Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV

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Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 1 of 19)

This table provides known or predicted information regarding PK interactions between PIs and non-ARV drugs. When information is available, interactions for PK-boosted (with either RTV or COBI) and unboosted ATV are listed separately. The term "All PIs" refers to both unboosted ATV and PIs boosted with either RTV or COBI, except the PIs noted below. For interactions between ARV agents and for dosing recommendations, refer to Tables 21c, 22a, and 22b.

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

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

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Alpha-Adrenergic Antagonists for Benign Prostatic Hyperplasia			
Alfuzosin	All PIs	↑ alfuzosin expected	**Contraindicated.**
Doxazosin	All PIs	↑ doxazosin possible	Initiate doxazosin at lowest dose and titrate while monitoring for clinical response/toxicity. Dose reduction may be necessary.
Tamsulosin	All PIs	↑ tamsulosin expected	**Coadministration is not recommended.** If coadministered, monitor for tamsulosin toxicities.
Terazosin	All PIs	↔ or ↑ terazosin possible	Initiate terazosin at lowest dose and titrate while monitoring for clinical response/toxicity. Dose reduction may be necessary.
Silodosin	All PIs	↑ silodosin expected	**Contraindicated.**
Acid Reducers			
Antacids	ATV, ATV/c, ATV/r	When given simultaneously, ↓ ATV expected	Give ATV at least 2 hours before or 1–2 hours after antacids or buffered medications.
	TPV/r	TPV AUC ↓ 27%	Give TPV at least 2 hours before or 1 hour after antacids.
H2 Receptor Antagonists	ATV (unboosted)	↓ ATV	H2 receptor antagonist single dose should not exceed a dose equivalent to famotidine 20 mg, and the total daily dose should not exceed a dose equivalent to famotidine 20 mg BID in PI-naive patients. Unboosted ATV plus famotidine should not be used in combination in PI-experienced patients. Give ATV at least 2 hours before and at least 10 hours after the H2 receptor antagonist.
	ATV/c, ATV/r	↓ ATV	H2 receptor antagonist dose should not exceed a dose equivalent to famotidine 40 mg BID in ART-naive patients or famotidine 20 mg BID in ART-experienced patients. Give ATV 300 mg plus (COBI 150 mg **or** RTV 100 mg) simultaneously with and/or ≥10 hours after the dose of H2 receptor antagonist. If using TDF and H2 receptor antagonist in ART-experienced patients, use ATV 400 mg plus (COBI 150 mg **or** RTV 100 mg).
	DRV/c, DRV/r, LPV/r	↔ demonstrated or expected	No dose adjustment necessary.

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 2 of 19)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers, continued			
PPIs	ATV (unboosted)	↓ ATV	**PPIs are not recommended in patients receiving unboosted ATV.** In these patients, consider alternative acid-reducing agents, RTV or COBI boosting, or alternative PIs.
	ATV/c, ATV/r	↓ ATV	PPIs should not exceed a dose equivalent to omeprazole 20 mg daily in PI-naive patients. PPIs should be administered at least 12 hours before ATV/c or ATV/r. **PPIs are not recommended in PI-experienced patients.**
	DRV/c, LPV/r	↔ expected	No dose adjustment necessary.
	DRV/r	Omeprazole AUC ↓ 42%	No dose adjustment necessary. If there is a lack of symptomatic relief, increase dose to no more than omeprazole 40 mg daily.
	TPV/r	Omeprazole AUC ↓ 70%	**Coadministration is not recommended.** If coadministration is necessary, dose increases of omeprazole may be considered based on clinical response.
Anticoagulants and Antiplatelets			
Apixaban	PI/c, PI/r	↑ apixaban expected	**Coadministration is not recommended** in patients who require apixaban 2.5 mg twice daily. In patients who require apixaban 5 mg or 10 mg twice daily, reduce apixaban dose by 50%.
Betrixaban	ATV/c, ATV/r, LPV/r	↑ betrixaban expected	Administer an initial single dose of betrixaban 80 mg followed by betrixaban 40 mg once daily.
	DRV/c, DRV/r	↔ betrixaban expected	No dose adjustment necessary.
	TPV/r	No data	No dosing recommendations available at this time. Consider alternative ARV or warfarin.
Dabigatran	ATV/c, ATV/r, LPV/r	↑ dabigatran expected With COBI 150 mg Alone: • Dabigatran AUC ↑ 110% to 127%	Dabigatran dosing recommendation depends on indication and renal function. Refer to dabigatran dosing instructions for concomitant use with P-gp inhibitors in dabigatran prescribing information.
	DRV/c, DRV/r	↔ dabigatran expected	No dose adjustment necessary.
	TPV/r	No data	No dosing recommendations available at this time. Consider alternative ARV or warfarin.
Edoxaban	ATV/c, ATV/r, LPV/r	↑ edoxaban expected	Stroke Prevention in Nonvalvular Atrial Fibrillation Indication: • No dose adjustment necessary. Deep Venous Thrombosis and Pulmonary Embolism Indication: • Administer edoxaban 30 mg once daily
	DRV/c, DRV/r	↔ edoxaban expected	No dose adjustment necessary.
	TPV/r	No data	No dosing recommendations available at this time. Consider alternative ARV or warfarin.
Rivaroxaban	PI/c, PI/r	↑ rivaroxaban expected	**Coadministration is not recommended.**
Ticagrelor	All PIs	↑ ticagrelor expected	**Coadministration is not recommended.**
Vorapaxar	All PIs	↑ vorapaxar expected	**Coadministration is not recommended.**

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticoagulants and Antiplatelets, continued			
Warfarin	PI/r	↓ warfarin possible	Monitor INR closely when stopping or starting PI/c and adjust warfarin dose accordingly. If switching between RTV and COBI, the effect of COBI on warfarin is not expected to be equivalent to RTV's effect on warfarin.
	PI/c	No data	
Anticonvulsants			
Carbamazepine	ATV (unboosted)	May ↓ PI levels substantially	**Do not coadminister.** Consider alternative anticonvulsant or ARV.
	ATV/r, LPV/r, TPV/r	↑ carbamazepine possible TPV/r ↑ carbamazepine AUC 26% May ↓ PI levels substantially	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. **Do not coadminister with LPV/r once daily.**
	DRV/r	Carbamazepine AUC ↑ 45% DRV: no significant change	Monitor anticonvulsant level and adjust dose accordingly.
	PI/c	↑ carbamazepine possible ↓ cobicistat expected ↓ PI levels expected	**Contraindicated.**
Eslicarbazepine, Oxcarbazepine	All PIs	↓ PI possible	Consider alternative anticonvulsant or ARV. If coadministration is necessary, monitor for virologic response. Consider monitoring anticonvulsant and PI concentration.
Ethosuximide	All PIs	↑ ethosuximide possible	Clinically monitor for ethosuximide toxicities.
Lamotrigine	ATV (unboosted)	Lamotrigine: no effect	No dose adjustment necessary.
	ATV/r	Lamotrigine AUC ↓ 32%	A dose increase of lamotrigine may be needed; consider monitoring lamotrigine concentration or consider alternative anticonvulsant.
	LPV/r	Lamotrigine AUC ↓ 50% LPV: no significant change	
	DRV/r, TPV/r	↓ lamotrigine possible	
	PI/c	No data	Monitor anticonvulsant level and adjust dose accordingly.
Phenobarbital	PI/c	↓ cobicistat expected ↓ PI levels expected	**Contraindicated.**
	ATV (unboosted), PI/r	May ↓ PI levels substantially	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. **Do not coadminister with LPV/r once daily or unboosted ATV.**

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 4 of 19)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticonvulsants, continued			
Phenytoin	ATV (unboosted)	May ↓ PI levels substantially	**Do not coadminister.** Consider alternative anticonvulsant or ATV/r.
	ATV/r, DRV/r, TPV/r	↓ phenytoin possible ↓ PI possible	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response.
	LPV/r	Phenytoin AUC ↓ 31% LPV/r AUC ↓ 33%	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. **Do not coadminister with LPV/r once daily.**
	PI/c	↓ cobicistat expected ↓ PI levels expected	**Contraindicated.**
Valproic Acid (VPA)	PI/c, PI/r	↓ or ↔VPA possible LPV AUC ↑ 75%	Monitor VPA levels and virologic response. Monitor for LPV-related toxicities.
Antidepressants, Anxiolytics, and Antipsychotics (also see Sedative/Hypnotics section below)			
Aripiprazole	PI/c, PI/r	↑ aripiprazole expected	Administer 25% of the usual aripiprazole dose. Titrate dose based on clinical monitoring for efficacy/toxicity. Refer to aripiprazole label for doses to use in patients who have major depressive disorder or who are known to be CYP2D6 poor metabolizers.
	ATV (unboosted)	↑ aripiprazole expected	Administer 50% of the usual aripiprazole dose. Titrate based on clinical monitoring for efficacy/toxicity. Refer to aripiprazole label for doses to use in patients who have major depressive disorder or who are known to be CYP2D6 poor metabolizers.
Brexpiprazole	PI/c, PI/r	↑ brexpiprazole expected	Administer 25% of the usual brexpiprazole dose. Titrate based on clinical monitoring for efficacy/toxicity. Refer to brexpiprazole label for doses to use in patients who have major depressive disorder or who are known to be CYP2D6 poor metabolizers.
	ATV (unboosted)	↑ brexpiprazole expected	Administer 50% of the usual brexpiprazole dose. Titrate based on clinical monitoring for efficacy/toxicity. Refer to brexpiprazole label for doses to use in patients who have major depressive disorder or who are known to be CYP2D6 poor metabolizers.
Bupropion	LPV/r	Bupropion AUC ↓ 57%	Titrate bupropion dose based on clinical response.
	TPV/r	Bupropion AUC ↓ 46%	
	ATV/r, DRV/r	↓ bupropion possible	
	PI/c	↔ bupropion expected	No dose adjustment necessary.
Buspirone	All PIs	↑ buspirone expected	Use a low dose of buspirone with caution and titrate buspirone dose based on clinical response.

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

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antifungals			
Fluconazole	PI/c, ATV/r, DRV/r, LPV/r	No significant effect observed or expected	No dose adjustment necessary.
	TPV/r	TPV AUC ↑ 50%	Fluconazole >200 mg daily is not recommended. If high-dose fluconazole is indicated, consider alternative ARV.
Isavuconazole	LPV/r	Isavuconazole AUC ↑ 96% LPV AUC ↓ 27% RTV AUC ↓ 31%	If coadministered, consider monitoring isavuconazole concentrations and toxicities and assessing virologic response.
	All PIs except LPV/r	↑ isavuconazole possible ↑ or ↓ PI possible	If coadministered, consider monitoring isavuconazole concentrations and toxicities. Monitor for PI toxicity and virologic response.
Itraconazole	All PIs	↑ itraconazole possible ↑ PI possible	Consider monitoring itraconazole level to guide dose adjustments. Doses >200 mg/day **are not recommended** with PI/r, ATV/c, or DRV/c unless dosing is guided by itraconazole levels.
Posaconazole	ATV/r	ATV AUC ↑ 146% ↑ posaconazole possible	If coadministered, monitor for PI adverse effects. Consider monitoring for posaconazole concentrations and toxicities.
	ATV	ATV AUC ↑ 268% ↑ posaconazole possible	
	ATV/c, DRV/c, DRV/r, LPV/r, TPV/r	↑ PI possible ↑ posaconazole possible	
Voriconazole	ATV (unboosted)	↑ voriconazole possible ↑ PI possible	Monitor for toxicities.
	All PI/r	RTV 100 mg BID ↓ voriconazole AUC 39%	Do not coadminister voriconazole and RTV or COBI unless benefit outweighs risk. If coadministered, consider monitoring voriconazole concentration and adjust dose accordingly.
	PI/c	Effect on voriconazole unknown	
Antihyperglycemics			
Canagliflozin	PI/r	↓ canagliflozin expected	If a patient is already tolerating canagliflozin 100 mg daily, has an eGFR >60 mL/min/1.73m^2, and requires additional glycemic control, consider increasing dose to canagliflozin 300 mg daily.
	PI/c	↓ canagliflozin possible	If used in combination, monitor glycemic control.
Saxagliptin	All PIs	↑ saxagliptin expected	Limit saxagliptin dose to 2.5 mg once daily
Dapagliflozin/ Saxagliptin	All PIs	↑ saxagliptin expected	**Do not coadminister**, as this coformulated drug contains 5 mg of saxagliptin.
Antimalarials			
Artemether/ Lumefantrine	DRV/r	Artemether AUC ↓ 16% DHA[a] AUC ↓ 18% Lumefantrine AUC ↑ 2.5-fold	Clinical significance unknown. If used, monitor closely for antimalarial efficacy and lumefantrine toxicity.
	DRV/c	↑ lumefantrine expected Effect on artemether unknown	
	LPV/r	Artemether AUC ↓ 40% DHA AUC ↓ 17% Lumefantrine AUC ↑ 470%	

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antimalarials, continued			
Artesunate/ Mefloquine	LPV/r	Dihydroartemisinin AUC ↓ 49% Mefloquine AUC ↓ 28% ↔ LPV	Clinical significance unknown. If used, monitor closely for antimalarial efficacy.
Atovaquone/ Proguanil	ATV/r, LPV/r	With ATV/r: • Atovaquone AUC ↓ 46% • Proguanil AUC ↓ 41% With LPV/r: • Atovaquone AUC ↓ 74% • Proguanil AUC ↓ 38%	No dose recommendation. Consider alternative drug for malaria prophylaxis, if possible.
Mefloquine	RTV	With RTV 200 mg BID: • RTV AUC ↓ 31%, C_{min} ↓ 43% ↔ mefloquine	Use with caution. Effect on exposure of RTV-boosted PIs is unknown.
Antimycobacterials (for treatment of *Mycobacterium tuberculosis* and nontuberculosis mycobacterial infections)			
Bedaquiline	All PIs	With LPV/r: • Bedaquiline AUC ↑ 1.9-fold With Other PI/r, ATV/c, or DRV/c: • ↑ bedaquiline possible	Clinical significance unknown. Use with caution if benefit outweighs the risk and monitor for QTc prolongation and liver function tests.
Clarithromycin	ATV (unboosted)	Clarithromycin AUC ↑ 94%	May cause QTc prolongation. Reduce clarithromycin dose by 50%. Consider alternative therapy (e.g., azithromycin).
	All PIs	↑ clarithromycin expected DRV/r ↑ clarithromycin AUC 57% LPV/r ↑ clarithromycin expected RTV 500 mg BID ↑ clarithromycin 77% TPV/r ↑ clarithromycin 19% Clarithromycin ↑ TPV 66%	Consider alternative macrolide (e.g., azithromycin). Monitor for clarithromycin-related toxicities or consider an alternative macrolide (e.g., azithromycin). Reduce clarithromycin dose by 50% in patients with CrCl 30−60 mL/min. Reduce clarithromycin dose by 75% in patients with CrCl <30 mL/min.

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 8 of 19)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antimycobacterials (for treatment of *Mycobacterium tuberculosis* and nontuberculosis mycobacterial infections), continued			
Rifabutin	ATV (unboosted)	↑ rifabutin AUC expected	Rifabutin 150 mg once daily or 300 mg three times a week. Monitor for antimycobacterial activity and consider therapeutic drug monitoring. PK data reported in this table are results from healthy volunteer studies. Lower rifabutin exposure has been reported in patients with HIV than in healthy study participants.
	ATV/r	Compared with Rifabutin (300 mg Once Daily) Alone, Rifabutin (150 mg Once Daily) plus ATV/r: • Rifabutin AUC ↑ 110% and metabolite AUC ↑ 2,101%	
	DRV/r	Compared with Rifabutin (300 mg Once Daily) Alone, Rifabutin (150 mg Every Other Day) plus DRV/r: • Rifabutin AUC ↔ and metabolite AUC ↑ 881%	
	LPV/r	Compared with Rifabutin (300 mg daily) Alone, Rifabutin (150 mg Once Daily) plus LPV/r: • Rifabutin AUC ↑ 203% and metabolite AUC ↑ 375%	
	TPV/r	Rifabutin AUC ↑ 190% and metabolite AUC ↑ 1,971%	
	PI/c	↑ rifabutin expected	
Rifampin	All PIs	↓ PI concentration by >75%	**Contraindicated.** Additional RTV does not overcome this interaction and may increase hepatotoxicity. Additional COBI is not recommended. Consider rifabutin if a rifamycin is indicated.
Rifapentine	All PIs	↓ PI expected	**Do not coadminister.**
Antipneumocystis and Antitoxoplasmosis Drug			
Atovaquone	ATV/r	↔ atovaquone	No dose adjustment necessary.
Cardiac Medications			
Amiodarone	TPV/r	↑ both amiodarone and PI possible	**Contraindicated.**
	All PIs except TPV/r	↑ both amiodarone and PI possible	Use with caution. Monitor for amiodarone toxicity and consider ECG and amiodarone drug levels.
Antiarrhythmics (e.g., disopyramide, dofetilide, lidocaine, mexiletine, propafenone)	ATV (unboosted)	↑ antiarrhythmic possible	Consider alternative antiarrhythmics or ARV. If coadministered, monitor for antiarrhythmic toxicities.
	PI/c, PI/r	↑ antiarrhythmic possible	**Do not coadminister.** Consider alternative antiarrhythmics or ARV.
Dronedarone	ATV (unboosted)	↑ dronedarone possible	**Do not coadminister.**
	PI/c, PI/r	↑ dronedarone expected	**Contraindicated.**
Flecanide	All PIs except TPV/r	↑ flecainide possible	**Do not coadminister.**
	TPV/r	↑ flecanide expected	**Contraindicated.**

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Cardiac Medications, continued			
Propafenone	All PIs except TPV/r	↑ propafenone possible	**Do not coadminister.**
	TPV/r	↑ propafenone expected	**Contraindicated.**
Quinidine	All PIs except TPV/r	↑ quinidine possible	**Do not coadminister.**
	TPV/r	↑ quinidine expected	**Contraindicated.**
Beta-Blockers (e.g., carvedilol, metoprolol, timolol)	All PIs	↑ beta-blockers possible	May need to decrease beta-blocker dose; adjust dose based on clinical response. Consider using beta-blockers that are not metabolized by CYP450 enzymes (e.g., atenolol, labetalol, nadolol, sotalol).
Bosentan	All PIs	LPV/r ↑ bosentan 48-fold (Day 4) and 5-fold (Day 10) ↓ ATV expected	**Do not coadminister bosentan and unboosted ATV.** In Patients on a PI (Other than Unboosted ATV) >10 Days: • Start bosentan at 62.5 mg once daily or every other day. In Patients on Bosentan who Require a PI (Other than Unboosted ATV): • Stop bosentan ≥36 hours before PI initiation and restart bosentan 10 days after PI initiation at 62.5 mg once daily or every other day. When Switching Between COBI and RTV: • Maintain same bosentan dose.
Calcium Channel Blockers (CCBs), Except Diltiazem	All PIs	↑ dihydropyridine possible ↑ verapamil possible	Use with caution. Titrate CCB dose and monitor closely. ECG monitoring is recommended when CCB is used with ATV.
Digoxin	PI/c , PI/r	RTV (200 mg BID) ↑ digoxin AUC 29% and ↑ half-life 43% DRV/r ↑ digoxin AUC 36% COBI ↑ digoxin C_{max} 41% and ↔ AUC	Use with caution. Monitor digoxin levels. Digoxin dose may need to be decreased. Titrate initial digoxin dose.
Diltiazem	ATV/c, ATV/r, ATV (unboosted)	Unboosted ATV ↑ diltiazem AUC 125% Greater ↑ likely with ATV/c or ATV/r	Decrease diltiazem dose by 50%. ECG monitoring is recommended.
	DRV/c, DRV/r, LPV/r, TPV/r	↑ diltiazem possible	Use with caution. Adjust diltiazem according to clinical response and toxicities.
Eplerenone	PI/c, PI/r	↑ eplerenone expected	**Contraindicated.**
Ranolazine	ATV (unboosted)	↑ ranolazine possible	**Do not coadminister.**
	PI/c, PI/r	↑ ranolazine expected	**Contraindicated.**
Ivabradine	All PIs	↑ ivabradine expected	**Contraindicated.**

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 10 of 19)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Corticosteroids			
Beclomethasone Inhaled or intranasal	DRV/r	↔ 17-BMP (active metabolite) AUC RTV 100 mg BID ↑ 17-BMP AUC 2-fold	No dose adjustment necessary.
	All PIs except DRV/r	↔ expected	No dose adjustment necessary.
Budesonide, Ciclesonide, Fluticasone, Mometasone Inhaled or intranasal	All PIs	↑ glucocorticoids possible RTV 100 mg BID ↑ fluticasone AUC 350-fold	Coadministration can result in adrenal insufficiency and Cushing's syndrome. **Do not coadminister unless potential benefits of inhaled or intranasal corticosteroid outweigh the risks of adverse effects associated with corticosteroids.** Consider an alternative corticosteroid (e.g., beclomethasone).
Betamethasone, Budesonide Systemic	All PIs	↑ glucocorticoids possible ↓ PI possible	Coadministration can result in adrenal insufficiency and Cushing's syndrome. **Do not coadminister unless potential benefits of systemic corticosteroid outweigh the risks of adverse effects associated with systemic corticosteroids.**
Dexamethasone Systemic	All PIs	↑ glucocorticoids possible ↓ PI possible	Consider alternative corticosteroid for long-term use. If coadministration is necessary, monitor virologic response to ART.
Prednisone, Prednisolone Systemic	LPV/r	↑ prednisolone AUC 31%	Coadministration may be considered if the potential benefits outweigh the risks of adverse effects associated with systemic corticosteroids. If coadministered, monitor for adrenal insufficiency, Cushing's syndrome, and other corticosteroid-associated toxicities.
	All PIs	↑ prednisolone possible	
Betamethasone, Methylprednisolone, Triamcinolone Local injections, including intra-articular, epidural, or intra-orbital	All PIs	↑ glucocorticoids expected	**Do not coadminister.** Coadministration can result in adrenal insufficiency and Cushing's syndrome.
Hepatitis C Direct-Acting Antiviral Agents			
Daclatasvir	ATV/c, ATV/r	↑ daclatasvir	Decrease daclatasvir dose to 30 mg once daily.
	ATV (unboosted), DRV/c, DRV/r, LPV/r	↔ daclatasvir	No dose adjustment necessary.
	TPV/r	No data	No dosing recommendations available at this time.
Dasabuvir plus Paritaprevir/ Ombitasvir/RTV	ATV (unboosted)	↔ ATV	ATV 300 mg alone, **without COBI or additional RTV**, should be given in the morning with dasabuvir plus paritaprevir/ombitasvir/ RTV.
	DRV	DRV C_{min} ↓ 43% to 48%	**Do not coadminister.**
	LPV/r	Paritaprevir AUC ↑ 117%	**Do not coadminister.**
	ATV/c, DRV/c, TPV/r	No data	**Do not coadminister.**

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 11 of 19)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hepatitis C Direct-Acting Antiviral Agents, continued			
Elbasvir/ Grazoprevir	ATV/r	Elbasvir AUC ↑ 4.8-fold Grazoprevir AUC ↑ 10.6-fold ATV ↔ by elbasvir ATV AUC ↑ 43% by grazoprevir	**Contraindicated.** May increase the risk of ALT elevations due to a significant increase in grazoprevir plasma concentrations caused by OATP1B1/3 inhibition.
	DRV/r	Elbasvir AUC ↑ 66% Grazoprevir AUC ↑ 7.5-fold ↔ DRV	
	LPV/r	Elbasvir AUC ↑ 3.7-fold Grazoprevir AUC ↑ 12.9-fold ↔ LPV	
	ATV (unboosted), ATV/c, DRV/c, TPV/r	↑ grazoprevir expected	
Glecaprevir/ Pibrentasvir	ATV (unboosted), ATV/c, ATV/r	When Given with ATV/r 300/100 mg Once Daily: • Glecaprevir AUC ↑ 6.5-fold • Pibrentasvir AUC ↑ 64%	**Contraindicated.**
	DRV/c, DRV/r	When Given with DRV/r 800/100 mg Once Daily: • Glecaprevir AUC ↑ 5-fold • ↔ pibrentasvir	**Do not coadminister.**
	LPV/r	Glecaprevir AUC ↑ 4-fold Pibrentasvir ↑ 2.5-fold	**Do not coadminister.**
	TPV/r	↑ glecaprevir and pibrentasvir expected	**Do not coadminister.**
Ledipasvir/ Sofosbuvir	ATV/r	ATV AUC ↑ 33% Ledipasvir AUC ↑ 113% ↔ sofosbuvir	No dose adjustment necessary. Coadministration of ledipasvir/sofosbuvir with TDF and a PI/r results in increased exposure to TDF. The safety of the increased TDF exposure has not been established. Consider alternative HCV or ARV drugs to avoid increased TDF toxicities. If coadministration is necessary, monitor for TDF-associated adverse reactions.
	DRV/r	↔ DRV expected ↔ ledipasvir/sofosbuvir	
	ATV (unboosted), ATV/c, DRV/c, LPV/r	↔ expected	
	TPV/r	↓ ledipasvir and sofosbuvir expected	**Do not coadminister.**

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 12 of 19)

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

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 13 of 19)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hormonal Therapies			
Hormonal Contraceptives Oral	ATV (unboosted)	Ethinyl estradiol AUC ↑ 48% Norethindrone AUC ↑ 110%	Prescribe oral contraceptive that contains no more than 30 mcg of ethinyl estradiol[b] or recommend alternative contraceptive method. Oral contraceptives containing less than 25 mcg of ethinyl estradiol or progestins other than norethindrone or norgestimate have not been studied.
	ATV/r	Ethinyl estradiol AUC ↓ 19% and C_{min} ↓ 37% Norgestimate ↑ 85% Norethindrone AUC ↑ 51% and C_{min} ↑ 67%	Oral contraceptive should contain at least 35 mcg of ethinyl estradiol.[c] Oral contraceptives containing progestins other than norethindrone or norgestimate have not been studied.
	ATV/c	Drospirenone AUC ↑ 2.3-fold Ethinyl estradiol AUC ↓ 22%	**Contraindicated with drospirenone-containing hormonal contraceptive due to potential for hyperkalemia.** Consider alternative or additional contraceptive method or alternative ARV drug.
	DRV/c	Drospirenone AUC ↑ 1.6-fold Ethinyl estradiol AUC ↓ 30%	Clinical monitoring is recommended due to the potential for hyperkalemia. Consider alternative or additional contraceptive method or alternative ARV.
	DRV/r, LPV/r, TPV/r	Ethinyl estradiol AUC ↓ 37% to 55% Norethindrone AUC ↓ 14% to 34% With TPV/r: • ↔ norethindrone AUC	Consider alternative or additional contraceptive method or alternative ARV drug.
Depot MPA Injectable	LPV/r	MPA AUC ↑ 46% No significant change in C_{min}	No dose adjustment necessary.
Etonogestrel-Releasing Subdermal Implant	LPV/r	Etonogestrel AUC ↑ 52% and C_{min} ↑ 34%	Use standard dose.
	All other PIs	No data	Consider alternative or additional contraceptive method or alternative ARV drug.
Etonogestrel/ Ethinyl Estradiol Vaginal Ring	ATV/r	Ethinyl estradiol AUC ↓ 26% Etonogestrel AUC ↑ 79%	Use standard dose.
Transdermal Ethinyl Estradiol/ Norelgestromin	LPV/r	↔ LPV Ethinyl estradiol AUC ↓ 45%, norelgestromin AUC ↑ 83%	Use standard dose.
	All other PIs	No data	Consider alternative or additional contraceptive method or alternative ARV drug.

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 14 of 19)

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

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 15 of 19)

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

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 16 of 19)

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

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 17 of 19)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
PDE5 Inhibitors			
Avanafil	All PIs except unboosted ATV	RTV (600 mg BID for 5 days) ↑ avanafil AUC 13-fold and ↑ C_{max} 2.4-fold	**Coadministration is not recommended.**
	ATV (unboosted)	No data	Avanafil dose should not exceed 50 mg once every 24 hours.
Sildenafil	All PIs	DRV/r plus sildenafil 25 mg similar to sildenafil 100 mg alone RTV 500 mg BID ↑ sildenafil AUC 1,000%	For Treatment of Erectile Dysfunction: • Start with sildenafil 25 mg every 48 hours and monitor for adverse effects of sildenafil. For Treatment of PAH: • **Contraindicated.**
Tadalafil	All PIs	RTV 200 mg BID ↑ tadalafil AUC 124% TPV/r (1st dose) ↑ tadalafil AUC 133% No significant effect on TPV/r steady state	For Treatment of Erectile Dysfunction: • Start with tadalafil 5-mg dose and do not exceed a single dose of tadalafil 10 mg every 72 hours. Monitor for adverse effects of tadalafil. For Treatment of PAH *In Patients on a PI >7 Days:* • Start with tadalafil 20 mg once daily and increase to tadalafil 40 mg once daily based on tolerability. *In Patients on Tadalafil who Require a PI:* • Stop tadalafil ≥24 hours before PI initiation. Seven days after PI initiation, restart tadalafil at 20 mg once daily and increase to tadalafil 40 mg once daily based on tolerability. *In Patients Switching between COBI and RTV:* • Maintain tadalafil dose. For Treatment of Benign Prostatic Hyperplasia: • Maximum recommended daily dose is tadalafil 2.5 mg per day.
Vardenafil	All PIs	RTV 600 mg BID ↑ vardenafil AUC 49-fold	Start with vardenafil 2.5 mg every 72 hours and monitor for adverse effects of vardenafil.
Sedative/Hypnotics			
Alprazolam, Clonazepam, Diazepam	All PIs	↑ benzodiazepine possible RTV (200 mg BID for 2 days) ↑ alprazolam half-life 222% and ↑ AUC 248%	Consider alternative benzodiazepines, such as lorazepam, oxazepam, or temazepam.
Lorazepam, Oxazepam, Temazepam	All PIs	No data	These benzodiazepines are metabolized via non-CYP450 pathways; thus, there is less interaction potential than with other benzodiazepines.
Midazolam	All PIs	↑ midazolam expected	**Oral midazolam is contraindicated with PIs.** Parenteral midazolam can be used with caution when given as a single dose in a monitored situation for procedural sedation.
Suvorexant	All PIs	↑ suvorexant expected	**Coadministration is not recommended.**

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 18 of 19)

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

[a] DHA is an active metabolite of artemether.

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

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

[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; ALT = alanine aminotransferase; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; AUC = area under the curve; BID = twice daily; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; CNS = central nervous system; COBI = cobicistat; CrCl = creatinine clearance; CV = cardiovascular; CYP = cytochrome P; DHA = dihydroartemisinin; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; FPV = fosamprenavir; HCV = hepatitis C virus; HRT = hormone replacement therapy; IDV = indinavir; INR = international normalized ratio; LPV = lopinavir; LPV/r = lopinavir/ritonavir; MPA = medroxyprogesterone acetate; NFV = nelfinavir; OATP = organic anion-transporting polypeptide; PAH = pulmonary arterial hypertension; PDE5 = Phosphodiesterase Type 5; PI = protease inhibitor; PI/c = protease inhibitor/cobicistat; PI/r = protease inhibitor/ritonavir; PK = pharmacokinetic; PPI = proton pump inhibitor; PTH = parathyroid hormone; QTc = QT corrected for heart rate; RTV = ritonavir; SQV = saquinavir; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; TPV/r = tipranavir/ritonavir