



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

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## Drug Interactions (Last updated May 1, 2014; last reviewed May 1, 2014)

Potential drug-drug and/or drug-food interactions should be taken into consideration when selecting an antiretroviral (ARV) regimen. A thorough review of concomitant medications can help in designing a regimen that minimizes undesirable interactions. In addition, the potential for drug interactions should be assessed when a new ARV is added to an existing ARV combination, as well as when any drug (including over-the-counter agents) is added to a patient's medication regimen. Most drug interactions with ARV drugs are mediated through inhibition or induction of hepatic drug metabolism.<sup>1</sup> The mechanisms of drug interactions with each ARV drug class are briefly summarized below. [Tables 17–19b](#) list significant drug interactions with different ARV agents and recommendations on contraindications, dose modifications, and alternative agents.

### Protease Inhibitors

All protease inhibitors (PIs) are metabolized in the liver by CYP3A isoenzymes; consequently their metabolic rates may be altered in the presence of CYP inducers or inhibitors. Co-administration of PIs with ritonavir (RTV), a potent CYP3A inhibitor, intentionally increases PI exposure (see [Pharmacokinetic Enhancing](#) below).

Co-administration of PIs with a potent CYP3A inducer may lead to suboptimal drug concentrations and reduced therapeutic effects of the PI. These drug combinations should be avoided if alternative agents can be used. If this is not possible, close monitoring of plasma HIV RNA, with or without ARV dosage adjustment, and therapeutic drug monitoring (TDM), may be warranted.

Some PIs may also induce or inhibit CYP isoenzymes, P-glycoprotein (P-gp), or other transporters in the gut and elsewhere. Tipranavir (TPV), for example, is a potent inducer of CYP3A4 and P-gp. However, the net effect of ritonavir-boosted TPV (TPV/r) on CYP3A in vivo appears to be enzyme inhibition. Thus, concentrations of drugs that are substrates for only CYP3A are most likely to be increased if the drugs are given with TPV/r. The net effect of TPV/r on a drug that is a substrate of both CYP3A and P-gp cannot be confidently predicted. Significant decreases in saquinavir (SQV), amprenavir (APV), and lopinavir (LPV) concentrations have been observed in vivo when the PIs were given with TPV/r.

The use of a CYP3A substrate that has a narrow margin of safety in the presence of a potent CYP3A inhibitor, such as the PIs, may lead to markedly prolonged elimination half-life ( $t_{1/2}$ ) and toxic drug accumulation. Avoidance of concomitant use or dose reduction of the affected drug, with close monitoring for dose-related toxicities or TDM if appropriate, may be warranted.

The list of drugs that may have significant interactions with PIs is extensive and is continuously expanding. Some examples of these drugs include lipid-lowering agents (e.g., statins), benzodiazepines, calcium channel blockers, immunosuppressants (e.g., cyclosporine, tacrolimus), anticonvulsants, rifamycins, erectile dysfunction agents (e.g., sildenafil), ergot derivatives, azole antifungals, macrolides, oral contraceptives, methadone, and HCV protease inhibitors. Herbal products, such as St. John's wort, can also cause interactions that increase the risk of adverse clinical effects. See [Table 18a](#) for dosage recommendations.

### Non-Nucleoside Reverse Transcriptase Inhibitors

All non-nucleoside reverse transcriptase inhibitors (NNRTIs) are metabolized in the liver by cytochrome P450 (CYP) 3A isoenzymes. In addition, efavirenz (EFV) and nevirapine (NVP) are substrates of CYP2B6 enzymes, and etravirine (ETR) is a substrate of CYP2C9 and 2C19 enzymes. Concomitantly administered drugs that induce or inhibit these enzymes can alter NNRTI drug concentrations, resulting in virologic failure or adverse effects. All NNRTIs, except rilpivirine (RPV), induce or inhibit CYP isoenzymes. EFV acts as a

mixed inducer and inhibitor, but similar to NVP, it primarily induces CYP3A and 2B6 enzymes. ETR also induces CYP3A but inhibits CYP2C9 and 2C19 enzymes. The inducing effects of NNRTIs can result in sub-therapeutic concentrations of concomitantly administered drugs that are metabolized by CYP enzymes. Examples of such interacting medications include azole antifungals, rifamycins (e.g., rifabutin), benzodiazepines, hepatitis C virus (HCV) protease inhibitors, HMG-CoA reductase inhibitors (statins), and methadone. See [Table 18b](#) for dosing recommendations.

## Integrase Strand Transfer Inhibitors

Raltegravir (RAL) is primarily eliminated by glucuronidation mediated by the uridine diphosphate (UDP)-glucuronosyltransferase (UGT) 1A1 enzymes. Strong inducers of UGT1A1 enzymes (e.g., rifampin) can significantly reduce the concentration of RAL.<sup>2</sup> Similar to RAL, dolutegravir (DTG) is also primarily metabolized by glucuronidation mediated by UGT1A1 and to a minor degree by CYP3A enzymes. DTG is also a substrate of UGT1A3, UGT1A9, and P-gp. Strong inducers of these proteins may reduce the concentration of DTG; alternatively, strong inhibitors of these proteins may increase the concentration of DTG. DTG does not appear to affect CYP or UGT enzymes or P-gp-mediated transport. *In vitro*, DTG has been shown to inhibit the renal organic cation transporter (OCT2), but does not appear to affect any additional transporter proteins.<sup>3</sup>

Elvitegravir (EVG) is metabolized largely by CYP3A enzymes but also undergoes glucuronidation by UGT 1A1/3 enzymes. It is available only as a fixed dose combination with cobicistat (cobi), tenofovir (TDF), and emtricitabine (FTC). Co-administration of EVG with cobin, a CYP3A inhibitor, increases EVG exposure (see [Pharmacokinetic Enhancing](#) below). Drugs that induce or inhibit CYP3A enzymes can alter concentrations of EVG. The co-formulation of EVG/cobi/TDF/FTC should not be co-administered with other ARVs because of potential drug interactions that may alter drug levels of EVG, cobin, or the concomitant drug.

[Table 18d](#) lists significant drug interactions and dosage recommendations when an INSTI is co-administered with other drugs.

## Nucleoside Reverse Transcriptase Inhibitors

Unlike PIs, NNRTIs, EVG, and maraviroc (MVC), nucleoside reverse transcriptase inhibitors (NRTIs) do not undergo hepatic transformation through the CYP metabolic pathway. Significant pharmacodynamic interactions of NRTIs and other drugs, such as additive bone marrow suppressive effects of zidovudine (ZDV) and ganciclovir, have been reported. Pharmacokinetic (PK) interactions have also been reported; for example, atazanavir (ATV) concentration can be reduced when it is co-administered with TDF.<sup>4</sup> However, the mechanisms underlying some of these interactions are still unclear. [Table 18c](#) lists significant interactions with NRTIs.

## CCR5 Antagonist

MVC is a substrate of CYP3A enzymes and P-gp. As a consequence, the concentrations of MVC can be significantly increased in the presence of strong CYP3A inhibitors (such as RTV, cobin, and other PIs, except for TPV/r) and are reduced when MVC is used with CYP3A inducers (such as EFV or rifampin). Dose adjustment is necessary when MVC is used in combination with these agents (see [Table 18e](#) or [Appendix B, Table 6](#) for dosage recommendations). MVC is neither an inducer nor an inhibitor of the CYP3A system and does not alter the PKs of the drugs evaluated in interaction studies to date.

## Fusion Inhibitor

The fusion inhibitor enfuvirtide (T20) is a 36-amino-acid peptide that does not enter human cells. T20 is expected to undergo catabolism to its constituent amino acids with subsequent recycling of the amino acids in the body pool. No clinically significant drug-drug interaction with T20 has been identified to date.

## Pharmacokinetic Enhancing

Pharmacokinetic (PK) enhancing is a strategy used in ARV treatment to increase the exposure of an ARV by concomitantly administering a drug that inhibits the specific drug metabolizing enzymes for which the ARV is a substrate. Currently two agents are used in clinical practice as PK enhancers: RTV and *cobi*.

**RTV** is an HIV PI that is primarily used in clinical practice at a lower than approved dose (100 to 400 mg per day) as a PK enhancer for other PIs because of its inhibitory effects on CYP450, predominantly CYP3A4, and Pgp. RTV increases the trough concentrations ( $C_{\min}$ ) and prolongs the half-life of the active PIs.<sup>5</sup> The higher  $C_{\min}$  allows for a greater  $C_{\min}$ : inhibitory concentration ratio, which reduces the risk that drug resistance will develop as a result of suboptimal drug exposure. The longer half-life of the PI allows for less frequent dosing, which may enhance medication adherence. Even though the primary role of RTV is as a potent inhibitor of 3A4, it may also, to a less extent, induce CYP2C9, which may result in complex drug-drug interactions when used with PIs, other ARVs or non ARV drugs. [Tables 18a](#) and [19a–b](#) list interactions between RTV-containing PI regimens and other medications, as well as comments on the clinical management of these interactions.

**cobi** is a specific, potent CYP3A inhibitor that has a weak to no effect on other CYP450 isoforms with no ARV activity. The high water solubility of *cobi* allows for its co-formulation with other agents.<sup>6</sup> *Cobi* is currently available only as part of a fixed dose combination of EVG/*cobi*/TDF/FTC. *cobi* is used to increase the plasma concentrations of EVG, an INSTI. Like RTV, *cobi* has a complex drug-drug interaction profile. It also is an inhibitor of P-gp-mediated transport, which appears to be the mechanism by which *cobi* increases the systemic exposure to TDF. [Table 18e](#) lists interactions with *cobi* identified in PK studies conducted to date, projected interactions, and drugs that should not be co-administered with *cobi*.

When using RTV- or *cobi*-containing regimens, clinicians should be vigilant in assessing the potential for adverse drug-drug interactions. This is especially important when prescribing CYP3A substrates for which no PK data are available.

## References

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**Table 17. Drugs That Should Not Be Used With Antiretroviral Agents (Last updated May 1, 2014; last reviewed May 1, 2014) (page 1 of 2)**

This table only lists drugs that should not be co-administered at any dose and regardless of RTV enhancing. See [Tables 18](#) and [19](#) for more detailed PK interaction data.

ARV Agents and Contraindicated Drugs by Drug Category										
ARV Agents <sup>a,b</sup>	Cardiac Agents	Lipid-Lowering Agents	Antimycobacterials	GI Drugs	Neuroleptics	Psychotropics	Ergot Derivatives (Vasoconstrictors)	Herbs	ARV Agents	Others
<b>ATV +/- RTV</b>	Amiodarone Dronedarone	Lovastatin Simvastatin	Rifampin Rifapentine <sup>c</sup>	Cisapride <sup>e</sup>	Pimozide	Midazolam <sup>f</sup> Triazolam	Dihydroergotamine Ergonovine Ergotamine Methylexgonovine	St. John's wort	ETR NVP	Alfuzosin Irinotecan Salmeterol Sildenafil for PAH
<b>DRV/r</b>	Amiodarone Dronedarone	Lovastatin Simvastatin	Rifampin Rifapentine <sup>c</sup>	Cisapride <sup>e</sup>	Pimozide	Midazolam <sup>f</sup> Triazolam	Dihydroergotamine Ergonovine Ergotamine Methylexgonovine	St. John's wort	None	Alfuzosin Salmeterol Sildenafil for PAH
<b>FPV +/- RTV</b>	Amiodarone Dronedarone Flecainide Propafenone	Lovastatin Simvastatin	Rifampin Rifapentine <sup>c</sup>	Cisapride <sup>e</sup>	Pimozide	Midazolam <sup>f</sup> Triazolam	Dihydroergotamine Ergonovine Ergotamine Methylexgonovine	St. John's wort	ETR	Alfuzosin Salmeterol Sildenafil for PAH
<b>LPV/r</b>	Amiodarone Dronedarone	Lovastatin Simvastatin	Rifampin <sup>d</sup> Rifapentine <sup>c</sup>	Cisapride <sup>e</sup>	Pimozide	Midazolam <sup>f</sup> Triazolam	Dihydroergotamine Ergonovine Ergotamine Methylexgonovine	St. John's wort	None	Alfuzosin Salmeterol Sildenafil for PAH
<b>SQV/r</b>	Amiodarone Dronedarone Dofetilide Flecainide Lidocaine Propafenone Quinidine	Lovastatin Simvastatin	Rifampin <sup>d</sup> Rifapentine <sup>c</sup>	Cisapride <sup>e</sup>	Pimozide	Midazolam <sup>f</sup> Triazolam Trazodone	Dihydroergotamine Ergonovine Ergotamine Methylexgonovine	St. John's wort Garlic supplements	None	Alfuzosin Salmeterol Sildenafil for PAH
<b>TPV/r</b>	Amiodarone Dronedarone Flecainide Propafenone Quinidine	Lovastatin Simvastatin	Rifampin Rifapentine <sup>c</sup>	Cisapride <sup>e</sup>	Pimozide	Midazolam <sup>f</sup> Triazolam	Dihydroergotamine Ergonovine Ergotamine Methylexgonovine	St. John's wort	ETR	Alfuzosin Salmeterol Sildenafil for PAH
<b>EFV</b>	None	None	Rifapentine <sup>c</sup>	Cisapride <sup>e</sup>	Pimozide	Midazolam <sup>f</sup> Triazolam	Dihydroergotamine Ergonovine Ergotamine Methylexgonovine	St. John's wort	Other NNRTIs	None
<b>ETR</b>	None	None	Rifampin Rifapentine <sup>c</sup>	None	None	None	None	St. John's wort	Unboosted PIs, ATV/r, FPV/r, or TPV/r  other NNRTIs	Carbamazepine Phenobarbital Phenytoin Clopidogrel
<b>NVP</b>	None	None	Rifapentine <sup>c</sup>	None	None	None	None	St. John's wort	ATV +/- RTV <b>DTG</b> other NNRTIs	Ketoconazole

**Table 17. Drugs That Should Not Be Used With Antiretroviral Agents (Last updated May 1, 2014; last reviewed May 1, 2014) (page 2 of 2)**

ARV Agents and Contraindicated Drugs by Drug Category										
ARV Agents <sup>a,b</sup>	Cardiac Agents	Lipid-Lowering Agents	Antimycobacterials	GI Drugs	Neuroleptics	Psychotropics	Ergot Derivatives (Vasoconstrictors)	Herbs	ARV Agents	Others
RPV	None	None	Rifabutin Rifampin Rifapentine <sup>c</sup>	Proton pump inhibitors	None	None	None	St. John's wort	Other NNRTIs	Carbamazepine Oxcarbazepine Phenobarbital Phenytoin
MVC	None	None	Rifapentine <sup>c</sup>	None	None	None	None	St. John's wort	None	None
EVG/ cobi/TDF/ FTC	None	Lovastatin Simvastatin	Rifabutin Rifampin Rifapentine <sup>c</sup>	Cisapride <sup>e</sup>	Pimozide	Midazolam <sup>f</sup> Triazolam	Dihydroergotamine Ergotamine Methylergonovine	St. John's wort	All other ARVs	Alfuzosin Salmeterol Sildenafil for PAH
DTG	Dofetilide	None	Rifapentine <sup>c</sup>	None	None	None	None	St. John's wort	NVP	Carbamazepine Oxcarbazepine Phenobarbital Phenytoin

<sup>a</sup> DLV, IDV, NFV, and RTV (as sole PI) are not included in this table. Refer to the appropriate FDA package insert for information regarding DLV-, IDV-, NFV-, and RTV (as sole PI)-related drug interactions.

<sup>b</sup> Certain listed drugs are contraindicated on the basis of theoretical considerations. Thus, drugs with narrow therapeutic indices and suspected metabolic involvement with CYP450 3A, 2D6, or unknown pathways are included in this table. Actual interactions may or may not occur in patients.

<sup>c</sup> HIV-infected patients who received rifapentine as part of a treatment regimen for TB had a higher rate of TB relapse and acquired rifamycin resistance than those treated with other rifamycin-based regimens. Therefore an alternative agent to rifapentine is recommended for TB treatment.

<sup>d</sup> A high rate of Grade 4 serum transaminase elevation was seen when a higher dose of RTV was added to LPV/r or SQV or when double-dose LPV/r was used with rifampin to compensate for rifampin's induction effect and therefore, these dosing strategies should not be used.

<sup>e</sup> The manufacturer of cisapride has a limited-access protocol for patients who meet specific clinical eligibility criteria.

<sup>f</sup> Use of oral midazolam is contraindicated. Parenteral midazolam can be used with caution as a single dose and can be given in a monitored situation for procedural sedation.

Suggested alternatives to:

- **Lovastatin, simvastatin:** Fluvastatin, pitavastatin, and pravastatin (except for pravastatin with DRV/r) have the least potential for drug-drug interactions (see [Table 18a](#)). Use atorvastatin and rosuvastatin with caution; start with the lowest possible dose and titrate based on tolerance and lipid-lowering efficacy.
- **Rifampin:** Rifabutin (with dosage adjustment, see [Tables 18a](#) and [18b](#))
- **Midazolam, triazolam:** temazepam, lorazepam, oxazepam

**Key to Acronyms:** ARV = antiretroviral; ATV = atazanavir; ATV/r = ritonavir-boosted atazanavir; coBI = cobicistat; CYP = cytochrome P; DLV = delavirdine; DRV/r = ritonavir-boosted darunavir; **DTG = dolutegravir**; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; FDA = Food and Drug Administration; FPV = fosamprenavir; FPV/r = ritonavir-boosted fosamprenavir; FTC = emtricitabine; IDV = indinavir; LPV/r = ritonavir-boosted lopinavir; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PAH = pulmonary arterial hypertension; PI = protease inhibitor; PK = pharmacokinetic; RPV = rilpivirine; RTV = ritonavir; SQV = saquinavir; SQV/r = ritonavir-boosted saquinavir; TB = tuberculosis; TDF = tenofovir disoproxil fumarate; TPV/r = ritonavir-boosted tipranavir

**Table 18a. Drug Interactions between Protease Inhibitors<sup>a</sup> and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 1 of 12)**

This table provides information relating to PK interactions between PIs and non-ARV drugs. When information is available, interactions with boosted and unboosted PIs are listed separately. For interactions between ARV agents and for dosing recommendations, refer to Tables 18c, 19a, and 19b.

<sup>a</sup> NFV and IDV are **not** included in this table. Please refer to the FDA product labels for NFV and IDV for information regarding drug interactions with these PIs.

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
<b>Acid Reducers</b>			
<b>Antacids</b>	ATV, ATV/r	When given simultaneously, ↓ ATV expected	Give ATV at least 2 hours before or 1 hour after antacids or buffered medications.
	FPV	APV AUC ↓ 18%; no significant change in APV C <sub>min</sub>	Give FPV simultaneously with (or at least 2 hours before or 1 hour after) antacids.
	TPV/r	TPV AUC ↓ 27%	Give TPV at least 2 hours before or 1 hour after antacids.
<b>H2 Receptor Antagonists</b>	<b>RTV-Boosted PIs</b>		
	ATV/r	↓ ATV	H2 receptor antagonist dose should not exceed a dose equivalent to famotidine 40 mg BID in ART-naive patients or 20 mg BID in ART-experienced patients.  Give ATV 300 mg + RTV 100 mg simultaneously with and/or ≥10 hours after the H2 receptor antagonist.  If using TDF and H2 receptor antagonist in ART-experienced patients, use ATV 400 mg + RTV 100 mg.
	DRV/r, LPV/r	No significant effect	No dosage adjustment necessary.
	<b>PIs without RTV</b>		
	ATV	↓ ATV	H2 receptor antagonist single dose should not exceed a dose equivalent of famotidine 20 mg or total daily dose equivalent of famotidine 20 mg BID in ART-naive patients.  Give ATV at least 2 hours before and at least 10 hours after the H2 receptor antagonist.
	FPV	APV AUC ↓ 30%; no significant change in APV C <sub>min</sub>	If concomitant use is necessary, give FPV at least 2 hours before H2 receptor antagonist. Consider boosting FPV with RTV.
<b>PPIs</b>	ATV	↓ ATV	<b>PPIs are not recommended in patients receiving unboosted ATV.</b> In these patients, consider alternative acid-reducing agents, RTV boosting, or alternative PIs.
	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/r.  <b>PPIs are not recommended in PI-experienced patients.</b>
	DRV/r, TPV/r	↓ omeprazole PI: no significant effect	May need to increase omeprazole dose when using TPV/r.
	FPV, FPV/r, LPV/r	No significant effect	No dosage adjustment necessary.
	SQV/r	SQV AUC ↑ 82%	Monitor for SQV toxicities.

**Table 18a. Drug Interactions between Protease Inhibitors<sup>a</sup> and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 2 of 12)**

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
<b>Anticoagulants</b>			
Warfarin	All PIs	↑ or ↓ warfarin possible	Monitor INR closely when stopping or starting PI and adjust warfarin dose accordingly.
Rivaroxaban	All PIs	↑ rivaroxaban	Avoid concomitant use. Co-administration is expected to result in increased rivaroxaban exposure, which may lead to risk of increased bleeding.
<b>Anticonvulsants</b>			
Carbamazepine	<b>RTV-Boosted PIs</b>		
	ATV/r, FPV/r, LPV/r, SQV/r, TPV/r	↑ carbamazepine possible TPV/r ↑ carbamazepine AUC 26% May ↓ PI levels substantially	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. <b>Do not co-administer with LPV/r once daily.</b>
	DRV/r	carbamazepine AUC ↑ 45% DRV: no significant change	Monitor anticonvulsant level and adjust dose accordingly.
	<b>PIs without RTV</b>		
	ATV, FPV	May ↓ PI levels substantially	<b>Do not co-administer.</b> Consider alternative anticonvulsant or RTV boosting for ATV and FPV.
Lamotrigine	LPV/r	Lamotrigine AUC ↓ 50% LPV: no significant change	A dose increase of lamotrigine may be needed and therapeutic concentration monitoring for lamotrigine may be indicated, particularly during dosage adjustment. Alternatively, consider another anticonvulsant.  A similar interaction is possible with other RTV-boosted PIs.
Phenobarbital	All PIs	May ↓ PI levels substantially	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response.  <b>Do not co-administer with LPV/r once daily, ATV without RTV, or FPV without RTV.</b>
Phenytoin	<b>RTV-Boosted PIs</b>		
	ATV/r, DRV/r, SQV/r, TPV/r	↓ phenytoin possible ↓ PI possible	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response.
	FPV/r	phenytoin AUC ↓ 22% APV AUC ↑ 20%	Monitor phenytoin level and adjust dose accordingly. No change in FPV/r dose recommended.
	LPV/r	phenytoin AUC ↓ 31% LPV/r AUC ↓ 33%	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. <b>Do not co-administer with LPV/r once daily.</b>
	<b>PIs without RTV</b>		
	ATV, FPV	May ↓ PI levels substantially	<b>Do not co-administer.</b> Consider alternative anticonvulsant or RTV boosting for ATV and FPV.
Valproic Acid	LPV/r	↓ or ↔ VPA possible LPV AUC ↑ 75%	Monitor VPA levels and virologic response. Monitor for LPV-related toxicities.

**Table 18a. Drug Interactions between Protease Inhibitors<sup>a</sup> and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 3 of 12)**

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
<b>Antidepressants</b>			
<b>Bupropion</b>	LPV/r	bupropion AUC ↓ 57%	Titrate bupropion dose based on clinical response.
	TPV/r	bupropion AUC ↓ 46%	
<b>Paroxetine</b>	DRV/r	paroxetine AUC ↓ 39%	Titrate paroxetine dose based on clinical response.
	FPV/r	paroxetine AUC ↓ 55%	
<b>Sertraline</b>	DRV/r	sertraline AUC ↓ 49%	Titrate sertraline dose based on clinical response.
<b>Trazodone</b>	ATV/r, ATV, DRV/r, FPV/r, FPV, LPV/r, TPV/r	RTV 200 mg BID (for 2 days) ↑ trazodone AUC 240%	Use lowest dose of trazodone and monitor for CNS and cardiovascular adverse effects.
	SQV/r	↑ trazodone expected	<b>Contraindicated. Do not co-administer.</b>
<b>Tricyclic Antidepressants</b> Amitriptyline, Desipramine, Imipramine, Nortriptyline	All RTV-boosted PIs	↑ TCA expected	Use lowest possible TCA dose and titrate based on clinical assessment and/or drug levels.
<b>Antifungals</b>			
<b>Fluconazole</b>	<b>RTV-Boosted PIs</b>		
	ATV/r	No significant effect	No dosage adjustment necessary.
	SQV/r	No data with RTV boosting SQV (1200 mg TID) AUC ↑ 50%	No dosage adjustment necessary.
	TPV/r	TPV AUC ↑ 50%	Fluconazole >200 mg daily is not recommended. If high-dose fluconazole is indicated, consider alternative PI or another class of ARV drug.
<b>Itraconazole</b>	All PIs	↑ itraconazole possible ↑ PI possible	Consider monitoring itraconazole level to guide dosage adjustments. High doses (>200 mg/day) are not recommended with RTV-boosted PIs unless dose is guided by itraconazole levels.
<b>Posaconazole</b>	ATV/r	ATV AUC ↑ 146%	Monitor for adverse effects of ATV.
	ATV	ATV AUC ↑ 268%	Monitor for adverse effects of ATV.
	FPV	Compared with FPV/r (700 mg/100 mg), FPV (1400 mg BID) ↓ posaconazole AUC 23%, ↓ APV AUC 65%	<b>Do not co-administer.</b>

**Table 18a. Drug Interactions between Protease Inhibitors<sup>a</sup> and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 4 of 12)**

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
<b>Antifungals, continued</b>			
Voriconazole	<b>RTV-Boosted PIs</b>		
	All RTV-boosted PIs	RTV 400 mg BID ↓ voriconazole AUC 82% RTV 100 mg BID ↓ voriconazole AUC 39%	<b>Do not co-administer voriconazole and RTV unless benefit outweighs risk.</b> If administered, consider monitoring voriconazole level and adjust dose accordingly.
	<b>PIs without RTV</b>		
	ATV, FPV	↑ voriconazole possible ↑ PI possible	Monitor for toxicities.
<b>Antimalarials</b>			
Artemether/ Lumefantrine	DRV/r	artemether AUC ↓ 16%; DHA <sup>a</sup> AUC ↓ 18%; lumefantrine AUC ↑ 2.5-fold	Clinical significance unknown. If used, monitor closely for anti-malarial efficacy and lumefantrine toxicity.
	LPV/r	artemether AUC ↓ 40%; DHA AUC ↓ 17%; lumefantrine AUC ↑ 470%	Clinical significance unknown. If used, monitor closely for anti-malarial efficacy and lumefantrine toxicity.
Atovaquone/ Proguanil	ATV/r, LPV/r	ATV/r ↓ atovaquone AUC 46% and ↓ proguanil AUC 41% LPV/r ↓ atovaquone AUC 74% and ↓ proguanil AUC 38%	No dosage recommendation. Consider alternative drug for malaria prophylaxis, if possible.
Mefloquine	RTV	With RTV 200 mg BID: RTV AUC ↓ 31%, C <sub>min</sub> ↓ 43%; ↔ mefloquine	Use with caution. Effect on exposure of RTV-boosted PIs is unknown.
<b>Antimycobacterials</b>			
Bedaquiline	All RTV-boosted PIs	With LPV/r: bedaquiline AUC ↑ 22%; C <sub>max</sub> ↔ With other PI/r: ↑ bedaquiline possible	Clinical significance unknown. Use with caution if benefit outweighs the risk and monitor for QTc prolongation and liver function tests.
Clarithromycin	ATV/r, ATV	clarithromycin AUC ↑ 94%	May cause QTc prolongation. Reduce clarithromycin dose by 50%. Consider alternative therapy (e.g., azithromycin).
	DRV/r, FPV/r, LPV/r, SQV/r, TPV/r	DRV/r ↑ clarithromycin AUC 57% FPV/r ↑ clarithromycin possible LPV/r ↑ clarithromycin expected RTV 500 mg BID ↑ clarithromycin 77% SQV unboosted ↑ clarithromycin 45% TPV/r ↑ clarithromycin 19% clarithromycin ↑ unboosted SQV 177% clarithromycin ↑ TPV 66%	Monitor for clarithromycin-related toxicities or consider alternative macrolide (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.
	FPV	APV AUC ↑ 18%	No dosage adjustment necessary.

**Table 18a. Drug Interactions between Protease Inhibitors<sup>a</sup> and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 5 of 12)**

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
<b>Antimycobacterials, continued</b>			
<b>Rifabutin</b>	<b>RTV-Boosted PIs</b>		
	ATV/r	Compared with rifabutin (300 mg daily) administered alone, when rifabutin (150 mg once daily) is administered with ATV/r, rifabutin AUC ↑ 110% and metabolite AUC ↑ 2101%	Rifabutin 150 mg once daily or 300 mg three times a week. Monitor for antimycobacterial activity and consider therapeutic drug monitoring.  PK data reported in this table are results from healthy volunteer studies. Lower rifabutin exposure has been reported in HIV-infected patients than in the healthy study participants.
	DRV/r	Compared with rifabutin (300 mg once daily) administered alone, when rifabutin (150 mg every other day) is administered with DRV/r, rifabutin AUC not significantly changed and metabolite AUC ↑ 881%	
	FPV/r	Compared with rifabutin (300 mg once daily) administered alone, when rifabutin (150 mg every other day) is administered with FPV/r, rifabutin and metabolite AUC ↑ 64%.	
	LPV/r	Compared with rifabutin (300 mg daily) administered alone, when rifabutin (150 mg once daily) is administered with LPV/r, rifabutin and metabolite AUC ↑ 473%.	
	SQV/r	↑ rifabutin with unboosted SQV	
	TPV/r	rifabutin and metabolite AUC ↑ 333%	
	<b>PIs without RTV</b>		
	ATV, FPV	↑ rifabutin AUC expected	Rifabutin 150 mg daily or 300 mg three times a week
<b>Rifampin</b>	All PIs	↓ PI concentration by >75%	<b>Do not co-administer rifampin and PIs.</b> Additional RTV does not overcome this interaction and increases hepatotoxicity. Consider rifabutin if a rifamycin is indicated.
<b>Rifapentine</b>	All PIs	↓ PI expected	<b>Do not co-administer rifapentine and PIs.</b>
<b>Benzodiazepines</b>			
<b>Alprazolam</b> <b>Diazepam</b>	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.
<b>Lorazepam</b> <b>Oxazepam</b> <b>Temazepam</b>	All PIs	No data	These benzodiazepines are metabolized via non-CYP450 pathways; there is less interaction potential than with other benzodiazepines.
<b>Midazolam</b>	All PIs	↑ midazolam expected SQV/r ↑ midazolam (oral) AUC 1144% and C <sub>max</sub> 327%	<b>Do not co-administer oral midazolam and PIs.</b>  Parenteral midazolam can be used with caution when given as a single dose in a monitored situation for procedural sedation.
<b>Triazolam</b>	All PIs	↑ triazolam expected RTV (200 mg BID) ↑ triazolam half-life 1200% and AUC 2000%	<b>Do not co-administer triazolam and PIs.</b>

**Table 18a. Drug Interactions between Protease Inhibitors<sup>a</sup> and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 6 of 12)**

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
<b>Cardiac Medications</b>			
<b>Bosentan</b>	All PIs	LPV/r ↑ bosentan 48-fold (day 4) and 5-fold (day 10) ↓ ATV expected	<b>Do not co-administer bosentan and ATV without RTV.</b> <u>In Patients on a PI (Other than Unboosted ATV) &gt;10 Days:</u> • Start bosentan at 62.5 mg once daily or every other day. <u>In Patients on Bosentan who Require a PI (Other than Unboosted ATV):</u> • Stop bosentan ≥36 hours before PI initiation and restart 10 days after PI initiation at 62.5 mg once daily or every other day.
<b>Digoxin</b>	RTV, SQV/r	RTV (200 mg BID) ↑ digoxin AUC 29% and ↑ half-life 43% SQV/r ↑ digoxin AUC 49%	Use with caution. Monitor digoxin levels. Digoxin dose may need to be decreased.
<b>Calcium Channel Blockers</b>	All PIs	↑ dihydropyridine possible	Use with caution. Titrate CCB dose and monitor closely. ECG monitoring is recommended when CCB used with ATV.
<b>Diltiazem</b>	ATV/r, ATV	diltiazem AUC ↑ 125%	Decrease diltiazem dose by 50%. ECG monitoring is recommended.
	DRV/r, FPV/r, FPV, LPV/r, SQV/r, TPV/r	↑ diltiazem possible	Use with caution. Adjust diltiazem according to clinical response and toxicities.
<b>Corticosteroids</b>			
<b>Beclomethasone Inhaled</b>	DRV/r	RTV 100 mg BID ↑ 17-BMP AUC 2-fold and ↑ C <sub>max</sub> 1.6-fold (DRV 600 mg plus RTV 100 mg) BID ↓ 17-BMP AUC 11% and ↓ C <sub>max</sub> 19%	No dosage adjustment necessary. Significant interaction between beclomethasone (inhaled or intranasal) and other RTV-boosted PIs is not expected.
<b>Budesonide Systemic</b>	All PIs	↓ PI levels possible ↑ glucocorticoids	Co-administration can result in adrenal insufficiency, including Cushing's syndrome. <b>Do not co-administer unless potential benefits of systemic budesonide outweigh the risks of systemic corticosteroid adverse effects.</b>
<b>Budesonide Inhaled or Intranasal</b>	All RTV-boosted PIs	↑ glucocorticoids	Co-administration can result in adrenal insufficiency, including Cushing's syndrome. <b>Do not co-administer unless potential benefits of inhaled or intranasal budesonide outweigh the risks of systemic corticosteroid adverse effects. Consider alternative therapy (e.g., beclomethasone).</b>
<b>Dexamethasone</b>	All PIs	↓ PI levels possible	Use systemic dexamethasone with caution or consider alternative corticosteroid for long-term use.

**Table 18a. Drug Interactions between Protease Inhibitors<sup>a</sup> and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 7 of 12)**

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
<b>Corticosteroids, continued</b>			
<b>Fluticasone</b> Inhaled or Intranasal	All RTV-boosted PIs	RTV 100 mg BID ↑ fluticasone AUC 350-fold and ↑ C <sub>max</sub> 25-fold	Co-administration can result in adrenal insufficiency, including Cushing's syndrome. <b>Do not co-administer unless potential benefits of inhaled or intranasal fluticasone outweigh the risks of systemic corticosteroid adverse effects.</b> Consider alternative therapy (e.g., beclomethasone).
<b>Prednisone</b>	LPV/r All PIs	↑ prednisolone AUC 31% ↑ prednisolone possible	Use with caution. Co-administration can result in adrenal insufficiency, including Cushing's syndrome. <b>Do not co-administer unless potential benefits of prednisone outweigh the risks of systemic corticosteroid adverse effects.</b>
<b>Methylprednisolone, Prednisolone, Triamcinolone</b> (local injections, including intra-articular, epidural, intra-orbital)	All RTV-boosted PIs	↑ glucocorticoids expected	Co-administration can result in adrenal insufficiency, including Cushing's syndrome. <b>Do not co-administer.</b> Consider alternative non-steroidal therapies. If intra-articular corticosteroid therapy required, change to alternative non-CYP3A-modulating ART (e.g., RAL, DTG).
<b>Hepatitis C NS3/4A Protease Inhibitors</b>			
<b>Boceprevir</b>	ATV/r	ATV AUC ↓ 35%, C <sub>min</sub> ↓ 49% RTV AUC ↓ 36% boceprevir AUC ↔	<b>Co-administration is not recommended.</b>
	DRV/r	DRV AUC ↓ 44%, C <sub>min</sub> ↓ 59% RTV AUC ↓ 26% boceprevir AUC ↓ 32%, C <sub>min</sub> ↓ 35%	<b>Co-administration is not recommended.</b>
	LPV/r	LPV AUC ↓ 34%, C <sub>min</sub> ↓ 43% RTV AUC ↓ 22% boceprevir AUC ↓ 45%, C <sub>min</sub> ↓ 57%	<b>Co-administration is not recommended.</b>
<b>Simeprevir</b>	All PIs	DRV/r 800/100 mg daily plus simeprevir 50 mg: simeprevir AUC ↑ 159% compared with simeprevir 150 mg alone RTV 100 mg BID ↑ simeprevir AUC 618%	<b>Co-administration is not recommended.</b>
<b>Telaprevir</b>	ATV/r	telaprevir AUC ↓ 20%	No dose adjustment necessary.
	DRV/r	telaprevir AUC ↓ 35% DRV AUC ↓ 40%	<b>Co-administration is not recommended.</b>
	FPV/r	telaprevir AUC ↓ 32% APV AUC ↓ 47%	<b>Co-administration is not recommended.</b>
	LPV/r	telaprevir AUC ↓ 54% LPV: no significant change	<b>Co-administration is not recommended.</b>

**Table 18a. Drug Interactions between Protease Inhibitors<sup>a</sup> and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 8 of 12)**

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
<b>Herbal Products</b>			
St. John's Wort	All PIs	↓ PI expected	<b>Do not co-administer.</b>
<b>Hormonal Contraceptives</b>			
<b>Hormonal Contraceptives</b>	<b>RTV-Boosted PIs</b>		
	ATV/r	ethinyl estradiol AUC ↓ 19% and C <sub>min</sub> ↓ 37% norgestimate ↑ 85%	Oral contraceptive should contain at least 35 mcg of ethinyl estradiol.  Oral contraceptives containing progestins other than norethindrone or norgestimate have not been studied. <sup>b</sup>
	DRV/r	ethinyl estradiol AUC ↓ 44% norethindrone AUC ↓ 14%	Recommend alternative or additional contraceptive method.
	FPV/r	ethinyl estradiol AUC ↓ 37% norethindrone AUC ↓ 34%	Recommend alternative or additional contraceptive method.
	LPV/r	ethinyl estradiol AUC ↓ 42% norethindrone AUC ↓ 17%	Recommend alternative or additional contraceptive method.
	SQV/r	↓ ethinyl estradiol	Recommend alternative or additional contraceptive method.
	TPV/r	ethinyl estradiol AUC ↓ 48% norethindrone: no significant change	Recommend alternative or additional contraceptive method.
	<b>Pis without RTV</b>		
	ATV	ethinyl estradiol AUC ↑ 48% norethindrone AUC ↑ 110%	Prescribe oral contraceptive that contains no more than 30 mcg of ethinyl estradiol or recommend alternative contraceptive method.  Oral contraceptives containing less than 25 mcg of ethinyl estradiol or progestins other than norethindrone or norgestimate have not been studied. <sup>c</sup>
	FPV	With APV: ↑ ethinyl estradiol and ↑ norethindrone C <sub>min</sub> ; APV C <sub>min</sub> ↓ 20%	Recommend alternative contraceptive method.
<b>HMG-CoA Reductase Inhibitors</b>			
<b>Atorvastatin</b>	ATV/r, ATV	↑ atorvastatin possible	Titrate atorvastatin dose carefully and use lowest dose necessary.
	DRV/r, FPV/r, FPV, SQV/r	DRV/r plus atorvastatin 10 mg similar to atorvastatin 40 mg administered alone; FPV +/- RTV ↑ atorvastatin AUC 130% to 153%; SQV/r ↑ atorvastatin AUC 79%	Titrate atorvastatin dose carefully and use the lowest necessary dose. Do not exceed 20 mg atorvastatin daily.
	LPV/r	LPV/r ↑ atorvastatin AUC 488%	Use with caution and use the lowest atorvastatin dose necessary.
	TPV/r	↑ atorvastatin AUC 836%	<b>Do not co-administer.</b>
<b>Lovastatin</b>	All PIs	Significant ↑ lovastatin expected	<b>Contraindicated. Do not co-administer.</b>

**Table 18a. Drug Interactions between Protease Inhibitors<sup>a</sup> and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 9 of 12)**

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
<b>HMG-CoA Reductase Inhibitors, continued</b>			
Pitavastatin	All PIs	ATV ↑ pitavastatin AUC 31% and C <sub>max</sub> ↑ 60% ATV: no significant effect DRV/r: no significant effect LPV/r ↓ pitavastatin AUC 20% LPV: no significant effect	No dose adjustment necessary.
	DRV/r	pravastatin AUC • ↑ 81% following single dose of pravastatin • ↑ 23% at steady state	Use lowest possible starting dose of pravastatin with careful monitoring.
Pravastatin	LPV/r	pravastatin AUC ↑ 33%	No dose adjustment necessary.
	SQV/r	pravastatin AUC ↓ 47% to 50%	No dose adjustment necessary.
Rosuvastatin	ATV/r, LPV/r	ATV/r ↑ rosuvastatin AUC 3-fold and C <sub>max</sub> ↑ 7-fold LPV/r ↑ rosuvastatin AUC 108% and C <sub>max</sub> ↑ 366%	Titrate rosuvastatin dose carefully and use the lowest necessary dose. Do not exceed 10 mg rosuvastatin daily.
	DRV/r	rosuvastatin AUC ↑ 48% and C <sub>max</sub> ↑ 139%	Titrate rosuvastatin dose carefully and use the lowest necessary dose while monitoring for toxicities.
	FPV +/- RTV	No significant effect on rosuvastatin	No dosage adjustment necessary.
	SQV/r	No data available	Titrate rosuvastatin dose carefully and use the lowest necessary dose while monitoring for toxicities.
	TPV/r	rosuvastatin AUC ↑ 26% and C <sub>max</sub> ↑ 123%	No dosage adjustment necessary.
Simvastatin	All PIs	Significant ↑ simvastatin level; SQV/r 400 mg/400 mg BID ↑ simvastatin AUC 3059%	<b>Contraindicated. Do not co-administer.</b>
<b>Immunosuppressants</b>			
Cyclosporine 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.
<b>Narcotics/Treatment for Opioid Dependence</b>			
Buprenorphine	ATV	buprenorphine AUC ↑ 93% norbuprenorphine <sup>d</sup> AUC ↑ 76% ↓ ATV possible	<b>Do not co-administer buprenorphine with unboosted ATV.</b>
	ATV/r	buprenorphine AUC ↑ 66% norbuprenorphine <sup>d</sup> AUC ↑ 105%	Monitor for sedation. Buprenorphine dose reduction may be necessary.
	DRV/r	buprenorphine: no significant effect norbuprenorphine <sup>d</sup> AUC ↑ 46% and C <sub>min</sub> ↑ 71%	No dosage adjustment necessary. Clinical monitoring is recommended.

**Table 18a. Drug Interactions between Protease Inhibitors<sup>a</sup> and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 10 of 12)**

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
<b>Narcotics/Treatment for Opioid Dependence, continued</b>			
<b>Buprenorphine, continued</b>	FPV/r	buprenorphine: no significant effect norbuprenorphine <sup>d</sup> AUC ↓ 15%	No dosage adjustment necessary. Clinical monitoring is recommended.
	LPV/r	No significant effect	No dosage adjustment necessary.
	TPV/r	buprenorphine: no significant effect norbuprenorphine <sup>d</sup> AUC, C <sub>max</sub> , and C <sub>min</sub> ↓ 80% TPV C <sub>min</sub> ↓ 19%–40%	Consider monitoring TPV level.
<b>Oxycodone</b>	LPV/r	oxycodone AUC ↑ 2.6-fold	Monitor for opioid-related adverse effects. Oxycodone dose reduction may be necessary.
<b>Methadone</b>	<b>RTV-Boosted PIs</b>		
	ATV/r, DRV/r, FPV/r, LPV/r, SQV/r, TPV/r	ATV/r, DRV/r, FPV/r: ↓ R-methadone <sup>e</sup> AUC 16% to 18%; LPV/r ↓ methadone AUC 26% to 53% SQV/r 1000/100 mg BID ↓ R-methadone <sup>e</sup> AUC 19% TPV/r ↓ R-methadone <sup>e</sup> AUC 48%	Opioid withdrawal unlikely but may occur. Dosage adjustment of methadone is not usually required, but monitor for opioid withdrawal and increase methadone dose as clinically indicated.
	<b>PIs without RTV</b>		
	ATV	No significant effect	No dosage adjustment necessary.
	FPV	No data with unboosted FPV APV ↓ R-methadone <sup>e</sup> C <sub>min</sub> 21%, AUC no significant change	Monitor and titrate methadone as clinically indicated. The interaction with FPV is presumed to be similar.
<b>Phosphodiesterase Type 5 (PDE5) Inhibitors</b>			
<b>Avanafil</b>	ATV, ATV/r, DRV/r, FPV/r, SQV/r, LPV/r	RTV (600 mg BID for 5 days) ↑ avanafil AUC 13-fold, C <sub>max</sub> 2.4-fold	<b>Co-administration is not recommended.</b>
	FPV	No data	Avanafil dose should not exceed 50 mg once every 24 hours.
<b>Sildenafil</b>	All PIs	DRV/r plus sildenafil 25 mg similar to sildenafil 100 mg alone; RTV 500 mg BID ↑ sildenafil AUC 1000% SQV unboosted ↑ sildenafil AUC 210%	<u>For Treatment of Erectile Dysfunction:</u> • Start with sildenafil 25 mg every 48 hours and monitor for adverse effects of sildenafil.  <u>For treatment of PAH:</u> • <b>Contraindicated</b>

**Table 18a. Drug Interactions between Protease Inhibitors<sup>a</sup> and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 11 of 12)**

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
<b>Phosphodiesterase Type 5 (PDE5) Inhibitors, continued</b>			
<b>Tadalafil</b>	All PIs	RTV 200 mg BID ↑ tadalafil AUC 124% TPV/r (1st dose) ↑ tadalafil AUC 133% TPV/r steady state: no significant effect	<p><u>For Treatment of Erectile Dysfunction:</u> Start with tadalafil 5-mg dose and do not exceed a single dose of 10 mg every 72 hours. Monitor for adverse effects of tadalafil.</p> <p><u>For Treatment of PAH:</u> <i>In Patients on a PI &gt;7 Days:</i></p> <ul style="list-style-type: none"> <li>• Start with tadalafil 20 mg once daily and increase to 40 mg once daily based on tolerability.</li> </ul> <p><i>In Patients on Tadalafil who Require a PI:</i></p> <ul style="list-style-type: none"> <li>• Stop tadalafil ≥24 hours before PI initiation, restart 7 days after PI initiation at 20 mg once daily, and increase to 40 mg once daily based on tolerability.</li> </ul> <p><u>For Treatment of Benign Prostatic Hyperplasia:</u></p> <ul style="list-style-type: none"> <li>• Maximum recommended daily dose is 2.5 mg per day</li> </ul>
<b>Vardenafil</b>	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.
<b>Miscellaneous Interactions</b>			
<b>Colchicine</b>	All PIs	RTV 100 mg BID ↑ colchicine AUC 296%, C <sub>max</sub> 184%  With all PIs: significant ↑ in colchicine AUC expected	<p><u>For Treatment of Gout Flares:</u></p> <ul style="list-style-type: none"> <li>• Colchicine 0.6 mg x 1 dose, followed by 0.3 mg 1 hour later. Do not repeat dose for at least 3 days.</li> </ul> <p><i>With FPV without RTV:</i></p> <ul style="list-style-type: none"> <li>• 1.2 mg x 1 dose and no repeat dose for at least 3 days</li> </ul> <p><u>For Prophylaxis of Gout Flares:</u></p> <ul style="list-style-type: none"> <li>• Colchicine 0.3 mg once daily or every other day</li> </ul> <p><i>With FPV without RTV:</i></p> <ul style="list-style-type: none"> <li>• Colchicine 0.3 mg BID or 0.6 mg once daily or 0.3 mg once daily</li> </ul> <p><u>For Treatment of Familial Mediterranean Fever:</u></p> <ul style="list-style-type: none"> <li>• Do not exceed colchicine 0.6 mg once daily or 0.3 mg BID.</li> </ul> <p><i>With FPV without RTV:</i></p> <ul style="list-style-type: none"> <li>• Do not exceed 1.2 mg once daily or 0.6 mg BID.</li> </ul> <p><b>Do not co-administer in patients with hepatic or renal impairment.</b></p>

**Table 18a. Drug Interactions between Protease Inhibitors<sup>a</sup> and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 12 of 12)**

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
<b>Miscellaneous Interactions, continued</b>			
<b>Quetiapine</b>	All PIs	↑ quetiapine AUC expected	<p><u>Initiation of Quetiapine in a Patient Receiving a PI:</u></p> <ul style="list-style-type: none"> <li>• Start quetiapine at the lowest dose and titrate up as needed. Monitor for quetiapine effectiveness and adverse effects.</li> </ul> <p><u>Initiation of a PI in a Patient Receiving a Stable Dose of Quetiapine:</u></p> <ul style="list-style-type: none"> <li>• Reduce quetiapine dose to 1/6 of the original dose. Closely monitor for quetiapine effectiveness and adverse effects.</li> </ul>
<b>Salmeterol</b>	All PIs	↑ salmeterol possible	<b>Do not co-administer</b> because of potential increased risk of salmeterol-associated cardiovascular events.

<sup>a</sup> DHA is an active metabolite of artemether.

<sup>b</sup> The following products contain at least 35 mcg of ethinyl estradiol combined with norethindrone or norgestimate (generic formulation may also be available): Ovcon 35, 50; Femcon Fe; Brevicon; Modicon; Ortho-Novum 1/35, 10/11, 7/7/7; Norinyl 1/35; Tri-Norinyl; Ortho-Cyclen; Ortho Tri-Cyclen.

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

<sup>d</sup> Norbuprenorphine is an active metabolite of buprenorphine.

<sup>e</sup> R-methadone is the active form of methadone.

**Key to Acronyms:** 17-BMP = beclomethasone 17-monopropionate; APV = amprenavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/r = ritonavir-boosted atazanavir; AUC = area under the curve; BID = twice daily; C<sub>max</sub> = maximum plasma concentration; C<sub>min</sub> = minimum plasma concentration; CNS = central nervous system; CrCl = creatinine clearance; CYP = cytochrome P; DHA = dihydroartemisinin; DRV = darunavir; DRV/r = ritonavir-boosted darunavir; DTG = dolutegravir; ECG = electrocardiogram; FDA = Food and Drug Administration; FPV = fosamprenavir; FPV/r = ritonavir-boosted fosamprenavir; IDV = indinavir; INR = international normalized ratio; LPV = lopinavir; LPV/r = ritonavir-boosted lopinavir; NFV = nelfinavir; PAH = pulmonary arterial hypertension; PDE5 = phosphodiesterase type 5; PI = protease inhibitor; PK = pharmacokinetic; PPI = proton pump inhibitor; RAL = raltegravir; RTV = ritonavir; SQV = saquinavir; SQV/r = ritonavir-boosted saquinavir; TDF = tenofovir disoproxil fumarate; TID = three times a day; TPV = tipranavir; TPV/r = ritonavir-boosted tipranavir

**Note:** FPV is a pro-drug of APV

**Table 18b. Drug Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors<sup>a</sup> and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 1 of 7)**

This table provides information relating to PK interactions between NNRTIs and non- ARV drugs. For interactions between ARV agents and for dosing recommendations, refer to Tables 18c, 19a, and 19b.

<sup>a</sup> DLV is **not** included in this table. Please refer to the DLV FDA package insert for information regarding drug interactions.

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

**Table 18b. Drug Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors<sup>a</sup> and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 2 of 7)**

Concomitant Drug Class/Name	NNRTI <sup>a</sup>	Effect on NNRTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
<b>Antifungals</b>			
<b>Fluconazole</b>	EFV	No significant effect	No dosage adjustment necessary.
	ETR	ETR AUC ↑ 86%	No dosage adjustment necessary. Use with caution.
	NVP	NVP AUC ↑ 110%	Increased risk of hepatotoxicity possible with this combination. Monitor NVP toxicity or use alternative ARV agent.
	RPV	↑ RPV possible	No dosage adjustment necessary. Clinically monitor for breakthrough fungal infection (RPV 150 mg/day reduces ketoconazole exposure; no data on interaction with fluconazole).
<b>Itraconazole</b>	EFV	itraconazole and OH-itraconazole AUC, C <sub>max</sub> and C <sub>min</sub> ↓ 35%–44%	Failure to achieve therapeutic itraconazole concentrations has been reported. Avoid this combination if possible. If co-administered, closely monitor itraconazole concentration and adjust dose accordingly.
	ETR	↓ itraconazole possible ↑ ETR possible	Dose adjustments for itraconazole may be necessary. Monitor itraconazole level and antifungal response.
	NVP	↓ itraconazole possible ↑ NVP possible	Avoid combination if possible. If co-administered, monitor itraconazole concentration and adjust dose accordingly.
	RPV	↑ RPV possible	No dosage adjustment necessary. Clinically monitor for breakthrough fungal infection. (RPV 150 mg/day reduces ketoconazole exposure; no data on interaction with itraconazole.)
<b>Posaconazole</b>	EFV	posaconazole AUC ↓ 50% ↔ EFV	Avoid concomitant use unless the benefit outweighs the risk. If co-administered, monitor posaconazole concentration and adjust dose accordingly.
	ETR	↑ ETR possible	No dosage adjustment necessary.
	RPV	↑ RPV possible	No dosage adjustment necessary. Clinically monitor for breakthrough fungal infection (RPV 150 mg/day reduces ketoconazole exposure; no data on interaction with posaconazole).

**Table 18b. Drug Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors<sup>a</sup> and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 3 of 7)**

Concomitant Drug Class/Name	NNRTI <sup>a</sup>	Effect on NNRTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
<b>Antifungals, continued</b>			
<b>Voriconazole</b>	EFV	voriconazole AUC ↓ 77% EFV AUC ↑ 44%	<b>Contraindicated at standard doses.</b> Dose: voriconazole 400 mg BID, EFV 300 mg daily.
	ETR	voriconazole AUC ↑ 14% ETR AUC ↑ 36%	No dosage adjustment necessary; use with caution. Consider monitoring voriconazole level.
	NVP	↓ voriconazole possible ↑ NVP possible	Monitor for toxicity and antifungal response and/or voriconazole level.
	RPV	↑ RPV possible	No dosage adjustment necessary. Clinically monitor for breakthrough fungal infection (RPV 150 mg/day reduces ketoconazole exposure; no data on interaction with voriconazole).
<b>Antimalarials</b>			
<b>Artemether/ Lumefantrine</b>	EFV	artemether AUC ↓ 79% DHA AUC ↓ 75% lumefantrine AUC ↓ 56%	Clinical significance unknown. If used, monitor closely for anti-malarial efficacy
	ETR	artemether AUC ↓ 38% DHA AUC ↓ 15% lumefantrine AUC ↓ 13% ETR AUC ↑ 10%	Clinical significance unknown. If used, monitor closely for anti-malarial efficacy
	NVP	artemether AUC ↓ 72% DHA AUC ↓ 37% lumefantrine: no difference in one study, but AUC ↑ 55.6% in another study	Clinical significance unknown. If used, monitor closely for anti-malarial efficacy and lumefantrine toxicity.
<b>Atovaquone/ Proguanil</b>	EFV	↓ atovaquone AUC 75% ↓ proguanil AUC 43%	No dosage recommendation. Consider alternative drug for malaria prophylaxis, if possible.
<b>Antimycobacterials</b>			
<b>Bedaquiline</b>	EFV, NVP	↔ bedaquiline AUC	No dosage adjustment necessary.
<b>Clarithromycin</b>	EFV	clarithromycin AUC ↓ 39%	Monitor for effectiveness or consider alternative agent, such as azithromycin, for MAC prophylaxis and treatment.
	ETR	clarithromycin AUC ↓ 39% ETR AUC ↑ 42%	Consider alternative agent, such as azithromycin, for MAC prophylaxis and treatment.
	NVP	clarithromycin AUC ↓ 31%	Monitor for effectiveness or use alternative agent, such as azithromycin, for MAC prophylaxis and treatment.
	RPV	↔ clarithromycin expected ↑ RPV possible	Consider alternative macrolide, such as azithromycin, for MAC prophylaxis and treatment.

**Table 18b. Drug Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors<sup>a</sup> and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 4 of 7)**

Concomitant Drug Class/Name	NNRTI <sup>a</sup>	Effect on NNRTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Rifabutin	EFV	rifabutin ↓ 38%	Dose: rifabutin 450–600 mg once daily or 600 mg 3 times a week if EFV is not co-administered with a PI.
	ETR	rifabutin and metabolite AUC ↓ 17% ETR AUC ↓ 37%	<b>If ETR is used with an RTV-boosted PI, rifabutin should not be co-administered.</b>  Dose: rifabutin 300 mg once daily <b>if</b> ETR is not co-administered with an RTV-boosted PI.
	NVP	rifabutin AUC ↑ 17% and metabolite AUC ↑ 24% NVP C <sub>min</sub> ↓ 16%	No dosage adjustment necessary. Use with caution.
	RPV	RPV AUC ↓ 46%	<b>Contraindicated. Do not co-administer.</b>
Rifampin	EFV	EFV AUC ↓ 26%	Maintain EFV dose at 600 mg once daily and monitor for virologic response. Consider therapeutic drug monitoring.  Some clinicians suggest EFV 800 mg dose in patients who weigh more than 60 kg.
	ETR	Significant ↓ ETR possible	<b>Do not co-administer.</b>
	NVP	NVP ↓ 20% to 58%	<b>Do not co-administer.</b>
	RPV	RPV AUC ↓ 80%	<b>Contraindicated. Do not co-administer.</b>
Rifapentine	EFV, ETR, NVP, RPV	↓ NNRTI expected	<b>Do not co-administer.</b>
<b>Benzodiazepines</b>			
Alprazolam	EFV, ETR, NVP, RPV	No data	Monitor for therapeutic effectiveness of alprazolam.
Diazepam	ETR	↑ diazepam possible	Decreased dose of diazepam may be necessary.
Lorazepam	EFV	lorazepam C <sub>max</sub> ↑ 16%, AUC ↔	No dosage adjustment necessary.
Midazolam	EFV	Significant ↑ midazolam expected	<b>Do not co-administer with oral midazolam.</b>  Parenteral midazolam can be used with caution as a single dose and can be given in a monitored situation for procedural sedation.
Triazolam	EFV	Significant ↑ triazolam expected	<b>Do not co-administer.</b>
<b>Cardiac Medications</b>			
Dihydropyridine Calcium Channel Blockers	EFV, NVP	↓ CCBs possible	Titrate CCB dose based on clinical response.
Diltiazem Verapamil	EFV	diltiazem AUC ↓ 69% ↓ verapamil possible	Titrate diltiazem or verapamil dose based on clinical response.
	NVP	↓ diltiazem or verapamil possible	
<b>Corticosteroids</b>			
Dexamethasone	EFV, ETR, NVP	↓ EFV, ETR, NVP possible	Consider alternative corticosteroid for long-term use. If dexamethasone is used with NNRTI, monitor virologic response.
	RPV	Significant ↓ RPV possible	<b>Contraindicated with more than a single dose of dexamethasone.</b>

**Table 18b. Drug Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors<sup>a</sup> and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 5 of 7)**

Concomitant Drug Class/Name	NNRTI <sup>a</sup>	Effect on NNRTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
<b>Hepatitis C NS3/4A—PIs</b>			
<b>Boceprevir</b>	EFV	EFV AUC ↑ 20% boceprevir AUC ↓ 19%, C <sub>min</sub> ↓ 44%	<b>Co-administration is not recommended.</b>
	ETR	ETR AUC ↓ 23% boceprevir AUC, C <sub>max</sub> ↑ 10%	No dosage adjustment necessary.
<b>Simeprevir</b>	EFV	Simeprevir AUC ↓ 71%, C <sub>min</sub> ↓ 91% EFV ↔	<b>Co-administration is not recommended.</b>
	ETR, NVP	↓ simeprevir expected	<b>Co-administration is not recommended.</b>
	RPV	Simeprevir ↔ and RPV ↔	No dosage adjustment necessary.
<b>Telaprevir</b>	EFV	EFV AUC ↔ telaprevir AUC ↓ 26%, C <sub>min</sub> ↓ 47% <u>With TDE:</u> • EFV AUC ↓ 15% to 18% • Telaprevir AUC ↓ 18% to 20%	Increase telaprevir dose to 1125 mg q8h.
	ETR	ETR AUC ↔ telaprevir AUC ↓ 16%, C <sub>min</sub> ↓ 25%	No dosage recommendation.
<b>Herbal Products</b>			
<b>St. John's Wort</b>	EFV, ETR, NVP, RPV	↓ NNRTI	<b>Do not co-administer.</b>
<b>Hormonal Contraceptives</b>			
<b>Hormonal Contraceptives</b>	EFV	ethinyl estradiol ↔ levonorgestrel AUC ↓ 83% norelgestromin AUC ↓ 64% ↓ etonogestrel (implant) possible	Use alternative or additional contraceptive methods. Norelgestromin and levonorgestrel are active metabolites of norgestimate.
	ETR	ethinyl estradiol AUC ↑ 22% norethindrone: no significant effect	No dosage adjustment necessary.
	NVP	ethinyl estradiol AUC ↓ 20% norethindrone AUC ↓ 19%	Use alternative or additional contraceptive methods.
		DMPA: no significant change	No dosage adjustment necessary.
	RPV	ethinyl estradiol AUC ↑ 14% norethindrone: no significant change	No dosage adjustment necessary.
<b>Levonorgestrel (for emergency contraception)</b>	EFV	levonorgestrel AUC ↓ 58%	Effectiveness of emergency post-coital contraception may be diminished.

**Table 18b. Drug Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors<sup>a</sup> and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 6 of 7)**

Concomitant Drug Class/Name	NNRTI <sup>a</sup>	Effect on NNRTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
<b>HMG-CoA Reductase Inhibitors</b>			
<b>Atorvastatin</b>	EFV, ETR	atorvastatin AUC ↓ 32% to 43%	Adjust atorvastatin according to lipid responses, not to exceed the maximum recommended dose.
	RPV	atorvastatin AUC ↔ atorvastatin metabolites ↑	No dosage adjustment necessary.
<b>Fluvastatin</b>	ETR	↑ fluvastatin possible	Dose adjustments for fluvastatin may be necessary.
<b>Lovastatin Simvastatin</b>	EFV	simvastatin AUC ↓ 68%	Adjust simvastatin dose according to lipid responses, not to exceed the maximum recommended dose. If EFV used with RTV-boosted PI, simvastatin and lovastatin should be avoided.
	ETR, NVP	↓ lovastatin possible ↓ simvastatin possible	Adjust lovastatin or simvastatin dose according to lipid responses, not to exceed the maximum recommended dose. If ETR or NVP used with RTV-boosted PI, simvastatin and lovastatin should be avoided.
<b>Pitavastatin</b>	EFV	pitavastatin AUC ↓ 11%, C <sub>max</sub> ↑ 20%	No dosage adjustment necessary.
	ETR, NVP, RPV	No data	No significant effect expected. No dosage adjustment necessary.
<b>Pravastatin Rosuvastatin</b>	EFV	pravastatin AUC ↓ 44% rosuvastatin: no data	Adjust statin dose according to lipid responses, not to exceed the maximum recommended dose.
	ETR	No significant effect expected	No dosage adjustment necessary.
<b>Immunosuppressants</b>			
<b>Cyclosporine Sirolimus Tacrolimus</b>	EFV, ETR, NVP	↓ immunosuppressant possible	Increase in immunosuppressant dose may be necessary. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with specialist as necessary.
<b>Narcotics/Treatment for Opioid Dependence</b>			
<b>Buprenorphine</b>	EFV	buprenorphine AUC ↓ 50% norbuprenorphine <sup>b</sup> AUC ↓ 71%	No dosage adjustment recommended; monitor for withdrawal symptoms.
	ETR	buprenorphine AUC ↓ 25%	No dosage adjustment necessary.
	NVP	No significant effect	No dosage adjustment necessary.
<b>Methadone</b>	EFV	methadone AUC ↓ 52%	Opioid withdrawal common; increased methadone dose often necessary.
	ETR	No significant effect	No dosage adjustment necessary.
	NVP	methadone AUC ↓ 37% to 51% NVP: no significant effect	Opioid withdrawal common; increased methadone dose often necessary.
	RPV	R-methadone <sup>c</sup> AUC ↓ 16%	No dosage adjustment necessary, but monitor for withdrawal symptoms.

**Table 18b. Drug Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors<sup>a</sup> and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 7 of 7)**

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

<sup>a</sup> Approved dose for RPV is 25 mg once daily. Most PK interaction studies were performed using 75 to 150 mg per dose.

<sup>b</sup> Norbuprenorphine is an active metabolite of buprenorphine.

<sup>c</sup> R-methadone is the active form of methadone.

**Key to Acronyms:** ARV = antiretroviral; AUC = area under the curve; BID = twice daily; C<sub>max</sub> = maximum plasma concentration; C<sub>min</sub> = minimum plasma concentration; **DHA = dihydroartemisinin**; DLV = delavirdine; DMPA = depot medroxyprogesterone acetate; EFV = efavirenz; ETR = etravirine; FDA = Food and Drug Administration; INR = international normalized ratio; MAC = *Mycobacterium avium* complex; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; OH-clarithromycin = active metabolite of clarithromycin; PDE5 = phosphodiesterase type 5; PI = protease inhibitor; PPI = proton pump inhibitor; RPV = rilpivirine; RTV = ritonavir; TDF = tenofovir disoproxil fumarate

**Table 18c. Drug Interactions between Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Including Antiretroviral Agents) (Last updated May 1, 2014; last reviewed May 1, 2014) (page 1 of 2)**

Concomitant Drug Class/Name	NRTI	Effect on NRTI or Concomitant Drug Concentrations	Dosage Recommendations and Clinical Comments
<b>Non-ARV—Antivirals</b>			
Adefovir	TDF	No data	<b>Do not co-administer.</b> Serum concentrations of TDF and/or other renally eliminated drugs may be increased.
Boceprevir	TDF	No significant effect	No dose adjustment necessary.
Ganciclovir	TDF	No data	Serum concentrations of these drugs and/or TDF may be increased. Monitor for dose-related toxicities.
Valganciclovir	ZDV	No significant effect	Potential increase in hematologic toxicities
Ribavirin	ddl	↑ intracellular ddl	<b>Contraindicated. Do not co-administer.</b> Fatal hepatic failure and other ddl-related toxicities have been reported with co-administration.
	ZDV	Ribavirin inhibits phosphorylation of ZDV.	Avoid co-administration if possible, or closely monitor HIV virologic response and possible hematologic toxicities.
Simeprevir	TDF	No significant PK effects	No dose adjustment necessary.
Telaprevir	TDF	TDF AUC ↑ 30%, C <sub>min</sub> ↑ 6% to 41%	Monitor for TDF-associated toxicity.
<b>INSTIs</b>			
DTG	TDF	TDF AUC ↑ 12%, C <sub>min</sub> ↑ 19% DTG ↔	No dosage adjustment necessary.
RAL	TDF	RAL AUC ↑ 49%	No dosage adjustment necessary.
<b>Narcotics/Treatment for Opioid Dependence</b>			
Buprenorphine	3TC, ddl, TDF, ZDV	No significant effect	No dosage adjustment necessary.
Methadone	ABC	methadone clearance ↑ 22%	No dosage adjustment necessary.
	d4T	d4T AUC ↓ 23%	No dosage adjustment necessary.
	ZDV	ZDV AUC ↑ 29% to 43%	Monitor for ZDV-related adverse effects.
<b>NRTIs</b>			
ddl	d4T	No significant PK interaction	<b>Do not co-administer.</b> Additive toxicities of peripheral neuropathy, lactic acidosis, and pancreatitis seen with this combination.
	TDF	ddl-EC AUC and C <sub>max</sub> ↑ 48% to 60%	<b>Avoid co-administration.</b>
<b>Other</b>			
Allopurinol	ddl	ddl AUC ↑ 113% <u>In Patients with Renal Impairment:</u> • ddl AUC ↑ 312%	<b>Contraindicated.</b> Potential for increased ddl-associated toxicities.
Atovaquone	ZDV	ZDV AUC ↑ 31%	Monitor for ZDV-related adverse effects.

**Table 18c. Drug Interactions between Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Including Antiretroviral Agents) (Last updated May 1, 2014; last reviewed May 1, 2014) (page 2 of 2)**

Concomitant Drug Class/Name	NRTI	Effect on NRTI or Concomitant Drug Concentrations	Dosage Recommendations and Clinical Comments
<b>PIs</b>			
<b>ATV</b>	ddl	With ddl-EC Plus ATV (with Food): • ddl AUC ↓ 34% • ATV no change	Administer ATV with food 2 hours before or 1 hour after ddl.
	TDF	ATV AUC ↓ 25%, C <sub>min</sub> ↓ 23% to 40% (higher C <sub>min</sub> with RTV than without RTV) TDF AUC ↑ 24% to 37%	Dose: ATV/r 300/100 mg daily co-administered with TDF 300 mg daily. Avoid concomitant use without RTV. If using TDF and H2 receptor antagonist in ART-experienced patients, use ATV/r 400 mg/100 mg daily. Monitor for TDF-associated toxicity.
	ZDV	ZDV C <sub>min</sub> ↓ 30%, no change in AUC	Clinical significance unknown.
<b>DRV/r</b>	TDF	TDF AUC ↑ 22%, C <sub>min</sub> ↑ 37%	Clinical significance unknown. Monitor for TDF toxicity.
<b>LPV/r</b>	TDF	LPV/r AUC ↓ 15% TDF AUC ↑ 34%	Clinical significance unknown. Monitor for TDF toxicity.
<b>TPV/r</b>	ABC	ABC AUC ↓ 35% to 44%	Appropriate doses for this combination have not been established.
	ddl	ddl-EC AUC ↔ and C <sub>min</sub> ↓ 34% TPV/r ↔	Separate doses by at least 2 hours.
	TDF	TDF AUC ↔ TPV/r AUC ↓ 9%–18%, C <sub>min</sub> ↓ 12% to 21%	No dosage adjustment necessary.
	ZDV	ZDV AUC ↓ 35% TPV/r AUC ↓ 31% to 43%	Appropriate doses for this combination have not been established.

**Key to Acronyms:** 3TC = lamivudine; ABC = abacavir; ART = antiretroviral; ARV = antiretroviral; ATV = atazanavir; ATV/r = ritonavir-boosted atazanavir; AUC = area under the curve; C<sub>max</sub> = maximum plasma concentration; C<sub>min</sub> = minimum plasma concentration; d4T = stavudine; ddl = didanosine; DRV/r = ritonavir-boosted darunavir; EC = enteric coated; LPV/r = ritonavir-boosted lopinavir; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PK = pharmacokinetic; RAL = raltegravir; RTV = ritonavir; TDF = tenofovir disoproxil fumarate; TPV/r = ritonavir-boosted tipranavir; ZDV = zidovudine

**Table 18d. Drug Interactions between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 1 of 8)**

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
<b>Acid Reducers</b>			
<b>Aluminium, Magnesium +/- Calcium Containing Antacids</b>  Please refer to the Miscellaneous Interactions section below for recommendations on use with other polyvalent cation products (e.g., iron, calcium supplements, multivitamins).	DTG	DTG AUC ↓ 74% if given simultaneously; DTG AUC ↓ 26% if given 2 hours before antacid	Give DTG at least 2 hours before or at least 6 hours after medications containing polyvalent cations.
	EVG/cobi/TDF/FTC	EVG AUC ↓ 40% to 50% if given simultaneously, ↓ 15% to 20% if given 2 hours before or after antacid; ↔ with 4-hour interval	Separate EVG/cobi/FTC/TDF and antacid administration by more than 2 hours.
	RAL	<u>Al-Mg Hydroxide Antacid:</u> • RAL C <sub>min</sub> ↓ 54% to 63% if given simultaneously or 2 hours before or after antacid  <u>CaCO<sub>3</sub> Antacid:</u> • RAL AUC ↓ 54%, C <sub>min</sub> ↓ 32%	<b>Do not co-administer RAL and Al-Mg hydroxide antacids either simultaneously or within 2 hours.</b>  No dosing separation necessary when co-administering RAL and CaCO <sub>3</sub> antacids.
<b>H2-Receptor Antagonists</b>	EVG/cobi/TDF/FTC	No significant effect	No dosage adjustment necessary.
<b>Proton Pump Inhibitors</b>	DTG	No significant effect	No dosage adjustment necessary.
	EVG/cobi/TDF/FTC	No significant effect	No dosage adjustment necessary.
	RAL	RAL AUC ↑ 212%, C <sub>min</sub> ↑ 46%	No dosage adjustment necessary.
<b>Anticoagulants</b>			
<b>Warfarin</b>	EVG/cobi/TDF/FTC	No data, but warfarin levels may be affected	Monitor INR and adjust warfarin dose accordingly.
<b>Anticonvulsants</b>			
<b>Carbamazepine</b>	DTG	↓ DTG possible	Consider alternative anticonvulsant.
<b>Oxcarbazepine</b>	EVG/cobi/TDF/FTC	↑ carbamazepine possible	Consider alternative anticonvulsant.
<b>Phenobarbital</b>		↓ EVG possible	
<b>Phenytoin</b>		↓ cobi possible	
<b>Ethosuximide</b>	EVG/cobi/TDF/FTC	↑ ethosuximide possible	Clinically monitor for ethosuximide toxicities.
<b>Antidepressants</b>			
<b>SSRIs</b>	EVG/cobi/TDF/FTC	↑ SSRI possible	Initiate with lowest dose of SSRI and titrate dose carefully based on antidepressant response.
<b>TCA's</b> Amitriptyline Desipramine Imipramine Nortriptyline	EVG/cobi/TDF/FTC	Desipramine AUC ↑ 65%	Initiate with lowest dose and titrate dose of TCA carefully.
<b>Trazodone</b>	EVG/cobi/TDF/FTC	↑ trazodone possible	Initiate with lowest dose and titrate dose of trazodone carefully.

**Table 18d. Drug Interactions between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 2 of 8)**

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
<b>Antifungals</b>			
<b>Itraconazole</b>	EVG/cobi/TDF/FTC	↑ itraconazole expected ↑ EVG and cobi possible	Consider monitoring itraconazole level to guide dosage adjustments. High doses (>200 mg/day) are not recommended unless dose is guided by itraconazole levels.
<b>Posaconazole</b>	EVG/cobi/TDF/FTC	↑ EVG and cobi possible ↑ posaconazole possible	If co-administered, monitor posaconazole concentrations
<b>Voriconazole</b>	EVG/cobi/TDF/FTC	↑ voriconazole expected ↑ EVG and cobi possible	Risk/benefit ratio should be assessed to justify use of voriconazole. If administered, consider monitoring voriconazole level. Adjust dose accordingly.
<b>Antimycobacterials</b>			
<b>Clarithromycin</b>	EVG/cobi/TDF/FTC	↑ clarithromycin possible ↑ cobi possible	<p><u>CrCl ≥60 mL/min:</u></p> <ul style="list-style-type: none"> <li>• No dose adjustment is necessary.</li> </ul> <p><u>CrCl 50–60 mL/min:</u></p> <ul style="list-style-type: none"> <li>• Reduce clarithromycin dose by 50%.</li> </ul> <p><u>CrCl &lt;50 mL/min:</u></p> <ul style="list-style-type: none"> <li>• EVG/cobi/TDF/FTC is not recommended.</li> </ul>
<b>Rifabutin</b>	<b>DTG</b>	<b>Rifabutin (300 mg once daily):</b> • DTG AUC ↔, C <sub>min</sub> ↓ 30%	No dosage adjustment necessary.
	EVG/cobi/TDF/FTC	Compared with rifabutin (300 mg daily) administered alone, when <b>rifabutin (150 mg every other day)</b> administered with EVG/cobi/TDF/FTC, no significant change in rifabutin AUC;  For 25-O-desacetyl-rifabutin, AUC ↑ 625%  EVG AUC ↓ 21%, C <sub>min</sub> ↓ 67%	<b>Do not co-administer.</b>
	<b>RAL</b>	RAL AUC ↑ 19%, C <sub>min</sub> ↓ 20%	No dosage adjustment necessary.

**Table 18d. Drug Interactions between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 3 of 8)**

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
<b>Antimycobacterials, continued</b>			
Rifampin	DTG	<p><u>Rifampin with DTG 50 mg BID Compared with DTG 50 mg BID Alone:</u></p> <ul style="list-style-type: none"> <li>• DTG AUC ↓ 54%, C<sub>min</sub> ↓ 72%</li> </ul> <p><u>Rifampin with DTG 50 mg BID Compared with DTG 50 mg Once Daily Alone:</u></p> <ul style="list-style-type: none"> <li>• DTG AUC ↑ 33%, C<sub>min</sub> ↑ 22%</li> </ul>	<p>Dose: DTG 50 mg BID (instead of 50 mg once daily) for patients without suspected or documented INSTI mutation.</p> <p><b>Avoid concomitant use in patients with certain suspected or determined INSTI-associated resistance substitutions. Consider using rifabutin.</b></p>
	EVG/cobi/TDF/FTC	Significant ↓ EVG and cobi expected	<b>Do not co-administer.</b>
	RAL	<p><u>RAL 400 mg:</u></p> <ul style="list-style-type: none"> <li>• RAL AUC ↓ 40%, C<sub>min</sub> ↓ 61%</li> </ul> <p><u>Compared with RAL 400 mg BID Alone. Rifampin with RAL 800 mg BID:</u></p> <ul style="list-style-type: none"> <li>• RAL AUC ↑ 27%, C<sub>min</sub> ↓ 53%</li> </ul>	<p>Dose: RAL 800 mg BID</p> <p>Monitor closely for virologic response or consider using rifabutin as an alternative rifamycin.</p>
Rifapentine	EVG/cobi/TDF/FTC	Significant ↓ EVG and cobi expected	<b>Do not co-administer.</b>
<b>Benzodiazepines</b>			
Clonazepam Clorazepate Diazepam Eszazolam Flurazepam	EVG/cobi/TDF/FTC	↑ benzodiazepines possible	<p>Dose reduction of benzodiazepine may be necessary. Initiate with low dose and clinically monitor.</p> <p>Consider alternative benzodiazepines to diazepam, such as lorazepam, oxazepam, or temazepam.</p>
Midazolam Triazolam	DTG	<p><u>DTG 25 mg:</u></p> <ul style="list-style-type: none"> <li>• midazolam AUC ↔</li> </ul>	No dosage adjustment necessary.
	EVG/cobi/TDF/FTC	<p>↑ midazolam expected</p> <p>↑ triazolam expected</p>	<p><b>Do not co-administer triazolam or oral midazolam and EVG/cobi/TDF/FTC.</b></p> <p>Parenteral midazolam can be used with caution in a closely monitored setting. Consider dose reduction, especially if more than one dose is administered.</p>
<b>Cardiac Medications</b>			
<p><b>Anti-Arrhythmics</b></p> <p>Amiodarone, bepridil, digoxin, disopyramide, dronedarone, flecainide, systemic lidocaine, mexilitine, propafenone, quinidine</p>	EVG/cobi/TDF/FTC	<p>↑ anti-arrhythmics possible</p> <p>digoxin C<sub>max</sub> ↑ 41%, AUC no significant change</p>	Use anti-arrhythmics with caution. Therapeutic drug monitoring, if available, is recommended for anti-arrhythmics.

**Table 18d. Drug Interactions between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 4 of 8)**

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
<b>Cardiac Medications, continued</b>			
<b>Bosentan</b>	EVG/cobi/TDF/FTC	↑ bosentan possible	<u>In Patients on EVG/cobi/FTC/TDF ≥10 Days:</u> <ul style="list-style-type: none"> <li>• Start bosentan at 62.5 mg once daily or every other day based on individual tolerability.</li> </ul> <u>In Patients on Bosentan who Require EVG/cobi/FTC/TDF:</u> <ul style="list-style-type: none"> <li>• Stop bosentan ≥36 hours before EVG/cobi/FTC/TDF initiation. After at least 10 days following initiation of EVG/cobi/FTC/TDF, resume bosentan at 62.5 mg once daily or every other day based on individual tolerability.</li> </ul>
<b>Beta-blockers</b>	EVG/cobi/TDF/FTC	↑ beta-blockers possible	Adjust beta-blockers according to clinical response. Beta-blocker dose may need to be decreased.  Some beta-blockers (e.g., metoprolol, timolol) are metabolized via CYP450 pathway. Consider using other beta-blockers (e.g., atenolol, labetalol, nadolol, sotalol) as these agents are not metabolized by CYP450 enzymes.
<b>Dofetilide</b>	DTG	↑ dofetilide expected	<b>Do not co-administer.</b>
<b>Dihydropyridine and Non-Dihydropyridine CCBs</b>	EVG/cobi/TDF/FTC	↑ CCBs possible	Co-administer with caution. Monitor for CCB efficacy and toxicities.
<b>Corticosteroids</b>			
<b>Dexamethasone</b>	EVG/cobi/TDF/FTC	↓ EVG and cobi possible	Co-administer with caution and monitor HIV virologic response.
<b>Fluticasone</b> Inhaled/Intranasal	EVG/cobi/TDF/FTC	↑ fluticasone possible	Co-administration may result in adrenal insufficiency, including Cushing's syndrome. Consider alternative therapy (e.g., beclomethasone), particularly for long-term use.
<b>Methylprednisolone, Prednisolone, Triamcinolone</b> Local injections, including intra-articular, epidural, intra-orbital	EVG/cobi/TDF/FTC	↑ glucocorticoids expected	Co-administration may result in adrenal insufficiency, including Cushing's syndrome. <b>Do not co-administer.</b>  Consider alternative non-steroidal therapies. If intra-articular corticosteroid therapy required, change to alternative non-CYP3A-modulating ART (e.g., RAL, DTG).
<b>Hepatitis C NS3/4A—PIs</b>			
<b>Boceprevir</b>	DTG	DTG AUC ↔	No dosage adjustment necessary.
	EVG/cobi/TDF/FTC	No data	<b>Do not co-administer.</b>
	RAL	No significant effect	No dosage adjustment necessary.

**Table 18d. Drug Interactions between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 5 of 8)**

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
<b>Hepatitis C NS3/4A—PIs, continued</b>			
Simeprevir	EVG/cobi/TDF/FTC	↑ simeprevir expected	<b>Co-administration is not recommended.</b>
	RAL	No significant effect	No dosage adjustment necessary.
Telaprevir	DTG	DTG AUC ↑ 25%	No dosage adjustment necessary.
	EVG/cobi/TDF/FTC	EVG AUC ↓ 31%, C <sub>min</sub> ↑ 29% Telaprevir AUC ↔	No dosage adjustment necessary.
	RAL	RAL AUC ↑ 31% Telaprevir ↔	No dosage adjustment necessary.
<b>Herbal Products</b>			
St. John's Wort	DTG	↓ DTG possible	<b>Do not co-administer.</b>
<b>Hormonal Contraceptives</b>			
Hormonal Contraceptives	RAL	No clinically significant effect	Safe to use in combination
Norgestimate/ethinyl estradiol	DTG	No significant effect	No dosage adjustment necessary.
	EVG/cobi/TDF/FTC	Norgestimate AUC, C <sub>max</sub> , C <sub>min</sub> ↑ >2-fold Ethinyl estradiol AUC ↓ 25%, C <sub>min</sub> ↓ 44%	The effects of increases in progestin (norgestimate) are not fully known and can include insulin resistance, dyslipidemia, acne, and venous thrombosis. Weigh the risks and benefits of the drug, and consider alternative contraceptive method.
<b>HMG-CoA Reductase Inhibitors</b>			
Atorvastatin	EVG/cobi/TDF/FTC	↑ atorvastatin possible	Titrate statin dose slowly and use the lowest dose possible.
Lovastatin	EVG/cobi/TDF/FTC	Significant ↑ lovastatin expected	<b>Contraindicated. Do not co-administer.</b>
Pitavastatin Pravastatin	EVG/cobi/TDF/FTC	No data	No dosage recommendation
Rosuvastatin	EVG/cobi/TDF/FTC	Rosuvastatin AUC ↑ 38%, C <sub>max</sub> ↑ 89%	Titrate statin dose slowly and use the lowest dose possible.
Simvastatin	EVG/cobi/TDF/FTC	Significant ↑ simvastatin expected	<b>Contraindicated. Do not co-administer.</b>
<b>Immunosuppressants</b>			
Cyclosporine Sirolimus Tacrolimus	EVG/cobi/TDF/FTC	↑ immunosuppressant possible	Initiate with an adjusted immunosuppressant dose to account for potential increased concentration and monitor for toxicities. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with specialist as necessary.

**Table 18d. Drug Interactions between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 6 of 8)**

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
<b>Narcotics/Treatment for Opioid Dependence</b>			
<b>Buprenorphine</b>	EVG/cobi/TDF/FTC	Buprenorphine: AUC ↑ 35%, C <sub>max</sub> ↑ 12%, C <sub>min</sub> ↑ 66% Norbuprenorphine: AUC ↑ 42%, C <sub>max</sub> ↑ 24%, C <sub>min</sub> ↑ 57%	No dosage adjustment necessary. Clinical monitoring is recommended.
	RAL	No significant effect	No dosage adjustment necessary.
<b>Methadone</b>	<b>DTG</b>	<b>No significant effect</b>	<b>No dosage adjustment necessary.</b>
	EVG/cobi/TDF/FTC	No significant effect	No dosage adjustment necessary.
	RAL	No significant effect	No dosage adjustment necessary.
<b>Neuroleptics</b>			
<b>Perphenazine</b> <b>Risperidone</b> <b>Thioridazine</b>	EVG/cobi/TDF/FTC	↑ neuroleptic possible	Initiate neuroleptic at a low dose. Decrease in neuroleptic dose may be necessary.
<b>PDE5 Inhibitors</b>			
<b>Avanafil</b>	EVG/cobi/TDF/FTC	No data	<b>Co-administration is not recommended.</b>
<b>Sildenafil</b>	EVG/cobi/TDF/FTC	↑ sildenafil expected	<u>For Treatment of Erectile Dysfunction:</u> • Start with sildenafil 25 mg every 48 hours and monitor for adverse effects of sildenafil.  <u>For treatment of PAH:</u> • <b>Contraindicated</b>
<b>Tadalafil</b>	EVG/cobi/TDF/FTC	↑ tadalafil expected	<u>For Treatment of Erectile Dysfunction:</u> • Start with tadalafil 5-mg dose and do not exceed a single dose of 10 mg every 72 hours. Monitor for adverse effects of tadalafil.  <u>For Treatment of PAH</u> <i>In Patients on EVG/cobi/TDF/FTC &gt;7 Days:</i> • Start with tadalafil 20 mg once daily and increase to 40 mg once daily based on tolerability.  <i>In Patients on Tadalafil who Require EVG/cobi/TDF/FTC:</i> • Stop tadalafil ≥24 hours before EVG/cobi/TDF/FTC initiation. Seven days after EVG/cobi/TDF/FTC initiation restart tadalafil at 20 mg once daily, and increase to 40 mg once daily based on tolerability.

**Table 18d. Drug Interactions between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 7 of 8)**

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
<b>PDE5 Inhibitors, continued</b>			
Vardenafil	EVG/cobi/TDF/FTC	↑ vardenafil expected	Start with vardenafil 2.5 mg every 72 hours and monitor for adverse effects of vardenafil.
<b>Sedatives/Hypnotics</b>			
Buspirone	EVG/cobi/TDF/FTC	↑ buspirone possible	Initiate buspirone at a low dose. Dose reduction may be necessary.
Zolpidem	EVG/cobi/TDF/FTC	↑ zolpidem possible	Initiate zolpidem at a low dose. Dose reduction may be necessary.
<b>Miscellaneous Interactions</b>			
Colchicine	EVG/cobi/TDF/FTC	↑ colchicine expected	<p><b>Do not co-administer in patients with hepatic or renal impairment.</b></p> <p><u>For Treatment of Gout Flares:</u></p> <ul style="list-style-type: none"> <li>Colchicine 0.6 mg for 1 dose, followed by 0.3 mg 1 hour later. Do not repeat dose for at least 3 days.</li> </ul> <p><u>For Prophylaxis of Gout Flares:</u></p> <ul style="list-style-type: none"> <li>If original regimen was colchicine 0.6 mg BID, the regimen should be decreased to 0.3 mg once daily. If regimen was 0.6 mg once daily, the regimen should be decreased to 0.3 mg every other day.</li> </ul> <p><u>For Treatment of Familial Mediterranean Fever:</u></p> <ul style="list-style-type: none"> <li>Do not exceed colchicine 0.6 mg once daily or 0.3 mg BID.</li> </ul>
Metformin	DTG	↑ metformin possible	Monitor clinically when starting or stopping DTG. Dose adjustment of metformin may be necessary.
<b>Polyvalent Cations</b> Mg, Al, Fe, Ca, Zn, including multivitamins with minerals	All INSTIs	↓ INSTI possible if co-administered with these products	<p>Give INSTI at least 2 hours before or at least 6 hours after medications containing polyvalent cations, including but not limited to the following products: cation-containing antacids or laxatives; iron, calcium, or magnesium supplements; and sucralfate.</p> <p>Many oral multivitamins also contain varying amounts of polyvalent cations.</p> <p>Exception: No dosing separation necessary when co-administering RAL and CaCO<sub>3</sub> antacids.</p>

**Table 18d. Drug Interactions between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated May 1, 2014; last reviewed May 1, 2014) (page 8 of 8)**

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
<b>Miscellaneous Interactions, continued</b>			
<b>Quetiapine</b>	EVG/cobi/TDF/FTC	↑ quetiapine AUC expected.	<p><u>Initiation of Quetiapine in a Patient Receiving EVG/cobi/TDF/FTC:</u></p> <ul style="list-style-type: none"> <li>• Start quetiapine at the lowest dose and titrate up as needed. Monitor for quetiapine efficacy and adverse effects.</li> </ul> <p><u>Initiation of EVG/cobi/TDF/FTC in a Patient Receiving a Stable Dose of Quetiapine:</u></p> <ul style="list-style-type: none"> <li>• Reduce quetiapine dose to 1/6 of the original dose, and closely monitor for quetiapine efficacy and adverse effects.</li> </ul>
<b>Salmeterol</b>	EVG/cobi/TDF/FTC	↑ salmeterol possible	<b>Do not co-administer</b> because of potential increased risk of salmeterol-associated cardiovascular events.

**Key to Acronyms:** Al = aluminum; ART = antiretroviral therapy; AUC = area under the curve; BID = twice daily; Ca = calcium; CaCO<sub>3</sub> = calcium carbonate; CCB = calcium channel blocker; C<sub>max</sub> = maximum plasma concentration; C<sub>min</sub> = minimum plasma concentration; cobi = cobicistat; CrCl = creatinine clearance; DTG = dolutegravir; EVG = elvitegravir; Fe = iron; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; Mg = magnesium; PAH = pulmonary arterial hypertension; RAL = raltegravir; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic anti-depressants; TDF = tenofovir disoproxil fumarate; Zn = zinc

**Table 18e. Drug Interactions between CCR5 Antagonist and Other Drugs (Including Antiretroviral Agents) (Last updated May 1, 2014; last reviewed May 1, 2014) (page 1 of 2)**

Concomitant Drug Class/Name	CCR5 Antagonist	Effect on CCR5 Antagonist or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
<b>Anticonvulsants</b>			
Carbamazepine Phenobarbital Phenytoin	MVC	↓ MVC possible	If used without a strong CYP3A inhibitor, use MVC 600 mg BID or an alternative antiepileptic agent.
<b>Antifungals</b>			
Itraconazole	MVC	↑ MVC possible	Dose: MVC 150 mg BID
Voriconazole	MVC	↑ MVC possible	Consider dose reduction to MVC 150 mg BID
<b>Antimycobacterials</b>			
Clarithromycin	MVC	↑ MVC possible	Dose: MVC 150 mg BID
Rifabutin	MVC	↓ MVC possible	If used without a strong CYP3A inducer or inhibitor, use MVC 300 mg BID. If used with a strong CYP3A inhibitor, use MVC 150 mg BID.
Rifampin	MVC	MVC AUC ↓ 64%	<b>Co-administration is not recommended.</b> If co-administration is necessary, use MVC 600 mg BID. If co-administered with a strong CYP3A inhibitor, use MVC 300 mg BID.
Rifapentine	MVC	↓ MVC expected	<b>Do not co-administer.</b>
<b>Hepatitis C NS3/4A—PIs</b>			
Boceprevir	MVC	MVC AUC ↑ 202%	Dose: MVC 150 mg BID
Telaprevir	MVC	MVC AUC ↑ 850%	<b>Co-administration is not recommended.</b>
<b>Herbal Products</b>			
St. John's Wort	MVC	↓ MVC possible	<b>Co-administration is not recommended.</b>
<b>Hormonal Contraceptives</b>			
Hormonal Contraceptives	MVC	No significant effect on ethinyl estradiol or levonorgestrel	Safe to use in combination
<b>Antiretroviral Drugs</b>			
<b>INSTIs</b>			
EVG/cobi/TDF/FTC	MVC	↑ MVC possible	<b>Do not co-administer.</b>
RAL	MVC	RAL AUC ↓ 37% MVC AUC ↓ 21%	Dose: standard
<b>NNRTIs</b>			
EFV	MVC	MVC AUC ↓ 45%	Dose: MVC 600 mg BID

**Table 18e. Drug Interactions between CCR5 Antagonist and Other Drugs (Including Antiretroviral Agents) (Last updated May 1, 2014; last reviewed May 1, 2014) (page 2 of 2)**

Concomitant Drug Class/Name	CCR5 Antagonist	Effect on CCR5 Antagonist or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
<b>NNRTIs, continued</b>			
ETR	MVC	MVC AUC ↓ 53%	Dose: MVC 600 mg BID in the absence of a potent CYP3A inhibitor
NVP	MVC	MVC AUC ↔	<u>Without HIV PI:</u> • MVC 300 mg BID  <u>With HIV PI (except TPV/r):</u> • MVC 150 mg BID
<b>PIs</b>			
ATV +/- RTV	MVC	<u>With Unboosted ATV:</u> • MVC AUC ↑ 257%  <u>With (ATV 300 mg and RTV 100 mg) Once Daily:</u> • MVC AUC ↑ 388%	Dose: MVC 150 mg BID
DRV/r	MVC	<u>With (DRV 600 mg and RTV 100 mg) BID:</u> • MVC AUC ↑ 305%  <u>With (DRV 600 mg and RTV 100 mg) BID and ETR:</u> • MVC AUC ↑ 210%	Dose: MVC 150 mg BID
FPV +/- RTV	MVC	<u>With (FPV 700 mg plus RTV 100 mg) BID plus MVC 300 mg BID:</u> • MVC AUC ↑ 149%, C <sub>min</sub> ↑ 374%  <u>With (FPV 1400 mg plus RTV 200 mg) Once Daily and MVC 300 mg Once Daily:</u> • MVC AUC ↑ 126%, C <sub>min</sub> ↑ 80%	Dose: MVC 150 mg BID
LPV/r	MVC	MVC AUC ↑ 295%  <u>With LPV/r and EFV:</u> • MVC AUC ↑ 153%	Dose: MVC 150 mg BID
RTV	MVC	<u>With RTV 100 mg BID:</u> • MVC AUC ↑ 161%	Dose: MVC 150 mg BID
SQV/r	MVC	<u>With SQV 1000 mg and RTV 100 mg BID:</u> • MVC: AUC ↑ 877%  <u>With SQV 1000 mg and RTV 100 mg BID plus EFV:</u> • MVC AUC ↑ 400%	Dose: MVC 150 mg BID
TPV/r	MVC	<u>With TPV 500 mg and RTV 200 mg) BID:</u> • MVC AUC ↔; • No data for TPV	Dose: MVC 300 mg BID

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

**Note:** FPV is a pro-drug of APV

**Table 19a. Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors, and Protease Inhibitors<sup>a</sup> (Last updated March 27, 2012; last reviewed May 1, 2014) (Page 1 of 2)**

<sup>a</sup> DLV, IDV, and NFV are **not** included in this table. Refer to the DLV, IDV, and NFV Food and Drug Administration package inserts for information regarding drug interactions.

PIs		NNRTIs			
		EFV	ETR	NVP	RPV <sup>a</sup>
ATV +/- RTV	PK data	<p><u>With Unboosted ATV:</u></p> <ul style="list-style-type: none"> <li>• ATV: AUC ↓ 74%</li> <li>• EFV: no significant change</li> </ul> <p><u>With ATV 300 mg plus RTV 100 mg Once Daily with Food:</u></p> <ul style="list-style-type: none"> <li>• ATV concentrations similar to those with unboosted ATV without EFV</li> </ul>	<p><u>With Unboosted ATV:</u></p> <ul style="list-style-type: none"> <li>• ETR: AUC ↑ 50%, C<sub>min</sub> ↑ 58%</li> <li>• ATV: AUC ↓ 17%, C<sub>min</sub> ↓ 47%</li> </ul> <p><u>With ATV 300 mg plus RTV 100 mg Once Daily:</u></p> <ul style="list-style-type: none"> <li>• ETR: AUC and C<sub>min</sub> ↑ approximately 30%</li> <li>• ATV: AUC ↓ 14%, C<sub>min</sub> ↓ 38%</li> </ul>	<p><u>With ATV 300 mg plus RTV 100 mg Once Daily:</u></p> <ul style="list-style-type: none"> <li>• ATV: AUC ↓ 42%, C<sub>min</sub> ↓ 72%</li> <li>• NVP: AUC ↑ 25%</li> </ul>	<p><u>With Boosted and Unboosted ATV:</u></p> <ul style="list-style-type: none"> <li>• ↑ RPV possible</li> </ul>
	Dose	<p><b>Do not co-administer with unboosted ATV.</b></p> <p><u>In ART-Naive Patients:</u></p> <ul style="list-style-type: none"> <li>• (ATV 400 mg plus RTV 100 mg) once daily</li> </ul> <p><b>Do not co-administer in ART-experienced patients.</b></p>	<p><b>Do not co-administer with ATV +/- RTV.</b></p>	<p><b>Do not co-administer with ATV +/- RTV.</b></p>	Standard
DRV  Always use with RTV	PK data	<p><u>With DRV 300 mg plus RTV 100 mg BID:</u></p> <ul style="list-style-type: none"> <li>• DRV: AUC ↓ 13%, C<sub>min</sub> ↓ 31%</li> <li>• EFV: AUC ↑ 21%</li> </ul>	<p><u>ETR 100 mg BID with DRV 600 mg plus RTV 100 mg BID:</u></p> <ul style="list-style-type: none"> <li>• DRV: no significant change</li> <li>• ETR: AUC ↓ 37%, C<sub>min</sub> ↓ 49%</li> </ul>	<p><u>With DRV 400 mg plus RTV 100 mg BID:</u></p> <ul style="list-style-type: none"> <li>• DRV: AUC ↑ 24%<sup>b</sup></li> <li>• NVP: AUC ↑ 27%, C<sub>min</sub> ↑ 47%</li> </ul>	<p><u>RPV 150 mg Once Daily with DRV 800 mg plus RTV 100 mg Once Daily:</u></p> <ul style="list-style-type: none"> <li>• DRV: no significant change</li> <li>• RPV: AUC ↑ 130%, C<sub>min</sub> ↑ 178%</li> </ul>
	Dose	<p>Clinical significance unknown. Use standard doses and monitor patient closely. Consider monitoring drug levels.</p>	<p>Standard (ETR 200 mg BID)</p> <p>Safety and efficacy of this combination, despite decreased ETR concentration, have been established in a clinical trial.</p>	Standard	Standard
FPV	PK data	<p><u>With FPV 1400 mg plus RTV 200 mg Once Daily:</u></p> <ul style="list-style-type: none"> <li>• APV: C<sub>min</sub> ↓ 36%</li> </ul>	<p><u>With FPV 700 mg plus RTV 100 mg BID:</u></p> <ul style="list-style-type: none"> <li>• APV: AUC ↑ 69%, C<sub>min</sub> ↑ 77%</li> </ul>	<p><u>With Unboosted FPV 1400 mg BID:</u></p> <ul style="list-style-type: none"> <li>• APV: AUC ↓ 33%</li> <li>• NVP: AUC ↑ 29%</li> </ul> <p><u>With FPV 700 mg plus RTV 100 mg BID:</u></p> <ul style="list-style-type: none"> <li>• NVP: C<sub>min</sub> ↑ 22%</li> </ul>	<p><u>With Boosted and Unboosted FPV:</u></p> <ul style="list-style-type: none"> <li>• ↑ RPV possible</li> </ul>
	Dose	<p>FPV 1400 mg plus RTV 300 mg once daily or FPV 700 mg plus RTV 100 mg BID</p> <p>EFV standard</p>	<p><b>Do not co-administer with FPV +/- RTV.</b></p>	<p>FPV 700 mg plus RTV 100 mg BID</p> <p>NVP standard</p>	Standard

**Table 19a. Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors, and Protease Inhibitors<sup>a</sup> (Last updated March 27, 2012; last reviewed May 1, 2014) (Page 2 of 2)**

PIs		NNRTIs			
		EFV	ETR	NVP	RPV <sup>a</sup>
LPV/r	PK data	With LPV/r Tablets 500/125 mg BID <sup>c</sup> plus EFV 600 mg: • LPV levels similar to LPV/r 400/100 mg BID without EFV	With LPV/r Tablets: • ETR: AUC ↓ 35% (comparable to the decrease with DRV/r) • LPV: AUC ↓ 13%	With LPV/r Capsules: • LPV: AUC ↓ 27%, C <sub>min</sub> ↓ 51%	RPV 150 mg Once Daily with LPV/r Capsules: • LPV: no significant change • RPV: AUC ↑ 52%, C <sub>min</sub> ↑ 74%
	Dose	LPV/r tablets 500/125 mg <sup>c</sup> BID; LPV/r oral solution 533/133 mg BID  EFV standard	Standard	LPV/r tablets 500/125 mg <sup>c</sup> BID; LPV/r oral solution 533/133 mg BID  NVP standard	Standard
RTV	PK data	Refer to information for boosted PI.	Refer to information for boosted PI.	Refer to information for boosted PI.	Refer to information for boosted PI.
	Dose				
SQV Always use with RTV	PK data	With SQV 1200 mg TID: • SQV: AUC ↓ 62% • EFV: AUC ↓ 12%	With SQV 1000 mg plus RTV 100 mg BID: • SQV: AUC unchanged • ETR: AUC ↓ 33%, C <sub>min</sub> ↓ 29%  Reduced ETR levels similar to reduction with DRV/r	With 600 mg TID: • SQV: AUC ↓ 24%  • NVP: no significant change	↑ RPV possible
	Dose	SQV 1000 mg plus RTV 100 mg BID	SQV 1000 mg plus RTV 100 mg BID	Dose with SQV/r not established	Standard
TPV Always use with RTV	PK data	With TPV 500 mg plus RTV 100 mg BID: • TPV: AUC ↓ 31%, C <sub>min</sub> ↓ 42% • EFV: no significant change  With TPV 750 mg plus RTV 200 mg BID: • TPV: no significant change • EFV: no significant change	With TPV 500 mg plus RTV 200 mg BID: • ETR: AUC ↓ 76%, C <sub>min</sub> ↓ 82% • TPV: AUC ↑ 18%, C <sub>min</sub> ↑ 24%	With (TPV 250 mg plus RTV 200 mg) BID and with (TPV 750 mg plus RTV 100 mg) BID: • NVP: no significant change • TPV: no data	↑ RPV possible
	Dose	Standard	<b>Do not co-administer.</b>	Standard	Standard

<sup>a</sup> Approved dose for RPV is 25 mg once daily. Most PK interaction studies were performed using 75 mg to 150 mg RPV per dose.

<sup>b</sup> Based on between-study comparison.

<sup>c</sup> 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 Acronyms:** APV = amprenavir; ART = antiretroviral therapy; ATV = atazanavir; AUC = area under the curve; BID = twice daily; C<sub>max</sub> = maximum plasma concentration; C<sub>min</sub> = minimum plasma concentration; CYP = cytochrome P; DLV = delavirdine; DRV = darunavir; DRV/r = ritonavir-boosted darunavir; EFV = efavirenz; ETR = etravirine; FDA = Food and Drug Administration; FPV = fosamprenavir; IDV = indinavir; LPV = lopinavir; LPV/r = ritonavir-boosted lopinavir; MVC = maraviroc; NfV = nelfinavir; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; RPV = rilpivirine; RTV = ritonavir; SQV = saquinavir; SQV/r = ritonavir-boosted saquinavir; TDF: tenofovir disoproxil fumarate; TID = three times a day; TPV = tipranavir

**Table 19b. Interactions between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors (Last updated May 1, 2014; last reviewed May 1, 2014) (page 1 of 3)**

Drug Class/ARV		INSTI		
		DTG	EVG/cobi/TDF/FTC	RAL
<b>NNRTIs</b>				
EFV	PK Data	<p><u>With DTG 50 mg Once Daily:</u></p> <ul style="list-style-type: none"> <li>DTG: AUC ↓ 57%, C<sub>min</sub> ↓ 75%</li> </ul>	↑ or ↓ EVG, cobi, EFV possible	EFV: AUC ↓ 36%
	Dose	<p>DTG 50 mg BID in patients without INSTI resistance</p> <p>Consider alternative combination in patients with certain INSTI-associated resistance<sup>a</sup> or clinically suspected INSTI resistance.</p>	<b>Do not co-administer.</b>	Standard
ETR	PK Data	<p><u>With ETR 200 mg BID plus DTG 50 mg Once Daily:</u></p> <ul style="list-style-type: none"> <li>DTG: AUC ↓ 71%, C<sub>min</sub> ↓ 88%</li> </ul> <p><u>With ETR 200 mg BID plus DRV/r 600/100 mg BID plus DTG 50 mg Once Daily:</u></p> <ul style="list-style-type: none"> <li>DTG: AUC ↓ 25%, C<sub>min</sub> ↓ 37%</li> </ul> <p><u>With ETR 200 mg BID plus LPV/r 400 mg/100 mg BID plus DTG 50 mg Once Daily:</u></p> <ul style="list-style-type: none"> <li>DTG: AUC ↑ 11%, C<sub>min</sub> ↑ 28%</li> </ul>	↑ or ↓ EVG, cobi, ETR possible	<p>ETR: C<sub>min</sub> ↓ 17%</p> <p>RAL: C<sub>min</sub> ↓ 34%</p>
	Dose	<p><b>Do not co-administer ETR and DTG without concurrently administering ATV/r, DRV/r, or LPV/r.</b></p> <p><u>In Patients without INSTI Resistance:</u></p> <ul style="list-style-type: none"> <li>DTG 50 mg daily with ETR (concurrently with ATV/r, DRV/r, or LPV/r)</li> </ul> <p><u>In Patients with Certain INSTI-Associated Resistance or Clinically Suspected INSTI Resistance:</u></p> <ul style="list-style-type: none"> <li>DTG 50mg BID with ETR (concurrently with ATV/r, DRV/r, or LPV/r)</li> </ul>	<b>Do not co-administer.</b>	Standard

**Table 19b. Interactions between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors (Last updated May 1, 2014; last reviewed May 1, 2014) (page 2 of 3)**

Drug Class/ARV		INSTI		
		DTG	EVG/cobi/TDF/FTC	RAL
<b>NNRTIs</b>				
NVP	PK Data	↓ DTG possible	↑ or ↓ EVG, cobi, NVP possible	No data
	Dose	<b>Do not co-administer.</b>	<b>Do not co-administer.</b>	Standard
RPV	PK Data	With DTG 50 mg Daily: • DTG: AUC ↔, C <sub>min</sub> ↑ 22% • RPV: AUC ↔, C <sub>min</sub> ↑ 21%	↑ or ↓ EVG, cobi, RPV possible	No data
	Dose	Standard	<b>Do not co-administer.</b>	No data
<b>PIs</b>				
ATV +/- RTV	PK Data	With Unboosted ATV plus DTG 30 mg Once Daily: • DTG: AUC ↑ 91%, C <sub>min</sub> ↑ 180%  With (ATV 300 mg plus RTV 100 mg) Once Daily plus DTG 30 mg Once Daily: • DTG: AUC ↑ 62%, C <sub>min</sub> ↑ 121%	↑ or ↓ EVG, cobi, ATV possible	With unboosted ATV: • RAL: AUC ↑ 72%  With ATV 300 mg plus RTV 100 mg Once Daily: • RAL: AUC ↑ 41%
	Dose	Standard	<b>Do not co-administer.</b>	Standard
DRV Always use with RTV	PK Data	With (DRV 600 mg plus RTV 100 mg) BID plus DTG 30 mg Once Daily: • DTG: AUC ↓ 22%, C <sub>min</sub> ↓ 38%	↑ or ↓ EVG, cobi, DRV possible	With DRV 600 mg plus RTV 100 mg BID: • RAL: AUC ↓ 29% and C <sub>min</sub> ↑ 38%
	Dose	Standard  Can use either once or twice daily dosing of DRV/r without dose adjustments.	<b>Do not co-administer.</b>	Standard
FPV +/- RTV	PK Data	With (FPV 700 mg plus RTV 100 mg) BID plus DTG 50 mg Once Daily: • DTG: AUC ↓ 35%, C <sub>min</sub> ↓ 49%	↑ or ↓ EVG, cobi, FPV possible	FPV: No significant effect
	Dose	DTG 50 mg BID in patients without INSTI resistance  <b>Consider alternative combination</b> in patients with certain INSTI-associated resistance <sup>a</sup> or clinically suspected INSTI resistance.	<b>Do not co-administer.</b>	Standard

**Table 19b. Interactions between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors (Last updated May 1, 2014; last reviewed May 1, 2014) (page 3 of 3)**

Drug Class/ARV		INSTI		
		DTG	EVG/cobi/TDF/FTC	RAL
PIs, continued				
LPV/r	PK Data	With LPV/r 400 mg/100 mg BID plus DTG 30 mg Once Daily: • DTG: no significant effect	↑ or ↓ EVG, cobi, LPV possible  RTV and cobi have similar effects on CYP3A.	↓ RAL  ↔ LPV/r
	Dose	Standard  Can use either once or twice daily dosing of LPV/r without dose adjustments.	<b>Do not co-administer.</b>	Standard
RTV	PK Data	No data with RTV alone	↑ or ↓ EVG, cobi possible  RTV and cobi have similar effects on CYP3A.	With RTV 100 mg BID: • RAL: AUC ↓ 16%
	Dose	Refer to other PI/r for dosage recommendation.	<b>Do not co-administer.</b>	Standard
SQV Always use with RTV	PK Data	No data	↑ or ↓ EVG, cobi, SQV possible  RTV and cobi have similar effects on CYP3A.	No data
	Dose	No dosage recommendation	<b>Do not co-administer.</b>	Standard
TPV Always use with RTV	PK Data	With (TPV 500 mg plus RTV 200 mg) BID plus DTG 50 mg Once Daily: • DTG: AUC ↓ 59%, C <sub>min</sub> ↓ 76%	↑ or ↓ EVG, cobi, TPV possible  RTV and cobi have similar effects on CYP3A.	With TPV 500 mg plus RTV 200 mg BID: • RAL: AUC ↓ 24%
	Dose	DTG: 50 mg BID in patients without INSTI resistance  <b>Consider alternative combination</b> in patients with certain INSTI-associated resistance or clinically suspected INSTI-associated resistance substitutions. <sup>a</sup>	<b>Do not co-administer.</b>	Standard

<sup>a</sup> Refer to Tivicay product label for details.

**Key to Acronyms:** APV = amprenavir; ART = antiretroviral therapy; ATV = atazanavir; AUC = area under the curve; BID = twice daily; cobi = cobicistat; C<sub>max</sub> = maximum plasma concentration; C<sub>min</sub> = minimum plasma concentration; CYP = cytochrome P; DLV = delavirdine; DRV = darunavir; DRV/r = ritonavir-boosted darunavir; **DTG = dolutegravir**; EFV = efavirenz; EVG = elvitegravir; ETR = etravirine; FDA = Food and Drug Administration; FPV = fosamprenavir; IDV = indinavir; **INSTI = integrase strand transfer inhibitor**; LPV = lopinavir; LPV/r = ritonavir-boosted lopinavir; MVC = maraviroc; NFV = nelfinavir; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQV = saquinavir; SQV/r = ritonavir-boosted saquinavir; TDF = tenofovir disoproxil fumarate; TID = three times a day; TPV = tipranavir