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

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Table 15a. Drug Interactions between Protease Inhibitors (PI)* and Other Drugs (Last updated February 12, 2013; last reviewed February 12, 2013) (page 1 of 10)

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

* Nelfinavir (NFV) and indinavir (IDV) are not included in this table. Please refer to the NFV and IDV FDA package inserts for information regarding drug interactions with these PIs.

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers			
Antacids	ATV, ATV/r	When given simultaneously, ↓ ATV expected	Give ATV at least 2 hours before or 1 hour after antacids or buffered medications.
	FPV	APV AUC ↓ 18%; no significant change in APV C_{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	**RTV-boosted PIs**		
	ATV/r	↓ ATV	H2 receptor antagonist dose should not exceed a dose equivalent to famotidine 40 mg BID in ART-naive patients or 20 mg BID in ART-experienced patients. Give ATV 300 mg + RTV 100 mg simultaneously with and/or ≥10 hours after the H2 receptor antagonist. If using TDF and H2 receptor antagonist in ART-experienced patients, use ATV 400 mg + RTV 100 mg.
	DRV/r, LPV/r	No significant effect	No dosage adjustment necessary.
	PIs without RTV		
	ATV	↓ ATV	H2 receptor antagonist single dose should not exceed a dose equivalent of famotidine 20 mg or total daily dose equivalent of famotidine 20 mg BID in ART-naive patients. Give ATV at least 2 hours before and at least 10 hours after the H2 receptor antagonist.
	FPV	APV AUC ↓ 30%; no significant change in APV C_{min}	If concomitant use is necessary, give FPV at least 2 hours before H2 receptor antagonist. Consider boosting FPV with RTV.
Proton Pump Inhibitors (PPIs)	ATV	↓ ATV	**PPIs are not recommended in patients receiving unboosted ATV.** In these patients, consider alternative acid-reducing agents, RTV boosting, or alternative PIs.
	ATV/r	↓ ATV	PPIs should not exceed a dose equivalent to omeprazole 20 mg daily in PI-naive patients. PPIs should be administered at least 12 hours before ATV/r. **PPIs are not recommended in PI-experienced patients.**
	DRV/r, TPV/r	↓ omeprazole PI: no significant effect	May need to increase omeprazole dose when using TPV/r.
	FPV, FPV/r, LPV/r	No significant effect	No dosage adjustment necessary.
	SQV/r	SQV AUC ↑ 82%	Monitor for SQV toxicities.

Table 15a. Drug Interactions between Protease Inhibitors (PI)* and Other Drugs (Last updated February 12, 2013; last reviewed February 12, 2013) (page 2 of 10)

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticoagulants			
Warfarin	ATV, ATV/r, DRV/r, FPV, FPV/r, LPV/r, SQV/r, TPV/r	↑ or ↓ warfarin possible DRV/r ↓ S-warfarin AUC 21%	Monitor INR closely when stopping or starting PI and adjust warfarin dose accordingly.
Rivaroxaban	All PIs	↑ rivaroxaban	Avoid concomitant use. Co-administration is expected to result in increased exposure of rivaroxaban which may lead to risk of increased bleeding.
Anticonvulsants			
Carbamazepine	**RTV-boosted PIs**		
	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 co-administer with LPV/r once daily.**
	DRV/r	carbamazepine AUC ↑ 45% DRV: no significant change	Monitor anticonvulsant level and adjust dose accordingly.
	PIs without RTV		
	ATV, FPV	May ↓ PI levels substantially	Monitor anticonvulsant level and virologic response. Consider alternative anticonvulsant, RTV boosting for ATV and FPV, and/or monitoring PI level.
Lamotrigine	LPV/r	lamotrigine AUC ↓ 50% LPV: no significant change	A dose increase of lamotrigine may be needed and therapeutic concentration monitoring for lamotrigine may be indicated; particularly during dosage adjustment or consider alternative anticonvulsant. A similar interaction is possible with other RTV-boosted PIs.
Phenobarbital	All PIs	May ↓ PI levels substantially	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. **Do not co-administer with LPV/r once daily.**
Phenytoin	**RTV-boosted PIs**		
	ATV/r, DRV/r, SQV/r, TPV/r	↓ phenytoin possible ↓ PI possible	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response.
	FPV/r	phenytoin AUC ↓ 22% APV AUC ↑ 20%	Monitor phenytoin level and adjust dose accordingly. No change in FPV/r dose recommended.
	LPV/r	phenytoin AUC ↓ 31% LPV/r AUC ↓ 33%	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. **Do not co-administer with LPV/r once daily.**
	PIs without RTV		
	ATV, FPV	May ↓ PI levels substantially	Consider alternative anticonvulsant, RTV boosting for ATV and FPV, and/or monitoring PI level. Monitor anticonvulsant level and virologic response.
Valproic Acid (VPA)	LPV/r	↓ or ⇔ VPA possible LPV AUC ↑ 75%	Monitor VPA levels and virologic response. Monitor for LPV-related toxicities.

Table 15a. Drug Interactions between Protease Inhibitors (PI)* and Other Drugs (Last updated February 12, 2013; last reviewed February 12, 2013) (page 3 of 10)

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antidepressants			
Bupropion	LPV/r	bupropion AUC ↓ 57%	Titrate bupropion dose based on clinical response.
	TPV/r	bupropion AUC ↓ 46%	
Paroxetine	DRV/r	paroxetine AUC ↓ 39%	Titrate paroxetine dose based on clinical response.
	FPV/r	paroxetine AUC ↓ 55%	
Sertraline	DRV/r	sertraline AUC ↓ 49%	Titrate sertraline dose based on clinical response.
Trazodone	ATV/r, ATV, DRV/r, FPV/r, FPV, LPV/r, TPV/r	RTV 200 mg BID (for 2 days) ↑ trazodone AUC 240%	Use lowest dose of trazodone and monitor for CNS and cardiovascular adverse effects.
	SQV/r	↑ trazodone expected	**Contraindicated. Do not co-administer.**
Tricyclic Antidepressants (TCAs) (Amitriptyline, Desipramine, Imipramine, Nortriptyline)	All RTV-boosted PIs	↑ TCA expected	Use lowest possible TCA dose and titrate based on clinical assessment and/or drug levels.
Antifungals			
Fluconazole	**RTV-boosted PIs**		
	ATV/r	No significant effect	No dosage adjustment necessary.
	SQV/r	No data with RTV boosting SQV (1200 mg TID) AUC ↑ 50%	No dosage adjustment necessary.
	TPV/r	TPV AUC ↑ 50%	Fluconazole >200 mg daily is not recommended. If high-dose fluconazole is indicated, consider alternative PI or another class of ARV drug.
Itraconazole	**RTV-boosted PIs**		
	ATV/r, DRV/r, FPV/r, TPV/r	↑ itraconazole possible ↑ PI possible	Consider monitoring itraconazole level to guide dosage adjustments. High doses (>200 mg/day) are not recommended unless dose is guided by itraconazole levels.
	LPV/r	↑ itraconazole	Consider monitoring itraconazole level to guide dosage adjustments. High doses (>200 mg/day) are not recommended unless dose is guided by itraconazole levels
	SQV/r	Bidirectional interaction has been observed	Dose not established, but decreased itraconazole dosage may be warranted. Consider monitoring itraconazole level.
	PIs without RTV		
	ATV, FPV	↑ itraconazole possible ↑ PI possible	Consider monitoring itraconazole level to guide dosage adjustments.

Table 15a. Drug Interactions between Protease Inhibitors (PI)* and Other Drugs (Last updated February 12, 2013; last reviewed February 12, 2013) (page 4 of 10)

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antifungals, continued			
Posaconazole	ATV/r	ATV AUC ↑ 146%	Monitor for adverse effects of ATV.
	ATV	ATV AUC ↑ 268%	Monitor for adverse effects of ATV.
	FPV	FPV (1400 mg BID) ↓ posaconazole AUC 23%; (compared with FPV/RTV 700 mg/100 mg) APV AUC ↓ 65%	**Do not co-administer.**
Voriconazole	**RTV-boosted PIs**		
	All RTV-boosted PIs	RTV 400 mg BID ↓ voriconazole AUC 82% RTV 100 mg BID ↓ voriconazole AUC 39%	**Do not co-administer** voriconazole and RTV unless benefit outweighs risk. If administered, consider monitoring voriconazole level and adjust dose accordingly.
	PIs without RTV		
	ATV, FPV	↑ voriconazole possible ↑ PI possible	Monitor for toxicities.
Antimycobacterials			
Clarithromycin	ATV/r, ATV	clarithromycin AUC ↑ 94%	May cause QTc prolongation. Reduce clarithromycin dose by 50%. Consider alternative therapy (e.g., azithromycin).
	DRV/r, FPV/r, LPV/r, SQV/r, TPV/r	DRV/r ↑ clarithromycin AUC 57% FPV/r ↑ clarithromycin possible LPV/r ↑ clarithromycin expected RTV 500 mg BID ↑ clarithromycin 77% SQV unboosted ↑ clarithromycin 45% TPV/r ↑ clarithromycin 19% clarithromycin ↑ unboosted SQV 177% clarithromycin ↑ TPV 66%	Monitor for clarithromycin-related toxicities or consider alternative macrolide (e.g., azithromycin). Reduce clarithromycin dose by 50% in patients with CrCl 30–60 mL/min. Reduce clarithromycin dose by 75% in patients with CrCl <30 mL/min.
	FPV	APV AUC ↑ 18%	No dosage adjustment necessary.
Rifabutin	**RTV-boosted PIs**		
	ATV/r	rifabutin (150 mg once daily) AUC ↑ 110% and metabolite AUC ↑ 2,101% compared with rifabutin (300 mg daily) administered alone	Rifabutin 150 mg once daily or 300 mg three times a week. Monitor for antimycobacterial activity and consider therapeutic drug monitoring. PK data reported in this table are results from healthy volunteer studies. Lower rifabutin exposure has been reported in HIV-infected patients than in the healthy study participants.
	DRV/r	rifabutin (150 mg every other day) AUC not significantly changed and metabolite AUC ↑ 881% compared with rifabutin (300 mg once daily) administered alone	
	FPV/r	rifabutin (150 mg every other day) and metabolite AUC ↑ 64% compared with rifabutin (300 mg once daily) administered alone	
	LPV/r	rifabutin (150 mg once daily) and metabolite AUC ↑ 473% compared with rifabutin (300 mg daily) administered alone	
	SQV/r	↑ rifabutin with unboosted SQV	
	TPV/r	rifabutin (150 mg x 1 dose) and metabolite AUC ↑ 333%	

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antimycobacterials, continued			
Rifabutin, continued	**PIs without RTV**		
	ATV, FPV	↑ rifabutin AUC expected	Rifabutin 150 mg daily or 300 mg three times a week
Rifampin	All PIs	↓ PI conc. by >75%	**Do not co-administer rifampin and PIs.** Additional RTV does not overcome this interaction and increases hepatotoxicity.
Rifapentine	All PIs	↓ PI expected	**Do not co-administer rifapentine and PIs.**
Benzodiazepines			
Alprazolam **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; there is less interaction potential than with other benzodiazepines.
Midazolam	All PIs	↑ midazolam expected SQV/r ↑ midazolam (oral) AUC 1,144% and C_{max} 327%	**Do not co-administer oral midazolam and PIs.** Parenteral midazolam can be used with caution when given as a single dose in a monitored situation for procedural sedation.
Triazolam	All PIs	↑ triazolam expected RTV (200 mg BID) ↑ triazolam half-life 1,200% and AUC 2,000%	**Do not co-administer triazolam and PIs.**
Cardiac Medications			
Bosentan	All PIs	LPV/r ↑ bosentan 48-fold (day 4) and 5-fold (day 10) ↓ ATV expected	**Do not co-administer bosentan and ATV without RTV.** 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 10 days after PI initiation at 62.5 mg once daily or every other day.
Digoxin	RTV, SQV/r	RTV (200 mg BID) ↑ digoxin AUC 29% and half-life 43% SQV/r ↑ digoxin AUC 49%	Use with caution. Monitor digoxin levels. Digoxin dose may need to be decreased.
Dihydropyridine Calcium Channel Blockers (CCBs)	All PIs	↑ dihydropyridine possible	Use with caution. Titrate CCB dose and monitor closely. ECG monitoring is recommended when CCB used with ATV.
Diltiazem	ATV/r, ATV	diltiazem AUC ↑ 125%	Decrease diltiazem dose by 50%. ECG monitoring is recommended.
	DRV/r, FPV/r, FPV LPV/r, SQV/r, TPV/r	↑ diltiazem possible	Use with caution. Adjust diltiazem according to clinical response and toxicities.

Table 15a. Drug Interactions between Protease Inhibitors (PI)* and Other Drugs (Last updated February 12, 2013; last reviewed February 12, 2013) (page 6 of 10)

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Corticosteroids			
Budesonide (systemic)	All PIs	↓ PI levels possible ↑ glucocorticoids	Use with caution. Co-administration can result in adrenal insufficiency, including Cushing's syndrome. **Do not co-administer unless potential benefits of systemic budesonide outweigh the risks of systemic corticosteroid adverse effects.**
Budesonide (inhaled or intranasal)	All RTV-boosted PIs	↑ glucocorticoids	Use with caution. Co-administration can result in adrenal insufficiency, including Cushing's syndrome. **Do not co-administer unless potential benefits of inhaled or intranasal budesonide outweigh the risks of systemic corticosteroid adverse effects.**
Dexamethasone	All PIs	↓ PI levels possible	Use systemic dexamethasone with caution or consider alternative corticosteroid for long-term use.
Fluticasone (inhaled or intranasal)	All RTV-boosted PIs	RTV 100 mg BID ↑ fluticasone AUC 350-fold and ↑ C_{max} 25-fold	Co-administration can result in adrenal insufficiency, including Cushing's syndrome. **Do not co-administer unless potential benefits of inhaled fluticasone outweigh the risks of systemic corticosteroid adverse effects.**
Prednisone	LPV/r	↑ prednisolone AUC 31% ↓ lopinavir	Use with caution. Co-administration can result in adrenal insufficiency, including Cushing's syndrome. **Do not co-administer unless potential benefits of prednisone outweigh the risks of systemic corticosteroid adverse effects.**
Hepatitis C NS3/4A Protease Inhibitors			
Boceprevir	ATV/r	ATV AUC ↓ 35%, C_{min} ↓ 49% RTV AUC ↓ 36% boceprevir AUC ⇔	**Co-administration is not recommended.**
	DRV/r	DRV AUC ↓ 44%, C_{min} ↓ 59% RTV AUC ↓ 26% boceprevir AUC ↓ 32%, C_{min} ↓ 35%	**Co-administration is not recommended.**
	LPV/r	LPV AUC ↓ 34%, C_{min} ↓ 43% RTV AUC ↓ 22% boceprevir AUC ↓ 45%, C_{min} ↓ 57%	**Co-administration is not recommended.**
Telaprevir	ATV/r	telaprevir AUC ↓ 20%	No dose adjustment necessary.
	DRV/r	telaprevir AUC ↓ 35% DRV AUC ↓ 40%	**Co-administration is not recommended.**
	FPV/r	telaprevir AUC ↓ 32% APV AUC ↓ 47%	**Co-administration is not recommended.**
	LPV/r	telaprevir AUC ↓ 54% LPV: no significant change	**Co-administration is not recommended.**

Table 15a. Drug Interactions between Protease Inhibitors (PI)* and Other Drugs (Last updated February 12, 2013; last reviewed February 12, 2013) (page 7 of 10)

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Herbal Products			
St. John's Wort	All PIs	↓ PI expected	**Do not co-administer.**
Hormonal Contraceptives			
Hormonal Contraceptives	**RTV-boosted PIs**		
	ATV/r	ethinyl estradiol AUC ↓ 19% and C_{min} ↓ 37% norgestimate ↑ 85%	Oral contraceptive should contain at least 35 mcg of ethinyl estradiol. Oral contraceptives containing progestins other than norethindrone or norgestimate have not been studied.[a]
	DRV/r	ethinyl estradiol AUC ↓ 44% norethindrone AUC ↓ 14%	Use alternative or additional contraceptive method.
	FPV/r	ethinyl estradiol AUC ↓ 37% norethindrone AUC ↓ 34%	Use alternative or additional contraceptive method.
	LPV/r	ethinyl estradiol AUC ↓ 42% norethindrone AUC ↓ 17%	Use alternative or additional contraceptive method.
	SQV/r	↓ ethinyl estradiol	Use alternative or additional contraceptive method.
	TPV/r	ethinyl estradiol AUC ↓ 48% norethindrone: no significant change	Use alternative or additional contraceptive method.
	PIs without RTV		
	ATV	ethinyl estradiol AUC ↑ 48% norethindrone AUC ↑ 110%	Use oral contraceptive that contains no more than 30 mcg of ethinyl estradiol or use alternative contraceptive method. Oral contraceptives containing less than 25 mcg of ethinyl estradiol or progestins other than norethindrone or norgestimate have not been studied.[b]
	FPV	With APV: ↑ ethinyl estradiol and ↑ norethindrone C_{min}; APV C_{min} ↓ 20%	Use alternative contraceptive method.
HMG-CoA Reductase Inhibitors			
Atorvastatin	ATV/r, ATV	↑ atorvastatin possible	Titrate atorvastatin dose carefully and use lowest dose necessary.
	DRV/r FPV/r, FPV, SQV/r	DRV/r + atorvastatin 10 mg similar to atorvastatin 40 mg administered alone; FPV +/– RTV ↑ atorvastatin AUC 130%–153%; SQV/r ↑ atorvastatin AUC 79%	Titrate atorvastatin dose carefully and use the lowest necessary dose. Do not exceed 20 mg atorvastatin daily.
	LPV/r	LPV/r ↑ atorvastatin AUC 488%	Use with caution and use the lowest atorvastatin dose necessary.
	TPV/r	↑ atorvastatin AUC 836%	**Do not co-administer.**
Lovastatin	All PIs	Significant ↑ lovastatin expected	**Contraindicated. Do not co-administer.**
Pitavastatin	All PIs	ATV ↑ pitavastatin AUC 31% and C_{max} ↑ 60% ATV: no significant effect LPV/r ↓ pitavastatin AUC 20% LPV: no significant effect	No dose adjustment necessary.

Table 15a. Drug Interactions between Protease Inhibitors (PI)* and Other Drugs (Last updated February 12, 2013; last reviewed February 12, 2013) (page 8 of 10)

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
HMG-CoA Reductase Inhibitors, continued			
Pravastatin	DRV/r	pravastatin AUC ↑ 81%	Use lowest possible starting dose of pravastatin with careful monitoring.
	LPV/r	pravastatin AUC ↑ 33%	No dose adjustment necessary.
	SQV/r	pravastatin AUC ↓ 47%–50%	No dose adjustment necessary.
Rosuvastatin	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 3,059%	**Contraindicated. Do not co-administer.**
Immunosuppressants			
Cyclosporine Sirolimus Tacrolimus	All PIs	↑ immunosuppressant possible	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/Treatment for Opioid Dependence			
Buprenorphine	ATV	buprenorphine AUC ↑ 93% norbuprenorphine[c] AUC ↑ 76% ↓ ATV possible	**Do not co-administer buprenorphine with unboosted ATV.**
	ATV/r	buprenorphine AUC ↑ 66% norbuprenorphine[c] AUC ↑ 105%	Monitor for sedation. Buprenorphine dose reduction may be necessary.
	DRV/r	buprenorphine: no significant effect norbuprenorphine[c] AUC ↑ 46% and C_{min} ↑ 71%	No dosage adjustment necessary. Clinical monitoring is recommended.
	FPV/r	buprenorphine: no significant effect norbuprenorphine[c] AUC ↓ 15%	No dosage adjustment necessary. Clinical monitoring is recommended.
	LPV/r	No significant effect	No dosage adjustment necessary.
	TPV/r	buprenorphine: no significant effect norbuprenorphine[c] AUC, C_{max}, and C_{min} ↓ 80% TPV C_{min} ↓ 19%–40%	Consider monitoring TPV level.

Table 15a. Drug Interactions between Protease Inhibitors (PI)* and Other Drugs (Last updated February 12, 2013; last reviewed February 12, 2013) (page 9 of 10)

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Narcotics/Treatment for Opioid Dependence, continued			
Oxycodone	LPV/r	oxycodone AUC ↑ 2.6 fold	Monitor for opioid-related adverse effects. Oxycodone dose reduction may be necessary.
Methadone	**RTV-boosted PIs**		
	ATV/r, DRV/r, FPV/r, LPV/r, SQV/r, TPV/r	ATV/r, DRV/r, FPV/r ↓ R-methadone[d] AUC 16%–18%; LPV/r ↓ methadone AUC 26%–53%; SQV/r 1000/100 mg BID ↓ R-methadone[d] AUC 19%; TPV/r ↓ R-methadone[d] 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.
	PIs without RTV		
	ATV	No significant effect	No dosage adjustment necessary.
	FPV	No data with unboosted FPV APV ↓ R-methadone[d] C_{min} 21%, AUC no significant change	Monitor and titrate methadone as clinically indicated. The interaction with FPV is presumed to be similar.
Phosphodiesterase Type 5 (PDE5) Inhibitors			
Avanafil	ATV, ATV/r, DRV/r, FPV/r, SQV/r, LPV/r	RTV (600 mg BID x 5 days) ↑ avanafil AUC 13-fold, C_{max} 2.4-fold	**Co-administration is not recommended.**
	FPV	No data	Avanafil dose should not exceed 50 mg once every 24 hours.
Sildenafil	All PIs	DRV/r + sildenafil 25 mg similar to sildenafil 100 mg alone; RTV 500 mg BID ↑ sildenafil AUC 1,000%; SQV unboosted ↑ sildenafil AUC 210%	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%; TPV/r steady state: no significant effect	For treatment of erectile dysfunction 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. For treatment of PAH *In patients on a PI >7 days:* Start with tadalafil 20 mg once daily and increase to 40 mg once daily based on tolerability. *In patients on tadalafil who require a PI:* Stop tadalafil ≥24 hours prior to PI initiation, restart 7 days after PI initiation at 20 mg once daily, and increase to 40 mg once daily based on tolerability. For treatment of benign prostatic hyperplasia Maximum recommended daily dose is 2.5 mg per day

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Phosphodiesterase Type 5 (PDE5) Inhibitors, continued			
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.
Miscellaneous Interactions			
Colchicine	All PIs	RTV 100 mg BID ↑ colchicine AUC 296%, C_{max} 184% With all PIs: significant ↑ in colchicine AUC expected	For treatment of gout flares Colchicine 0.6 mg x 1 dose, followed by 0.3 mg 1 hour later. Do not repeat dose for at least 3 days. *With FPV without RTV:* 1.2 mg x 1 dose and no repeat dose for at least 3 days For prophylaxis of gout flares Colchicine 0.3 mg once daily or every other day *With FPV without RTV:* colchicine 0.3 mg BID or 0.6 mg once daily or 0.3 mg once daily For treatment of familial Mediterranean fever Do not exceed colchicine 0.6 mg once daily or 0.3 mg BID. *With FPV without RTV:* Do not exceed 1.2 mg once daily or 0.6 mg BID. **Do not co-administer in patients with hepatic or renal impairment.**
Salmeterol	All PIs	↑ salmeterol possible	**Do not co-administer** because of potential increased risk of salmeterol-associated cardiovascular events.
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.

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

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

[c] Norbuprenorphine is an active metabolite of buprenorphine.

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

Acronyms: APV = amprenavir, ART = antiretroviral therapy, ARV = antiretroviral, ATV = atazanavir, ATV/r = atazanavir + ritonavir, AUC = area under the curve, BID = twice daily, CCB = calcium channel blocker, C_{max} = maximum plasma concentration, C_{min} = minimum plasma concentration, CNS = central nervous system, CrCl = creatinine clearance, CYP = cytochrome P, DRV = darunavir, DRV/r = darunavir + ritonavir, ECG = electrocardiogram, FDA = Food and Drug Administration, FPV = fosamprenavir (FPV is a pro-drug of APV), FPV/r = fosamprenavir + ritonavir, IDV = indinavir, INR = international normalized ratio, LPV = lopinavir, LPV/r = lopinavir + ritonavir, NFV = nelfinavir, PAH = pulmonary arterial hypertension, PDE5 = phosphodiesterase type 5, PI = protease inhibitor, PK = pharmacokinetic, PPI = proton pump inhibitor, RTV = ritonavir, SQV = saquinavir, SQV/r = saquinavir + ritonavir, TCA = tricyclic antidepressant, TDF = tenofovir disoproxil fumarate, TID = three times a day, TPV = tipranavir, TPV/r = tipranavir + ritonavir, VPA = valproic acid