



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

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

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

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

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

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

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

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

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

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

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antidepressants, Anxiolytics, and Antipsychotics (Also see Sedative/Hypnotics section below.)			
Bupropion	LPV/r	bupropion AUC ↓ 57%	Titrate bupropion dose based on clinical response.
	TPV/r	bupropion AUC ↓ 46%	
Buspirone	All PIs	↑ buspirone expected	Use a low dose of buspirone with caution and titrate buspirone dose based on clinical response.
Fluvoxamine	All PIs	↑ or ↓ PI possible	Consider alternative therapeutic agent.
Other Selective Serotonin Reuptake Inhibitors (SSRIs) (eg, citalopram, escitalopram, fluoxetine, paroxetine, sertraline)	RTV	escitalopram ↔	Titrate SSRI dose based on clinical response.
	DRV/r	paroxetine AUC ↓ 39%	
		sertraline AUC ↓ 49%	
	FPV/r	paroxetine AUC ↓ 55%	
	ATV/r, LPV/r, SQV/r, TPV/r	No data	Titrate SSRI dose using the lowest available initial or maintenance dose.
ATV/c, DRV/c	Effects unknown		
Quetiapine	All PIs	↑ quetiapine expected	<p><u>Starting quetiapine in a patient receiving a PI:</u></p> <ul style="list-style-type: none"> • Start quetiapine at the lowest dose and titrate up as needed. Monitor for quetiapine effectiveness and adverse effects. <p><u>Starting a PI in a patient receiving a stable dose of quetiapine:</u></p> <ul style="list-style-type: none"> • Reduce quetiapine dose to 1/6 of the original dose. Closely monitor for quetiapine effectiveness and adverse effects.
Other Antipsychotics (eg, perphenazine, risperidone, thioridazine)	ATV/c DRV/c, All PI/r	↑ antipsychotic possible	Titrate antipsychotic dose using the lowest initial dose, or adjust maintenance dose accordingly. Monitor for toxicities.
Trazodone	All PIs except SQV/r	RTV 200 mg BID (for 2 days) ↑ trazodone AUC 240%	Use lowest dose of trazodone and monitor for CNS and cardiovascular adverse effects.
	SQV/r	↑ trazodone expected	Contraindicated. Do not coadminister.
Tricyclic Antidepressants Amitriptyline, Desipramine, Doxepin, Imipramine, Nortriptyline	All PI/r, ATV/c, DRV/c	↑ TCA expected	Use lowest possible TCA dose and titrate based on clinical assessment and/or drug levels.

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

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

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

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

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

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

Table 19a. Drug Interactions between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 8 of 15)

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

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

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

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

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

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

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

Table 19a. Drug Interactions between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 12 of 15)

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

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

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

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

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

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

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

^a DHA is an active metabolite of artemether.

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

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

^d Norbuprenorphine is an active metabolite of buprenorphine.

^e R-methadone is the active form of methadone.

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

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

Note: FPV is a prodrug of APV.