

Please refer to the **Drug Interactions** section of the Adult Guidelines for more detailed discussions.

Table 15a. Drug Interactions Between Protease Inhibitors (PIs) and Other Drugs

This table provides information relating to pharmacokinetic interactions between PIs and non-antiretroviral drugs. When information is available, interactions with boosted and unboosted PIs are listed separately. For interactions among antiretroviral agents and dosing recommendations, please refer to [Table 16a](#).

Concomitant Drug Class/Name	Protease Inhibitor (PI)	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers			
Antacids	ATV ± RTV	No data	↓ ATV concentrations expected when given simultaneously. Give ATV at least 2 hrs before or 1 hr after antacids or buffered medications.
	FPV	APV AUC ↓ 18%; C _{min} : no significant change	Can be given simultaneously or separated at least 2 hrs before or 1 hr after antacids.
	DRV/r, FPV/r, IDV ± RTV, LPV/r, NFV, SQV/r	No data	
	TPV/r	↓ TPV ~30%	Give TPV at least 2 hrs before or 1 hr after antacids.
H₂ Receptor Antagonists	RTV-boosted PI		
	ATV/r	↓ ATV	H ₂ receptor antagonist dose should not exceed a dose equivalent to famotidine 40mg BID in treatment-naïve patients or 20mg BID in treatment-experienced patients. ATV 300mg + RTV 100mg should be administered simultaneously with and/or ≥10 hours after the H ₂ receptor antagonist. In treatment-experienced patients, if TDF is used with H ₂ receptor antagonists, ATV 400mg + RTV 100mg should be used.
	DRV/r, LPV/r	No effect	
	FPV/r, SQV/r, TPV/r	No data	
	PIs without RTV:		
	ATV	↓ ATV	H ₂ receptor antagonist single dose should not exceed a dose equivalent of famotidine 20mg or total daily dose equivalent of famotidine 20mg BID in treatment-naïve patients. ATV should be administered ≥2 hours before and/or ≥10 hours after the H ₂ receptor antagonist.
	FPV	APV AUC ↓ 30%; C _{min} : unchanged	Separate administration if coadministration is necessary. Consider boosting with RTV.
	IDV, NFV	No data	
Proton Pump Inhibitors (PPIs)	ATV	↓ ATV	PPIs are not recommended in patients receiving unboosted ATV. In these patients, consider alternative acid-reducing agents, ritonavir-boosting, or alternative PIs.
	ATV/r	↓ ATV	PPIs should not exceed a dose equivalent to omeprazole 20mg daily in treatment-naïve patients. PPIs should be administered ≥ 12 hrs prior to ATV/r. PPIs are not recommended in treatment-experienced patients.
	DRV/r, FPV ± RTV, LPV/r,	No effect	
	IDV ± RTV	No data	
	NFV	NFV AUC ↓ 36% M8 AUC ↓ 92%	Do not coadminister PPIs and NFV.
	SQV/r	SQV AUC ↑ 82%	Monitor for SQV toxicities.
	TPV/r	↓ omeprazole, TPV: no effect	May need to increase omeprazole dose.

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Concomitant Drug Class/Name	Protease Inhibitor (PI)	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antifungals			
Fluconazole	RTV-boosted PI		
	ATV/r	No effect	
	DRV/r, FPV/r, IDV/r, LPV/r	No data	
	SQV/r	No data with RTV-boosting; SQV AUC ↑ 50%, Cmax ↑ 56% with SQV 1200mg TID	
	TPV/r	TPV AUC ↑ 50%, Cmax ↑ 32%, Cmin ↑ 69%	Fluconazole >200mg daily not recommended.
	PIs without RTV		
ATV, FPV, NFV	No data		
IDV	No effect		
Itraconazole	RTV-boosted PI		
	ATV/r, DRV/r, FPV/r, IDV/r, TPV/r	No data	Potential for bi-directional inhibition between itraconazole and PIs. Consider monitoring itraconazole level to guide dosage adjustments. High doses (>200 mg/day) are not recommended.
	LPV/r	↑ itraconazole	Consider not exceeding 200mg itraconazole daily, or monitor itraconazole level.
	SQV/r	Bi-directional interaction has been observed.	Dose not established, but decreased itraconazole dosage may be warranted. Consider monitoring itraconazole level.
	PIs without RTV:		
	ATV, FPV, NFV	No data	Potential for bi-directional inhibition between itraconazole and PIs. Consider monitoring itraconazole level to guide dosage adjustments.
IDV	↑ IDV IDV 600mg Q8H + itraconazole 200mg BID: AUC similar to IDV 800mg Q8H	Dose: IDV 600mg Q8H (without ritonavir); Do not exceed 200mg itraconazole BID. Dosing of IDV when used with ritonavir and itraconazole not established.	
Ketoconazole	RTV-boosted PI:		
	ATV/r, FPV/r	↑ ketoconazole levels	Use with caution. Do not exceed 200mg ketoconazole daily.
	DRV/r	DRV AUC ↑ 42%, ketoconazole ↑ 3-fold	
	IDV/r	No data	
	LPV/r	May ↑ or ↓ LPV, ketoconazole ↑ 3-fold	Potential for bidirectional interaction between ketoconazole & IDV/r, SQV/r, TPV/r.
	SQV/r	SQV ↑ 3x (when ketoconazole used with unboosted SQV)	
	TPV/r	No data	
	PIs without RTV:		
	ATV, NFV		No dosage adjustment necessary.
	FPV	No data with FPV ↑ APV ↑ ketoconazole	Consider ketoconazole dose reduction if dose is >400mg/day. Presumably similar interaction as seen with APV: APV ↑ 31%; ketoconazole ↑ 44%
IDV	↑ IDV	Dose: IDV 600mg Q8H. Levels: IDV ↑ 68% IDV dosage when used with ritonavir and ketoconazole has not been established.	
Posaconazole	All PIs	No data	
Voriconazole	RTV-boosted PI		
	ATV/r, DRV/r, FPV/r, IDV/r, LPV/r, SQV/r, TPV/r	voriconazole AUC ↓ 82% with RTV 400mg BID and ↓ 39% with RTV 100mg BID	Administration of voriconazole and RTV 100mg once daily or BID is not recommended unless benefit outweighs risk. Consider monitoring voriconazole level. Administration of voriconazole and RTV 400mg BID or higher is contraindicated.
	PIs without RTV:		
	ATV FPV NFV	No data	Potential for bi-directional inhibition between voriconazole and PIs. Monitor for toxicities.
IDV	No significant effect	No dose adjustment.	

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Concomitant Drug Class/Name	Protease Inhibitor (PI)	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticonvulsants			
Carbamazepine Phenobarbital Phenytoin	RTV-boosted PI		
	ATV/r, DRV/r, IDV/r, LPV/r, SQV/r, TPV/r	↑ carbamazepine ↓ PI level	Consider alternative anticonvulsant or monitor levels of both drugs.
	FPV/r	↓ phenytoin ↑ APV	Monitor anticonvulsant level, and adjust dose accordingly. No change in FPV/r dose recommended.
	LPV/r	↓ phenytoin ↓ phenobarbital ↓ LPV/r level May ↓ other PI levels	Consider alternative anticonvulsant or monitor levels of both drugs.
	PIs without RTV:		
	ATV FPV NFV	No data May ↓ PI levels substantially NFV ↓ phenytoin	Monitor anticonvulsant level and virologic response. Consider alternative anticonvulsant, RTV boosting for ATV and FPV, and/or monitoring PI level.
IDV	↓ IDV	Consider alternative anticonvulsant, RTV boosting, and/or monitoring IDV level.	
Anti-mycobacterials			
Clarithromycin	ATV ± RTV	clarithromycin AUC ↑ 94%	May cause QTc prolongation. Reduce clarithromycin dose by 50%. Consider alternative therapy.
	DRV/r IDV ± RTV LPV/r SQV/r TPV/r	DRV/r ↑ Clar AUC 57%; IDV ↑ Clar AUC 53%; LPV/r ↑ Clar AUC 77%; RTV ↑ Clar 77%; SQV ↑ Clar 45%; Clar ↑ SQV 177%; TPV/r ↑ Clar 19% and ↓ active metabolite 97%; Clar ↑ TPV 66%	Reduce clarithromycin dose by 50% in patients with CrCl 30-60mL/min. Reduce clarithromycin dose by 75% in patients with CrCl <30mL/min.
	FPV	↑ APV	No dose adjustment.
	NFV	No data	
	RTV-boosted PI:		
Rifabutin	ATV ± RTV FPV/r DRV/r IDV/r LPV/r SQV/r TPV/r	ATV ↑ rifabutin AUC 2.5-fold; FPV/r, DRV/r, IDV/r: no PK data, expect ↑ rifabutin; RTV (500mg bid) ↑ rifabutin 4X; LPV/r ↑ rifabutin AUC 3-fold, ↑ 25-O-desacetyl metabolite 47.5-fold; Rifabutin ↓ unboosted SQV 40%; TPV/r ↑ rifabutin AUC 2.9-fold, ↑ 25-O-desacetyl metabolite 20.7-fold	Rifabutin 150mg QOD or 3x/week. Acquired rifamycin resistance has been reported in patients with inadequate rifabutin levels while on 150mg twice weekly and RTV-boosted PIs. May consider therapeutic drug monitoring and adjust dose accordingly.
	PIs without RTV:		
	FPV	↑ rifabutin	Rifabutin 150mg daily or 300mg 3x/week
	IDV	↑ rifabutin ↓ IDV	Rifabutin 150mg daily or 300mg 3x/week + IDV 1,000mg q8h or consider RTV boosting. Levels: rifabutin ↑ 2X, IDV ↓ 32%
	NFV	↑ rifabutin 2X; ↓ NFV 750mg Q8H 32%	Rifabutin 150mg daily or 300mg 3x/week
Rifampin	All PIs	Approximately >75% ↓ in PI concentrations	Do not coadminister rifampin and PIs.
Benzodiazepines			
Alprazolam Diazepam	All PIs	May ↑ benzodiazepine levels RTV 200mg BID x 2 days ↑ alprazolam half-life 200% and AUC 248%	Consider alternative benzodiazepines such as lorazepam, oxazepam, or temazepam
Lorazepam Oxazepam Temazepam	All PIs	No data	Metabolism of these benzodiazepines via non-CYP450 pathways decreases interaction potential compared with other benzodiazepines.

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Concomitant Drug Class/Name	Protease Inhibitor (PI)	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Midazolam	All PIs	↑ midazolam SQV/r ↑ midazolam (oral) AUC 1144%, ↑ Cmax 327%	Do not coadminister oral midazolam and PIs. Parenteral midazolam can be used with caution as a single dose and can be given in a monitored situation for procedural sedation.
Triazolam	All PIs	RTV 200mg BID: ↑ triazolam AUC by 20x; Other PIs: No data; may significantly ↑ triazolam concentration	Do not coadminister triazolam and PIs.
Calcium Channel Blockers			
Dihydropyridine	ATV ± RTV	No data	Caution warranted with ATV. Dose titration should be considered as well as ECG monitoring.
	DRV/r, FPV ± RTV, NFV, TPV/r	No data	
	IDV/r	↑ amlodipine	Monitor closely.
	LPV/r SQV/r	↑ dihydropyridine	Caution is warranted and clinical monitoring of patients is recommended.
Diltiazem	ATV ± RTV	↑ diltiazem AUC 125%	Decrease diltiazem dose by 50%. ECG monitoring is recommended.
	DRV/r, FPV ± RTV, IDV ± RTV, LPV/r, NFV, TPV/r	No data	Potential for ↑ diltiazem level.
	SQV/r	↑ diltiazem	Caution is warranted, and clinical monitoring of patients is recommended.
Herbal Products			
St. John's wort	All PIs	↓ PI	Administration of St. John's wort with PIs is not recommended.
Hormonal Contraceptives			
Hormonal Contraceptives	RTV-boosted PI:		
	ATV/r	↓ ethinyl estradiol ↑ progestin	Oral contraceptive should contain at least 35mcg of ethinyl estradiol. Oral contraceptives containing progestins other than norethindrone or norgestimate have not been studied.
	DRV/r, IDV/r	No data	Use alternative or additional method because of possible interaction.
	FPV/r	↓ ethinyl estradiol AUC 37%; ↓ norethindrone AUC 34%; APV: no change	Use alternative or additional method.
	LPV/r	↓ ethinyl estradiol 42%	Use alternative or additional method.
	SQV/r	↓ ethinyl estradiol	Use alternative or additional method.
	TPV/r	↓ ethinyl estradiol Cmax & AUC ↓ ~50%	Use alternative or additional method. Used as hormone replacement therapy, monitor clinically for signs of estrogen deficiency.
	PIs without RTV:		
	ATV	↑ ethinyl estradiol AUC 48%; ↑ norethindrone AUC 110%	Oral contraceptive should contain no more than 30mcg of ethinyl estradiol, or use alternate method. Oral contraceptives containing less than 25mcg of ethinyl estradiol or progestins other than norethindrone or norgestimate have not been studied.
	FPV	With APV: ↑ ethinyl estradiol, ↑ norethindrone, ↓ APV 20%	Use alternative method.
	IDV	↑ ethinyl estradiol; ↑ norethindrone	No dose adjustment.
	NFV	ethinyl estradiol ↓ 47%; norethindrone ↓ 18%	Use alternative or additional method.
HMG-CoA Reductase Inhibitors			
Atorvastatin	All PIs	↑ atorvastatin; DRV/r + atorvastatin 10mg similar to atorvastatin 40mg alone; FPV ↑ atorvastatin AUC 150%; LPV/r ↑ atorvastatin AUC 5.88-fold; NFV ↑ atorvastatin AUC 74%; SQV/r ↑ atorvastatin levels 450%; TPV/r ↑ atorvastatin AUC 9-fold	Use lowest possible starting dose with careful monitoring, or consider other HMG-CoA reductase inhibitors with less potential for interaction.

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Concomitant Drug Class/Name	Protease Inhibitor (PI)	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Lovastatin	All PIs	Significant ↑ lovastatin level	Contraindicated – do not coadminister.
Pravastatin	DRV/r	Mean ↑ in pravastatin AUC 81% & up to 5-fold in some patients	Use lowest possible starting dose with careful monitoring.
	LPV/r	↑ pravastatin	No dose adjustment necessary.
	NFV, SQV/r	↓ pravastatin	No dose adjustment necessary.
	TPV/r ATV, FPV, IDV	No data	
Rosuvastatin	ATV +/- RTV, DRV/r, FPV +/- RTV, IDV +/- RTV, NFV, SQV/r	No data Potential for ↑ rosuvastatin level.	Use lowest possible starting dose with careful monitoring, or consider other HMG-CoA reductase inhibitors with less potential for interaction.
	LPV/r	rosuvastatin AUC ↑ 2.1-fold and Cmax ↑ 4.7-fold	Use lowest possible starting dose with careful monitoring for rosuvastatin toxicities, or consider other HMG-CoA reductase inhibitors with less potential for interaction.
	TPV/r	rosuvastatin AUC ↑ 37% and Cmax ↑ 123%	Use lowest possible starting dose with monitoring for rosuvastatin toxicities, or consider other HMG-CoA reductase inhibitors with less potential for interaction.
Simvastatin	All PIs	Significant ↑ simvastatin level; NFV ↑ simvastatin AUC 505%	Contraindicated – do not coadminister.
Methadone			
Methadone	RTV-boosted PI:		
	ATV/r, FPV/r, DRV/r, IDV/r, LPV/r, SQV/r, TPV/r	↓ methadone levels: ATV/r ↓ R-methadone AUC 16%; DRV/r ↓ R-methadone AUC 16%; FPV/r ↓ R-methadone AUC 18% ; LPV/r ↓ methadone AUC 26%–53%; SQV/r 1,000/100mg BID ↓ methadone AUC 19%; TPV/r ↓ R-methadone AUC 48%	Opiate withdrawal unlikely but may occur. No adjustment in methadone usually required but monitor for opiate withdrawal and increase methadone dose as clinically indicated. R-methadone is the active form of methadone.
	PIs without RTV:		
	ATV, IDV	No effect	
	FPV	No data with FPV ; with APV, R-methadone levels ↓ 13%	Monitor and titrate methadone as clinically indicated. The interaction with FPV is presumed to be similar.
NFV	NFV ↓ methadone AUC 40%	Opiate withdrawal rarely occurs. Monitor and titrate dose as clinically indicated. May require ↑ methadone dose.	
Phosphodiesterase Type 5 Inhibitors			
Sildenafil	All PIs	↑ sildenafil; APV ↑ sildenafil AUC 2- to 11-fold; DRV/r + sildenafil 25mg similar to sildenafil 100mg alone; IDV ↑ sildenafil AUC 3-fold; LPV/r ↑ sildenafil 11-fold; NFV ↑ sildenafil 2- to 11-fold; RTV ↑ sildenafil AUC 11-fold	Sildenafil: start with 25mg every 48 hours and monitor for adverse effects of sildenafil.
Tadalafil	All PIs	LPV/r ↑ tadalafil AUC 124%	Tadalafil: start with 5mg dose and do not exceed a single dose of 10mg every 72 hours. Monitor for adverse effects of tadalafil.
Vardenafil	All PIs	↑ vardenafil; IDV ↑ vardenafil AUC 16-fold, ↓ IDV AUC 30%; RTV ↑ vardenafil AUC 49-fold, ↓ RTV AUC 20%	Vardenafil: start with 2.5mg every 72 hours and monitor for adverse effects of vardenafil.

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Drug-Specific Interactions

Protease Inhibitor (PI)	Concomitant Drug Class/Name	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
DRV/r	Paroxetine Sertraline	↓ paroxetine ↓ sertraline	Monitor closely for antidepressant response. Carefully titrate SSRI dose based on clinical assessment.
IDV	Grapefruit juice Vitamin C >1 g/day	↓ IDV ↓ IDV	Monitor for virologic responses.
RTV	Desipramine	RTV ↑ desipramine 145%	Reduce desipramine dose.
	Trazodone	RTV 200mg BID ↑ trazodone AUC 2.4-fold.	Use lowest dose of trazodone, and monitor for CNS and CV adverse effects.
	Theophylline	RTV ↓ theophylline 47%.	Monitor theophylline levels.
SQV	Grapefruit juice	↑ SQV	
	Dexamethasone	↓ SQV	

Abbreviations: APV = amprenavir, ATV = atazanavir, ATV/r = atazanavir + ritonavir, DRV/r = darunavir + ritonavir, FPV = fosamprenavir, FPV/r = fosamprenavir + ritonavir, IDV = indinavir, IDV/r = indinavir + ritonavir, LPV/r = lopinavir/ritonavir, NFV = nelfinavir, RTV = ritonavir, SQV/r = saquinavir + ritonavir, TPV/r = tipranavir + ritonavir.