels than ABC or TAF.	EFV: ↑ TG, ↑ LDL, ↑ HDL	All RTV- or COBI-Boosted PIs: ↑ TG, ↑ LDL, ↑ HDL LPV/r and FPV/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 (e.g., diarrhea, nausea, vomiting) NFV and LPV/r > DRV/r and ATV/r: Diarrhea	EVG/c: Nausea and diarrhea	IBA: 8% of patients reported diarrhea in a study of 40 people.
Hepatic Effects	**Reported with most NRTIs.** ZDV, d4T, and ddI: Steatosis ddI: Prolonged exposure linked to noncirrhotic portal hypertension and esophageal varices. When TAF, TDF, 3TC, and FTC are Withdrawn in Patients with HBV/HIV Coinfection or When HBV Resistance Develops: Patients with HBV/HIV coinfection may develop severe hepatic flares.	EFV: Most cases relate to an increase in transaminases. Fulminant hepatitis leading to death or hepatic failure requiring transplantation have been reported. NVP: Severe hepatotoxicity associated with skin rash or hypersensitivity. A 2-week NVP dose escalation may reduce risk. Risk is greater for women with pre-NVP CD4 counts >250 cells/mm^3 and men with pre-NVP CD4 counts >400 cells/mm^3. NVP should **never** be used for post-exposure prophylaxis. EFV and NVP **are not recommended** in patients with hepatic insufficiency (Child-Pugh class B or C).	All PIs: Drug-induced hepatitis and hepatic decompensation have been reported; greatest frequency occurs with TPV/r. TPV/r: **Contraindicated** in patients with hepatic insufficiency (Child Pugh class B or C). IDV and ATV: Jaundice due to indirect hyperbilirubinemia	N/A	MVC: Hepatotoxicity with or without rash or HSRs reported.

Table 15. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy (page 3 of 5)

Adverse Effect	Drug Class				
	NRTIs	NNRTIs	PIs	INSTIs	EIs
Hypersensitivity Reaction Excluding rash alone or Stevens-Johnson syndrome	ABC: **Contraindicated** if patient is HLA-B*5701 positive. Median onset for HSR is 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 should not be rechallenged with ABC if HSR is suspected, regardless of their HLA-B*5701 status.	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 counts >250 cells/mm^3 and men with pre-NVP CD4 counts >400 cells/mm^3. Overall, risk is higher for women than men. A 2-week dose escalation of NVP reduces risk.	N/A	RAL: HSR reported when RAL is given with other drugs also known to cause HSRs. All ARVs should be stopped if HSR occurs. DTG: Reported in <1% of patients in clinical development program	MVC: HSR 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
Lipodystrophy	Lipoatrophy: d4T > ZDV. More likely when NRTIs are coadministered with EFV than with an RTV-boosted PI.	Lipohypertrophy: Trunk fat increase observed with EFV-, PI-, and RAL-containing regimens; however, causal relationship has not been established.			N/A

Table 15. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy (page 4 of 5)

Adverse Effect	Drug Class				
	NRTIs	NNRTIs	PIs	INSTIs	EIs
Myopathy/ Elevated Creatine Phosphokinase	ZDV: Myopathy	N/A	N/A	RAL and DTG: ↑ CPK, rhabdomyolysis, and myopathy or myositis have been reported.	N/A
Nervous System/ Psychiatric Effects	d4T > ddI: Peripheral neuropathy (can be irreversible) d4T: Associated with rapidly progressive, ascending neuromuscular weakness resembling Guillain-Barré syndrome (rare)	Neuropsychiatric Events: EFV > RPV, DOR > ETR EFV: Somnolence, insomnia, abnormal dreams, dizziness, impaired concentration, depression, psychosis, and suicidal ideation. Symptoms usually subside or diminish after 2–4 weeks. Bedtime dosing may reduce symptoms. Risk factors include presence of 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 was found in a retrospective analysis of comparative trials. RPV: Depression, suicidality, sleep disturbances DOR: Sleep disorders and disturbances, dizziness, altered sensorium; depression and suicidality/self-harm	N/A	All INSTIs: Insomnia, depression, and suicidality have been reported with INSTI use, primarily in patients with pre-existing psychiatric conditions.	N/A
Rash	FTC: Hyperpigmentation	All NNRTIs	ATV, DRV, FPV, LPV/r, and TPV	All INSTIs	MVC, IBA

Table 15. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy (page 5 of 5)

Adverse Effect	Drug Class				
	NRTIs	NNRTIs	PIs	INSTIs	EIs
Renal Effects/ Urolithiasis	TDF: ↑ SCr, proteinuria, hypophosphatemia, urinary phosphate wasting, glycosuria, hypokalemia, and 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.	RPV: Inhibits Cr secretion without reducing renal glomerular function.	ATV and LPV/r: Associated with increased risk of chronic kidney disease in a large cohort study. IDV: ↑ SCr, pyuria, renal atrophy, or hydronephrosis IDV, ATV: Stone or crystal formation. Adequate hydration may reduce risk. COBI (as a Boosting Agent for DRV or ATV): Inhibits Cr secretion without reducing renal glomerular function.	DTG, COBI (as a Boosting Agent for EVG), and BIC: Inhibits Cr secretion without reducing renal glomerular function	IBA: SCr abnormalities ≥Grade 3 reported in 10% of trial participants.
Stevens-Johnson Syndrome/ Toxic Epidermal Necrosis	Some reported cases for ddI and ZDV.	NVP > DLV, EFV, ETR, RPV	Some reported cases for FPV, DRV, IDV, LPV/r, and ATV.	RAL	N/A

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ART= antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/r = atazanavir/ritonavir; BIC = bictegravir; BMD = bone mineral density; CD4 = CD4 T lymphocyte; Cr = creatinine; CNS = central nervous system; COBI = cobicistat; CPK = creatine phosphokinase; CVD = cardiovascular disease; d4T = stavudine; ddI = didanosine; DLV = delavirdine; DOR = doravirine; DRV = darunavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; ECG = electrocardiogram; EFV = efavirenz; EI = entry inhibitor; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FPV = fosamprenavir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; GI = gastrointestinal; HBV = hepatitis B virus; HDL = high-density lipoprotein; HSR = hypersensitivity reaction; IBA = ibalizumab; 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; TC = total cholesterol; TDF = tenofovir disoproxil fumarate; TG = triglycerides; TPV = tipranavir; TPV/r = tipranavir/ritonavir; ZDV = zidovudine

Switching Antiretroviral Therapy Due to Adverse Effects

Some patients experience treatment-limiting toxicities associated with ART. In these cases, ART must be modified. ART-associated adverse events can range from acute and potentially life-threatening to chronic and insidious. Serious life-threatening events (e.g., hypersensitivity reaction due to ABC, symptomatic hepatotoxicity, or severe cutaneous reactions) require the immediate discontinuation of all ARV drugs and re-initiation of an alternative regimen without overlapping toxicity. Toxicities that are not life-threatening (e.g., urolithiasis with ATV or renal tubulopathy with TDF) can usually be managed by substituting another ARV agent for the presumed causative agent without interrupting ART. Other chronic, non–life-threatening adverse events (e.g., dyslipidemia) can be addressed either by switching the potentially causative agent for another agent or by managing the adverse event with additional pharmacological or nonpharmacological interventions. Management strategies must be individualized for each patient.

Switching from an effective ARV regimen (or agent) to a new regimen (or agent) must be done carefully and only when the potential benefits of the change outweigh the potential complications of altering treatment. The fundamental principle of regimen switching is to maintain viral suppression. When selecting a new agent or regimen, providers should be aware that resistance mutations are archived in HIV reservoirs, regardless of when the mutations were identified by genotypic resistance testing. Even if resistance mutations are absent from subsequent resistance test results, they may reappear under selective drug pressure. It is critical that providers review the following information before implementing any treatment switch:

- The patient's medical and complete ARV history, including prior virologic responses to ART;
- All previous resistance test results;
- Viral tropism (if MVC is being considered);
- HLA-B*5701 status (if ABC is being considered);
- Comorbidities;
- The patient's pregnancy status, ability to use effective contraceptives, and desire for pregnancy (if DTG is being considered for patients of child-bearing potential);
- HBV status, since patients with evidence of chronic HBV infection should not discontinue TDF or TAF unless a regimen contains another agent that is active against HBV;
- Adherence history;
- Prior intolerances to any ARVs; and
- Concomitant medications and supplements, taking into consideration any potential drug interactions with ARVs.

A patient's willingness to accept new requirements for food or dosing must also be assessed. In some cases, medication costs may also be a factor to consider before switching treatment. Signs and symptoms of comorbidities, adverse effects of concomitant medications, or HIV itself may mimic adverse effects caused by ART. Therefore, clinicians should investigate all potential causes for an adverse event. In the case of a severe adverse event, it may be necessary to discontinue or switch ARVs pending the outcome of such an investigation. For the first few months after an ART switch, the patient should be closely monitored for any new adverse events. The patient's viral load should also be monitored to assure continued viral suppression.

Table 16 lists several major ART-associated adverse events and the options for appropriate switches between agents in an ARV regimen. The table focuses on the ARVs most commonly used in the United States and lists substitutions that are supported by ARV switch studies, the findings of comparative ARV trials and observational cohort studies, or expert opinion. Switching agents in a successful ARV regimen should be done carefully and only when the potential benefits of the change outweigh the potential complications of altering treatment.

Table 16. Antiretroviral Therapy-Associated Adverse Events That Can Be Managed with Substitution of Alternative Antiretroviral Agent (page 1 of 3)

Adverse Event	ARV Agent(s) or Drug Class		Comments
	Switch from	Switch to	
Bone Density Effects	TDF[a]	TAF or ABC[b] NRTI-sparing regimens or regimens using only 3TC or FTC as the 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 patients show improvement in BMD upon switching to TAF. 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.
Cardiac QTc Interval Prolongation	EFV, RPV	A PI- or INSTI-based regimen	High EFV and RPV exposures may cause QT prolongation. Consider switching from EFV- or RPV-based regimens if patient is taking other medications with known risk of Torsades de Pointes, or in patients at higher risk of Torsades de Pointes.
Cardiovascular Events Myocardial infarction, ischemic stroke	ABC	TDF, TAF, FTC, or 3TC	ABC use has been associated with CV disease and cardiac events in some, but not all, observational studies. TDF has been associated with lower lipid levels than TAF.
	RTV- or COBI-boosted PI regimens, EFV, EVG/c	RAL, DTG, BIC, or RPV	RAL, DTG, BIC, and RPV have less effect on lipids than RTV- or COBI-boosted PI regimens, EFV, and EVG/c. Large observation cohorts have found an association between some PIs (DRV, FPV, IDV, LPV/r) and an increased risk of CV events. However, this association has not been seen with ATV. Further study is needed.
Central Nervous System, Neuropsychiatric Side Effects Dizziness, suicidal ideation, abnormal dreams, depression	EFV, RPV	ETR, PI/c, or PI/r INSTIs may be used, but monitoring is recommended (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, and EFV	RAL, DTG, BIC, or 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]

Table 16. Antiretroviral Therapy-Associated Adverse Events That Can Be Managed with Substitution of Alternative Antiretroviral Agent (page 2 of 3)

Adverse Event	ARV Agent(s) or Drug Class		Comments
	Switch from	Switch to	
Gastrointestinal Effects Nausea, diarrhea	LPV/r	ATV/c, ATV/r, DRV/c, DRV/r, RAL, DTG, BIC, or 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 they are persistent and intolerable.
	Other RTV- or COBI-boosted regimens	RAL, DTG, BIC, or 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	Non-INSTI ART	Reactions to NVP, ETR, RAL, DTG, and MVC may be accompanied by elevated liver transaminases.
	MVC	Suitable alternative ART	
Insulin Resistance	LPV/r, FPV/r	INSTI, NNRTI	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 the 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.
Lipoatrophy Subcutaneous fat wasting of limbs, face, buttocks	d4T, ZDV	TDF, TAF, or ABC[b]	Peripheral lipoatrophy is associated with 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, dorsocervical, and breast fat has been observed during ART, particularly during use of older PI-based regimens (e.g., 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 that develop 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 (e.g., INSTI)	Mild rashes following DRV/r use may resolve without modification of therapy. For more severe reactions, change to an alternative boosted PI or an agent from another drug class.

Table 16. Antiretroviral Therapy-Associated Adverse Events That Can Be Managed with Substitution of Alternative Antiretroviral Agent (page 3 of 3)

Adverse Event	ARV Agent(s) or Drug Class		Comments
	Switch from	Switch to	
Renal Effects Including proximal renal tubulopathy and elevated creatinine	TDF[a]	ABC,[b] TAF (for patients with CrCl >30 mL/min), NRTI-sparing regimens, or regimens using only 3TC or FTC as the 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, BIC, RAL, or NNRTI	COBI, DTG, BIC, and, to a lesser extent, RPV, can increase SCr through inhibition of creatinine secretion. This effect does not affect glomerular filtration. However, assess patient 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	This switch should be made if the clinician believes ATV is the cause of the stones.

[a] In patients with chronic active HBV infection, another agent that is 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 coadministered with TDF.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; BMD = bone mineral density; CD4 = CD4 T lymphocyte; CNS = central nervous system; COBI = cobicistat; CrCl = creatine clearance; CV = cardiovascular; d4T = stavudine; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; FPV = fosamprenavir; 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; NRTI = 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; TC = total cholesterol; TDF = tenofovir disoproxil fumarate; TG = triglycerides; ZDV = zidovudine

References

1. O'Brien ME, Clark RA, Besch CL, et al. Patterns and correlates of discontinuation of the initial HAART regimen in an urban outpatient cohort. *J Acquir Immune Defic Syndr*. 2003;34(4):407-414. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14615659.
2. den Brinker M, Wit FW, Wertheim-van Dillen PM, et al. Hepatitis B and C virus co-infection and the risk for hepatotoxicity of highly active antiretroviral therapy in HIV-1 infection. *AIDS*. 2000;14(18):2895-2902. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11153671.
3. Saves M, Raffi F, Clevenbergh P, et al. Hepatitis B or hepatitis C virus infection is a risk factor for severe hepatic cytolysis after initiation of a protease inhibitor-containing antiretroviral regimen in human immunodeficiency virus-infected patients. The APROCO Study Group. *Antimicrob Agents Chemother*. 2000;44(12):3451-3455. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11083658.
4. Harris M, Larsen G, Montaner JS. Exacerbation of depression associated with starting raltegravir: a report of four cases. *AIDS*. 2008;22(14):1890-1892. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18753871.
5. Kheloufi F, Allemand J, Mokhtari S, Default A. Psychiatric disorders after starting dolutegravir: report of four cases. *AIDS*. 2015;29(13):1723-1725. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26372287.

6. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med*. 2008;358(6):568-579. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18256392.
7. Saag M, Balu R, Phillips E, et al. High sensitivity of human leukocyte antigen-b*5701 as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients. *Clin Infect Dis*. 2008;46(7):1111-1118. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18444831.
8. Gounden V, van Niekerk C, Snyman T, George JA. Presence of the CYP2B6 516G> T polymorphism, increased plasma efavirenz concentrations and early neuropsychiatric side effects in South African HIV-infected patients. *AIDS Res Ther*. 2010;7:32. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20723261.
9. Abdelhady AM, Shugg T, Thong N, et al. Efavirenz inhibits the human ether-a-go-go related current (hERG) and induces QT interval prolongation in CYP2B6*6*6 allele carriers. *J Cardiovasc Electrophysiol*. 2016;27(10):1206-1213. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27333947.
10. Rodriguez-Novoa S, Martin-Carbonero L, Barreiro P, et al. Genetic factors influencing atazanavir plasma concentrations and the risk of severe hyperbilirubinemia. *AIDS*. 2007;21(1):41-46. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17148966.

Cost Considerations and Antiretroviral Therapy (Last updated July 14, 2016; last reviewed July 14, 2016)

Although antiretroviral therapy (ART) is expensive (see Table 16 below), the cost-effectiveness of ART has been demonstrated in analyses of older[1] and newer regimens,[2,3] as well as for treatment-experienced patients with drug-resistant HIV.[4] Given the recommendations for immediate initiation of lifelong treatment and the increasing number of patients taking ART, the Panel now introduces cost-related issues pertaining to medication adherence and cost-containment strategies, as discussed below.

Costs as They Relate to Adherence from a Patient Perspective

Cost sharing: Cost sharing is where the patient is responsible for some of the medication cost burden (usually accomplished via copayments, coinsurance, or deductibles); these costs are often higher for branded medications than for generic medications. In one comprehensive review, increased patient cost sharing resulted in decreased medical adherence and more frequent drug discontinuation; for patients with chronic diseases, increased cost sharing was also associated with increased use of the medical system.[5] Conversely, copayment reductions, such as those that might be used to incentivize prescribing of generic drugs, have been associated with improved adherence in patients with chronic diseases.[6] Whereas cost sharing disproportionately affects low-income patients, resources (e.g., the Ryan White AIDS Drug Assistance Program [ADAP]) are available to assist eligible patients with copays and deductibles. Given the clear association between out-of-pocket costs for patients with chronic diseases and the ability of those patients to pay for and adhere to medications, clinicians should minimize patients' out-of-pocket drug-related expenses whenever possible.

Prior authorizations: As a cost-containment strategy, some programs require that clinicians obtain prior authorizations or permission before prescribing newer or more costly treatments rather than older or less expensive drugs. Although there are data demonstrating that prior authorizations do reduce spending, several studies have also shown that prior authorizations result in fewer prescriptions filled and increased nonadherence.[7-9] Prior authorizations in HIV care specifically have been reported to cost over $40 each in provider personnel time (a hidden cost) and have substantially reduced timely access to medications.[10]

Generic ART: The impact of the availability of generic antiretroviral (ARV) drugs on selection of ART in the United States is unknown. Because U.S. patent laws currently limit the coformulation of some generic alternatives to branded drugs, generic options may result in increased pill burden. To the extent that pill burden, rather than drug frequency, results in reduced adherence, generic ART could lead to decreased costs but at the potential expense of worsening virologic suppression rates and poorer clinical outcomes.[11,12] Furthermore, prescribing the individual, less-expensive generic components of a branded coformulated product rather than the branded product itself could, under some insurance plans, lead to higher copays—an out-of-pocket cost increase that may reduce medication adherence.

Potential Cost Containment Strategies from a Societal Perspective

Given resource constraints, it is important to maximize the use of resources without sacrificing clinical outcomes. Evidence-based revisions to these guidelines recommend tailored laboratory monitoring for patients with long-term virologic suppression on ART as one possible way to provide overall cost savings. Data suggest that continued CD4 monitoring yields no clinical benefit for patients whose viral loads are suppressed and whose CD4 counts exceed 200 cells/mm^3 after 48 weeks of therapy.[13] A reduction in laboratory use from biannual to annual CD4 monitoring could save ~$10 million per year in the United States[14] (see Laboratory Monitoring). Although this is a small proportion of the overall costs associated with HIV care, such a strategy could reduce patients' personal expenses if they have deductibles for laboratory tests. The present and future availability of generic formulations of certain ARV drugs, despite the potential caveats of increased pill burden and reduced adherence, offers other money-saving possibilities on a much

greater scale. One analysis suggests the possibility of saving approximately $900 million nationally in the first year of switching from a branded fixed-dose combination product to a three-pill regimen containing generic efavirenz.[3]

In summary, understanding HIV and ART related-costs in the United States is complicated because of the wide variability in medical coverage, accessibility, and expenses across regions, insurance plans, and pharmacies. In an effort to retain excellent clinical outcomes in an environment of cost-containment strategies, providers should remain informed of current insurance and payment structures, ART costs (see Table 16 below for estimates of drugs' average wholesale prices), discounts among preferred pharmacies, and available generic ART options. Providers should work with patients and their case managers and social workers to understand their patients' particular pharmacy benefit plans and potential financial barriers to filling their prescriptions. Additionally, providers should familiarize themselves with ARV affordability resources (such as ADAP and pharmaceutical company patient assistance programs for patients who qualify) and refer patients to such assistance if needed.

Table 17. Monthly Average Prices of Commonly Used Antiretroviral Drugs (Last updated November 26, 2018; last reviewed October 25, 2018) (page 1 of 5)

Prescription drug pricing in the United States involves complex systems of negotiations, rebates, discounts, and reimbursement rates. Much of the information used to determine drug prices is confidential, and prices can vary depending on the purchaser, the type of public or private insurance coverage in use, and the number of generic competitors. In addition, price increases that exceed rates of inflation can trigger additional rebates for Medicaid and 340B Drug Discount Program entities. Table 17 includes three benchmark prices, rounded to the nearest dollar, for commonly used antiretroviral (ARV) drugs[a] as a general reference for health care providers when considering the cost of HIV treatment. Health care providers should contact patients' pharmacies or payors regarding actual prices, comparative cost savings, and related formulary restrictions.

Wholesale acquisition cost (WAC) is the list price published by manufacturers for prescription drugs or biologics sold to wholesalers. The WAC price approximates what retail pharmacies pay wholesalers for single-source (e.g., brand-name) drugs. There is a range of WAC prices for generic ARVs, as these are multiple-source products with variable list prices. With increasing competition, actual transactional prices of generic drugs among wholesalers and pharmacies decrease substantially. **Average wholesale price (AWP)** has historically been used as the basis for setting public (e.g., Medicaid) and private (e.g., commercial insurer) reimbursement rates for pharmacies. Neither WAC nor AWP include variable price concessions along supply and payment chains, including discounts and rebates to wholesalers, pharmacies, federal purchasers (e.g., the Veterans' Administration), pharmacy benefit managers, commercial insurers, Medicaid, 340B pharmacies, and AIDS Drug Assistance Programs. The availability of these discounts and rebates depends on product demand, market competition, and WAC price increases set by manufacturers.

Maximum prices are assigned to generic products with three or more therapeutically and pharmaceutically equivalent products, as determined by the Food and Drug Administration. This federally established price is the **federal upper limit (FUL)**. Federal Medicaid will reimburse state Medicaid programs up to this limit for multiple-source drugs (plus the dispensing fee); commercial insurers set their own reimbursement upper limits with pharmacies. Whereas WACs and AWPs are generally set annually, FULs are adjusted monthly, particularly for multiple-source drugs with fluctuating pharmacy acquisition costs. In the table below, the FUL for a drug is described as "pending" if a generic drug currently lacks the competition required to trigger a FUL.

ARV Drug (Generic and Brand Names)	Strength, Formulation	Tablets, Capsules, or mLs per Month	WAC (Monthly)[b]	AWP (Monthly)[b]	FUL (As of 9/1/2018)[c]
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)					
Abacavir					
• Generic	300 mg tablet	60 tablets	$150 to $482	$579 to $603	$44
• Ziagen	300 mg tablet	60 tablets	$559	$670	
Emtricitabine					
• Emtriva	200 mg capsules	30 capsules	$537	$644	N/A
Lamivudine					
• Generic	300 mg tablet	30 tablets	$75 to $343	$429 to $430	$83
• Epivir	300 mg tablet	30 tablets	$416	$499	

Table 17. Monthly Average Prices of Commonly Used Antiretroviral Drugs (Last updated November 26, 2018; last reviewed October 25, 2018) (page 2 of 5)

ARV Drug (Generic and Brand Names)	Strength, Formulation	Tablets, Capsules, or mLs per Month	WAC (Monthly)[b]	AWP (Monthly)[b]	FUL (As of 9/1/2018)[c]
Nucleoside Reverse Transcriptase Inhibitors (NRTIs), continued					
Tenofovir Disoproxil Fumarate					
• Generic	300 mg tablet	30 tablets	$58 to $922	$110 to $1,216	Pending
• Viread	300 mg tablet	30 tablets	$1,140	$1,368	
Zidovudine					
• Generic	300 mg tablet	60 tablets	$36 to $54	$54 to $365	$13
NRTI Combination Products					
Abacavir/Lamivudine					
• Generic	600 mg/300 mg tablets	30 tablets	$185 to $1,116	$1,395	$356
• Epzicom	600 mg/300 mg tablets	30 tablets	$1,292	$1,550	
Tenofovir Alafenamide/Emtricitabine					
• Descovy	25 mg/200 mg tablet	30 tablets	$1,676	$2,011	N/A
Tenofovir Disoproxil Fumarate/Emtricitabine					
• Truvada	300 mg/200 mg tablet	30 tablets	$1,676	$2,011	N/A
Tenofovir Disoproxil Fumarate/Lamivudine					
• Cimduo	300 mg/300 mg tablet	30 tablets	$1,005	$1,207	N/A
Zidovudine/Lamivudine					
• Generic	300 mg/150 mg tablet	60 tablets	$134 to $578	$878 to $932	$47
• Combivir	300 mg/150 mg tablet	60 tablets	$901	$1,082	
Abacavir Sulfate/Zidovudine/Lamivudine					
• Generic	300 mg/300 mg/150 mg tablet	60 tablets	$1,391	$1,738	Pending
• Trizivir	300 mg/300 mg/150 mg tablet	60 tablets	$1,610	$1,932	
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)					
Efavirenz					
• Generic	600 mg tablet	30 tablets	$894	$1,118	Pending
• Sustiva	600 mg tablet	30 tablets	$981	$1,177	
Doravirine					
• Pifeltro	100 mg tablet	30 tablets	$1,380	$1,656	N/A

Table 17. Monthly Average Prices of Commonly Used Antiretroviral Drugs (Last updated November 26, 2018; last reviewed October 25, 2018) (page 3 of 5)

ARV Drug (Generic and Brand Names)	Strength, Formulation	Tablets, Capsules, or mLs per Month	WAC (Monthly)[b]	AWP (Monthly)[b]	FUL (As of 9/1/2018)[c]
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), continued					
Etravirine					
• Intelence	200 mg tablet	60 tablets	$1,296	$1,523	N/A
Nevirapine					
• Generic	200 mg tablet	60 tablets	$10 to $45	$648 to $651	$37
• Viramune	200 mg tablet	60 tablets	$855	$1,026	
• Generic XR	400 mg tablet	30 tablets	$246 to $565	$678 to $706	$231
• Viramune XR	400 mg tablet	30 tablets	$793	$951	
Rilpivirine					
• Edurant	25 mg tablet	30 tablets	$1043	$1,252	N/A
Protease Inhibitors (PIs)					
Atazanavir					
• Generic	200 mg capsule	60 capsules	$878 to $1,264	$1,580 to $1,668	Pending
• Reyataz	200 mg capsule	60 capsules	$1,463	$1,756	
• Generic	300 mg capsule	30 capsules	$870 to $1,252	$1,565 to $1,652	Pending
• Reyataz	300 mg capsule	30 capsules	$1,449	$1,739	
Atazanavir/Cobicistat					
• Evotaz	300/150 mg tablet	30 tablets	$1,605	$1,927	N/A
Darunavir					
• Prezista	600 mg tablet	60 tablets	$1,581	$1,897	N/A
• Prezista	800 mg tablet	30 tablets	$1,581	$1,897	N/A
• Prezista	100 mg/mL suspension	200 mL	$878	$1,054	N/A
Darunavir/Cobicistat					
• Prezcobix	800 mg/150 mg tablet	30 tablets	$1,806	$2,168	N/A
Lopinavir/Ritonavir					
• Kaletra	200 mg/50 mg tablet	120 tablets	$1,024	$1,229	N/A
Tipranavir					
• Aptivus	250 mg capsule	120 capsules	$1,578	$1,894	N/A

Table 17. Monthly Average Prices of Commonly Used Antiretroviral Drugs (Last updated November 26, 2018; last reviewed October 25, 2018) (page 4 of 5)

ARV Drug (Generic and Brand Names)	Strength, Formulation	Tablets, Capsules, or mLs per Month	WAC (Monthly)[b]	AWP (Monthly)[b]	FUL (As of 9/1/2018)[c]
Integrase Strand Transfer Inhibitors (INSTIs)					
Dolutegravir					
• Tivicay	50 mg tablet	30 tablets	$1,658	$1,989	N/A
• Tivicay	50 mg tablet	60 tablets	$3,315	$3,978	N/A
Raltegravir					
• Isentress	400 mg tablet	60 tablets	$1,500	$1,800	N/A
• Isentress HD	600 mg tablet	60 tablets	$1,500	$1,800	N/A
Fusion Inhibitor					
Enfuvirtide					
• Fuzeon	90 mg injection kit	60 doses (1 kit)	$3,586	$4,303	N/A
CCR5 Antagonist					
Maraviroc					
• Selzentry	150 mg tablet	60 tablets	$1,511	$1,813	N/A
• Selzentry	300 mg tablet	60 tablets	$1,511	$1,813	N/A
• Selzentry	300 mg tablet	120 tablets	$3,022	$3,626	N/A
CD4-Directed Post-Attachment Inhibitor					
Ibalizumab-uiyk					
• Trogarzo	200 mg vials	8 vials	$9,080	$10,896	N/A
Coformulated Combination Products as Single Tablet Regimens					
Bictegravir/Tenofovir Alafenamide/Emtricitabine					
• Biktarvy	50 mg/25 mg/200 mg	30 tablets	$2,946	$3,535	N/A
Darunavir/Cobicistat/Tenofovir Alafenamide/Emtricitabine					
• Symtuza	600 mg/150 mg/10 mg/200 mg	30 tablets	$3,482	$4,178	N/A
Dolutegravir/Abacavir/Lamivudine					
• Triumeq	50 mg/600 mg/300 mg tablet	30 tablets	$2,805	$3,366	N/A
Dolutegravir/Rilpivirine					
• Juluca	50 mg/25 mg	30 tablets	$2,579	$3,095	N/A
Doravirine/Tenofovir Disoproxil Fumarate/Lamivudine					
• Delstrigo	100 mg/300 mg/300 mg	30 tablets	$2,100	$2,520	N/A

Table 17. Monthly Average Prices of Commonly Used Antiretroviral Drugs (Last updated November 26, 2018; last reviewed October 25, 2018) (page 5 of 5)

ARV Drug (Generic and Brand Names)	Strength, Formulation	Tablets, Capsules, or mLs per Month	WAC (Monthly)[b]	AWP (Monthly)[b]	FUL (As of 9/1/2018)[c]
Coformulated Combination Products as Single Tablet Regimens, continued					
Efavirenz/Tenofovir Disoproxil Fumarate/Emtricitabine					
• Atripla	600 mg/300 mg/200 mg tablet	30 tablets	$2,724	$3,269	N/A
Efavirenz/Tenofovir Disoproxil Fumarate/Lamivudine					
• Symfi	600 mg/300 mg/300 mg tablet	30 tablets	$1,634	$1,961	N/A
• Symfi Lo	400 mg/300 mg/300 mg tablet	30 tablets	$1,634	$1,961	N/A
Elvitegravir/Cobicistat/Tenofovir Alafenamide/Emtricitabine					
• Genvoya	150 mg/150 mg/10 mg/200 mg tablet	30 tablets	$2,946	$3,535	N/A
Elvitegravir/Cobicistat/Tenofovir Disoproxil Fumarate/ Emtricitabine					
• Stribild	150 mg/150 mg/300 mg/200 mg tablet	30 tablets	$3,090	$3,708	N/A
Rilpivirine/Tenofovir Alafenamide/Emtricitabine					
• Odefsey	25 mg/25 mg/200 mg tablet	30 tablets	$2,681	$3,217	N/A
Rilpivirine/Tenofovir Disoproxil Fumarate/Emtricitabine					
• Complera	25 mg/300 mg/200 mg tablet	30 tablets	$2,681	$3,217	N/A
Pharmacokinetic Enhancers (Boosters)					
Cobicistat					
• Tybost	150 mg tablet	30 tablets	$219	$264	N/A
Ritonavir					
• Generic	100 mg tablet	30 tablets	$222	$278	Pending
• Norvir	100 mg tablet	30 tablets	$257	$309	

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

[b] Source: IBM Watson Health. Micromedex Red Book [database]. 2018. Available at: https://www.micromedexsolutions.com

[c] Source: Medicare & Medicaid Services. Federal Upper Limits—September 2018 [database]. 2018 September 1. Available at: https://www.medicaid.gov/medicaid/prescription-drugs/pharmacy-pricing/index.html.

References

1. Freedberg KA, Losina E, Weinstein MC, et al. The cost effectiveness of combination antiretroviral therapy for HIV disease. *N Engl J Med*. Mar 15 2001;344(11):824-831. Available at https://www.ncbi.nlm.nih.gov/pubmed/11248160.
2. Mauskopf J, Brogan AJ, Talbird SE, Martin S. Cost-effectiveness of combination therapy with etravirine in treatment-experienced adults with HIV-1 infection. *AIDS*. Jan 28 2012;26(3):355-364. Available at http://www.ncbi.nlm.nih.gov/pubmed/22089378.
3. Walensky RP, Sax PE, Nakamura YM, et al. Economic savings versus health losses: the cost-effectiveness of generic antiretroviral therapy in the United States. *Ann Intern Med*. Jan 15 2013;158(2):84-92. Available at http://www.ncbi.nlm.nih.gov/pubmed/23318310.
4. Bayoumi AM, Barnett PG, Joyce VR, et al. Cost-effectiveness of newer antiretroviral drugs in treatment-experienced patients with multidrug-resistant HIV disease. *J Acquir Immune Defic Syndr*. Dec 1 2013;64(4):382-391. Available at http://www.ncbi.nlm.nih.gov/pubmed/24129369.
5. Goldman DP, Joyce GF, Zheng Y. Prescription drug cost sharing: associations with medication and medical utilization and spending and health. *JAMA*. Jul 4 2007;298(1):61-69. Available at http://www.ncbi.nlm.nih.gov/pubmed/17609491.
6. Maciejewski ML, Farley JF, Parker J, Wansink D. Copayment reductions generate greater medication adherence in targeted patients. *Health Aff*. Nov 2010;29(11):2002-2008. Available at http://www.ncbi.nlm.nih.gov/pubmed/21041739.
7. Abdelgawad T, Egbuonu-Davis L. Preferred drug lists and Medicaid prescriptions. *Pharmacoeconomics*. 2006;24 Suppl 3:55-63. Available at http://www.ncbi.nlm.nih.gov/pubmed/17266388.
8. Ridley DB, Axelsen KJ. Impact of Medicaid preferred drug lists on therapeutic adherence. *Pharmacoeconomics*. 2006;24 Suppl 3:65-78. Available at http://www.ncbi.nlm.nih.gov/pubmed/17266389.
9. Wilson J, Axelsen K, Tang S. Medicaid prescription drug access restrictions: exploring the effect on patient persistence with hypertension medications. *Am J Manag Care*. Jan 2005;11 Spec No:SP27-34. Available at http://www.ncbi.nlm.nih.gov/pubmed/15760907.
10. Raper JL, Willig JH, Lin HY, et al. Uncompensated medical provider costs associated with prior authorization for prescription medications in an HIV clinic. *Clin Infect Dis*. Sep 15 2010;51(6):718-724. Available at http://www.ncbi.nlm.nih.gov/pubmed/20695800.
11. Hanna DB, Hessol NA, Golub ET, et al. Increase in Single-Tablet Regimen Use and Associated Improvements in Adherence-Related Outcomes in Hiv-Infected Women. *J Acquir Immune Defic Syndr*. Dec 8 2013. Available at http://www.ncbi.nlm.nih.gov/pubmed/24326606.
12. Nachega JB, Parienti JJ, Uthman OA, et al. Lower pill burden and once-daily antiretroviral treatment regimens for HIV infection: A meta-analysis of randomized controlled trials. *Clin Infect Dis*. May 2014;58(9):1297-1307. Available at https://www.ncbi.nlm.nih.gov/pubmed/24457345.
13. Girard PM, Nelson M, Mohammed P, Hill A, van Delft Y, Moecklinghoff C. Can we stop CD4+ testing in patients with HIV-1 RNA suppression on antiretroviral treatment? *AIDS*. Nov 13 2013;27(17):2759-2763. Available at http://www.ncbi.nlm.nih.gov/pubmed/23842127.
14. Hyle EP, Sax PE, Walensky RP. Potential savings by reduced CD4 monitoring in stable patients with HIV receiving antiretroviral therapy. *JAMA Intern Med*. Oct 14 2013;173(18):1746-1748. Available at http://www.ncbi.nlm.nih.gov/pubmed/23978894.

Drug-Drug Interactions (Last updated October 25, 2018; last reviewed October 25, 2018)

Pharmacokinetic (PK) drug-drug interactions between antiretroviral (ARV) drugs and concomitant medications are common and may lead to increased or decreased drug exposure. In some instances, changes in drug exposure may increase toxicities or affect therapeutic responses. When prescribing or switching one or more drugs in an ARV regimen, clinicians must consider the potential for drug-drug interactions—both those affecting ARVs and those affecting the other drugs a patient is taking. A thorough review of concomitant medications in consultation with an expert in ARV pharmacology can help in designing a regimen that minimizes undesirable interactions. Recommendations for managing a particular drug interaction may differ depending on whether a new ARV is being initiated in a patient on a stable concomitant medication or a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly. When it is necessary to prescribe interacting drugs, clinicians should be vigilant in monitoring for therapeutic efficacy and/or concentration-related toxicities.

Mechanisms of Pharmacokinetic Interactions

PK interactions may occur during absorption, metabolism, or elimination of the ARV and/or the interacting drugs. The most common mechanisms of interactions are described below and listed for each ARV drug in Table 18.

Pharmacokinetic Interactions Affecting Drug Absorption

The extent of oral absorption of drugs can be affected by the following mechanisms:

- Acid-reducing agents, such as proton pump inhibitors, H2 antagonists, or antacids, can reduce the absorption of ARV drugs that require gastric acidity for optimal absorption (i.e., atazanavir [ATV] and rilpivirine [RPV]).
- Products that contain polyvalent cations, such as supplements, iron products, or antacids that contain aluminum, calcium, or magnesium, can bind to integrase strand transfer inhibitors (INSTIs) and reduce absorption of these ARV agents.
- Drugs that induce or inhibit the enzyme cytochrome P450 3A4 (CYP3A4) or efflux transporter p-glycoprotein in the intestines may reduce or promote the absorption of other drugs.

Pharmacokinetic Interactions Affecting Hepatic Metabolism

Two major enzyme systems are most frequently responsible for clinically significant drug interactions.

- The cytochrome P450 enzyme system is responsible for the metabolism of many drugs, including the non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), the CCR5 antagonist maraviroc (MVC), and the INSTI elvitegravir (EVG). CYP3A4 is the most common enzyme responsible for drug metabolism, though multiple enzymes may be involved in the metabolism of a drug. ARV drugs and concomitant medications may be inducers, inhibitors, and/or substrates of these enzymes.
- The uridine diphosphate glucuronosyltransferase (UGT) 1A1 enzyme is the primary enzyme responsible for the metabolism of the INSTIs dolutegravir (DTG) and raltegravir (RAL). Drugs that induce or inhibit the UGT enzyme can affect the PKs of these INSTIs.

Pharmacokinetic Enhancers (Boosters)

PK enhancing is a strategy used to increase exposure of an ARV by concomitantly administering a drug that inhibits the enzymes that metabolize the ARV. Currently, two agents are used as PK enhancers: ritonavir

(RTV) and cobicistat (COBI). Both of these drugs are potent inhibitors of the CYP3A4 enzyme, resulting in higher systemic exposures of the coadministered ARV that is metabolized by this pathway. Importantly, RTV and COBI have different effects on other CYP- or UGT-metabolizing enzymes and drug transporters. Complex or unknown mechanisms of PK-based interactions preclude extrapolation of RTV drug interactions to certain COBI interactions, such as interactions with warfarin, phenytoin, voriconazole, oral contraceptives, and certain HMG-CoA reductase inhibitors (or statins).

Other Mechanisms of Pharmacokinetic Interactions

Knowledge of drug transporters is evolving, elucidating additional drug interaction mechanisms. For example, DTG decreases the renal clearance of metformin by inhibiting organic cation transporters in renal tubular cells. Similar transporters aid hepatic, renal, and biliary clearance of drugs and may be susceptible to drug interactions. ARVs and concomitant medications may be inducers, inhibitors, and/or substrates of these drug transporters.

Tables 19a through 20b provide information on known or suspected drug interactions between ARV agents and commonly prescribed medications based on published PK data or information from product labels. The tables provide general guidance on drugs that should not be coadministered and recommendations for dose modifications or alternative therapy.

Role of Therapeutic Drug Monitoring in Managing Drug-Drug Interactions

Therapeutic drug monitoring (TDM) can guide the dosing of certain medications by using measured drug concentrations to improve the likelihood of desired therapeutic and safety outcomes. Drugs suitable for TDM are characterized by a known exposure-response relationship and a therapeutic range of concentrations. The therapeutic range is a range of concentrations established through clinical investigations that are associated with a greater likelihood of achieving the desired therapeutic response and/or reducing the frequency of drug-associated adverse reactions.

When concomitant use of an ARV drug and another medication is likely to result in a clinically important PK drug-drug interaction, the first step is to assess whether there are other, equally effective treatment options that can be used in order to avoid the interaction. If that is not possible, TDM may be useful in assessing whether a dose adjustment is needed.

Assays for some ARV drug concentrations are commercially available; however, it may take 1 week or longer for the results to be reported. When interpreting the results, clinicians should take into account the patient's medication adherence, the timing of last dose and blood draw, and the time elapsed since coadministration of the interacting drug combination. If needed, a specialist in ARV clinical pharmacology should be consulted when interpreting the results and deciding what actions to take. If a dose adjustment is needed, it is necessary to repeat TDM after the adjusted drug reaches steady state in order to assure appropriate dosing.

TDM information should not be used alone; it must be integrated with other clinical information, including virologic responses and signs and symptoms of drug toxicities, to assure safe and effective therapy.

Table 18. Mechanisms of Antiretroviral-Associated Drug Interactions (Last updated October 25, 2018; last reviewed October 25, 2018) (page 1 of 2)

PK 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 (e.g., transporters); however, the table lists the most common mechanisms of known interactions and focuses on absorption and CYP- and UGT1A1-mediated interactions.

Note: N/A indicates that there are no clinically relevant interactions by these mechanisms. Identified mechanisms are specific to individual ARV drugs and not combinations of ARV drugs.

ARV Drugs by Drug Class	Mechanisms That May Affect Oral Absorption of ARV Drugs			Enzymes That Metabolize or are Induced or Inhibited by ARV Drugs				Other Mechanisms of Known Drug Interactions
	Increasing Gastric pH	Cationic Chelation	P-glyco-protein	CYP Substrate	CYP Inhibitor	CYP Inducer	UGT1A1	
INSTIs								
BIC	N/A	Concentration decreased by products that contain polyvalent cations (e.g., Ca, Mg, Al, Fe, Zn)	Substrate	3A4	N/A	N/A	Substrate	Inhibitor of renal transporters OCT2 and MATE1
DTG	N/A		Substrate	3A4 (minor)	N/A	N/A	Substrate	Inhibitor of renal transporters OCT2 and MATE1
EVG	N/A		N/A	3A4	N/A	2C9	Substrate	N/A
RAL	N/A		N/A	N/A	N/A	N/A	Substrate	N/A
PK Enhancers (Boosters)								
COBI	N/A	N/A	Inhibitor	3A4	3A4, 2D6	N/A	N/A	N/A
RTV	N/A	N/A	Substrate, inhibitor	3A4, 2D6	3A4, 2D6	1A2, 2B6, 2C8, 2C9, 2C19	Inducer	N/A
PIs **Note:** When PIs are coadministered with PK enhancers (boosters), the pharmacologic properties of both agents should be considered when assessing potential drug interactions.								
ATV	Concentration decreased	N/A	Substrate, inducer, inhibitor	3A4	3A4	N/A	Inhibitor	OATP inhibitor
DRV	N/A	N/A	Substrate, inducer	3A4	3A4	2C9	N/A	OATP inhibitor
FPV	Concentration decreased by H2 antagonist	N/A	Substrate, inhibitor	3A4	3A4	N/A	N/A	N/A
LPV	N/A	N/A	Substrate	3A4	3A4	N/A	N/A	OATP inhibitor
SQV	N/A	N/A	Substrate, inhibitor	3A4	3A4	N/A	N/A	OATP inhibitor
TPV	N/A	N/A	Substrate, inducer	3A4	2D6	3A4, 1A2, 2C19	N/A	OATP inhibitor
NNRTIs								
DOR	N/A	N/A	N/A	3A4, 3A5	N/A	N/A	N/A	N/A
EFV	N/A	N/A	N/A	2B6 (primary), 2A6, 3A4	3A4	3A4, 2B6, 2C19	N/A	N/A

Table 18. Mechanisms of Antiretroviral-Associated Drug Interactions (Last updated October 25, 2018; last reviewed October 25, 2018) (page 2 of 2)

ARV Drugs by Drug Class	Mechanisms That May Affect Oral Absorption of ARV Drugs			Enzymes That Metabolize or are Induced or Inhibited by ARV Drugs				Other Mechanisms of Known Drug Interactions
	Increasing Gastric pH	Cationic Chelation	P-glyco-protein	CYP Substrate	CYP Inhibitor	CYP Inducer	UGT1A1	
NNRTIs, continued								
ETR	N/A	N/A	N/A	3A4, 2C9, 2C19	2C9, 2C19	3A4	N/A	N/A
NVP	N/A	N/A	N/A	3A4, 2B6	N/A	3A4, 2B6	N/A	N/A
RPV	Concentration decreased	N/A	N/A	3A4	N/A	N/A	N/A	N/A
NRTIs								
ABC	N/A	N/A	N/A	N/A	N/A	N/A	Substrate	Alcohol dehydrogenase substrate
FTC	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
3TC	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
TAF	N/A	N/A	Substrate	N/A	N/A	N/A	N/A	OATP substrate
TDF	N/A	N/A	Substrate	N/A	N/A	N/A	N/A	Competition of active renal tubular secretion
ZDV	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Glucuronidation
CCR5 Antagonist								
MVC	N/A	N/A	Substrate	3A4	N/A	N/A	N/A	N/A
Fusion Inhibitor								
T-20	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; Al = aluminum; ARV = antiretroviral; ATV = atazanavir; BIC = bictegravir; Ca = calcium; COBI = cobicistat; CYP = cytochrome P; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; Fe = iron; FPV = fosamprenavir; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; LPV = lopinavir; MATE = multidrug and toxin extrusion transporter; Mg = magnesium; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitors; NRTI = nucleoside reverse transcriptase inhibitors; NVP = nevirapine; OCT2 = organic cation transporter 2; OATP = organic anion-transporting polypeptide; PK = pharmacokinetic; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQV = saquinavir; T-20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; UGT = uridine diphosphate glucuronosyltransferase; ZDV = zidovudine; Zn = zinc

Table 19a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 1 of 19)

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

Recommendations for managing a particular drug interaction may differ depending on whether a new ARV drug is being initiated in a patient on a stable concomitant medication or if a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly.

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

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Alpha-Adrenergic Antagonists for Benign Prostatic Hyperplasia			
Alfuzosin	All PIs	↑ alfuzosin expected	**Contraindicated.**
Doxazosin	All PIs	↑ doxazosin possible	Initiate doxazosin at lowest dose and titrate while monitoring for clinical response/toxicity. Dose reduction may be necessary.
Tamsulosin	All PIs	↑ tamsulosin expected	**Coadministration is not recommended.** If coadministered, monitor for tamsulosin toxicities.
Terazosin	All PIs	↔ or ↑ terazosin possible	Initiate terazosin at lowest dose and titrate while monitoring for clinical response/toxicity. Dose reduction may be necessary.
Silodosin	All PIs	↑ silodosin expected	**Contraindicated.**
Acid Reducers			
Antacids	ATV, ATV/c, ATV/r	When given simultaneously, ↓ ATV expected	Give ATV at least 2 hours before or 1–2 hours after antacids or buffered medications.
	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 PI-naive patients. Unboosted ATV plus famotidine should not be used in combination in PI-experienced 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 famotidine 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	↔ demonstrated or expected	No dose adjustment necessary.

Table 19a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 2 of 19)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers, continued			
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, LPV/r	↔ expected	No dose adjustment necessary.
	DRV/r	Omeprazole AUC ↓ 42%	No dose adjustment necessary. If there is a lack of symptomatic relief, increase dose to no more than omeprazole 40 mg daily.
	TPV/r	Omeprazole AUC ↓ 70%	**Coadministration is not recommended.** If coadministration is necessary, dose increases of omeprazole may be considered based on clinical response.
Anticoagulants and Antiplatelets			
Apixaban	PI/c, PI/r	↑ apixaban expected	**Coadministration is not recommended** in patients who require apixaban 2.5 mg twice daily. In patients who require apixaban 5 mg or 10 mg twice daily, reduce apixaban dose by 50%.
Betrixaban	ATV/c, ATV/r, LPV/r	↑ betrixaban expected	Administer an initial single dose of betrixaban 80 mg followed by betrixaban 40 mg once daily.
	DRV/c, DRV/r	↔ betrixaban expected	No dose adjustment necessary.
	TPV/r	No data	No dosing recommendations available at this time. Consider alternative ARV or warfarin.
Dabigatran	ATV/c, ATV/r, LPV/r	↑ dabigatran expected With COBI 150 mg Alone: • Dabigatran AUC ↑ 110% to 127%	Dabigatran dosing recommendation depends on indication and renal function. Refer to dabigatran dosing instructions for concomitant use with P-gp inhibitors in dabigatran prescribing information.
	DRV/c, DRV/r	↔ dabigatran expected	No dose adjustment necessary.
	TPV/r	No data	No dosing recommendations available at this time. Consider alternative ARV or warfarin.
Edoxaban	ATV/c, ATV/r, LPV/r	↑ edoxaban expected	Stroke Prevention in Nonvalvular Atrial Fibrillation Indication: • No dose adjustment necessary. Deep Venous Thrombosis and Pulmonary Embolism Indication: • Administer edoxaban 30 mg once daily
	DRV/c, DRV/r	↔ edoxaban expected	No dose adjustment necessary.
	TPV/r	No data	No dosing recommendations available at this time. Consider alternative ARV or warfarin.
Rivaroxaban	PI/c, PI/r	↑ rivaroxaban expected	**Coadministration is not recommended.**
Ticagrelor	All PIs	↑ ticagrelor expected	**Coadministration is not recommended.**
Vorapaxar	All PIs	↑ vorapaxar expected	**Coadministration is not recommended.**

Table 19a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 3 of 19)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticoagulants and Antiplatelets, continued			
Warfarin	PI/r	↓ warfarin possible	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.
	PI/c	No data	
Anticonvulsants			
Carbamazepine	ATV (unboosted)	May ↓ PI levels substantially	**Do not coadminister.** Consider alternative anticonvulsant or ARV.
	ATV/r, LPV/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 once daily.**
	DRV/r	Carbamazepine AUC ↑ 45% DRV: no significant change	Monitor anticonvulsant level and adjust dose accordingly.
	PI/c	↑ carbamazepine possible ↓ cobicistat expected ↓ PI levels expected	**Contraindicated.**
Eslicarbazepine, Oxcarbazepine	All PIs	↓ PI possible	Consider alternative anticonvulsant or ARV. If coadministration is necessary, monitor for virologic response. Consider monitoring anticonvulsant and PI concentration.
Ethosuximide	All PIs	↑ ethosuximide possible	Clinically monitor for ethosuximide 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	
	DRV/r, TPV/r	↓ lamotrigine possible	
	PI/c	No data	Monitor anticonvulsant level and adjust dose accordingly.
Phenobarbital	PI/c	↓ cobicistat expected ↓ PI levels expected	**Contraindicated.**
	ATV (unboosted), 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 once daily or unboosted ATV.**

Table 19a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 4 of 19)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticonvulsants, continued			
Phenytoin	ATV (unboosted)	May ↓ PI levels substantially	**Do not coadminister.** Consider alternative anticonvulsant or ATV/r.
	ATV/r, DRV/r, TPV/r	↓ phenytoin possible ↓ PI possible	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response.
	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.**
	PI/c	↓ cobicistat expected ↓ PI levels expected	**Contraindicated.**
Valproic Acid (VPA)	PI/c, PI/r	↓ or ↔ VPA possible LPV AUC ↑ 75%	Monitor VPA levels and virologic response. Monitor for LPV-related toxicities.
Antidepressants, Anxiolytics, and Antipsychotics (also see Sedative/Hypnotics section below)			
Aripiprazole	PI/c, PI/r	↑ aripiprazole expected	Administer 25% of the usual aripiprazole dose. Titrate dose based on clinical monitoring for efficacy/toxicity. Refer to aripiprazole label for doses to use in patients who have major depressive disorder or who are known to be CYP2D6 poor metabolizers.
	ATV (unboosted)	↑ aripiprazole expected	Administer 50% of the usual aripiprazole dose. Titrate based on clinical monitoring for efficacy/toxicity. Refer to aripiprazole label for doses to use in patients who have major depressive disorder or who are known to be CYP2D6 poor metabolizers.
Brexpiprazole	PI/c, PI/r	↑ brexpiprazole expected	Administer 25% of the usual brexpiprazole dose. Titrate based on clinical monitoring for efficacy/toxicity. Refer to brexpiprazole label for doses to use in patients who have major depressive disorder or who are known to be CYP2D6 poor metabolizers.
	ATV (unboosted)	↑ brexpiprazole expected	Administer 50% of the usual brexpiprazole dose. Titrate based on clinical monitoring for efficacy/toxicity. Refer to brexpiprazole label for doses to use in patients who have major depressive disorder or who are known to be CYP2D6 poor metabolizers.
Bupropion	LPV/r	Bupropion AUC ↓ 57%	Titrate bupropion dose based on clinical response.
	TPV/r	Bupropion AUC ↓ 46%	
	ATV/r, DRV/r	↓ bupropion possible	
	PI/c	↔ bupropion expected	No dose adjustment necessary.
Buspirone	All PIs	↑ buspirone expected	Use a low dose of buspirone with caution and titrate buspirone dose based on clinical response.

Table 19a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 5 of 19)

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), continued			
Cariprazine	All PIs	↑ cariprazine expected	Starting Cariprazine in a Patient Already Receiving a PI: • Administer cariprazine 1.5 mg on Day 1 and Day 3, with no dose given on Day 2. From Day 4 onward, administer cariprazine 1.5 mg daily. Dose can be increased to a maximum dose of cariprazine 3 mg daily. If the PI is withdrawn, cariprazine dose may need to be increased. Starting a PI in a Patient Already Receiving Cariprazine: • For patients receiving cariprazine 3 mg or cariprazine 6 mg daily, reduce dose by half. For patients taking cariprazine 4.5 mg daily, the dose should be reduced to cariprazine 1.5 mg or cariprazine 3 mg daily. For patients taking cariprazine 1.5 mg daily, change to cariprazine 1.5 mg every other day. If PI is withdrawn, cariprazine dose may need to be increased.
Fluvoxamine	All PIs	↑ fluvoxamine possible	Titrate fluvoxamine dose based on clinical response.
Lurasidone	PI/c, PI/r	↑ lurasidone expected	**Contraindicated.**
	ATV (unboosted)	↑ lurasidone expected	Consider alternative therapy. If coadministration is necessary, reduce lurasidone dose by 50%.
Pimavanserin	All PIs	↑ pimavanserin expected	Reduce dose from pimavanserin 34 mg daily to pimavanserin 17 mg daily.
Pimozide	All PIs	↑ pimozide expected	**Contraindicated.**
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.
Trazodone	All PIs	RTV 200 mg BID (for 2 days) ↑ trazodone AUC 240%	Use lowest dose of trazodone and monitor for CNS and CV adverse effects.
Tricyclic Antidepressants (TCA) Amitriptyline, desipramine, doxepin, imipramine, nortriptyline	All PIs	↑ TCA expected	Use lowest possible TCA dose and titrate based on clinical assessment and/or drug levels.
Other Antipsychotics (CYP3A4 and/or CYP2D6 substrates)	PI/c, PI/r	↑ antipsychotic possible	Titrate antipsychotic dose using the lowest initial dose, or adjust maintenance dose accordingly. Monitor for toxicities.
Other Selective Serotonin Reuptake Inhibitors (SSRIs) (e.g., citalopram, escitalopram, fluoxetine, paroxetine, sertraline)	DRV/r	Paroxetine AUC ↓ 39% Sertraline AUC ↓ 49%	Titrate SSRI dose based on clinical response.
	ATV/r, LPV/r, TPV/r	No data	
	PI/c	Effects unknown	Titrate SSRI dose using the lowest available initial or maintenance dose.

Table 19a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 6 of 19)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antifungals			
Fluconazole	PI/c, ATV/r, DRV/r, LPV/r	No significant effect observed or expected	No dose 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% RTV AUC ↓ 31%	If coadministered, consider monitoring isavuconazole concentrations and toxicities and assessing virologic response.
	All PIs except LPV/r	↑ isavuconazole possible ↑ or ↓ PI possible	If coadministered, consider monitoring isavuconazole concentrations and toxicities. Monitor for PI toxicity and virologic response.
Itraconazole	All PIs	↑ itraconazole possible ↑ PI possible	Consider monitoring itraconazole level to guide dose 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/r	ATV AUC ↑ 146% ↑ posaconazole possible	If coadministered, monitor for PI adverse effects. Consider monitoring for posaconazole concentrations and toxicities.
	ATV	ATV AUC ↑ 268% ↑ posaconazole possible	
	ATV/c, DRV/c, DRV/r, LPV/r, TPV/r	↑ PI possible ↑ posaconazole possible	
Voriconazole	ATV (unboosted)	↑ voriconazole possible ↑ PI possible	Monitor for toxicities.
	All PI/r	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.
	PI/c	Effect on voriconazole unknown	
Antihyperglycemics			
Canagliflozin	PI/r	↓ canagliflozin expected	If a patient is already tolerating canagliflozin 100 mg daily, has an eGFR >60 mL/min/1.73m², and requires additional glycemic control, consider increasing dose to canagliflozin 300 mg daily.
	PI/c	↓ canagliflozin possible	If used in combination, monitor glycemic control.
Saxagliptin	All PIs	↑ saxagliptin expected	Limit saxagliptin dose to 2.5 mg once daily
Dapagliflozin/ Saxagliptin	All PIs	↑ saxagliptin expected	**Do not coadminister**, as this coformulated drug contains 5 mg of saxagliptin.
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 October 25, 2018; last reviewed October 25, 2018) (page 7 of 19)

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	With ATV/r: • Atovaquone AUC ↓ 46% • Proguanil AUC ↓ 41% With LPV/r: • Atovaquone AUC ↓ 74% • Proguanil AUC ↓ 38%	No dose 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 nontuberculosis mycobacterial infections)			
Bedaquiline	All PIs	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 (e.g., azithromycin).
	All PIs	↑ clarithromycin expected DRV/r ↑ clarithromycin AUC 57% LPV/r ↑ clarithromycin expected RTV 500 mg BID ↑ clarithromycin 77% TPV/r ↑ clarithromycin 19% Clarithromycin ↑ TPV 66%	Consider alternative macrolide (e.g., azithromycin). Monitor for clarithromycin-related toxicities or consider an alternative macrolide (e.g., 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.

Table 19a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 8 of 19)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antimycobacterials (for treatment of *Mycobacterium tuberculosis* and nontuberculosis mycobacterial infections), continued			
Rifabutin	ATV (unboosted)	↑ rifabutin AUC 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 patients with HIV than in healthy study participants.
	ATV/r	Compared with Rifabutin (300 mg Once Daily) Alone, Rifabutin (150 mg Once Daily) plus ATV/r: • Rifabutin AUC ↑ 110% and metabolite AUC ↑ 2,101%	
	DRV/r	Compared with Rifabutin (300 mg Once Daily) Alone, Rifabutin (150 mg Every Other Day) plus DRV/r: • Rifabutin AUC ↔ and metabolite AUC ↑ 881%	
	LPV/r	Compared with Rifabutin (300 mg daily) Alone, Rifabutin (150 mg Once Daily) plus LPV/r: • Rifabutin AUC ↑ 203% and metabolite AUC ↑ 375%	
	TPV/r	Rifabutin AUC ↑ 190% and metabolite AUC ↑ 1,971%	
	PI/c	↑ rifabutin expected	
Rifampin	All PIs	↓ PI concentration by >75%	**Contraindicated.** 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 dose adjustment necessary.
Cardiac Medications			
Amiodarone	TPV/r	↑ both amiodarone and PI possible	**Contraindicated.**
	All PIs except TPV/r	↑ both amiodarone and PI possible	Use with caution. Monitor for amiodarone toxicity and consider ECG and amiodarone drug levels.
Antiarrhythmics (e.g., disopyramide, dofetilide, lidocaine, mexiletine, propafenone)	ATV (unboosted)	↑ antiarrhythmic possible	Consider alternative antiarrhythmics or ARV. If coadministered, monitor for antiarrhythmic toxicities.
	PI/c, PI/r	↑ antiarrhythmic possible	**Do not coadminister.** Consider alternative antiarrhythmics or ARV.
Dronedarone	ATV (unboosted)	↑ dronedarone possible	**Do not coadminister.**
	PI/c, PI/r	↑ dronedarone expected	**Contraindicated.**
Flecanide	All PIs except TPV/r	↑ flecainide possible	**Do not coadminister.**
	TPV/r	↑ flecanide expected	**Contraindicated.**

Table 19a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 9 of 19)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Cardiac Medications, continued			
Propafenone	All PIs except TPV/r	↑ propafenone possible	**Do not coadminister.**
	TPV/r	↑ propafenone expected	**Contraindicated.**
Quinidine	All PIs except TPV/r	↑ quinidine possible	**Do not coadminister.**
	TPV/r	↑ quinidine expected	**Contraindicated.**
Beta-Blockers (e.g., carvedilol, 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 (e.g., 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 restart bosentan 10 days after PI initiation at 62.5 mg once daily or every other day. When Switching Between COBI and RTV: • Maintain same bosentan dose.
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 is used with ATV.
Digoxin	PI/c , PI/r	RTV (200 mg BID) ↑ digoxin AUC 29% and ↑ half-life 43% DRV/r ↑ digoxin AUC 36% COBI ↑ digoxin C_{max} 41% and ↔ 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)	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, LPV/r, TPV/r	↑ diltiazem possible	Use with caution. Adjust diltiazem according to clinical response and toxicities.
Eplerenone	PI/c, PI/r	↑ eplerenone expected	**Contraindicated.**
Ranolazine	ATV (unboosted)	↑ ranolazine possible	**Do not coadminister.**
	PI/c, PI/r	↑ ranolazine expected	**Contraindicated.**
Ivabradine	All PIs	↑ ivabradine expected	**Contraindicated.**

Table 19a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 10 of 19)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Corticosteroids			
Beclomethasone Inhaled or intranasal	DRV/r	↔ 17-BMP (active metabolite) AUC RTV 100 mg BID ↑ 17-BMP AUC 2-fold	No dose adjustment necessary.
	All PIs except DRV/r	↔ expected	No dose adjustment necessary.
Budesonide, Ciclesonide, Fluticasone, Mometasone Inhaled or intranasal	All PIs	↑ glucocorticoids possible RTV 100 mg BID ↑ fluticasone AUC 350-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 adverse effects associated with corticosteroids.** Consider an alternative corticosteroid (e.g., beclomethasone).
Betamethasone, Budesonide Systemic	All PIs	↑ glucocorticoids possible ↓ PI possible	Coadministration can result in adrenal insufficiency and Cushing's syndrome. **Do not coadminister unless potential benefits of systemic corticosteroid outweigh the risks of adverse effects associated with systemic corticosteroids.**
Dexamethasone Systemic	All PIs	↑ glucocorticoids possible ↓ PI possible	Consider alternative corticosteroid for long-term use. If coadministration is necessary, monitor virologic response to ART.
Prednisone, Prednisolone Systemic	LPV/r	↑ prednisolone AUC 31%	Coadministration may be considered if the potential benefits outweigh the risks of adverse effects associated with systemic corticosteroids. If coadministered, monitor for adrenal insufficiency, Cushing's syndrome, and other corticosteroid-associated toxicities.
	All PIs	↑ prednisolone possible	
Betamethasone, Methylprednisolone, Triamcinolone Local injections, including intra-articular, epidural, or intra-orbital	All PIs	↑ glucocorticoids expected	**Do not coadminister.** Coadministration can result in adrenal insufficiency and Cushing's syndrome.
Hepatitis C Direct-Acting Antiviral Agents			
Daclatasvir	ATV/c, ATV/r	↑ daclatasvir	Decrease daclatasvir dose to 30 mg once daily.
	ATV (unboosted), DRV/c, DRV/r, LPV/r	↔ daclatasvir	No dose adjustment necessary.
	TPV/r	No data	No dosing recommendations available at this time.
Dasabuvir plus Paritaprevir/ Ombitasvir/RTV	ATV (unboosted)	↔ ATV	ATV 300 mg alone, **without COBI or additional RTV**, should be given in the morning with dasabuvir plus paritaprevir/ombitasvir/ RTV.
	DRV	DRV C_{min} ↓ 43% to 46%	**Do not coadminister.**
	LPV/r	Paritaprevir AUC ↑ 117%	**Do not coadminister.**
	ATV/c, DRV/c, TPV/r	No data	**Do not coadminister.**

Table 19a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 11 of 19)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hepatitis C Direct-Acting Antiviral Agents, continued			
Elbasvir/ Grazoprevir	ATV/r	Elbasvir AUC ↑ 4.8-fold Grazoprevir AUC ↑ 10.6-fold ATV ↔ by elbasvir ATV AUC ↑ 43% by grazoprevir	**Contraindicated.** 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 (unboosted), ATV/c, DRV/c, TPV/r	↑ grazoprevir expected	
Glecaprevir/ Pibrentasvir	ATV (unboosted), ATV/c, ATV/r	When Given with ATV/r 300/100 mg Once Daily • Glecaprevir AUC ↑ 6.5-fold • Pibrentasvir AUC ↑ 64%	**Contraindicated.**
	DRV/c, DRV/r	When Given with DRV/r 800/100 mg Once Daily • Glecaprevir AUC ↑ 5-fold • ↔ pibrentasvir	**Do not coadminister.**
	LPV/r	Glecaprevir AUC ↑ 4-fold Pibrentasvir ↑ 2.5-fold	**Do not coadminister.**
	TPV/r	↑ glecaprevir and pibrentasvir expected	**Do not coadminister.**
Ledipasvir/ Sofosbuvir	ATV/r	ATV AUC ↑ 33% Ledipasvir AUC ↑ 113% ↔ sofosbuvir	No dose 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 expected ↔ ledipasvir/sofosbuvir	
	ATV (unboosted), ATV/c, DRV/c, LPV/r	↔ expected	
	TPV/r	↓ ledipasvir and sofosbuvir expected	**Do not coadminister.**

Table 19a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 12 of 19)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hepatitis C Direct-Acting Antiviral Agents, continued			
Simeprevir	All PIs	Compared with Simeprevir 150 mg Alone: Simeprevir 50 mg plus DRV/r 800 mg/100 mg Daily: • Simeprevir AUC ↑ 159% RTV 100 mg BID ↑ simeprevir AUC 618%	**Do not coadminister.**
Sofosbuvir	TPV/r	↓ sofosbuvir expected	**Do not coadminister.**
Sofosbuvir/ Velpatasvir	ATV/r	↔ ATV/r ↔ sofosbuvir Velpatasvir AUC ↑ 2.4-fold	No dose adjustment necessary.
	DRV/r	↔ DRV/r Sofosbuvir AUC ↓ 28% ↔ velpatasvir	No dose adjustment necessary.
	ATV (unboosted), ATV/c, DRV/c, LPV/r	↔ sofosbuvir and velpatasvir expected	No dose adjustment necessary.
	TPV/r	↓ sofosbuvir expected ↓ velpatasvir expected	**Do not coadminister.**
Sofosbuvir/ Velpatasvir/ Voxilaprevir	ATV (unboosted), ATV/c, ATV/r	When Given with ATV/r: • Voxilaprevir AUC ↑ 4.3-fold • Velpatasvir AUC ↑ 93% • Sofosbuvir AUC ↑ 40%	**Do not coadminister.**
	LPV/r	↑ voxilaprevir expected	**Do not coadminister.**
	DRV/c , DRV/r	When Given with DRV/r: • Voxilaprevir AUC ↑ 2.4-fold • ↔ DRV/r, velpatasvir, and sofosbuvir	No dose adjustment needed.
	TPV/r	↓ sofosbuvir expected ↓ velpatasvir expected Effect on voxilaprevir is unknown.	**Do not coadminister.**
Herbal Products			
St. John's Wort	All PIs	↓ PI expected	**Contraindicated.**

Table 19a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 13 of 19)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hormonal Therapies			
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[b] 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.
	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.[c] Oral contraceptives containing progestins other than norethindrone or norgestimate have not been studied.
	ATV/c	Drospirenone AUC ↑ 2.3-fold Ethinyl estradiol AUC ↓ 22%	**Contraindicated with drospirenone-containing hormonal contraceptive due to potential for hyperkalemia.** Consider alternative or additional contraceptive method or alternative ARV drug.
	DRV/c	Drospirenone AUC ↑ 1.6-fold Ethinyl estradiol AUC ↓ 30%	Clinical monitoring is recommended due to the potential for hyperkalemia. Consider alternative or additional contraceptive method or alternative ARV.
	DRV/r, LPV/r, TPV/r	Ethinyl estradiol AUC ↓ 37% to 55% Norethindrone AUC ↓ 14% to 34% With TPV/r: • ↔ norethindrone AUC	Consider alternative or additional contraceptive method or alternative ARV drug.
Depot MPA Injectable	LPV/r	MPA AUC ↑ 46% No significant change in C_{min}	No dose adjustment necessary.
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.
Etonogestrel/ Ethinyl Estradiol Vaginal Ring	ATV/r	Ethinyl estradiol AUC ↓ 26% Etonogestrel AUC ↑ 79%	Use standard dose.
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.

Table 19a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 14 of 19)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hormonal Therapies, continued			
Menopausal Hormone Replacement Therapy (HRT)	All PIs	↓ estrogen possible with estradiol or conjugated estrogen (equine and synthetic)	Adjust estrogen dosage as needed based on clinical effects.
	All PIs	↑ drospirenone possible ↑ medroxyprogesterone ↑ micronized progesterone See Hormonal Contraceptives for other progestin-PI interactions	Adjust progestin/progesterone dosage as needed based on clinical effects. Because drospirenone is prescribed as a lower dose for menopausal HRT than the products used for hormonal contraceptives, it is not contraindicated with ATV/c products.
Gender-Affirming Hormone Therapy	All PIs	↓ estradiol possible	Adjust estradiol dosage as needed based on clinical effects and endogenous hormone concentrations.
	All PIs	↔ finasteride, goserelin, leuprolide acetate, and spironolactone expected	No dose adjustment necessary.
	All PIs	↑ dutasteride possible	Adjust dutasteride dosage as needed based on clinical effects and endogenous hormone concentrations.
	All PIs	↓ testosterone possible	Adjust testosterone dosage as needed based on clinical effects and endogenous hormone concentrations.
HMG-CoA Reductase Inhibitors			
Atorvastatin	ATV (unboosted), ATV/r	↑ atorvastatin possible	Titrate atorvastatin dose carefully and use lowest dose necessary while monitoring for toxicities.
	ATV/c	Atorvastatin AUC ↑ 9.2-fold, C_{max} ↑ 18.9-fold	**Coadministration is not recommended.**
	DRV/r	DRV/r plus atorvastatin 10 mg similar to atorvastatin 40 mg administered alone	Titrate atorvastatin dose carefully and use the lowest dose necessary while monitoring for toxicities. Do not exceed 20 mg atorvastatin daily.
	DRV/c	Atorvastatin AUC ↑ 3.9-fold, C_{max} ↑ 4.2-fold	Titrate atorvastatin dose carefully and use lowest dose necessary while monitoring for toxicities. Do not exceed 20 mg atorvastatin daily.
	LPV/r	Atorvastatin AUC ↑ 5.9-fold, C_{max} ↑ 4.7-fold	Titrate atorvastatin dose carefully and use lowest dose necessary while monitoring for toxicities. Do not exceed 20 mg atorvastatin daily.
	TPV/r	Atorvastatin AUC ↑ 9.4-fold, C_{max} ↑ 8.6-fold	**Do not coadminister.**
Lovastatin	All PIs	Significant ↑ lovastatin expected	**Contraindicated.**
Pitavastatin	All PIs	ATV ↑ pitavastatin AUC 31% and C_{max} ↑ 60% ↔ ATV DRV/r ↓ pitavastatin AUC 26% ↔ DRV/r LPV/r ↓ pitavastatin AUC 20% ↔ LPV	No dose adjustment necessary.

Table 19a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 15 of 19)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
HMG-CoA Reductase Inhibitors, continued			
Pravastatin	ATV/c, ATV/r	No data	Titrate pravastatin dose carefully while monitoring for toxicities.
	DRV/c, DRV/r	With DRV/r: • Pravastatin AUC ↑ 81% following single dose of pravastatin • Pravastatin AUC ↑ 23% at steady state	Titrate pravastatin dose carefully while monitoring for toxicities.
	LPV/r	Pravastatin AUC ↑ 33%	No dose adjustment necessary.
Rosuvastatin	ATV/r	Rosuvastatin AUC ↑ 3-fold, C_{max} ↑ 7-fold	Titrate rosuvastatin dose carefully and use lowest dose necessary while monitoring for toxicities. Do not exceed rosuvastatin 10 mg daily.
	ATV/c	Rosuvastatin AUC ↑ 3.4-fold, C_{max} ↑ 10.6-fold	
	DRV/c	Rosuvastatin AUC ↑ 1.9-fold, C_{max} ↑ 3.8-fold	Titrate rosuvastatin dose carefully and use the lowest dose necessary while monitoring for toxicities. Do not exceed rosuvastatin 20 mg daily.
	DRV/r	Rosuvastatin AUC ↑ 48%, C_{max} ↑ 2.4-fold	Titrate rosuvastatin dose carefully and use the lowest necessary dose while monitoring for toxicities.
	LPV/r	Rosuvastatin AUC ↑ 2.1-fold, C_{max} ↑ 4.7-fold	Titrate rosuvastatin dose carefully and use the lowest necessary dose. Do not exceed rosuvastatin 10 mg daily.
	TPV/r	Rosuvastatin AUC ↑ 26%, C_{max} ↑ 2.2-fold	No dose adjustment necessary.
Simvastatin	All PIs	Significant ↑ simvastatin expected	**Contraindicated.**
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.

Table 19a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 16 of 19)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Narcotics and Treatment for Opioid Dependence			
Buprenorphine Sublingual, buccal, or implant	ATV (unboosted)	Buprenorphine AUC ↑ 93% Norbuprenorphine[d] AUC ↑ 76% ↓ ATV possible	**Do not coadminister.**
	ATV/r	Buprenorphine AUC ↑ 66% Norbuprenorphine[d] AUC ↑ 105%	Monitor for sedation and other signs or symptoms of over-medication. Buprenorphine dose reduction may be necessary. It may be necessary to remove implant and treat with a formulation that permits dose adjustments.
	DRV/r	No significant effect on buprenorphine Norbuprenorphine[d] AUC ↑ 46% and C_{min} ↑ 71%	No dose adjustment necessary. Clinical monitoring is recommended. When transferring buprenorphine from transmucosal delivery to implantation, monitor to ensure buprenorphine effect is adequate and not excessive.
	LPV/r	No significant effect	
	TPV/r	No significant effect on buprenorphine Norbuprenorphine[d] AUC, C_{max}, and C_{min} ↓ 80% TPV C_{min} ↓ 19% to 40%	Consider monitoring TPV level. When transferring buprenorphine from transmucosal delivery to implantation, monitor to ensure buprenorphine effect is adequate and not excessive.
	PI/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.
Fentanyl	All PIs	↑ fentanyl possible	Clinical monitoring is recommended, including for potentially fatal respiratory depression.
Methadone	ATV (unboosted)	No significant effect	No dose adjustment necessary.
	PI/c	Effects unknown	Titrate methadone dose using the lowest feasible initial dose. Dose adjustment of methadone may be needed. Clinical monitoring is recommended.
	All PI/r	ATV/r and DRV/r ↓ R-methadone[e] AUC 16% to 18% LPV/r ↓ methadone AUC 26% to 53% TPV/r ↓ R-methadone[e] AUC 48%	Opioid withdrawal is 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	All PIs	Oxycodone AUC ↑ 2.6-fold with LPV/r	Monitor for opioid-related adverse effects. Oxycodone dose reduction may be necessary.
Tramadol	All PIs	↑ tramadol possible	Tramadol dose reduction may be necessary. Monitor for tramadol toxicities and clinical response.

Table 19a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 17 of 19)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
PDE5 Inhibitors			
Avanafil	All PIs except unboosted ATV	RTV (600 mg BID for 5 days) ↑ avanafil AUC 13-fold and ↑ C_{max} 2.4-fold	**Coadministration is not recommended.**
	ATV (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%	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.**
Tadalafil	All PIs	RTV 200 mg BID ↑ tadalafil AUC 124% TPV/r (1st dose) ↑ tadalafil AUC 133% No significant effect on TPV/r steady state	For Treatment of Erectile Dysfunction: • Start with tadalafil 5-mg dose and do not exceed a single dose of tadalafil 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 tadalafil 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 tadalafil 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 tadalafil 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	**Oral midazolam is contraindicated with 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.**

Table 19a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 18 of 19)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Sedative/Hypnotics, continued			
Triazolam	All PIs	↑ triazolam expected RTV (200 mg BID) ↑ triazolam half-life 1,200% and AUC 2,000%	**Contraindicated.**
Zolpidem	PI/c, PI/r	↑ zolpidem possible	Initiate zolpidem at a low dose. Dose reduction may be necessary.
Miscellaneous Drugs			
Calcifediol	All PIs	↑ calcifediol possible	Dose adjustment of calcifediol may be required, and serum 25-hydroxyvitamin D, intact PTH, and serum calcium concentrations should be closely monitored.
Cisapride	All PIs	↑ cisapride expected	**Contraindicated.**
Colchicine	All PIs	RTV 100 mg BID ↑ colchicine AUC 296% and C_{max} 184% Significant ↑ colchicine expected with all PIs, with or without COBI or RTV	For Treatment of Gout Flares: • Administer a single dose of colchicine 0.6 mg, followed by colchicine 0.3 mg 1 hour later. Do not repeat dose for at least 3 days. For Prophylaxis of Gout Flares: • Administer colchicine 0.3 mg once daily or every other day. For Treatment of Familial Mediterranean Fever: • Do not exceed colchicine 0.6 mg once daily or colchicine 0.3 mg BID. **Do not coadminister in patients with hepatic or renal impairment.**
Dronabinol	All PIs	↑ dronabinol possible	Monitor for increased dronabinol-related adverse reactions.
Eluxadoline	All PIs	↑ eluxadoline expected	Administer eluxadoline at a dose of 75 mg twice daily and monitor for eluxadoline-related adverse effects.
Enzalutamide	All PIs	↓ PI expected	**Contraindicated.**
Ergot Derivatives	All PIs	↑ dihydroergotamine, ergotamine, methylergonovine expected	**Contraindicated.**
Flibanserin	All PIs	↑ flibanserin expected	**Contraindicated.**
Irinotecan	ATV (unboosted), ATV/c, ATV/r	↑ irinotecan expected	**Contraindicated.**
Mitotane	All PIs	↓ PI expected	**Contraindicated.**
Salmeterol	All PIs	↑ salmeterol possible	**Do not coadminister** because of potential increased risk of salmeterol-associated CV events.

Table 19a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 19 of 19)

[e] DHA is an active metabolite of artemether.

[f] The following products contain no more than 30 mcg of ethinyl estradiol combined with norethindrone or norgestimate (generic formulations 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.

[g] The following products contain at least 35 mcg of ethinyl estradiol combined with norethindrone or norgestimate (generic formulations 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.

[h] Norbuprenorphine is an active metabolite of buprenorphine.

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

Key to Symbols:

↑ = increase

↓ = decrease

↔ = no change

Key to Acronyms: 17-BMP = beclomethasone 17-monopropionate; ALT = alanine aminotransferase; 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; CV = cardiovascular; CYP = cytochrome P; DHA = dihydroartemisinin; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; FPV = fosamprenavir; HCV = hepatitis C virus; HRT = hormone replacement therapy; IDV = indinavir; INR = international normalized ratio; LPV = lopinavir; LPV/r = lopinavir/ritonavir; MPA = medroxyprogesterone acetate; NFV = nelfinavir; OATP = organic anion-transporting polypeptide; PAH = pulmonary arterial hypertension; PDE5 = Phosphodiesterase Type 5; PI = protease inhibitor; PI/c = protease inhibitor/cobicistat; PI/r = protease inhibitor/ritonavir; PK = pharmacokinetic; PPI = proton pump inhibitor; PTH = parathyroid hormone; QTc = QT corrected for heart rate; RTV = ritonavir; SQV = saquinavir; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; TPV/r = tipranavir/ritonavir

Table 19b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 1 of 10)

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. Recommendations for managing a particular drug interaction may differ depending on whether a new ARV drug is being initiated in a patient on a stable concomitant medication or if a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly.

Note: DLV is **not** included in this table. Please refer to the DLV FDA package insert for information regarding drug interactions. The term "All NNRTIs" in this table refers to all NNRTIs except for DLV.

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% and C_{min} ↓ 33%	**Contraindicated. Do not coadminister.**
Alpha-Adrenergic Antagonists for Benign Prostatic Hyperplasia			
Alfuzosin, Doxazosin, Silodosin	EFV, ETR, NVP	↓ alpha antagonist expected	Consider alternative therapy. If coadministration is necessary, monitor for therapeutic effectiveness of alpha antagonist.
Tamsulosin	EFV, ETR, NVP	↓ tamsulosin expected	Monitor for therapeutic effectiveness of tamsulosin after 2 to 4 weeks of dosing. May need to increase to tamsulosin 0.8 mg once daily for patients who fail to respond to the 0.4 mg dose.
Anticoagulants/Antiplatelets			
Apixaban	EFV, ETR, NVP	↓ apixaban possible	Consider alternative therapy.
Betrixaban	All NNRTIs	↔ betrixaban expected	No dose adjustment necessary.
Clopidogrel	EFV, ETR	↓ activation of clopidogrel possible	ETR may prevent metabolism of clopidogrel (inactive) to its active metabolite. Avoid coadministration, if possible.
	DOR, NVP, RPV	↔ clopidogrel expected	No dose adjustment necessary.
Dabigatran	All NNRTIs	↔ dabigatran expected	No dose adjustment necessary.
Edoxaban	All NNRTIs	↔ edoxaban expected	No dose adjustment necessary.
Prasugrel	All NNRTIs	↔ prasugrel expected	No dose adjustment necessary.
Rivaroxaban	EFV, ETR, NVP	↓ rivaroxaban possible	Consider alternative therapy.
Ticagrelor	EFV, ETR, NVP	↓ ticagrelor expected	Consider alternative therapy.
Warfarin	EFV, ETR, NVP	↑ or ↓ warfarin possible	Monitor INR and adjust warfarin dose accordingly.

Table 19b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 2 of 10)

Concomitant Drug Class/ Name	NNRTI[a]	Effect on NNRTI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticonvulsants			
Carbamazepine, Phenobarbital, Phenytoin	EFV	Carbamazepine plus EFV: • Carbamazepine AUC ↓ 27% • EFV AUC ↓ 36% Phenytoin plus EFV: • ↓ EFV • ↓ phenytoin possible	Monitor anticonvulsant and EFV concentrations 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 concentrations and virologic responses or consider alternative anticonvulsant.
	DOR, RPV	↓ NNRTI possible	**Contraindicated. Do not coadminister.** Consider alternative anticonvulsant.
Eslicarbazepine	All NNRTIs	↓ NNRTI possible	Monitor virologic outcomes and consider monitoring plasma concentrations of ARVs, or consider alternative anticonvulsant or ARV drug.
Oxcarbazepine	DOR, RPV	↓ NNRTI possible	**Contraindicated. Do not coadminister.** Consider alternative anticonvulsant.
Ethosuximide, Lacosamide, Tiagabine, Zonisamide,	ETR, EFV	↓ anticonvulsant possible	Monitor seizure control and plasma concentrations of anticonvulsants (when available).
Lamotrigine	EFV	↓ lamotrigine possible	Monitor seizure control and plasma concentrations of lamotrigine.
Antidepressants			
Bupropion	EFV, NVP	Bupropion AUC ↓ 55% ↓ bupropion possible	Titrate bupropion dose based on clinical response.
Citalopram, Escitalopram	EFV, ETR, NVP	↓ antidepressant possible	Titrate antidepressant dose based on clinical response.
Fluoxetine, Fluvoxamine	All NNRTIs	↔ antidepressant expected	No dose adjustment necessary.
Paroxetine	EFV, ETR	↔ paroxetine observed with EFV or ETR	No dose adjustment necessary.
	DOR, NVP, RPV	↔ expected with DOR, NVP or RPV	No dose adjustment necessary.
Nefazodone	EFV, ETR, NVP	↓ nefazodone expected ↑ NNRTI possible	Monitor the antidepressant effect and titrate dose as necessary. Monitor for ARV-related adverse events.
	DOR, RPV	↑ NNRTI possible	Monitor for ARV-related adverse events.
Sertraline	EFV	Sertraline AUC ↓ 39%	Titrate sertraline dose based on clinical response.
Trazodone	EFV, ETR, NVP	↓ trazodone possible	Monitor the therapeutic effect of trazodone and titrate dose as necessary.

Table 19b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 3 of 10)

Concomitant Drug Class/ Name	NNRTI[a]	Effect on NNRTI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antifungals			
Fluconazole	EFV	↔ fluconazole or EFV	No dose adjustment necessary.
	ETR	ETR AUC ↑ 86%	No dose 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.
	DOR,RPV	↑ NNRTI possible	No dose adjustment necessary.
Isavuconazole	EFV, ETR, NVP	↓ isavuconazole possible	Dose adjustments for isavuconazole may be necessary. Consider monitoring isavuconazole concentration and antifungal response.
	DOR, RPV	↑ NNRTI possible	No dose adjustment necessary.
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 AUC ↓ 61% ↑ NVP possible	Avoid this combination if possible. If coadministered, monitor itraconazole concentration and adjust dose accordingly.
	DOR, RPV	↑ NNRTI possible	No dose adjustment necessary.
Posaconazole	EFV	Posaconazole AUC ↓ 50% ↔ EFV	Avoid concomitant use unless the benefit outweighs the risk. If coadministered, monitor posaconazole concentration and adjust dose accordingly.
	DOR, ETR, NVP, RPV	↑ NNRTI possible	Monitor for NNRTI toxicities.
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 ETR AUC ↑ 36%	No dose adjustment necessary.
	NVP	↓ voriconazole possible ↑ NVP possible	Monitor for toxicity and antifungal response and/or voriconazole concentration.
	DOR, RPV	↑ NNRTI possible	No dose adjustment necessary.
Antihyperglycemics			
Canagliflozin, Dapagliflozin, Empagliflozin, Sitagliptin	All NNRTIs	↔ antihyperglycemic expected	No dose adjustment necessary.
Linagliptin, Saxagliptin	EFV, ETR, NVP	↓ antihyperglycemic possible	Monitor glycemic control.

Table 19b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 4 of 10)

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.
	ETR	Artemether AUC ↓ 38% ↔ DHA AUC ↔ Lumefantrine AUC ↔ ETR AUC	Clinical significance of the reduced antimalarial drug concentrations unknown. If used in combination with ETR, monitor for antimalarial efficacy.
	NVP	Artemether AUC ↓ 67% to 72% DHA: • Study results are conflicting. DHA 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 dose recommendation. Consider alternative drug for malaria prophylaxis, if possible.
Antimycobacterials			
Bedaquiline	EFV, ETR	↓ bedaquiline possible	**Do not coadminister.**
	NVP	↔ bedaquiline AUC	No dose 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% NVP AUC ↑ 26%	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	DOR	DOR AUC ↓ 50%	Increase DOR dose to 100 mg twice daily. No dose adjustment for 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 ETR AUC ↓ 37%	**Do not coadminister ETR plus PI/r with rifabutin.** Use rifabutin 300 mg once daily if ETR is administered without PI/r

Table 19b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 5 of 10)

Concomitant Drug Class/ Name	NNRTI*	Effect on NNRTI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antimycobacterials, continued			
Rifabutin, continued	NVP	Rifabutin AUC ↑ 17% and metabolite AUC ↑ 24% NVP C_{min} ↓ 16%	No dose adjustment necessary. Use with caution.
	RPV	Rifabutin plus RPV 50 mg Once Daily Compared to RPV 25 mg Once Daily Alone: • ↔ RPV AUC and C_{min}	Increase RPV dose to 50 mg once daily. No dose adjustment for rifabutin.
Rifampin	DOR	DOR AUC ↓ 88%	**Contraindicated.**
	EFV	EFV AUC ↓ 26%	**Do not use EFV 400 mg with rifampin.** Maintain EFV dose at 600 mg once daily and monitor for virologic response.
	ETR	Significant ↓ ETR possible	**Do not coadminister.**
	NVP	NVP ↓ 20% to 58%	**Do not coadminister.**
	RPV	RPV AUC ↓ 80%	**Contraindicated.**
Rifapentine	EFV	↔ EFV concentrations	No dose adjustment necessary.
	ETR, NVP	↓ NNRTI possible	**Do not coadminister.**
	DOR, RPV	↓ NNRTI expected	**Contradindicated.**
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.
Antipsychotics			
Aripiprazole	EFV, ETR, NVP	↓ aripiprazole expected	Monitor effectiveness of antipsychotic. Consider doubling usual dose of aripiprazole over 1–2 weeks. Refer to aripiprazole prescribing information for dosing recommendations.
Brexpiprazole	EFV, ETR, NVP	↓ brexpiprazole expected	Monitor effectiveness of antipsychotic. Consider doubling the usual dose of brexpiprazole and making further adjustments based on clinical response. Refer to brexpiprazole prescribing information.
Cariprazine	EFV, ETR, NVP	↓ cariprazine and ↑ or ↓ active metabolite possible	Coadministration is not recommended.
Olanzapine	EFV	↓ olanzapine possible	Monitor effect of olanzapine.
	DOR, ETR, NVP, RPV	↔ olanzapine expected	No dose adjustment necessary.
Pimozide	EFV, ETR, NVP	↓ pimozide possible	Monitor therapeutic effectiveness of pimozide
Lurasidone, Pimavanserin, Quetiapine, Thioridazine	EFV, ETR, NVP	↓ antipsychotic possible	Monitor effect of antipsychotic.

Table 19b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 6 of 10)

Concomitant Drug Class/ Name	NNRTI[a]	Effect on NNRTI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Benzodiazepines			
Alprazolam	EFV, ETR, NVP	↓ alprazolam possible	Monitor for therapeutic effectiveness of alprazolam.
Diazepam	EFV, NVP	↓ diazepam possible	Monitor for therapeutic effectiveness of diazepam.
	ETR	↑ diazepam possible	Decreased dose of diazepam may be necessary. Monitor for diazepam toxicity.
Lorazepam	EFV	↔ lorazepam AUC	No dose adjustment necessary.
	ETR, NVP	↔ lorazepam expected	
Midazolam	EFV	↑ or ↓ midazolam possible	Monitor therapeutic effectiveness and toxicity of midazolam.
	ETR	Midazolam AUC ↓ 31% Midazolam active metabolite C_{max} ↑ 57%	Monitor therapeutic effectiveness of midazolam.
	NVP	↓ midazolam possible	Monitor therapeutic effectiveness of midazolam.
Triazolam	EFV, ETR, NVP	↓ triazolam possible	Monitor therapeutic effectiveness of triazolam.
Cardiac Medications			
Dihydropyridine CCBs	EFV, ETR, 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.
	ETR, NVP	↓ diltiazem or verapamil possible	
Corticosteroids			
Dexamethasone	DOR, EFV, ETR, NVP	↓ NNRTI 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 120 mg Once Daily plus EFV 600 mg Daily Compared with Daclatasvir 60 mg Alone: • Daclatasvir C_{min} ↓ 17%, AUC ↑ 37%	The recommended dose is daclatasvir 90 mg once daily.
	DOR, RPV	No data	No dose adjustment necessary.
Dasabuvir plus Paritaprevir/ Ombitasivir/RTV	DOR	↑ DOR possible	No dose adjustment necessary.
	EFV	No data	**Contraindicated.**
	ETR, NVP	↓ DAAs possible	**Do not coadminister.**
	RPV	RPV AUC ↑ 150% to 225%	**Do not coadminister,** due to potential for QT interval prolongation with higher concentrations of RPV.

Table 19b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 7 of 10)

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			
Elbasvir/ Grazoprevir	EFV	Elbasvir AUC ↓ 54% Grazoprevir AUC ↓ 83% EFV ↔ by grazoprevir EFV ↔ AUC by elbasvir	**Contraindicated.**
	ETR, NVP	↓ elbasvir and grazoprevir expected	**Do not coadminister.**
	DOR, RPV	↔ Elbasvir, grazoprevir ↔ DOR, RPV	No dose adjustment necessary.
Glecaprevir/ Pibrentasvir	DOR	↑ DOR expected	No dose adjustment necessary.
	EFV	↓ glecaprevir and pibrentasvir expected	**Do not coadminister.**
	ETR , NVP	↓ glecaprevir and pibrentasvir possible	
	RPV	↔ glecaprevir, pibrentasvir RPV AUC ↑ 84%	No dose adjustment necessary.
Ledipasvir/ Sofosbuvir	EFV	Ledipasvir AUC, C_{min}, and C_{max} ↓ 34% ↔ sofosbuvir	No dose adjustment necessary.
	ETR, NVP	No significant effect expected	
	DOR, RPV	↔ Ledipasvir, sofosbuvir ↔ DOR, RPV	
Simeprevir	DOR	No significant effect expected.	No dose adjustment necessary.
	EFV	Simeprevir AUC ↓ 71%, C_{min} ↓ 91% ↔ EFV	**Do not coadminister.**
	ETR, NVP	↓ simeprevir expected	**Do not coadminister.**
	RPV	↔ simeprevir and RPV	No dose adjustment necessary.
Sofosbuvir/ Velpatasvir	EFV	Velpatasvir AUC ↓ 43%, C_{max} ↓ 37% and C_{min} ↓ 47%	**Do not coadminister.**
	ETR, NVP	↓ velpatasvir expected	**Do not coadminister.**
	DOR, RPV	No significant effect expected	No dose adjustment necessary.
Sofosbuvir/ Velpatasvir/ Voxilaprevir	EFV	Velpatasvir AUC ↓ 43% , C_{max} ↓ 37%, and C_{min} ↓ 47% ↓ voxilaprevir expected	**Do not coadminister.**
	ETR, NVP	↓ voxilaprevir expected ↓ velpatasvir expected	**Do not coadminister.**
	DOR, RPV	No signficant effect expected	No dose adjustment necessary.

Table 19b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 8 of 10)

Concomitant Drug Class/ Name	NNRTI[a]	Effect on NNRTI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Herbal Products			
St. John's Wort	EFV, ETR, NVP	↓ EFV, ETR, and NVP expected	**Do not coadminister.**
	DOR, RPV	↓ NNRTI expected	**Contraindicated.**
Hormonal Therapies			
Hormonal Contraceptives, Oral	EFV	↔ Ethinyl estradiol Etonogestrel (metabolite of oral desogestrel) C_{min} ↓ 61% Levonorgestrel (metabolite of oral norgestimate) AUC ↓ 83% Norelgestromin (metabolite of oral norgestimate) AUC ↓ 64%	Use alternative or additional contraceptive methods.
	ETR	Ethinyl estradiol AUC ↑ 22% No significant effect on norethindrone	No dose adjustment necessary.
	NVP	Ethinyl estradiol AUC ↓ 29%, C_{min} ↓ 58% Norethindrone AUC ↓ 18% Etonogestrel (metabolite of oral desogestrel) C_{min} ↓ 22%	Based on clinical data demonstrating no change in effectiveness, no dose adjustment necessary.
	RPV	↔ Ethinyl estradiol ↔ Norethindrone	No dose adjustment necessary.
	DOR	↔ Ethinyl estradiol ↔ Levonorgestrel	No dose adjustment necessary.
Depot Medroxy-progesterone Acetate (MPA) Injectable	EFV, NVP	DMPA: no significant change	No dose adjustment necessary.
Etonogestrel-Releasing Subdermal Implant	EFV	Etonogestrel AUC ↓ 63% to 82%	Use alternative or additional contraceptive methods.
	NVP	Etonogestrel: no significant change	No dose adjustment necessary.
Etonogestrel/ Ethinyl Estradiol Vaginal Ring	EFV	Ethinyl estradiol (intravaginal ring) AUC ↓ 56% Etonogestrel (intravaginal ring) AUC ↓ 81%	Use alternative or additional contraceptive methods.
Levonorestrel-Releasing Subdermal Implant	EFV	Levonorgestrel AUC ↓ 47%	Use alternative or additional contraceptive methods. Unintended pregnancies were observed in women who used EFV and levonorgestrel implant concomitantly.
	NVP	Levonorgestrel AUC ↑ 35%	No dose adjustment necessary.
Levonorgestrel For emergency contraception	EFV	Levonorgestrel AUC ↓ 58%	Effectiveness of emergency postcoital contraception may be diminished.

Table 19b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 9 of 10)

Concomitant Drug Class/ Name	NNRTI[a]	Effect on NNRTI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hormonal Therapies, continued			
Menopausal Hormone Replacement Therapy	EFV, ETR, NVP	↓ estrogen possible with estradiol or conjugated estrogen (equine and synthetic) ↓ medroxyprogesterone possible ↓ micronized progesterone possible ↓ drospirenone possible See Hormonal Contraceptives for other progestin-NNRTI interactions	Monitor menopausal symptoms. Titrate to the dose of hormonal therapy that achieves menopausal symptom relief.
Gender-Affirming Hormone Therapy	EFV, ETR, NVP	↓ estradiol possible ↔ goserelin, leuprolide acetate, and spironolactone expected ↓ dutasteride and finasteride possible	Monitor feminizing effects of estrogen and antiandrogen therapy and titrate dosing as necessary to achieve therapeutic goals.
	EFV, ETR, NVP	↓ testosterone possible	Monitor masculinizing effects of testosterone and titrate testosterone dose as necessary to achieve therapeutic goals.
HMG-CoA Reductase Inhibitors			
Atorvastatin	EFV, ETR	Atorvastatin AUC ↓ 32% to 43%	Adjust atorvastatin dose according to lipid response, but do not exceed the maximum recommended dose.
	NVP	↓ atorvastatin possible	Adjust atorvastatin dose according to lipid response, but do not exceed the maximum recommended dose.
	DOR, RPV	↔ atorvastatin AUC	No dose adjustment necessary.
Fluvastatin	EFV, ETR	↑ fluvastatin possible	Dose adjustments for fluvastatin may be necessary. Monitor for fluvastatin toxicity.
Lovastatin, Simvastatin	EFV	Simvastatin AUC ↓ 68% Simvastatin active metabolite AUC ↓ 60%	Adjust simvastatin dose according to lipid response, but do not 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 but do not 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	No dose adjustment necessary.
	DOR, ETR, NVP, RPV	↔ pitavastatin expected	No dose adjustment necessary.
Pravastatin	EFV	Pravastatin AUC ↓ 44%	Adjust statin dose according to lipid responses, but do not exceed the maximum recommended dose.
	ETR	↓ pravastatin possible	
Rosuvastatin	EFV, ETR, NVP	↔ rosuvastatin expected	No dose adjustment necessary.

Table 19b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 10 of 10)

Concomitant Drug Class/ Name	NNRTI[a]	Effect on NNRTI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Immunosuppressants			
Cyclosporine, Everolimus, 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 or buccal	EFV	Buprenorphine AUC ↓ 50% Norbuprenorphine[b] AUC ↓ 71%	No dose adjustment recommended; monitor for withdrawal symptoms.
	ETR	Buprenorphine AUC ↓ 25%	No dose adjustment necessary.
	NVP	No significant effect	No dose 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.
	DOR, ETR	No significant effect	No dose adjustment necessary.
	NVP	Methadone AUC ↓ 37% to 51% No significant effect on NVP	Opioid withdrawal is common; increased methadone dose is often necessary.
	RPV	R-methadone[c] AUC ↓ 16%	No dose adjustment necessary, but monitor for withdrawal symptoms.
PDE5 Inhibitors			
Sildenafil	DOR, RPV	↔ sildenafil expected	No dose adjustment necessary.
	ETR	Sildenafil AUC ↓ 57%	May need to titrate sildenafil dose based on clinical effect.
	EFV, NVP	↓ sildenafil possible	
Tadalafil	EFV, ETR, NVP	↓ tadalafil possible	May need to titrate tadalafil dose based on clinical effect.
	RPV	↔ tadalafil	No dose adjustment necessary.
Avanafil, Vardenafil	EFV, ETR, NVP	↓ PDE5 inhibitor possible	May need to increase PDE5 inhibitor dose based on clinical effect.
Miscellaneous Drugs			
Enzalutamide	All NNRTIs	↓ NNRTI expected	**Contraindicated.**
Mitotane	All NNRTIs	↓ NNRTI expected	**Contraindicated.**

[a] Approved dose for RPV is 25 mg once daily. Most PK interaction studies were performed using 75 mg 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 blocker; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; DAA = direct-acting antiviral; DHA = dihydroartemisinin; DMPA = depot medroxyprogesterone acetate; DOR = doravirine; EFV = efavirenz; ETR = etravirine; 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 jirovecii* pneumonia; PDE5 = phosphodiesterase type 5; PI = protease inhibitor; PI/r = protease inhibitor/ritonavir; 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 October 25, 2018; last reviewed October 25, 2018) (page 1 of 3)

Recommendations for managing a particular drug interaction may differ depending on whether a new ARV drug is being initiated in a patient on a stable concomitant medication or whether a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly.

Note: Interactions associated with ddI and d4T are **not** included in this table. Please refer to FDA product labels for information regarding interactions between ddI or d4T and other concomitant drugs.

Concomitant Drug Class/ Name	NRTI	Effect on NRTI and/or Concomitant Drug Concentrations	Dosage Recommendations and Clinical Comments
Cytomegalovirus and Hepatitis B Antivirals			
Adefovir	TDF	No data	**Do not coadminister.** Serum concentrations of TDF and/or other renally eliminated drugs may increase.
Ganciclovir, Valganciclovir	TAF, TDF	No data	Serum concentrations of ganciclovir and/or TFV may increase. Monitor for dose-related toxicities.
	ZDV	No significant effect	Potential increase in hematologic toxicities.
Hepatitis C Antiviral Agents			
Glecaprevir/Pibrentasvir	TAF, TDF	No significant effect	No dose adjustment necessary.
Ledipasvir/Sofosbuvir, Sofosbuvir/Velpatasvir, Sofosbuvir/Velpatasvir/ Voxilaprevir	TAF	No significant effect	No dose adjustment.
	TDF	Ledipasvir ↑ TFV AUC 40% to 98% when TDF is given with RPV and EFV Further ↑ TFV possible if TDF is given with PIs	No dose adjustment necessary. The safety of increased TFV exposure when ledipasvir/sofosbuvir is coadministered with TDF plus a PI/r or PI/c has not been established. Consider alternative HCV or ARV drugs to avoid increased TFV toxicities. Consider using TAF in patients at risk of TDF-associated adverse events. If TDF is used in these patients, monitor for TDF toxicity. **Coadministration of ledipasvir/sofosbuvir with EVG/c/TDF/FTC is not recommended.**
Ribavirin	TDF	With Sofosbuvir 400 mg: • ↔ TFV AUC	No dose adjustment necessary.
	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 dose adjustment necessary.
	TDF	↔ TDF AUC ↔ DTG AUC	No dose adjustment necessary.
RAL	TDF	RAL AUC ↑ 49%	No dose adjustment necessary.
Narcotics/Treatment for Opioid Dependence			
Buprenorphine	3TC, TDF, TAF, ZDV	No significant effect	No dose adjustment necessary.

Table 19c. Drug Interactions Between Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Including Antiretroviral Agents) (Last updated October 25, 2018; last reviewed October 25, 2018)
(page 2 of 3)

Concomitant Drug Class/ Name	NRTI	Effect on NRTI and/or Concomitant Drug Concentrations	Dosage Recommendations and Clinical Comments
Narcotics/Treatment for Opioid Dependence, continued			
Methadone	ABC	Methadone clearance ↑ 22%	No dose adjustment necessary.
	ZDV	ZDV AUC ↑ 29% to 43%	Monitor for ZDV-related adverse effects.
Other			
Atovaquone	ZDV	ZDV AUC ↑ 31%	Monitor for ZDV-related adverse effects.
Anticonvulsants Carbamazepine, oxcarbazepine, phenobarbital, phenytoin	TAF	With Carbamazepine: • TAF AUC ↓ 55% ↓ TAF possible with other anticonvulsants	**Coadministration is not recommended.**
Antimycobacterial Rifampin	TAF	TAF AUC ↓ 55% TFV-DP (intracellular active moiety) AUC ↓ 36% TAF plus Rifampin Compared with TDF Alone: • TFV-DP (intracellular active moiety) AUC ↑ 4.2-fold With Twice-Daily TAF 25 mg Compared with Once-Daily TAF without Rifampin: • TAF AUC ↓ 14% • TFV-DP (intracellular active moiety) AUC ↓ 24%	**Coadministration is not recommended.**
	TDF	↔ AUC TFV	No dose adjustment necessary.
Rifabutin, Rifapentine	TAF	↓ TAF possible	**Coadministration is not recommended.**
St. John's Wort	TAF	↓ TAF possible	**Coadministration is not recommended.**
PIs (HIV)			
ATV (Unboosted), ATV/c, ATV/r	TAF	TAF 10 mg with ATV/r: • TAF AUC ↑ 91% TAF 10 mg with ATV/c: • TAF AUC ↑ 75%	No dose adjustment (use TAF 25 mg).
	TDF	With ATV (Unboosted): • ATV AUC ↓ 25% and C_{min} ↓ 23% to 40% (higher C_{min} with RTV than without RTV) TFV 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 an ART-experienced patient, 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 ↔ ZDV AUC	Clinical significance unknown.

Table 19c. Drug Interactions Between Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Including Antiretroviral Agents) (Last updated October 25, 2018; last reviewed October 25, 2018)
(page 3 of 3)

Concomitant Drug Class/ Name	NRTI	Effect on NRTI and/or Concomitant Drug Concentrations	Dosage Recommendations and Clinical Comments
PIs (HIV), continued			
DRV/c	TAF	TAF 25 mg with DRV/c: • ↔ TAF	No dose adjustment necessary.
	TDF	↑ TDF possible	Monitor for TDF-associated toxicity.
DRV/r	TAF	TAF 10 mg with DRV/r: • ↔ TAF	No dose adjustment necessary.
	TDF	TFV AUC ↑ 22% and C_{min} ↑ 37%	Clinical significance unknown. Monitor for TDF-associated toxicity.
LPV/r	TAF	TAF 10 mg with DRV/r: • TAF AUC ↑ 47%	No dose adjustment necessary.
	TDF	↔ LPV/r AUC TFV AUC ↑ 32%	Clinical significance unknown. Monitor for TDF-associated toxicity.
TPV/r	ABC	ABC AUC ↓ 35% to 44%	Appropriate doses for this combination have not been established.
	TAF	↓ TAF expected	**Coadministration is not recommended.**
	TDF	↔ TDF AUC TPV AUC ↓ 9% to 18% and C_{min} ↓ 12% to 21%	No dose adjustment necessary.
	ZDV	ZDV AUC ↓ 31% to 42% ↔ TFV AUC	Appropriate doses for this combination have not been established.

Key to Symbols:

↑ = increase

↓ = decrease

↔ = no change

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; AUC = area under the curve; C_{min} = minimum plasma concentration; COBI = cobicistat; d4T = stavudine; ddI = didanosine; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FDA = Food and Drug Administration; FTC = emtricitabine; HCV = hepatitis C virus; INSTI = integrase strand transfer inhibitors; LPV/r = lopinavir/ritonavir; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PI/c = protease inhibitor/cobicistat; PI/r = protease inhibitor/ritonavir; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TFV = tenofovir; TFV-DP = tenofovir diphosphate; TPV/r = tipranavir/ritonavir; ZDV = zidovudine

Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 1 of 15)

This table provides information on known or predicted PK interactions between INSTIs (BIC, DTG, EVG, or RAL) and non-ARV drugs. EVG is always coadministered with COBI. Recommendations for managing a particular drug interaction may differ depending on whether a new ARV drug is being initiated in a patient on a stable concomitant medication or whether a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly.

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Alpha-Adrenergic Antagonists for Benign Prostatic Hyperplasia			
Alfuzosin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ alfuzosin expected	**Contraindicated.**
Doxazosin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ doxazosin possible	Initiate doxazosin at lowest dose and titrate while monitoring for clinical response/toxicity. Dose reduction may be necessary.
Tamsulosin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ tamsulosin expected	**Coadministration is not recommended.** If coadministered, monitor for tamsulosin toxicities.
Terazosin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ terazosin possible	Initiate terazosin at lowest dose and titrate while monitoring for clinical response/toxicity. Dose reduction may be necessary.
Silodosin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ silodosin expected	**Contraindicated.**
Acid Reducers			
Al, Mg, +/- Ca-Containing Antacids Please refer to the Miscellaneous Drugs section of this table for recommendations on use with other polyvalent cation products (e.g., Fe, Ca supplements, multivitamins).	BIC	↔ BIC AUC if antacid is given 2 hours after BIC and under fasting conditions BIC AUC ↓ 79% if given simultaneously with antacid BIC AUC ↓ 52% if antacid is given 2 hours before BIC	With Antacids Containing Al/Mg or Ca: • BIC can be taken under fasting conditions at least 2 hours before antacids containing Al/Mg or Ca. Do not coadminister BIC simultaneously with, or 2 hours after, antacids containing Al/Mg or Ca.
	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 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 >2 hours.

Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 2 of 15)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers, continued			
Al, Mg, +/- Ca-Containing Antacids, continued Please refer to the Miscellaneous Drugs section of this table for recommendations on use with other polyvalent cation products (e.g., Fe, Ca supplements, multivitamins).	RAL	Al/Mg Hydroxide Antacid: • RAL C_{min} ↓ 49% to 63% $CaCO_3$ Antacid: • RAL (400 mg BID) C_{min} ↓ 32% • RAL (1200 mg once daily) C_{min} ↓ 48% to 57%	**Do not coadminister RAL and Al-Mg hydroxide antacids.** Use alternative acid reducing agent. With $CaCO_3$ Antacids: • RAL 1200 mg once daily: **Do not coadminister.** • RAL 400 mg BID: No dose adjustment or separation necessary.
H2-Receptor Antagonists	BIC, DTG, EVG/c	No significant effect	No dose adjustment necessary.
	RAL	RAL AUC ↑ 44% and C_{max} ↑ 60%	No dose adjustment necessary.
PPIs	BIC, DTG, EVG/c	No significant effect	No dose adjustment necessary.
	RAL	RAL AUC ↑ 37% and C_{min} ↑ 24%	No dose adjustment necessary.
Anticoagulants and Antiplatelets			
Apixaban	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ apixaban expected	In Patients Requiring Apixaban 2.5 mg Twice Daily: • **Coadministration is not recommended.** In Patients Requiring Apixaban 5 mg or 10 mg Twice Daily: • Reduce apixaban dose by 50%.
Betrixaban	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ betrixaban expected	Administer initial single dose of betrixaban 80 mg, followed by betrixaban 40 mg once daily.
Dabigatran	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ dabigatran expected Dabigatran AUC ↑ 110% to 127% with COBI 150 mg alone	Dabigatran dosing recommendation depends on indication and renal function. Refer to dabigatran prescribing information for dosing instruction when used with P-gp inhibitors.
Edoxaban	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↔ or ↑ edoxaban expected	For Stroke Prevention in Nonvalvular Atrial Fibrillation: • No dose adjustment necessary. For Deep Venous Thrombosis and Pulmonary Embolism: • Administer edoxaban 30 mg once daily.
Rivaroxaban	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ rivaroxaban expected	**Coadministration is not recommended.**

Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 3 of 15)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticoagulants and Antiplatelets, continued			
Ticagrelor	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ ticagrelor expected	**Coadministration is not recommended.**
Vorapaxar	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ vorapaxar expected	**Coadministration is not recommended.**
Warfarin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ or ↓ warfarin possible	Monitor INR and adjust warfarin dose accordingly.
Anticonvulsants			
Carbamazepine	BIC	↓ BIC possible	Consider using an alternative anticonvulsant or ARV.
	DTG	DTG AUC ↓ 49%	Increase DTG dose to 50 mg BID in treatment-naive or treatment-experienced, INSTI-naive patients. Use alternative anticonvulsant for INSTI-experienced patients with known or suspected INSTI resistance.
	EVG/c	Carbamazepine AUC ↑ 43% EVG AUC ↓ 69% and C_{min} ↓ >99% ↓ COBI expected	**Contraindicated.**
	RAL	↓ or ↔ RAL possible	**Coadministration is not recommended.**
Eslicarbazepine	All INSTIs	↓ INSTI possible ↓ COBI possible	Consider using an alternative anticonvulsant or ARV.
Ethosuximide	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ ethosuximide possible	Clinically monitor for ethosuximide toxicities.
Lamotrigine	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	No data	Monitor anticonvulsant level and adjust dose accordingly.
Oxcarbazepine	All INSTIs	↓ INSTI possible ↓ COBI possible	Consider using an alternative anticonvulsant or ARV.
Phenobarbital **Phenytoin**	BIC	↓ BIC possible	**Coadministration is not recommended.**
	DTG	↓ DTG possible	**Coadministration is not recommended.**
	EVG/c	↓ EVG/c expected	**Contraindicated.**
	RAL	↓ or ↔ RAL possible	**Coadministration is not recommended.**
Valproic Acid	All INSTIs	No data	Monitor valproic acid concentration and virologic response.

Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 4 of 15)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antidepressants/Anxiolytics/Antipsychotics Also see Sedative/Hypnotics section below.			
Aripiprazole	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ aripiprazole expected	Administer 25% of the usual aripiprazole dose. Titrate based on clinical monitoring for efficacy and toxicity. Refer to aripiprazole label for dosing recommendations in patients who are known to be CYP2D6 poor metabolizers or who have major depressive disorder.
Brexpiprazole	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ brexpiprazole expected	Administer 25% of the usual brexpiprazole dose. Titrate based on clinical monitoring for efficacy/toxicity. Refer to brexpiprazole label for dosing recommendations in patients who are known to be CYP2D6 poor metabolizers or who have major depressive disorder.
Bupropion	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ bupropion possible	Titrate bupropion dose based on clinical response.
Buspirone	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ buspirone possible	Initiate buspirone at a low dose. Dose reduction may be necessary.
Cariprazine	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ cariprazine expected	Starting Cariprazine in a Patient Already on EVG/c: • Administer cariprazine 1.5 mg on Day 1 and Day 3, with no dose given on Day 2. • From Day 4 onward, administer 1.5 mg daily. Can be increased to a maximum dose of 3 mg daily. • If EVG/c is withdrawn, cariprazine dose may need to be increased. Starting EVG/c in a Patient Already on Cariprazine: • For patients receiving cariprazine 3 mg or 6 mg daily, reduce cariprazine dose by half. • For patients taking cariprazine 4.5 mg daily, the dose should be reduced to 1.5 mg or 3 mg daily. • For patients taking cariprazine 1.5 mg daily, change to 1.5 mg every other day. • If EVG/c is withdrawn, cariprazine dose may need to be increased.

Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 5 of 15)

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.			
Fluvoxamine	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ or ↓ EVG possible	Consider alternative antidepressant or ARV.
Lurasidone	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ lurasidone expected	**Contraindicated.**
Pimavanserin	BIC, DTG, RAL	↔ expected	Standard doses.
	EVG/c	↑ pimavanserin expected	Reduce pimavanserin dose by 50%. Titrate dose based on efficacy and toxicity.
Pimozide	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ pimozide expected	**Contraindicated.**
Quetiapine	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ 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.
SSRIs Citalopram, escitalopram, fluoxetine, paroxetine, sertraline	EVG/c	↔ EVG ↔ sertraline	No dose adjustment necessary.
		↑ other SSRI possible	Initiate with lowest dose of SSRI and titrate dose carefully based on antidepressant response.
	BIC, DTG, RAL	↔ BIC, DTG, RAL expected ↔ SSRI expected	No dose adjustment necessary.
TCAs Amitriptyline, desipramine, doxepin, imipramine, nortriptyline	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	Desipramine AUC ↑ 65%	Initiate with lowest dose of TCA and titrate dose carefully.
		↑ TCA expected	Initiate with lowest dose of TCA and titrate dose carefully based on antidepressant response and/or drug levels.
Trazodone	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ trazodone possible	Initiate with lowest dose of trazodone and titrate dose carefully.
Other Antipsychotics (CYP3A4 and/or CYP2D6 substrates)	EVG/c	↑ antipsychotic possible	Initiate antipsychotic at a low dose. Decrease in antipsychotic dose may be necessary.

Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 6 of 15)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antifungals			
Isavuconazole	BIC	↑ BIC possible	No dose adjustment necessary.
	EVG/c	↑ isavuconazole expected ↑ EVG and COBI possible	If coadministered, consider monitoring isavuconazole concentrations and assess virologic response.
Itraconazole	BIC	↑ BIC expected	No dose adjustment necessary.
	DTG, RAL	↔ expected	No dose adjustment necessary.
	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.
Posaconazole	BIC	↑ BIC expected	No dose adjustment necessary.
	DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ EVG and COBI possible ↑ posaconazole possible	If coadministered, monitor posaconazole concentrations.
Voriconazole	BIC	↑ BIC possible	No dose adjustment necessary.
	DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ voriconazole expected ↑ EVG and COBI possible	**Do not coadminister voriconazole and COBI unless benefit outweighs risk.** If coadministered, consider monitoring voriconazole concentrations and adjust dose accordingly.
Antihyperglycemics			
Metformin	BIC	Metformin AUC ↑ 39%	Monitor for metformin adverse effects.
	DTG	DTG 50 mg Once Daily plus Metformin 500 mg BID: • Metformin AUC ↑ 79% and C_{max} ↑ 66% DTG 50 mg BID plus Metformin 500 mg BID: • Metformin AUC ↑ 2.4-fold and C_{max} ↑ 2-fold	Start metformin at lowest dose and titrate based on glycemic control. Monitor for metformin adverse effects. When starting/stopping DTG in patients on metformin, dose adjustment of metformin may be necessary to maintain optimal glycemic control and/or minimize adverse effects of metformin.
	RAL	↔ expected	No dose adjustment necessary.
Saxagliptin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ saxagliptin expected	Limit saxagliptin dose to 2.5 mg once daily.
Dapagliflozin/ Saxagliptin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ saxagliptin expected	**Do not coadminister**, as this coformulated drug contains 5 mg of saxagliptin.
Antimycobacterials			
Clarithromycin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	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.**

Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 7 of 15)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antimycobacterials, continued			
Rifabutin	BIC	Rifabutin (300 mg Once Daily): • BIC AUC ↓ 38% and C_{min} ↓ 56%	**Do not coadminister.**
	DTG	Rifabutin (300 mg Once Daily): • DTG AUC ↔ and C_{min} ↓ 30%	No dose 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% and C_{min} ↓ 67%	**Do not coadminister.**
	RAL	RAL AUC ↑ 19% and C_{min} ↓ 20%	No dose adjustment necessary.
Rifampin	BIC	BIC AUC ↓ 75%	**Contraindicated.**
	DTG	Rifampin with DTG 50 mg BID Compared to DTG 50 mg BID Alone: • DTG AUC ↓ 54% and C_{min} ↓ 72% Rifampin with DTG 50 mg BID Compared to DTG 50 mg Once Daily Alone: • DTG AUC ↑ 33% and 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	Significant ↓ EVG and COBI expected	**Contraindicated.**
	RAL	RAL 400 mg: • RAL AUC ↓ 40% and C_{min} ↓ 61% Rifampin with RAL 800 mg BID Compared to RAL 400 mg BID Alone: • RAL AUC ↑ 27% and C_{min} ↓ 53%	Dose: • RAL 800 mg BID, instead of 400 mg BID **Do not coadminister RAL 1200 mg once daily with rifampin.** Monitor closely for virologic response or consider using rifabutin as an alternative rifamycin.
Rifapentine	BIC, DTG, EVG/c	Significant ↓ BIC, DTG, EVG, and COBI expected	**Do not coadminister.**
	RAL	Rifapentine 900 mg Once Weekly: • RAL AUC ↑ 71% and C_{min} ↓ 12% Rifapentine 600 mg Once Daily: • RAL C_{min} ↓ 41%	For once-weekly rifapentine, use standard RAL 400 mg BID doses. **Do not coadminister with once-daily rifapentine.**

Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 8 of 15)

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, mexiletine, propafenone, quinidine	BIC, DTG	↔ expected for the listed antiarrhythmics, except for disopyramide ↑ disopyramide possible	No dose adjustment necessary. Coadminister with caution. Clinical monitoring is recommended.
	RAL	↔ expected for the listed antiarrhythmics	No dose adjustment necessary.
	EVG/c	↑ antiarrhythmics possible Digoxin C_{max} ↑ 41% and no significant change in AUC	Use antiarrhythmics with caution. TDM, if available, is recommended for antiarrhythmics.
Bosentan	BIC, DTG	↓ BIC, DTG possible	Standard doses.
	RAL	↔ expected	No dose adjustment necessary.
	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.
Beta-blockers (e.g., metoprolol, timolol)	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ 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 (e.g., atenolol, labetalol, nadolol, sotalol).
CCBs	BIC	↑ BIC possible with diltiazem ↔ expected for all other CCBs	No dose adjustment necessary.
	DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ CCBs possible	Coadminister with caution. Titrate CCB dose and monitor for CCB efficacy and toxicities. Refer to Table 19a for diltiazem plus ATV/r recommendations.
Dofetilide	BIC, DTG	↑ dofetilide expected	**Contraindicated.**
	RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ dofetilide possible	**Do not coadminister.**
Eplerenone	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ eplerenone expected	**Contraindicated.**
Ranolazine	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ ranolazine expected	**Contraindicated.**
Ivabradine	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ ivabradine expected	**Contraindicated.**

Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 9 of 15)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Corticosteroids			
Beclomethasone Inhaled or intranasal	BIC, DTG, EVG/c, RAL	↔ expected	No dose adjustment necessary.
Budesonide, Ciclesonide, Fluticasone, Mometasone Inhaled or intranasal	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ glucocorticoid possible	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 an alternative corticosteroid (e.g., beclomethasone).
Betamethasone, Budesonide Systemic	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ glucocorticoids possible ↓ EVG possible	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.**
Dexamethasone Systemic	BIC	↓ BIC possible	Consider an alternative corticosteroid for long-term use or an alternative ARV. If coadministration is necessary, monitor virologic response to ART.
	DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↓ EVG and COBI possible	Consider an alternative corticosteroid for long-term use or alternative ART. If coadministration is necessary, monitor virologic response to ART.
Prednisone, Prednisolone Systemic	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ prednisolone possible	Coadministration may be considered if the potential benefits outweigh the risks of systemic corticosteroid adverse effects. If coadministered, monitor for adrenal insufficiency and Cushing's syndrome.
Betamethasone, Methylprednisolone, Prednisolone, Triamcinolone Local injections, including intra-articular, epidural, or intra-orbital	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ glucocorticoids expected	**Do not coadminister.** Coadministration may result in adrenal insufficiency and Cushing's syndrome.
Hepatitis C Direct Acting Antivirals			
Daclatasvir	DTG	↔ daclatasvir	No dose adjustment necessary.
	EVG/c	↑ daclatasvir	Decrease daclastavir dose to 30 mg once daily.
	BIC, RAL	No data	No dose adjustment necessary.
Dasabuvir plus Ombitasvir/ Paritaprevir/RTV	BIC, DTG	No data	No dose adjustment necessary.
	EVG/c	No data	**Do not coadminister.**
	RAL	RAL AUC ↑ 134%	No dose adjustment necessary.

Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 10 of 15)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hepatitis C Direct Acting Antivirals, continued			
Elbasvir/Grazoprevir	BIC	↔ BIC expected	No dose adjustment necessary.
	DTG	↔ elbasvir ↔ grazoprevir ↔ DTG	No dose adjustment necessary.
	EVG/c	↑ elbasvir and ↑ grazoprevir expected	**Coadministration is not recommended.**
	RAL	↔ elbasvir ↔ grazoprevir ↔ RAL with elbasvir RAL AUC ↑ 43% with grazoprevir	No dose adjustment necessary.
Glecaprevir/ Pibrentasvir	BIC	↔ BIC expected	No dose adjustment necessary.
	DTG, RAL	No significant effect	No dose adjustment necessary.
	EVG/c	Glecaprevir AUC ↑ 3-fold Pibrentasvir AUC ↑ 57% EVG AUC ↑ 47%	No dose adjustment necessary.
Ledipasvir/ Sofosbuvir	EVG/c/TDF/ FTC	↑ TDF and ↑ ledipasvir expected	**Do not coadminister.**
	EVG/c/TAF/ FTC	↔ EVG/c/TAF/FTC expected	No dose adjustment necessary.
	BIC, DTG, RAL	↔ DTG or RAL	No dose adjustment necessary.
Simeprevir	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ simeprevir expected	**Coadministration is not recommended.**
Sofosbuvir	All INSTIs	↔ expected	No dose adjustment necessary.
Sofosbuvir/ Velpatasvir	All INSTIs	↔ expected	No dose adjustment necessary.
Sofosbuvir/ Velpatasvir/ Voxilaprevir	EVG/c	When Given with Sofosbuvir/Velpatasvir/ Voxilaprevir (400 mg/100 mg/100 mg) plus Voxilaprevir 100 mg: • Sofosbuvir AUC ↑ 22% • ↔ velpatasvir • Voxilaprevir AUC ↑ 2-fold	No dose adjustment necessary.
	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
Herbal Products			
St. John's Wort	BIC, DTG	↓ BIC and DTG possible	**Do not coadminister.**
	EVG/c	↓ EVG and COBI possible	**Contraindicated.**

Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 11 of 15)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hormonal Therapies			
Hormonal Contraceptives Oral	BIC, DTG, RAL	↔ ethinyl estradiol, norgestimate, and DTG or RAL	No dose 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 using an alternative contraceptive method.
		↑ drospirenone possible	Clinical monitoring is recommended, due to the potential for hyperkalemia.
Hormonal Contraceptives Non-oral	All INSTIs	No data	No drug-drug interaction studies have been conducted with INSTIs and non-oral routes of hormone administration. It is unclear if oral drug-drug interaction data can be extrapolated beyond oral routes of administration.
Menopausal Hormone Replacement Therapy	BIC, DTG, RAL	With Estradiol or Conjugated Estrogen (Equine and Synthetic): • ↔ estrogen expected ↔ drospirenone, medroxyprogesterone, or micronized progesterone expected	No dose adjustment necessary.
	EVG/c	↓ estrogen expected ↑ drospirenone possible ↑ oral medroxyprogesterone possible ↑ oral micronized progesterone possible	Adjust estrogen and progestin dose as needed based on clinical effects.
Gender-Affirming Hormone Therapy	BIC, DTG, RAL	↔ estrogen expected	No dose adjustment necessary.
	BIC, DTG, EVG/c, RAL	↔ finasteride, goserelin, leuprolide acetate, spironolactone expected	
	EVG/c	↓ estradiol expected ↑ dutasteride possible	Adjust dutasteride dosage as needed based on clinical effects and endogenous hormone concentrations.
	EVG/c	↑ testosterone possible	Monitor masculinizing effects of testosterone and for adverse effects and adjust testosterone dose as necessary.
	BIC, DTG, RAL	↔ testosterone expected	No dose adjustment necessary.
HMG-CoA Reductase Inhibitors			
Atorvastatin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	Atorvastatin AUC ↑ 2.6-fold and C_{max} ↑ 2.3-fold	Titrate statin dose carefully and use the lowest dose necessary while monitoring for toxicities. Do not exceed 20 mg atorvastatin daily.
Lovastatin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	Significant ↑ lovastatin expected	**Contraindicated.**
Pitavastatin, Pravastatin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	No data	No dose recommendation.

Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 12 of 15)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
HMG-CoA Reductase Inhibitors, continued			
Rosuvastatin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	Rosuvastatin AUC ↑ 38% and C_{max} ↑ 89%	Titrate statin dose carefully and use the lowest dose necessary while monitoring for toxicities.
Simvastatin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	Significant ↑ simvastatin expected	**Contraindicated.**
Immunosuppressants			
Cyclosporine, Everolimus, Sirolimus, Tacrolimus	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ 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 a specialist as necessary.
Narcotics/Treatment for Opioid Dependence			
Buprenorphine Sublingual, buccal, or implant	BIC, DTG	↔ expected	No dose adjustment necessary.
	EVG/c	Buprenorphine AUC ↑ 35% and C_{min} ↑ 66% Norbuprenorphine AUC ↑ 42% and C_{min} ↑ 57%	No dose adjustment necessary. Clinical monitoring is recommended. When transferring buprenorphine from transmucosal administration to implantation, monitor to ensure buprenorphine effect is adequate and not excessive.
	RAL	↔ observed (sublingual) ↔ expected (implant)	No dose adjustment necessary.
Methadone	All INSTIs	No significant effect	No dose adjustment necessary.
PDE5 Inhibitors			
Avanafil	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	No data	**Coadministration is not recommended.**
Sildenafil	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ 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 October 25, 2018; last reviewed October 25, 2018) (page 13 of 15)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
PDE5 Inhibitors, continued			
Tadalafil	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ tadalafil expected	For Treatment of Erectile Dysfunction: • Start with tadalafil 5-mg dose and do not exceed a single dose of tadalafil 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 tadalafil 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 tadalafil 40 mg once daily based on tolerability.
Vardenafil	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ 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	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ 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	BIC, RAL	↔ expected	No dose adjustment necessary.
	DTG	With DTG 25 mg: • ↔ Midazolam AUC	No dose adjustment necessary.
	EVG/c	↑ midazolam expected ↑ triazolam expected	**Contraindicated. Do not coadminister triazolam or oral midazolam and EVG/c.** Parenteral midazolam can be used with caution in a closely monitored setting. Consider dose reduction, especially if >1 dose is administered.
Suvorexant	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ suvorexant expected	**Coadministration is not recommended.**
Zolpidem	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ 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 October 25, 2018; last reviewed October 25, 2018) (page 14 of 15)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Miscellaneous Drugs			
Calcifediol	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ calcifediol possible	Dose adjustment of calcifediol may be required, and serum 25-hydroxyvitamin D, intact PTH, and serum Ca concentrations should be closely monitored.
Cisapride	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ cisapride expected	**Contraindicated.**
Colchicine	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ colchicine expected	**Do not coadminister in patients with hepatic or renal impairment.** For Treatment of Gout Flares: • Administer colchicine 0.6 mg for 1 dose, followed by colchicine 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.
Enzalutamide	DTG	↓ DTG possible	Monitor for ARV efficacy.
	BIC, EVG/c	↓ BIC, EVG/c expected	**Contraindicated.**
	RAL	↔ expected	No dose adjustment necessary.
Ergot Derivatives	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ dihydroergotamine, ergotamine, methylergonovine expected	**Contraindicated.**
Dronabinol	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ dronabinol possible	Monitor for dronabinol-related adverse effects.
Eluxadoline	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ eluxadoline possible	Monitor for eluxadoline-related adverse effects.
Flibanserin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ flibanserin expected	**Contraindicated.**
Mitotane	BIC, EVG/c	↓ BIC and ↓ EVG/c expected	**Contraindicated.**
	DTG	↓ DTG possible	Monitor for ARV efficacy.
	RAL	↔ expected	No dose adjustment necessary.

Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 15 of 15)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Miscellaneous Drugs, continued			
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.	BIC	↔ BIC AUC if given simultaneously with Fe or Ca and food BIC AUC ↓ 33% if given simultaneously with $CaCO_3$ under fasting conditions BIC AUC ↓ 63% if given simultaneously with Fe under fasting conditions	With Supplements that Contain Ca or Fe: • BIC and supplements containing Ca or Fe can be taken together with food. **Do not coadminister BIC under fasting conditions simultaneously with, or 2 hours after, supplements containing Ca or Fe.**
	DTG	DTG AUC ↓ 39% if given simultaneously with calcium carbonate under fasting conditions DTG AUC ↓ 54% if given simultaneously with Fe under fasting conditions ↔ DTG when administered with Ca or Fe supplement simultaneously with food	With Supplements That Contain Ca or Fe: • DTG and supplements containing Ca or Fe can be taken together with food; alternately, administer DTG at least 2 hours before or at least 6 hours after supplement. **Do not coadminister DTG under fasting conditions simultaneously with, or 2 hours after, supplements containing Ca or Fe.**
	EVG/c, RAL	↓ INSTI possible	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. Many oral multivitamins also contain varying amounts of polyvalent cations; the extent and significance of chelation is unknown.
Salmeterol	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ salmeterol possible	**Do not coadminister**, due to potential increased risk of salmeterol-associated cardiovascular events.

Key to Symbols:

↑ = increase

↓ = decrease

↔ = no change

Key to Acronyms: Al = aluminum; ART = antiretroviral therapy; ARV = antiretroviral; ATV/r = atazanavir/ritonavir; AUC = area under the curve; BIC = bictegravir; BID = twice daily; Ca = calcium; $CaCO_3$ = calcium carbonate; CCB = calcium channel blocker; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; COBI = cobicistat; CrCl = creatinine clearance; CYP = cytochrome P; DTG = dolutegravir; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; Fe = iron; FTC = emtricitabine; INR= international normalized ratio; INSTI = integrase strand transfer inhibitor; Mg = magnesium; PAH = pulmonary arterial hypertension; PI = protease inhibitor; PK = pharmacokinetic; PTH = parathyroid hormone; RAL = raltegravir; RTV = ritonavir; SSRI = selective serotonin reuptake inhibitors; TAF = tenofovir alafenamide; TCA = tricyclic antidepressants; TDF = tenofovir disoproxil fumarate; TDM = therapeutic drug monitoring; Zn = zinc

Table 19e. Drug Interactions between CCR5 Antagonist (Maraviroc) and Other Drugs (Including Antiretroviral Agents) (Last updated October 25, 2018; last reviewed October 25, 2018) (page 1 of 3)

In the table below, "No dose adjustment necessary" indicates that the FDA-approved dose of MVC 300 mg twice daily should be used. Recommendations for managing a particular drug interaction may differ depending on whether a new ARV is being initiated in a patient on a stable concomitant medication or whether a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly.

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, no dose adjustment is necessary. If used with a strong CYP3A inhibitor, use MVC 150 mg BID.
Rifampin	MVC	MVC AUC ↓ 64%	Dose: • MVC 600 mg BID If used 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 necessary.
Dasabuvir plus Ombitasvir/Paritaprevir/ RTV	MVC	↑ MVC expected	**Do not coadminister.**
Elbasvir/Grazoprevir	MVC	↔ MVC expected	No dose adjustment necessary.
Ledipasvir/Sofosbuvir	MVC	↔ MVC expected	No dose adjustment necessary.
Glecaprevir/Pibrentasvir	MVC	↔ MVC expected	No dose adjustment necessary.
Simeprevir	MVC	↔ MVC expected	No dose adjustment necessary.
Sofosbuvir	MVC	↔ MVC expected	No dose adjustment necessary.
Sofosbuvir/Velpatasvir	MVC	↔ MVC expected	No dose adjustment necessary.

Table 19e. Drug Interactions between CCR5 Antagonist (Maraviroc) and Other Drugs (Including Antiretroviral Agents) (Last updated October 25, 2018; last reviewed October 25, 2018) (page 2 of 3)

Concomitant Drug Class/ Name	CCR5 Antagonist	Effect on CCR5 Antagonist and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hepatitis C Direct-Acting Antivirals, continued			
Sofosbuvir/Velpatasvir/ Voxilaprevir	MVC	↔ MVC expected	No dose adjustment necessary.
Herbal Products			
St. John's Wort	MVC	↓ MVC expected	**Do not coadminister.**
Hormonal Therapies			
Hormonal Contraceptives	MVC	↔ Ethinyl estradiol or levonorgestrel	No dose adjustment necessary.
Menopausal Hormone Replacement Therapy	MVC	↔ MVC or hormone replacement therapies expected	No dose adjustment necessary.
Gender-Affirming Hormone Therapies	MVC	↔ MVC or gender-affirming hormones expected	No dose adjustment necessary.
ARV Drugs			
INSTIs			
BIC, DTG	MVC	↔ MVC expected	No dose adjustment necessary.
EVG/c	MVC	↑ MVC possible	Dose: • MVC 150 mg BID
RAL	MVC	MVC AUC ↓ 21% RAL AUC ↓ 37%	No dose adjustment necessary.
NNRTIs			
DOR, RPV	MVC	↔ MVC expected	No dose adjustment necessary.
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 with or without RTV or COBI	MVC	With Unboosted ATV: • MVC AUC ↑ 257% With (ATV/r 300 mg/100 mg) Once Daily: • MVC AUC ↑ 388%	Dose: • MVC 150 mg BID

Table 19c. Drug Interactions between CCR5 Antagonist (Maraviroc) and Other Drugs (Including Antiretroviral Agents) (Last updated October 25, 2018; last reviewed October 25, 2018) (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			
DRV/c or **DRV/r**	MVC	With (DRV/r 600 mg/100 mg) BID: • MVC AUC ↑ 305% With (DRV/r 600 mg/100 mg) BID and ETR: • MVC AUC ↑ 210%	Dose: • MVC 150 mg BID
LPV/r	MVC	MVC AUC ↑ 295% With LPV/r and EFV: • MVC AUC ↑ 153%	Dose: • MVC 150 mg BID
RTV	MVC	With RTV 100 mg BID: • MVC AUC ↑ 161%	Dose: • MVC 150 mg BID
TPV/r	MVC	With (TPV/r 500 mg/200 mg) BID: • ↔ MVC AUC	No dose adjustment necessary.

Key to Symbols:

↑ = increase

↓ = decrease

↔ = no change

Key to Acronyms: ARV = antiretroviral; ATV = atazanavir; ATV/r = atazanavir/ritonavir; AUC = area under the curve; BIC = bictegravir; BID = twice daily; COBI = cobicistat; CYP = cytochrome P; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; FDA = Food and Drug Administration; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; TPV = tipranavir; TPV/r = tipranavir/ritonavir

Table 20a. Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Protease Inhibitors (Last updated October 25, 2018; last reviewed October 25, 2018) (page 1 of 2)

Note: Delavirdine (DLV), fosamprenavir (FPV), indinavir (IDV), nelfinavir (NFV), and saquinavir (SQV) are **not** included in this table. Please refer to the Food and Drug Administration product labels for DLV, FPV, IDV, NFV, and SQV for information regarding drug interactions.

PIs		NNRTIs				
		DOR	EFV	ETR	NVP	RPV[a]
ATV Unboosted	PK Data	↑ DOR expected ↔ ATV expected	↔ EFV ATV AUC ↓ 74%	ETR AUC ↑ 50% and C_{min} ↑ 58% ATV AUC ↓ 17% and C_{min} ↓ 47%	↓ ATV possible	↑ RPV possible
	Dose	Standard doses	**Do not coadminister.**	**Do not coadminister.**	**Do not coadminister.**	Standard doses
ATV/c	PK Data	↑ DOR expected ↔ ATV expected	↓ ATV possible ↓ COBI possible	↓ ATV possible ↓ COBI possible	↓ ATV possible ↓ COBI possible	↑ RPV possible ↔ ATV expected
	Dose	Standard doses	EFV standard dose In ART-Naive Patients: • ATV 400 mg plus COBI 150 mg once daily • **Do not use coformulated ATV/c 300 mg/150 mg.** In ART-Experienced Patients: • **Do not coadminister.**	**Do not coadminister.**	**Do not coadminister.**	Standard doses
ATV/r	PK Data	↑ DOR expected ↔ ATV expected	(ATV 400 mg plus RTV 100 mg) Once Daily: • ATV concentrations similar to (ATV 300 mg plus RTV 100 mg) without EFV	(ATV 300 mg plus RTV 100 mg) Once Daily: • ETR AUC and C_{min} both ↑ ~30% • ↔ ATV AUC and C_{min}	(ATV 300 mg plus RTV 100 mg) Once Daily: • ATV AUC ↓ 42% and C_{min} ↓ 72% • NVP AUC ↑ 25%	↑ RPV possible
	Dose	Standard doses	EFV standard dose In ART-Naive Patients: • (ATV 400 mg plus RTV 100 mg) once daily In ART-Experienced Patients: • **Do not coadminister.**	ETR standard dose (ATV 300 mg plus RTV 100 mg) once daily	**Do not coadminister.**	Standard doses
DRV/c	PK Data	↑ DOR expected ↔ DRV expected	↓ DRV possible ↓ COBI possible	ETR 400 mg Once Daily with (DRV 800 mg plus COBI 150 mg) Once Daily: • ↔ ETR AUC and C_{min} • ↔ DRV AUC and C_{min} ↓ 56% • COBI AUC ↓ 30% and C_{min} ↓ 66%	↓ DRV possible ↓ COBI possible	↔ DRV expected ↑ RPV possible
	Dose	Standard doses	**Do not coadminister.**	**Do not coadminister.**	**Do not coadminister.**	Standard doses

Table 20a. Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Protease Inhibitors (Last updated October 25, 2018; last reviewed October 25, 2018) (page 2 of 2)

PIs		NNRTIs				
		DOR	EFV	ETR	NVP	RPV[a]
DRV/r	PK Data	↑ DOR expected ↔ DRV expected	With (DRV 300 mg plus RTV 100 mg) BID: • EFV AUC ↑ 21% • ↔ DRV AUC 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	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
	Dose	Standard doses	Clinical significance unknown. Use standard doses and monitor patient closely. Consider monitoring drug levels.	Standard doses Despite reduced ETR concentration, safety and efficacy of this combination have been established in a clinical trial.	Standard doses	Standard doses
LPV/r	PK Data	↑ DOR expected ↔ LPV expected	With LPV/r Tablets 500 mg/125 mg[c] BID: • LPV concentration similar to that of LPV/r 400 mg/100 mg BID without EFV	With LPV/r Tablets: • ETR AUC ↓ 35% (comparable to the decrease with DRV/r) • ↔ LPV AUC	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
	Dose	Standard doses	LPV/r tablets 500 mg/125 mg[c] BID; LPV/r oral solution 533 mg/133 mg BID EFV standard dose	Standard doses	LPV/r tablets 500 mg/125 mg[c] BID; LPV/r oral solution 533 mg/133 mg BID NVP standard dose	Standard doses
TPV/r Always use TPV with RTV	PK Data	↑ DOR expected ↔ TPV expected	With (TPV 500 mg plus RTV 100 mg) BID: • ↔ EFV • TPV AUC ↓ 31% and C_{min} ↓ 42% With (TPV 750 mg plus RTV 200 mg) BID: • ↔ EFV and TPV	With (TPV 500 mg plus RTV 200 mg) BID: • ETR AUC ↓ 76% and C_{min} ↓ 82% • ↔ TPV AUC and C_{min} ↑ 24%	With (TPV 250 mg plus RTV 200 mg) BID *or* with (TPV 750 mg plus RTV 100 mg) BID: • ↔ NVP • ↔ TPV expected	↑ RPV possible
	Dose	Standard doses	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 RPV 75 mg to 150 mg per dose.

[b] DRV concentration was compared to a historic control.

[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: ART = antiretroviral therapy; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; AUC = area under the curve; BID = twice daily; C_{min} = minimum plasma concentration; COBI = cobicistat; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; EFV = efavirenz; ETR = etravirine; LPV = lopinavir; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; RPV = rilpivirine; RTV = ritonavir; TPV = tipranavir

Table 20b. Interactions between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors (Last updated October 25, 2018; last reviewed October 25, 2018) (page 1 of 3)

Recommendations for managing a particular drug interaction may differ depending on whether a new ARV is being initiated in a patient on a stable concomitant medication or if a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly.

ARV Drugs by Drug Class		INSTIs			
		BIC	DTG	EVG/c	RAL
NNRTIs					
DOR	**PK Data**	↔ DOR, BIC expected	↔ DOR DTG AUC ↑ 36% and C_{min} ↑ 27%	↑ DOR expected ↔ EVG	↔ DOR, RAL expected
	Dose	Standard doses	Standard doses	Standard doses	Standard doses
EFV	**PK Data**	↓ BIC expected	With DTG 50 mg Once Daily: • DTG AUC ↓ 57% and C_{min} ↓ 75%	↑ or ↓ EVG, COBI, EFV possible	With RAL 400 mg BID: • RAL AUC ↓ 36% and C_{min} ↓ 21% With RAL 1200 mg Once Daily: • RAL AUC ↓ 14% and ↔ C_{min}
	Dose	**Do not coadminister.**	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.**	Standard doses
ETR	**PK Data**	↓ BIC expected	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	ETR 200 mg BID plus RAL 400 mg BID: • ETR C_{min} ↑ 17% • RAL C_{min} ↓ 34%

Table 20b. Interactions between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors (Last updated October 25, 2018; last reviewed October 25, 2018) (page 2 of 3)

ARV Drugs by Drug Class		INSTIs			
		BIC	DTG	EVG/c	RAL
NNRTIs, continued					
ETR, continued	Dose	**Do not coadminister.**	**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 Resistancea or Clinically Suspected INSTI Resistance: • DTG 50 mg BID with ETR (concurrently with ATV/r, DRV/r, or LPV/r)	**Do not coadminister.**	RAL 400 mg BID **Coadministration with RAL 1200 mg once daily is not recommended.**
NVP	PK Data	↓ BIC expected	With DTG 50 mg Once Daily: • DTG AUC ↓ 19% and C_{min} ↓ 34%	↑ or ↓ EVG, COBI, NVP possible	No data
	Dose	**Do not coadminister.**	Standard doses	**Do not coadminister.**	Standard doses
RPV	PK Data	No 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 RAL C_{min} ↑ 27%
	Dose	Standard doses	Standard doses	**Do not coadminister.**	Standard doses
PIs					
ATV/c	PK Data	BIC AUC ↑ 305%	No data	No data	No data
	Dose	**Do not coadminister.**	Standard doses	**Do not coadminister.**	Standard doses
ATV +/- RTV	PK Data	BIC AUC ↑ 310%	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	With Unboosted ATV: • RAL AUC ↑ 72% With Unboosted ATV and RAL 1200 mg: • RAL AUC ↑ 67% With (ATV 300 mg plus RTV 100 mg) Once Daily: • RAL AUC ↑ 41%
	Dose	**Do not coadminister.**	Standard doses	**Do not coadminister.**	Standard doses
DRV/c	PK Data	BIC AUC ↑ 74%	DRV/c plus DTG Once Daily: • ↔ DTG, DRV, COBI DTG 50 mg Once Daily and DRV/r Once Daily Switched to DRV/c: • DTG C_{min} ↑ 100%	DRV/c plus EVG/c: • ↓ EVG possible	No data
	Dose	Standard doses	Standard doses	**Do not coadminister.**	Standard doses

Table 20b. Interactions between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors (Last updated October 25, 2018; last reviewed October 25, 2018) (page 3 of 3)

ARV Drugs by Drug Class		INSTIs			
		BIC	DTG	EVG/c	RAL
PIs, continued					
DRV/r	**PK Data**	No 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	With (DRV 600 mg plus RTV 100 mg) BID: • RAL AUC ↓ 29% and C_{min} ↑ 38%
	Dose	Standard doses	Standard doses	**Do not coadminister.**	Standard doses
LPV/r	**PK Data**	No data	With (LPV 400 mg plus RTV 100 mg) BID and DTG 30 mg Once Daily: • ↔ DTG	↑ or ↓ EVG, COBI, LPV possible RTV and COBI have similar effects on CYP3A.	↓ RAL ↔ LPV/r
	Dose	**Consider alternative combination.**	Standard doses	**Do not coadminister.**	Standard doses
TPV/r	**PK Data**	↓ BIC possible	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.	With (TPV 500 mg plus RTV 200 mg) BID and RAL 400 mg BID: • RAL AUC ↓ 24% and C_{min} ↓ 55%
	Dose	**Do not coadminister.**	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.**	RAL 400 mg BID **Coadministration with RAL 1200 mg once daily is not recommended.**

[a] Refer to DTG product labeling for details.

Key to Symbols:

↑ = increase

↓ = decrease

↔ = no change

Key to Acronyms: ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; AUC = area under the curve; BIC = bictegravir; BID = twice daily; C_{min} = minimum plasma concentration; COBI = cobicistat; CYP = cytochrome P; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; INSTI = integrase strand transfer inhibitor; LPV = lopinavir; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; TPV = tipranavir; TPV/r = tipranavir/ritonavir

Conclusion (Last updated January 28, 2016; last reviewed January 28, 2016)

The Panel has carefully reviewed results from clinical HIV therapy trials and considered how they affect appropriate care guidelines. HIV care is complex and rapidly evolving. Where possible, the Panel has based recommendations on the best evidence from prospective trials with defined endpoints. Absent such evidence, the Panel has attempted to base recommendations on reasonable options for HIV care.

HIV care requires partnerships and open communication. Guidelines are only a starting point for medical decision making involving informed providers and patients. Although guidelines can identify some parameters of high-quality care, they cannot substitute for sound clinical judgment.

As further research is conducted and reported, these guidelines will be modified. The Panel anticipates continued progress in refining antiretroviral therapy regimens and strategies. The Panel hopes these guidelines are useful and is committed to their continued revision and improvement.

Appendix A: Key to Acronyms (Last updated October 25, 2018; last reviewed October 25, 2018)

Drug Name Abbreviations

Abbreviation	Full Name
3TC	lamivudine
ABC	abacavir
APV	amprenavir
ATV	atazanavir
BIC	bictegravir
COBI or c	cobicistat
d4T	stavudine
ddI	didanosine
DLV	delavirdine
DOR	doravirine
DRV	darunavir
DTG	dolutegravir
EFV	efavirenz
ETR	etravirine
EVG	elvitegravir
FPV	fosamprenavir
FTC	emtricitabine
IBA	ibalizumab
IDV	indinavir
LPV	lopinavir
MVC	maraviroc
NFV	nelfinavir
NVP	nevirapine
RAL	raltegravir
RPV	rilpivirine
RTV or r	ritonavir
SQV	saquinavir
T-20	enfuvirtide
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TPV	tipranavir
ZDV	zidovudine

General Terms

Abbreviation	Definition
17-BMP	beclomethasone 17-monopropionate
ADAP	AIDS drug assistance program

Ag/Ab	antigen/antibody
Al	aluminum
ALT	alanine aminotransferase
aOR	adjusted odds ratio
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
AUC	area under the curve
AV	atrioventricular
AWP	average wholesale price
BID	twice daily
BMD	bone mineral density
BUN	blood urea nitrogen
Ca	calcium
$CaCO_3$	calcium carbonate
CAPD	chronic ambulatory peritoneal dialysis
CBC	complete blood count
CCB	calcium channel blockers
CD4	CD4 T lymphocyte
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CKD	chronic kidney disease
Cl	chloride
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CNS	central nervous system
CPK	creatine phosphokinase
Cr	creatinine
CrCl	creatinine clearance
CSF	cerebrospinal fluid
CV	cardiovascular
CVD	cardiovascular disease
CYP	cytochrome P450
CYP3A4	cytochrome P450 3A4
DAA	direct-acting antiviral
DHA	dihydroartemisinin
DILI	drug-induced liver injury
DMPA	depot medroxyprogesterone acetate
DOT	directly observed therapy

EBV	Epstein-Barr virus
EC	enteric coated
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
FDC	fixed-dose combination
Fe	iron
FI	fusion inhibitor
FUL	federal upper limit
GAZT	azidothymidine glucuronide
GI	gastrointestinal
HAD	HIV-associated dementia
HAV	hepatitis A virus
HBcAb	hepatitis B core antibody
HBeAg	hepatitis B e antigen
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCO_3	bicarbonate
HCV	hepatitis C virus
HD	hemodialysis
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
HIV RNA	HIV viral load
HIV-1	human immunodeficiency virus type 1
HIV-2	human immunodeficiency virus type 2
HIVAN	HIV-associated nephropathy
HLA	human leukocyte antigen
HMG-CoA	hydroxy-methylglutaryl-coenzyme A
HRT	hormone replacement therapy
HSR	hypersensitivity reaction
HTLV-1	human T-lymphotropic virus-1
INR	international normalized ratio
INSTI	integrase strand transfer inhibitor
IRIS	immune reconstitution inflammatory syndrome
K	potassium
KS	Kaposi's sarcoma
LDL	low-density lipoprotein
LLOD	lower limits of detection

MAC	*Mycobacterium avium* complex
MATE	multidrug and toxin extrusion transporter
Mg	magnesium
MI	myocardial infarction
MPA	medroxyprogesterone acetate
MRI	magnetic resonance imaging
msec	millisecond
MTR	multi-tablet regimen
Na	sodium
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
OATP	organic anion-transporting polypeptide
OCT2	organic cation transporter 2
OH-itraconazole	active metabolite of itraconazole
OI	opportunistic infection
OR	odds ratio
PAH	pulmonary arterial hypertension
PCP	*Pneumocystis jirovecii* pneumonia
PCR	polymerase chain reaction
PDE5	phosphodiesterase type 5
PI	protease inhibitor
PI/c	cobicistat-boosted protease inhibitor
PI/r	ritonavir-boosted protease inhibitor
PK	pharmacokinetic
PO	orally
PPI	proton pump inhibitor
PR	protease
PrEP	pre-exposure prophylaxis
PTH	parathyroid hormone
q(n)d	every (n) days
q(n)h	every (n) hours
QTc	QT corrected for heart rate
RNA	ribonucleic acid
RR	relative risk
RT	reverse transcriptase
SCr	serum creatinine
SJS	Stevens-Johnson syndrome
SSRI	selective serotonin reuptake inhibitor
STI	sexually transmitted infection

STR	single-tablet regimen
TB	tuberculosis
TCA	tricyclic antidepressant
TDM	therapeutic drug monitoring
TEN	toxic epidermal necrosis
TG	triglyceride
TID	three times a day
UGT	uridine diphosphate glucuronosyltransferase
VPA	valproic acid
WAC	wholesale acquisition cost
WHO	World Health Organization
XR	extended release
Zn	zinc

Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (Last updated October 25, 2018; last reviewed October 25, 2018) (page 1 of 6)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum/ Intracellular Half-Lives	Adverse Events[b]
Abacavir (ABC) *Ziagen* **Note:** Generic tablet formulation is available.	Ziagen: • 300 mg tablet • 20 mg/mL oral solution	Ziagen: • 600 mg once daily, or • 300 mg BID Take without regard to meals.	Metabolized by alcohol dehydrogenase and glucuronyl transferase Renal excretion of metabolites: 82% Dose adjustment for ABC is recommended in patients with hepatic insufficiency (see Appendix B, Table 8).	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 a 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.
(ABC/3TC) *Epzicom* **Note:** Generic formulation is available.	Epzicom: • (ABC 600 mg plus 3TC 300 mg) tablet	Epzicom: • 1 tablet once daily			
(ABC/DTG/3TC) *Triumeq*	Triumeq: • (ABC 600 mg plus 3TC 300 mg plus DTG 50 mg) tablet	Triumeq: • 1 tablet once daily			
(ABC/ZDV/3TC) *Trizivir* **Note:** Generic formulation is available.	Trizivir: • (ABC 300 mg plus ZDV 300 mg plus 3TC 150 mg) tablet	Trizivir: • 1 tablet BID			
Didanosine (ddI) *Videx* *Videx EC* **Note:** Generic is available as delayed-release capsules; dose is the same as Videx EC.	Videx EC: • 125, 200, 250, and 400 mg capsules Videx: • 10 mg/mL oral solution	Body Weight ≥60 kg: • ddI 400 mg once daily *With TDF:* • ddI 250 mg once daily Body Weight <60 kg: • ddI 250 mg once daily *With TDF:* • ddI 200 mg once daily Take 1/2 hour before or 2 hours after a meal. **Note:** Preferred dosing with oral solution is BID (with the total daily dose divided into 2 doses).	Renal excretion: 50% Dose adjustment is recommended in patients with renal insufficiency (see Appendix B, Table 8).	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 noncirrhotic 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 October 25, 2018; last reviewed October 25, 2018) (page 2 of 6)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum/ Intracellular Half-Lives	Adverse Events[b]
Emtricitabine (FTC) *Emtriva*	Emtriva: • 200 mg hard gelatin capsule • 10 mg/mL oral solution	Emtriva *Capsule:* • FTC 200 mg once daily *Oral Solution:* • FTC 240 mg (24 mL) once daily Take without regard to meals.	Renal excretion: 86% Dose adjustment is recommended in patients with renal insufficiency (see Appendix B, Table 8)	10 hours/ >20 hours	• Minimal toxicity • Hyperpigmentation/skin discoloration • Severe acute exacerbation of hepatitis may occur in HBV coinfected patients who discontinue FTC.
(FTC/TAF) *Descovy*	Descovy: • (FTC 200 mg plus TAF 25 mg) tablet	Descovy: • 1 tablet once daily			
(FTC/TDF) *Truvada*	Truvada: • (FTC 200 mg plus TDF 300 mg) tablet	Truvada: • 1 tablet once daily			
(FTC/BIC/TAF) *Biktarvy*	Biktarvy: • (FTC 200 mg plus BIC 50 mg plus TAF 25 mg) tablet	Biktarvy: • 1 tablet once daily			
(FTC/DRV/c/TAF) *Symtuza*	Symtuza: • (FTC 200 mg plus DRV 800 mg plus COBI 150 mg plus TAF 10 mg) tablet	Symtuza: • 1 tablet once daily with food			
(FTC/EFV/TDF) *Atripla*	Atripla: • (FTC 200 mg plus EFV 600 mg plus TDF 300 mg) tablet	Atripla: • 1 tablet once daily on an empty stomach, preferably at bedtime			
(FTC/EVG/c/ TAF) *Genvoya*	Genvoya: • (FTC 200 mg plus EVG 150 mg plus COBI 150 mg plus TAF 10 mg) tablet	Genvoya: • 1 tablet once daily with food			
(FTC/EVG/c/ TDF) *Stribild*	Stribild: • (FTC 200 mg plus EVG 150 mg plus COBI 150 mg plus TDF 300 mg) tablet	Stribild: • 1 tablet once daily with food			
(FTC/RPV/TDF) *Complera*	Complera: • (FTC 200 mg plus RPV 25 mg plus TDF 300 mg) tablet	Complera: • 1 tablet once daily with a meal			

Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (Last updated October 25, 2018; last reviewed October 25, 2018) (page 3 of 6)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum/ Intracellular Half-Lives	Adverse Events[b]
Lamivudine (3TC) *Epivir* **Note:** Generic is available.	Epivir: • 150 and 300 mg tablets • 10 mg/mL oral solution	Epivir: • 3TC 300 mg once daily, *or* • 3TC 150 mg BID	Renal excretion: 70% Dose adjustment in patients with renal insufficiency is recommended (see Appendix B, Table 8).	5–7 hours/ 18–22 hours	• Minimal toxicity • Severe acute exacerbation of hepatitis may occur in HBV coinfected patients who discontinue 3TC.
(3TC/ABC) *Epzicom* **Note:** Generic is available.	Epzicom: • (3TC 300 mg plus ABC 600 mg) tablet	Epzicom: • 1 tablet once daily			
(3TC/TDF) *Cimduo*	Cimduo: • (3TC 300 mg plus TDF 300 mg) tablet	Cimduo: • 1 tablet once daily			
(3TC/ZDV) *Combivir* **Note:** Generic is available.	Combivir: • (3TC 150 mg plus ZDV 300 mg) tablet	Combivir: • 1 tablet BID			
(3TC/ABC/ZDV) *Trizivir* **Note:** Generic is available.	Trizivir: • (3TC 150 mg plus ZDV 300 mg plus ABC 300 mg) tablet	Trizivir: • 1 tablet BID			
(3TC/DOR/TDF) *Delstrigo*	Delstrigo: • (3TC 300 mg plus DOR 100 mg plus TDF 300 mg) tablet	Delstrigo: • 1 tablet once daily			
(3TC/DTG/ABC) *Triumeq*	Triumeq: • (3TC 300 mg plus ABC 600 mg plus DTG 50 mg) tablet	Triumeq: • 1 tablet once daily			
(3TC/EFV/TDF) *Symfi*	Symfi: • (3TC 300 mg plus EFV 600 mg plus TDF 300 mg) tablet	Symfi: • 1 tablet once daily on an empty stomach, preferably at bedtime			
(3TC/EFV/TDF) *Symfi Lo*	Symfi Lo: • (3TC 300 mg plus EFV 400 mg plus TDF 300 mg) tablet	Symfi Lo: • 1 tablet once daily on an empty stomach, preferably at bedtime			

Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (Last updated October 25, 2018; last reviewed October 25, 2018) (page 4 of 6)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum/ Intracellular Half-Lives	Adverse Events[b]
Stavudine (d4T) *Zerit* **Note:** Generic is available.	Zerit: • 15, 20, 30, and 40 mg capsules • 1 mg/mL oral solution	Body Weight ≥60 kg: • d4T 40 mg BID Body Weight <60 kg: • d4T 30 mg BID Take without regard to meals. **Note:** WHO recommends 30 mg BID dosing regardless of body weight.	Renal excretion: 50% Dose adjustment is recommended in patients with renal insufficiency (see Appendix B, Table 8).	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)
Tenofovir Alafenamide (TAF) *Vemlidy* **Note:** Available as a 25-mg tablet for the treatment of HBV.	See FDCs for HIV treatment below.	See FDCs for HIV treatment below.	Metabolized by cathepsin A. Not recommended in patients with CrCl <30 mL/min.	0.5 hours/ 150–180 hours	• Renal insufficiency, Fanconi syndrome, proximal renal tubulopathy are less likely to occur with TAF than with TDF. • Osteomalacia, decrease in bone mineral density are less likely to occur with TAF than with TDF. • Severe acute exacerbation of hepatitis may occur in HBV coinfected patients who discontinue TAF. • Diarrhea, nausea, headache
(FTC/TAF) *Descovy*	Descovy: • (FTC 200 mg plus TAF 25 mg) tablet	Descovy: • 1 tablet once daily			
(TAF/BIC/FTC) *Biktarvy*	Biktarvy: • (TAF 25 mg plus BIC 50 mg plus FTC 200 mg) tablet	Biktarvy: • 1 tablet once daily			
(TAF/DRV/c/FTC) *Symtuza*	Symtuza: • (TAF 10 mg plus DRV 800 mg plus COBI 150 mg plus FTC 200 mg) tablet	Symtuza: • 1 tablet once daily with food			
(TAF/EVG/c/ FTC) *Genvoya*	Genvoya: • (TAF 10 mg plus EVG 150 mg plus COBI 150 mg plus FTC 200 mg) tablet	Genvoya: • 1 tablet once daily with food			
(TAF/RPV/FTC) *Odefsey*	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 October 25, 2018; last reviewed October 25, 2018) (page 5 of 6)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum/ Intracellular Half-Lives	Adverse Events[b]
Tenofovir Disoproxil Fumarate (TDF) *Viread* Note: Generic is available.	Viread: • 150, 200, 250, and 300 mg tablets • 40 mg/g oral powder Generic: • 300 mg tablet	Viread: • TDF 300 mg once daily, *or* • 7.5 level scoops of oral powder once daily (dosing scoop dispensed with each prescription; 1 level scoop contains 1g 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. Dose adjustment is recommended in patients with renal insufficiency (see Appendix B, Table 8).	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
(TDF/3TC) *Cimduo*	Cimduo: • (TDF 300 mg plus 3TC 300 mg) tablet	Cimduo: • 1 tablet once daily			
(TDF/FTC) *Truvada*	Truvada: • (TDF 300 mg plus FTC 200 mg) tablet	Truvada: • 1 tablet once daily • Take without regard to meals.			
(TDF/DOR/3TC) *Delstrigo*	Delstrigo: • (TDF 300 mg plus DOR 100 mg plus 3TC 300 mg) tablet	Delstrigo: • 1 tablet once daily			
(TDF/EFV/FTC) *Atripla*	Atripla: • (TDF 300 mg plus EFV 600 mg plus FTC 200 mg) tablet	Atripla: • 1 tablet once daily on an empty stomach, preferably at bedtime			
(TDF/EFV/3TC) *Symfi*	Symfi: • (TDF 300 mg plus EFV 600 mg plus 3TC 300 mg) tablet	Symfi: • 1 tablet once daily on an empty stomach, preferably at bedtime			
(TDF/EFV/3TC) *Symfi Lo*	Symfi Lo: • (TDF 300 mg plus EFV 400 mg plus 3TC 300 mg) tablet	Symfi Lo: • 1 tablet once daily on an empty stomach, preferably at bedtime			
(TDF/EVG/c/ FTC) *Stribild*	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.			
(TDF/RPV/FTC) *Complera*	Complera: • (TDF 300 mg plus RPV 25 mg plus FTC 200 mg) tablet	Complera: • 1 tablet once daily • Take with a meal.			

Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (Last updated October 25, 2018; last reviewed October 25, 2018) (page 6 of 6)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum/ Intracellular Half-Lives	Adverse Events[b]
Zidovudine (ZDV) *Retrovir* **Note:** Generic is available.	Retrovir: • 100 mg capsule • 300 mg tablet (only available as generic) • 10 mg/mL intravenous solution • 10 mg/mL oral solution	Retrovir: • ZDV 300 mg BID, *or* • ZDV 200 mg TID • Take without regard to meals.	Metabolized to GAZT Renal excretion of GAZT Dose adjustment is recommended in patients with renal insufficiency (see Appendix B, Table 8).	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
(ZDV/3TC) *Combivir* **Note:** Generic is available.	Combivir: • (ZDV 300 mg plus 3TC 150 mg) tablet	Combivir: • 1 tablet BID • Take without regard to meals.			
(ZDV/3TC/ABC) *Trizivir* **Note:** Generic is 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 dose adjustments in patients with renal or hepatic insufficiency, see Appendix B, Table 8.

[b] Also see Table 15.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; BIC = bictegravir; BID = twice daily; COBI = cobicistat; CrCl = creatinine clearance; d4T = stavudine; ddI = didanosine; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; EC = enteric coated; EFV = efavirenz; EVG = elvitegravir; FDC = fixed-dose combination; 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 October 25, 2018; last reviewed October 25, 2018) (page 1 of 2)

Note: 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]
Doravirine (DOR) *Pifeltro*	Pifeltro: • 100 mg tablet	Pifeltro: • 1 tablet once daily	CYP3A4/5 substrate	15 hours	• Nausea • Dizziness • Abnormal dreams
(DOR/TDF/3TC) *Delstrigo*	Delstrigo: • (DOR 100 mg plus TDF 300 mg plus 3TC 300 mg) tablet	Delstrigo: • 1 tablet once daily			
Efavirenz (EFV) Sustiva **Note:** Generic product is available.	Sustiva: • 50 and 200 mg capsules • 600 mg tablet Generic: • 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 • QT interval prolongation
(EFV/TDF/FTC) *Atripla*	Atripla: • (EFV 600 mg plus TDF 300 mg plus FTC 200 mg) tablet	Atripla: • 1 tablet once daily on an empty stomach, preferably at bedtime			
(EFV/TDF/3TC) *Symfi*	Symfi: • (EFV 600 mg plus TDF 300 mg plus 3TC 300 mg) tablet	Symfi: • 1 tablet once daily on an empty stomach, preferably at bedtime			
(EFV/TDF/3TC) *Symfi Lo*	Symfi Lo: • (EFV 400 mg plus TDF 300 mg plus 3TC 300 mg) tablet	Symfi Lo: • 1 tablet once daily on an empty stomach, preferably at bedtime			
Etravirine (ETR) *Intelence*	Intelence: • 25, 100, and 200 mg tablets	Intelence: • 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[e] • HSRs, characterized by rash, constitutional findings, and sometimes organ dysfunction (including hepatic failure) have been reported. • Nausea

Appendix B, Table 2. Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors (Last updated October 25, 2018; last reviewed October 25, 2018) (page 2 of 2)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/Metabolic Pathway	Serum Half-Life	Adverse Events[b]

Nevirapine (NVP) *Viramune or Viramune XR*
Note: Generic is 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 do not administer for longer than 28 days total.
			CYP450 substrate, inducer of 3A4 and 2B6; 80% excreted in urine (glucuronidated metabolites, <5% unchanged); 10% in feces
			Contraindicated in patients with moderate to severe hepatic impairment.
			Dose adjustment is recommended in patients on hemodialysis (see Appendix B, Table 8).
				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.

Rilpivirine (RPV) *Edurant*	Edurant: • 25 mg tablet	Edurant: • 25 mg once daily • Take with a meal.	CYP3A4 substrate	50 hours	• Rash[c] • Depression, insomnia, headache • Hepatotoxicity • QT interval prolongation
(RPV/DTG) *Juluca*	Juluca: • (RPV 25 mg plus DTG 50 mg) tablet	Juluca: • 1 tablet once daily • Take with a meal.			
(RPV/TAF/FTC) *Odefsey*	Odefsey: • (RPV 25 mg plus TAF 25 mg plus FTC 200 mg) tablet	Odefsey: • 1 tablet once daily • Take with a meal.			
(RPV/TDF/FTC) *Complera*	Complera: • (RPV 25 mg plus TDF 300 mg plus FTC 200 mg) tablet	Complera: • 1 tablet once daily • Take with a meal.			

[a] For dose adjustments in patients with renal or hepatic insufficiency, see Appendix B, Table 8.

[b] Also see Table 15.

[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 Acronyms: 3TC = lamivudine; ARV = antiretroviral; BID = twice daily; CD4 = CD4 T lymphocyte; CYP = cytochrome P; DLV = delavirdine; DOR = doravirine; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; 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 October 25, 2018; last reviewed October 25, 2018) (page 1 of 6)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/Metabolic Pathway	Serum Half-Life	Adverse Events[b]
Atazanavir (ATV) *Reyataz* **Note:** Generic is available for capsule formulations.	Reyataz: • 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 dosing recommendations with H2 antagonists and PPIs, refer to Table 19a.	CYP3A4 inhibitor and substrate; weak CYP2C8 inhibitor; UGT1A1 inhibitor Dose adjustment is recommended in patients with hepatic insufficiency (see Appendix B, Table 8).	7 hours	• Indirect hyperbilirubinemia • PR interval prolongation: First degree symptomatic AV block reported. Use with caution in patients who have underlying conduction defects or who are 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)
(ATV/c) *Evotaz*	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 8 for the equation for calculating CrCl).	ATV: as above COBI: CYP3A inhibitor and substrate; CYP2D6 inhibitor		

Appendix B, Table 3. Characteristics of Protease Inhibitors (Last updated October 25, 2018; last reviewed October 25, 2018) (page 2 of 6)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/Metabolic Pathway	Serum Half-Life	Adverse Events[b]
Darunavir (DRV) *Prezista*	Prezista: • 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)	• Skin rash (10%): DRV has a sulfonamide moiety; Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and erythema multiforme have been reported. • Hepatotoxicity • Diarrhea, nausea • Headache • Hyperlipidemia • Serum transaminase elevation • Hyperglycemia • Fat maldistribution • Increase in serum creatinine (with COBI)
(DRV/c) *Prezcobix*	Prezcobix: • (DRV 800 mg plus COBI 150 mg) tablet	Prezcobix: • 1 tablet once daily • Take with food. **Not recommended** for patients with 1 or more DRV resistance-associated mutations. With TDF: • **Not recommended** for patients with baseline CrCl <70 mL/min (see Appendix B, Table 8 for the equation for calculating CrCl).	DRV: CYP3A4 inhibitor and substrate; CYP2C9 inducer COBI: CYP3A inhibitor and substrate; CYP2D6 inhibitor	7 hours (when combined with COBI)	
(DRV/c/TAF/FTC) *Symtuza*	Symtuza: • (DRV 800 mg plus COBI 150 mg plus TAF 10 mg plus FTC 200 mg) tablet	Symtuza: • 1 tablet once daily with food **Not recommended** for patients with 1 or more DRV resistance-associated mutations. **Not recommended** for patients with CrCl <30 mL/min. **Not recommended** in patients with severe hepatic impairment.	DRV: CYP3A4 inhibitor and substrate; CYP2C9 inducer COBI: CYP3A inhibitor and substrate; CYP2D6 inhibitor		

Appendix B, Table 3. Characteristics of Protease Inhibitors (Last updated October 25, 2018; last reviewed October 25, 2018) (page 3 of 6)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/Metabolic Pathway	Serum Half-Life	Adverse Events[b]
Fosamprenavir (FPV, a prodrug of APV) *Lexiva* **Note:** Generic is available.	Lexiva: • 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. Dose adjustment is recommended in patients with hepatic insufficiency (see Appendix B, Table 8).	7.7 hours (APV)	• Skin rash (reported in 12% to 19% of patients on FPV); FPV has a sulfonamide moiety. • Diarrhea, nausea, vomiting • Headache • Hyperlipidemia • Serum transaminase elevation • Hyperglycemia • Fat maldistribution • Possible increase in the frequency of bleeding episodes in patients with hemophilia • Nephrolithiasis
Indinavir (IDV) *Crixivan*	Crixivan: • 200 and 400 mg capsules	Crixivan: • IDV 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. Drink at least 48 oz of water daily.	CYP3A4 inhibitor and substrate Dose adjustment is recommended in patients with hepatic insufficiency (see Appendix B, Table 8).	1.5–2 hours	• 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 increase in the frequency of bleeding episodes in patients with hemophilia

Appendix B, Table 3. Characteristics of Protease Inhibitors (Last updated October 25, 2018; last reviewed October 25, 2018) (page 4 of 6)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/Metabolic Pathway	Serum Half-Life	Adverse Events[b]
Lopinavir/ Ritonavir (LPV/r) *Kaletra*	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.	Kaletra: • (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	• GI intolerance, nausea, vomiting, diarrhea • Pancreatitis • Asthenia • Hyperlipidemia (especially hypertriglyceridemia) • Serum transaminase elevation • Hyperglycemia • Insulin resistance/diabetes mellitus • Fat maldistribution • Possible increase in the frequency of 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*	Viracept: • 250 and 625 mg tablets	Viracept: • NFV 1250 mg BID, or • NFV 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	• Diarrhea • Hyperlipidemia • Hyperglycemia • Fat maldistribution • Possible increase in the frequency of bleeding episodes in patients with hemophilia • Serum transaminase elevation

Appendix B, Table 3. Characteristics of Protease Inhibitors (Last updated October 25, 2018; last reviewed October 25, 2018) (page 5 of 6)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/Metabolic Pathway	Serum Half-Life	Adverse Events[b]
Ritonavir (RTV) *Norvir* **Note:** Generic is available.	Norvir: • 100 mg tablet • 100 mg soft gel capsule • 80 mg/mL oral solution • 100 mg single packet oral powder Oral solution contains 43% alcohol.	As PK Booster (or Enhancer) for Other PIs: • RTV 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 UGT1A1 and CYPs 1A2, 2C8, 2C9, and 2C19	3–5 hours	• GI intolerance, nausea, vomiting, diarrhea • Paresthesia (circumoral and extremities) • Hyperlipidemia (especially hypertriglyceridemia) • Hepatitis • Asthenia • Taste perversion • Hyperglycemia • Fat maldistribution • Possible increase in the frequency of bleeding episodes in patients with hemophilia
Saquinavir (SQV) *Invirase*	Invirase: • 500 mg tablet • 200 mg capsule	Invirase: • (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	• GI intolerance, nausea, and diarrhea • Headache • Serum transaminase elevation • Hyperlipidemia • Hyperglycemia • Fat maldistribution • Possible increase in the frequency of 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.

Appendix B, Table 3. Characteristics of Protease Inhibitors (Last updated October 25, 2018; last reviewed October 25, 2018) (page 6 of 6)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/Metabolic Pathway	Serum Half-Life	Adverse Events[b]
Tipranavir (TPV) *Aptivus*	Aptivus: • 250 mg capsule • 100 mg/mL oral solution	Aptivus: • (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.	CYP3A4 inducer and substrate CYP2D6 inhibitor; CYP3A4, 1A2, and 2C19 inducer Net effect of combining TPV and RTV is a CYP3A4 and 2D6 inhibitor	6 hours after single dose of TPV/r	• Hepatotoxicity: clinical hepatitis (including hepatic decompensation and hepatitis-associated fatalities) has been reported; monitor patients closely, especially those with underlying liver diseases. • Skin rash: 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 anticoagulant or antiplatelet agents (including vitamin E). • Hyperlipidemia • Hyperglycemia • Fat maldistribution • Possible increase in the frequency of bleeding episodes in patients with hemophilia

[a] For dose adjustments in patients with hepatic insufficiency, see Appendix B, Table 8.

[b] Also see Table 15.

Key to Acronyms: APV = amprenavir; ARV = antiretroviral; ATV = atazanavir; AV = atrioventricular; BID = twice daily; COBI = cobicistat; CrCl = creatinine clearance; CYP = cytochrome P; DRV = darunavir; DRV/c = darunavir/cobicistat; EFV = efavirenz; FPV = fosamprenavir; FTC = emtricitabine; 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; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TID = three times a day; TPV = tipranavir; UGT = uridine diphosphate glucuronosyltransferase

Appendix B, Table 4. Characteristics of Integrase Inhibitors (Last updated October 25, 2018; last reviewed October 25, 2018) (page 1 of 2)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/Metabolic Pathways	Serum Half-Life	Adverse Events[b]
Bictegravir (BIC) **Note:** BIC is only available as a component of an FDC. (BIC/TAF/FTC) *Biktarvy*	Biktarvy: • (BIC 50 mg plus TAF 25 mg plus FTC 200 mg) tablet	Biktarvy: • 1 tablet once daily	BIC: • CYP3A4 substrate • UGT1A1 mediated glucuronidation	BIC: ~17 hours	• Diarrhea • Nausea • Headache
Dolutegravir (DTG) *Tivicay*	Tivicay: • 50 mg tablet	In ARV-Naive or ARV-Experienced, INSTI-Naive Patients: • 50 mg once daily In ARV-Naive or ARV-Experienced, INSTI-Naive Patients when Coadministered 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	• Insomnia • Headache • Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions) • Hepatotoxicity • Preliminary data suggest increased rate of neural tube defects in infants born to mothers who were taking DTG at the time of conception. • HSRs, including rash, constitutional symptoms, and organ dysfunction (including liver injury) have been reported.
(DTG/ ABC/3TC) *Triumeq*	Triumeq: • (DTG 50 mg plus ABC 600 mg plus 3TC 300 mg) tablet	Triumeq: • 1 tablet once daily			
(DTG/RPV) *Juluca*	Juluca: • (DTG 50 mg plus RPV 25 mg) tablet	Juluca: • 1 tablet once daily with a meal			

Appendix B, Table 4. Characteristics of Integrase Inhibitors (Last updated October 25, 2018; last reviewed October 25, 2018) (page 2 of 2)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/Metabolic Pathways	Serum Half-Life	Adverse Events[b]
Elvitegravir (EVG) **Note:** EVG is only available as a component of an FDC.	N/A	N/A	N/A	N/A	• Nausea • Diarrhea • Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions)
(EVG/c/FTC/ TAF) *Genvoya*	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 8 for the equation for calculating CrCl). **Not recommended for use with other ARV drugs.**	EVG: CYP3A, UGT1A1/3 substrate COBI: CYP3A inhibitor and substrate; CYP2D6 inhibitor	~13 hours (EVG/c)	
(EVG/c/FTC/ TDF) *Stribild*	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 8 for the equation for calculating CrCl). **Not recommended for use with other ARV drugs.**			
Raltegravir (RAL) *Isentress Isentress HD*	• 400 mg tablet • 600 mg tablet (HD) • 25 and 100 mg chewable tablets • 100 mg single packet for oral suspension	In ARV-Naive Patients or ARV-Experienced Patients: • Isentress: 400 mg BID In ARV-Naive or ARV-Experienced Patients with Virologic Suppression on a Regimen of RAL 400 mg BID: • Isentress HD: 1200 mg (two 600-mg tablets) once daily With Rifampin: • Isentress: 800 mg BID • Isentress HD: **Not recommended** 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 patients with hepatic insufficiency, see Appendix B, Table 6.

[b] Also see Table 15.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; BIC = bictegravir; BID = twice daily; COBI = cobicistat; CPK = creatine phosphokinase; CrCl = creatinine clearance; CYP = cytochrome P; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDC = fixed-dose combination; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; HSR = hypersensitivity reaction; INSTI = integrase strand transfer inhibitor; RAL = raltegravir; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TPV/r = tipranavir/ritonavir; UGT = uridine diphosphate glucosyltransferase

Appendix B, Table 5. Characteristics of the Fusion Inhibitor (Last updated January 29, 2008; last reviewed October 25, 2018)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendation	Serum Half-Life	Elimination	Adverse Events[a]
Enfuvirtide (T-20) *Fuzeon*	Fuzeon: • Injectable; supplied as lyophilized powder • Each vial contains 108 mg of T-20; reconstitute with 1.1 mL of sterile water for injection for delivery of approximately 90 mg/1 mL. • Refer to prescribing information for storage instruction.	Fuzeon • 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	• Local injection site reactions (e.g., pain, erythema, induration, nodules and cysts, pruritus, ecchymosis) occur 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. **Rechallenge is not recommended.**

[a] Also see Table 15.

Key to Abbreviations: BID = twice daily; HSR = hypersensitivity reaction; T-20 = enfuvirtide

Appendix B, Table 6. Characteristics of CCR5 Antagonist (Last updated March 27, 2012; last reviewed October 25, 2018)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Serum Half-Life	Elimination/ Metabolic Pathway	Adverse Events[b]
Maraviroc (MVC) *Selzentry*	Selzentry: • 150 and 300 mg tablets	Selzentry: • **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, T-20, 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 8.

[b] Also see Table 15.

Key to Acronyms: BID = twice daily; CYP = cytochrome P; EFV = efavirenz; ETR = etravirine; MVC = maraviroc; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; T-20 = enfuvirtide; TPV/r = tipranavir/ritonavir

Appendix B, Table 7. Characteristics of CD4 Post-Attachment Inhibitor (Last updated October 25, 2018; last reviewed October 25, 2018)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Serum Half-Life	Elimination/ Metabolic Pathway	Adverse Events
Ibalizumab (IBA) *Trogarzo*	Trogarzo: • Single-dose 2 mL vial containing 200 mg/1.33 mL (150 mg/mL) of ibalizumab	Trogarzo: • Administer a single loading dose of IBA 2000 mg IV infusion over 30 minutes, followed by a maintenance dose of IBA 800 mg IV infusion over 15 minutes every 2 weeks. • See prescribing information for additional instruction in preparation, storage, administration, and monitoring.	~64 hours	Not well defined.	• Diarrhea • Dizziness • Nausea • Rash

Key to Acronyms: IBA = ibalizumab; IV = intravenous

Appendix B, Table 8. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated October 25, 2018; last reviewed October 25, 2018) (page 1 of 7)

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

ARVs Generic Name (Abbreviation) *Trade Name*	Usual Daily Dose[a]	Dosing in Patients with Renal Insufficiency[b]	Dosing in Patients with Hepatic Impairment
NRTIs Stribild should not be initiated in patients with CrCl <70 mL/min. The following FDCs **are not recommended** in patients with CrCl <50 mL/min: Atripla, Combivir, Complera, Delstrigo, Epzicom, Triumeq, or Trizivir. Biktarvy, Descovy, Genvoya, Odefsey, Symtuza, and Truvada **are not recommended** in patients with CrCl <30 mL/min.			
Abacavir (ABC) *Ziagen*	• 300 mg PO BID, *or* • 600 mg PO once daily	No dose adjustment necessary.	Child-Pugh Class A: • 200 mg PO BID (use oral solution) Child-Pugh Class B or C: • **Contraindicated**
Didanosine EC (ddI) *Videx EC*	Body Weight ≥60 kg: • 400 mg PO once daily Body Weight <60 kg: • 250 mg PO once daily	**Once-Daily Dose by Body Weight** **CrCl (mL/min)** / **≥60 kg** / **<60 kg** 30–59 / 200 mg / 125 mg 10–29 / 125 mg / 125 mg <10, HD,[c] or CAPD / 125 mg / 75 mg oral solution	No dose adjustment necessary.
Didanosine Oral Solution (ddI) *Videx*	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	**Once-Daily Dose by Body Weight** **CrCl (mL/min)** / **≥60 kg** / **<60 kg** 30–59 / 200 mg / 150 mg 10–29 / 150 mg / 100 mg <10, HD,[c] or CAPD / 100 mg / 75 mg	No dose adjustment necessary.
Emtricitabine (FTC) *Emtriva*	• 200 mg oral capsule once daily, *or* • 240 mg (24 mL) oral solution once daily	**Dose** **CrCl (mL/min)** / **Capsule** / **Solution** 30–49 / 200 mg q48h / 120 mg q24h 15–29 / 200 mg q72h / 80 mg q24h <15 or on HD[c] / 200 mg q96h / 60 mg q24h	No dose recommendation.
Lamivudine (3TC) *Epivir*	• 300 mg PO once daily, *or* • 150 mg PO BID	**CrCl (mL/min)** / **Dose** 30–49 / 150 mg q24h 15–29 / 1 x 150 mg, then 100 mg q24h 5–14 / 1 x 150 mg, then 50 mg q24h <5 or on HD[c] / 1 x 50 mg, then 25 mg q24h	No dose adjustment necessary.
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 dose recommendation

Appendix B, Table 8. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated October 25, 2018; last reviewed October 25, 2018) (page 2 of 7)

ARVs Generic Name (Abbreviation) *Trade Name*	Usual Daily Dose[a]	Dosing in Patients with Renal Insufficiency[b]	Dosing in Patients with Hepatic Impairment
NRTIs, continued			
Tenofovir Alafenamide/ Emtricitabine (TAF/FTC) *Descovy*	• TAF for HIV treatment is only available as a component of FDCs (i.e., Descovy, Genvoya, Odefsey, Biktarvy, and Symtuza). • TAF 10 mg PO daily with EVG/c (Genvoya) or DRV/c (Symtuza) • 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 dose adjustment Child-Pugh Class C: • No dose 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 dose 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 dose recommendation.
Tenofovir Disoproxil Fumarate/Lamivudine (TDF/3TC) *Cimduo*	• 1 tablet PO once daily	**CrCl (mL/min)** — **Dose** <50 or on HD — Not recommended	No dose recommendation.
Zidovudine (ZDV) *Retrovir*	• 300 mg PO BID	**CrCl (mL/min)** — **Dose** <15 or on HD[c] — 100 mg TID or 300 mg once daily	No dose recommendation.
NNRTIs			
Doravirine (DOR) *Pifeltro*	• 1 tablet PO once daily	No dose adjustment required in mild, moderate, or severe renal impairment. Has not been studied in ESRD or HD.	Child-Pugh Class A or B: • No dose adjustment Child-Pugh Class C: • Not studied
Doravine/Tenofovir Disoproxil Fumarate/ Lamivudine (DOR/TDF/3TC) *Delstrigo*	• 1 tablet PO once daily	Not recommended if CrCl <50 mL/min.	Child-Pugh Class A or B: • No dose adjustment Child-Pugh Class C: • Not studied
Efavirenz (EFV) *Sustiva*	• 600 mg PO once daily, on an empty stomach, preferably at bedtime	No dose adjustment necessary.	No dose recommendation; use with caution in patients with hepatic impairment.
Efavirenz/Tenofovir Disoproxil Fumarate/ Emtricitabine (EFV/TDF/FTC) *Atripla*	• 1 tablet once daily on an empty stomach, preferably at bedtime	Not recommended if CrCl <50 mL/min. Instead, use the individual drugs and adjust TDF and FTC doses according to CrCl level.	No dose recommendation; use with caution in patients with hepatic impairment.

Appendix B, Table 8. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated October 25, 2018; last reviewed October 25, 2018) (page 3 of 7)

ARVs Generic Name (Abbreviation) *Trade Name*	Usual Daily Dose[a]	Dosing in Patients with Renal Insufficiency[b]	Dosing in Patients with Hepatic Impairment
Efavirenz 600 mg/ Tenofovir Disoproxil Fumarate/Lamivudine (EFV/TDF/3TC) *Symfi*	• 1 tablet once daily on an empty stomach, preferably at bedtime	Not recommended if CrCl <50 mL/min or if patient is on HD. Instead, use the individual drugs and adjust TDF and 3TC doses according to CrCl level.	Not recommended for patients with moderate or severe hepatic impairment. Use caution in patients with mild hepatic impairment.
Efavirenz 400 mg/ Tenofovir Disoproxil Fumarate/Lamivudine (EFV/TDF/3TC) *Symfi Lo*	• 1 tablet once daily on an empty stomach, preferably at bedtime	Not recommended if CrCl <50 mL/min or if patient is on HD. Instead, use the individual drugs and adjust TDF and 3TC doses according to CrCl level.	Not recommended for patients with moderate or severe hepatic impairment. Use caution in patients with mild hepatic impairment.
Etravirine (ETR) *Intelence*	• 200 mg PO BID	No dose adjustment necessary.	Child-Pugh Class A or B: • No dose adjustment Child-Pugh Class C: • No dose recommendation
Nevirapine (NVP) *Viramune* or *Viramune XR*	• 200 mg PO BID, or • 400 mg PO once daily (using Viramune XR formulation)	No dose adjustment for patients with renal impairment. Patients on HD should receive an additional dose of 200 mg following each dialysis treatment.	Child-Pugh Class A: • No dose adjustment Child-Pugh Class B or C: • **Contraindicated**
Rilpivirine (RPV) *Edurant*	• 25 mg PO once daily	No dose adjustment necessary.	Child-Pugh Class A or B: • No dose adjustment Child-Pugh Class C: • No dose recommendation
Rilpivirine/Tenofovir Alafenamide/ Emtricitabine (RPV/TAF/FTC) *Odefsey*	• 1 tablet PO once daily	Not recommended if CrCl <30 mL/min.	Child-Pugh Class A or B: • No dose adjustment Child-Pugh Class C: • No dose recommendation
Rilpivirine/Tenofovir Disoproxil Fumarate/ Emtricitabine (RPV/TDF/FTC) *Complera*	• 1 tablet PO once daily	Not recommended if CrCl <50 mL/min. Instead, use the individual drugs and adjust TDF and FTC doses according to CrCl level.	Child-Pugh Class A or B: • No dose adjustment Child-Pugh Class C: • No dose recommendation
Rilpivirine/ Dolutegravir (RPV/DTG) *Juluca*	• 1 tablet PO once daily with food	No dose adjustment necessary. In patients with CrCl <30 mL/min, monitor closely for adverse effects.	Child-Pugh Class A or B: • No dose adjustment Child-Pugh Class C: • No dose recommendation
PIs			
Atazanavir (ATV) *Reyataz*	• 400 mg PO once daily, or • (ATV 300 mg plus RTV 100 mg) PO once daily	No dose adjustment for patients with renal dysfunction who do not require HD. In ARV-Naive Patients on HD: • (ATV 300 mg plus RTV 100 mg) once daily In ARV-Experienced Patients on HD: • ATV or ATV/r not recommended	Child-Pugh Class B: • 300 mg once daily (unboosted) for ARV-naive patients only Child-Pugh Class C: • Not recommended RTV boosting **is not recommended** in patients with hepatic impairment.

Appendix B, Table 8. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated October 25, 2018; last reviewed October 25, 2018) (page 4 of 7)

ARVs Generic Name (Abbreviation) *Trade Name*	Usual Daily Dose[a]	Dosing in Patients with Renal Insufficiency[b]	Dosing in Patients with Hepatic Impairment
PIs, continued			
Atazanavir/Cobicistat (ATV/c) *Evotaz*	• 1 tablet PO once daily	If Used with TDF: • Not recommended if CrCl <70 mL/min	Not recommended in patients with hepatic impairment.
Darunavir (DRV) *Prezista*	In ARV-Naive Patients and ARV-Experienced Patients with No DRV Resistance Mutations: • (DRV 800 mg plus RTV 100 mg) PO once daily with food In ARV-Experienced Patients with at Least 1 DRV Resistance Mutation: • (DRV 600 mg plus RTV 100 mg) PO BID	No dose adjustment necessary.	In Patients with Mild-to-Moderate Hepatic Impairment: • No dose adjustment In Patients with Severe Hepatic Impairment: • Not recommended
Darunavir/Cobicistat (DRV/c) *Prezcobix*	• 1 tablet PO once daily	If Used with TDF: • Not recommended if CrCl <70 mL/min	Child-Pugh Class A or B: • No dose adjustment Child-Pugh Class C: • Not recommended
Darunavir/ Cobicistat/Tenofovir Alafenamide/ Emtricitabine (DRV/c/TAF/FTC) *Symtuza*	• 1 tablet PO once daily	Not recommended if CrCl <30 mL/min.	Not recommended for patients with severe hepatic impairment.
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 dose adjustment necessary.	In PI-Naive Patients Only *Child-Pugh Score 5–9:* • 700 mg BID *Child-Pugh Score 10–15:* • 350 mg BID In PI-Naive or PI-Experienced Patients *Child-Pugh Score 5–6:* • (FPV 700 mg BID plus RTV 100 mg) once daily *Child-Pugh Score 7–9:* • (FPV 450 mg BID plus RTV 100 mg) once daily *Child-Pugh Score 10–15:* • (FPV 300 mg BID plus RTV 100 mg) once daily

Appendix B, Table 8. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated October 25, 2018; last reviewed October 25, 2018) (page 5 of 7)

ARVs Generic Name (Abbreviation) *Trade Name*	Usual Daily Dose[a]	Dosing in Patients with Renal Insufficiency[b]	Dosing in Patients with Hepatic Impairment
PIs, continued			
Indinavir (IDV) *Crixivan*	• 800 mg PO q8h	No dose adjustment necessary.	In Patients with Mild-to-Moderate Hepatic Insufficiency Due to Cirrhosis: • 600 mg q8h
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 dose recommendation; use with caution in patients with hepatic impairment.
Nelfinavir (NFV) *Viracept*	• 1250 mg PO BID	No dose adjustment necessary.	In Patients with Mild Hepatic Impairment: • No dose adjustment In Patients with Moderate-to-Severe Hepatic Impairment: • Not recommended
Ritonavir (RTV) *Norvir*	As a PI-Boosting Agent: • 100–400 mg per day	No dose adjustment necessary.	Refer to recommendations for the primary PI.
Saquinavir (SQV) *Invirase*	• (SQV 1000 mg plus RTV 100 mg) PO BID	No dose adjustment necessary.	In Patients with Mild-to-Moderate Hepatic Impairment: • Use with caution In Patients with Severe Hepatic Impairment: • **Contraindicated**
Tipranavir (TPV) *Aptivus*	• (TPV 500 mg plus RTV 200 mg) PO BID	No dose adjustment necessary.	Child-Pugh Class A: • Use with caution Child-Pugh Class B or C: • **Contraindicated**
INSTIs			
Bictegravir/Tenofovir Alafenamide/ Emtricitabine (BIC/TAF/FTC) *Biktarvy*	• 1 tablet once daily	Not recommended for use in patients with CrCl <30 mL/min.	Child-Pugh Class C: • Not recommended
Dolutegravir (DTG) *Tivicay*	• 50 mg once daily, *or* • 50 mg BID	No dose adjustment necessary.	Child-Pugh Class A or B: • No dose adjustment Child-Pugh Class C: • Not recommended

Appendix B, Table 8. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated October 25, 2018; last reviewed October 25, 2018) (page 6 of 7)

ARVs Generic Name (Abbreviation) *Trade Name*	Usual Daily Dose[a]	Dosing in Patients with Renal Insufficiency[b]	Dosing in Patients with Hepatic Impairment
INSTIs, continued			
Dolutegravir/Abacavir/ Lamivudine (DTG/ABC/3TC) *Triumeq*	• 1 tablet once daily	Not recommended if CrCl <50 mL/min. Instead, use the individual drugs and adjust 3TC dose according to CrCl.	Child-Pugh Class A: • Patients with mild hepatic impairment require a dose reduction of ABC. Use the individual drugs instead of the fixed-dose combination in these patients. Child-Pugh Class B or C: • **Contraindicated**, due to the ABC component
Dolutegravir/ Rilpivirine (DTG/RPV) *Juluca*	• 1 tablet PO once daily with food	No dose adjustment necessary. In patients with CrCl <30 mL/min, monitor closely for adverse effects.	Child-Pugh Class A or B: • No dose adjustment Child-Pugh Class C: • No dose recommendation
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.	In Patients with Mild-to-Moderate Hepatic Insufficiency: • No dose adjustment necessary In Patients with Severe Hepatic Insufficiency: • Not recommended
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.	In Patients with Mild-to-Moderate Hepatic Insufficiency: • No dose adjustment necessary In Patients with Severe Hepatic Insufficiency: • Not recommended
Raltegravir (RAL) *Isentress* *Isentress HD*	• 400 mg BID (using Isentress formulation), *or* • 1200 mg once daily (use Isentress HD formulation only)	No dose adjustment necessary.	In Patients with Mild-to-Moderate Hepatic Insufficiency: • No dose adjustment necessary In Patients with Severe Hepatic Insufficiency: • No recommendation
Fusion Inhibitor			
Enfuvirtide (T-20) *Fuzeon*	• 90 mg subcutaneous BID	No dose adjustment necessary.	No dose adjustment necessary.

Appendix B, Table 8. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated October 25, 2018; last reviewed October 25, 2018) (page 7 of 7)

ARVs Generic Name (Abbreviation) *Trade Name*	Usual Daily Dose[a]	Dosing in Patients with Renal Insufficiency[b]	Dosing in Patients with Hepatic Impairment
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.	In Patients with CrCl <30 mL/min or Patients Who Are 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 dose recommendations. MVC concentrations will likely be increased in patients with hepatic impairment.
CD4 Post-Attachment Inhibitor			
Ibalizumab (IBA) *Trogarzo*	• Loading dose of 2000 mg IV, followed by a maintenance dose of 800 mg IV every 2 weeks	No dose adjustment recommended.	No recommendation.

[a] Refer to Appendix B, Tables 1–7 for additional dosing information.

[b] Including patients who are on CAPD and HD.

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

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; AZT = zidovudine; BIC = bictegravir; BID = twice daily; CAPD = chronic ambulatory peritoneal dialysis; COBI = cobicistat; CrCl = creatinine clearance; CYP = cytochrome P; d4T = stavudine; ddI = didanosine; DLV = delavirdine; DRV = darunavir; DRV/c = darunavir/cobicistat; DTG = dolutegravir; DOR = doravirine; EC = enteric coated; EFV = efavirenz; ESRD = end stage renal disease; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDC = fixed-dose combination; FPV = fosamprenavir; FTC = emtricitabine; HD = hemodialysis; IBA = ibalizumab; IDV = indinavir; INSTI = integrase strand transfer inhibitor; IV=intravenous; LPV = lopinavir; 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; T-20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TID = three times daily; TPV = tipranavir; XR = extended release; ZDV = 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–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