DRUG INTERACTIONS WITH SECONDARY PROTEASE INHIBITORS

	Amprenavir (Agenerase®)	Indinavir (Crixivan®)	Nelfinavir (Viracept®)	Saquinavir hgc-(Invirase®) sgc-(Fortovase®)	Tipranavir (Aptivus®)
I) DOSING	**INFORMATION**				
Usual Dose	Amprenavir: 1200 mg po BID *NB: Amprenavir is 14% less bioavailable from liquid vs. capsules; therefore not interchangeable on a mg-per-mg basis.*	800 mg po q8h	Adults: 750 mg po TID or 1250 mg po BID Children (2-13 years old): 20-30 mg/kg/dose TID	hgc: 600 mg po q8h sgc: 1200 mg TID or 1600 mg BID	500 mg/200 mg ritonavir BID
Kinetic Characteristics	Primarily metabolized by CYP3A4. Inhibitor of CYP3A4 (similar potency as indinavir and nelfinavir)[1]; also induces CYP3A4[2].	Primarily metabolized by CYP3A4. Inhibitor of CYP3A4; may also be weak inhibitor of CYP2D6.[3, 4] Requires acidic pH for optimal absorption.	Metabolized by CYP3A4 and CYP2C19. Inhibitor of CYP3A4.[5, 6] Induces CYP2B6, 2C8 and 2C9.[7]	Primarily metabolized by CYP3A4. Weak inhibitor of CYP3A4.[3]	Substrate of CYP3A4 and P-gp. Inducer of CYP3A4, P-gp, glucuronyl transferase, slight inducer of CYP2C9, moderate inducer of CYP1A2, and potent inhibitor of CYP2D6.[8] When co-administered with ritonavir, net effect is CYP3A inhibition.[9] Capsules contain alcohol; avoid use of disulfiram and metronidazole.
Food (NB: **garlic**: see entries for Saquinavir and Ritonavir)	May be taken with or without food. Avoid taking with high-fat meal.[1] Administer amprenavir liquid solution at least 1 hour apart from other medications that contain sorbitol.	Take on empty stomach or with light meal. (77% ↓ AUC with full meal)[10]	Take with meal or light snack (2-5 fold ↑ in Cmax, AUC). Highest nelfinavir levels observed with greater food intake, i.e., 500-1000 kCal and 20-50% fat.[11]	Take within 2 hours of meal (almost 7-fold ↑ AUC with food). In a kinetic study of healthy volunteers, chronic **garlic** administration plus saquinavir-sgc 1200 mg TID led to a 51% ↓ saquinavir AUC. Use caution when combining garlic supplements with saquinavir used as a sole protease inhibitor.[12]	Take with food. When given as a single dose (without ritonavir) with a high-fat meal, tipranavir absorption ↑ 32%. Tipranavir capsules: When tipranavir 500 mg/ritonavir 200 mg BID was administered with food, tipranavir bioavailability was not altered compared to when TPV/r was administered in a fasting state.[13]
Grapefruit juice	No significant changes in amprenavir concentrations when administered with 200 mL grapefruit juice.[14]	No change in indinavir concentrations when administered with 6 oz. Double-strength grapefruit juice.[15]	Not studied.	40-100% ↑ saquinavir AUC. Take 150 mL juice with each dose.[16]	
Vitamins	**Vitamin E:** Each amprenavir capsule contains 109 IU **vitamin E** ∴ avoid additional vit. E supplements.	**Vitamin C:** In a study of healthy volunteers, Vit C 1 g daily resulted in a significant ↓ in IDV			

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		C_{max} (-20%, p = 0.04) and steady-state AUC_{8hr} (-14%, p <0.05); IDV C_{min} was 32% lower with Vit C (265 vs. 181 ng/mL, p = 0.09). Clinical significance unclear, use combination with caution.[17]			
II) ANTI-	**RETROVIRAL**	**INTERACTIONS**			
Amprenavir (APV), fos-amprenavir (FPV)		Single dose study: 31%↑ Cmax and 18% ↑ AUC of amprenavir, 35% ↓ AUC and 23% ↓ Cmax of indinavir. Multiple-dose study: 33% ↑ APV AUC, 38% ↓ IDV AUC, 27% ↓ Cmin. No dosage adjustments recommended for either drug.[18]	Amprenavir 800 mg q8h + nelfinavir 750 mg po q8h: 2.89-fold ↑ Cmin of APV (but no overall change in AUC) , 15%↑ NFV AUC. No dosage adjustment required for either drug.[18]	*Amprenavir:* In a randomized, prospective study of 11 HIV+ subjects, SQV AUC ↓ 81% and C_{12} ↓ 61% when given in a regimen of SQV 1000/rtv 100/APV 600 mg BID vs. SQV 1000/rtv 100 mg BID in the absence of APV. APV exposure was not affected. When doses were adjusted to **SQV 1400/rtv 200/APV 600 mg BID**, SQV exposure returned to baseline.[19] May wish to consider TDM if using RTV 100 mg BID dose with this combination.	Pharmacokinetic analysis in treatment-experienced subjects taking TPV 500 mg/APV 600 mg/rtv 200 mg BID showed 45% ↓ AUC, 40% ↓ Cmax, 56% ↓ Cmin of APV compared to APV 600/rtv 200 mg BID alone.[20] In a series of HIV-positive patients receiving TPV 500/FPV 1400/rtv200 mg BID, therapeutic LPV levels (>1.25 ug/mL) were observed in 67% of subjects.[21] Use combination with caution, and consider therapeutic drug monitoring if available.
Atazanavir (ATV)	Combination of ATV with amprenavir in HIV-infected peripheral blood mononuclear cells yielded additive to moderately synergistic antiviral effects.[22] In a series of expanded access subjects (n=30), combination of ATV 400 mg QD, APV 1200 mg/d, and tenofovir 300 mg/d led to lower ATV Ctrough (0.073 ug/mL) vs. either	Combination ATV with indinavir in HIV-infected peripheral blood mononuclear cells yielded additive to moderately synergistic antiviral effects.[22] However, **combination not recommended** due to the risk for additive hyperbilirubinemia.[24]	Combination of ATV with nelfinavir in HIV-infected peripheral blood mononuclear cells yielded additive to moderately synergistic antiviral effects.[22]	Additive-synergistic antiviral activity in vitro.[22] In healthy volunteers, ATV 400 mg QD plus **saquinavir-sgc 800, 1200, or 1600 mg QD** resulted in 5.4- to 7.1-fold ↑ AUC and 6.6- to 17.6-fold ↑ Cmin of saquinavir; ATV kinetics not affected.[25]	Healthy volunteer study of steady-state atazanavir 300/100 mg, tipranavir 500/100 mg BID, or tipranavir 500/100 mg BID + atazanavir 300 mg QD showed 68% ↓ AUC, 81% ↓ Cmin of ATV, and 20% ↑ AUC, 75% ↑ Cmin of TPV when drugs were coadministered. [26] Combination not recommended.

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	ATV/APV or ATV alone (0.11 and 0.251 ug/mL, respectively).[23]				
Brecanavir (BCV)					In healthy adults, a study of brecanavir 600 mg BID plus tipranavir 500/rtv 200 mg BID was stopped prior to collection of steady-state data due to asymptomatic LFT ↑ (all grades 1-2 except one subject with grade 3-4). All LFTs returned to baseline following study discontinuation. Do not co-administer this combination.[27]
Capravirine			Healthy volunteer, multi-dose study of CPV 1400 mg BID + nelfinavir 1250 mg BID with food: ↑ CPV Cmax 84%, AUC ↑ 138%, Cmin ↑ 263%, NFV kinetics unchanged.[28]	Addition of SQV 1000 mg BID to dual PI regimen of CPV 400 mg BID plus LPV/r 400/100 mg BID or CPV 700 mg BID plus LPV/r 533/133 mg BID did not affect PK of either SQV or LPV. No further dosage adjustment needed.[29]	
Cobicistat (GS-9350, a CYP3A4 inhibitor lacking anti-HIV activity)					In a fixed-sequence crossover study, healthy volunteers received **tipranavir 500 mg BID** boosted **with** either **cobicistat 150 mg BID** or ritonavir 200 mg BID. In the presence of tipranavir, cobicistat AUC ↓ 90% vs. cobicistat 150 mg BID and tipranavir AUC ↓ 54%, Cmax ↓ 38%, Ctrough ↓ 86%.[30]
Darunavir, TMC114 *(substrate of CYP3A4)*				Saquinavir-sgc: Single dose SQV-sgc 1200 mg plus 1200 mg TMC-114 BID led to 5-fold ↑ SQV AUC and Cmax and 1.4-fold ↑ TMC AUC.	
Delavirdine	Amprenavir 1200 mg	IDV 600 mg q8h +	Interaction data in	Delavirdine 400 mg	

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	+/- delavirdine 600 mg BID (healthy volunteer study) significantly increased amprenavir concentrations (4-fold ↑ AUC, 6-fold ↑ Cmin, 1.3 fold ↑ Cmax); no change in delavirdine concentrations.[31] In a separate healthy volunteer multi-dose study, administration of APV 600 mg BID +/- DLV 600 mg BID resulted in ↑ APV Cmin 133% & AUC 117%; however, median DLV Cmin ↓ 88%. Suggest avoiding this dosage combination until further data available.[32]	DLV: ↑ IDV AUC, Cmin vs. IDV 800 mg q8h alone.[33, 34] Thus, ↓ IDV to 600 mg q8h with delavirdine. Healthy volunteer study of IDV/DLV BID regimens: a) 800/600 mg BID: similar AUC, Cmax, but Cmin IDV ↓ 35-40% (vs. IDV 800 mg q8h) b) 1200/600 mg BID: similar Cmin, ↑ AUC (50-70%), ↑ Cmax (20-50%) Thus, 1200/600 mg BID may be preferable (NB: risk nephrolithiasis?); may take +/- food.[35]	HIV subjects taking DLV 600 mg TID + standard NFV: approx. 2-fold ↑ NFV AUC, and DLV Cmin similar to that with DLV 400 mg TID alone. [36] Recommendations on dosage adjustments not available. Use together with caution and monitor for drug toxicities, incl. Neutropenia. Regimens currently being studied: NFV 750 mg TID + DLV 600 mg TID, and NFV 1250 mg BID + DLV 600mg BID.	TID + saquinavir-hgc 600 mg TID in healthy volunteers: 5-fold ↑ SQV AUC, Cmin, Cmax; monitor LFTs during initial weeks of combination therapy. Dosage adjustments not necessary.[37] In a randomized study in HIV-subjects (n=10), these regimens were compared: • SQV-sgc 1200 mg TID • SQV-sgc 1400 mg + delavirdine 600 mg BID • SQV-sgc 1000 mg + delavirdine 400 mg TID When combined with DLV, SQV exposure was ↑ vs. SQV alone; SQV Cmin was higher in the TID vs. BID arm, both were greater than Cmin SQV alone.[38]	
Didanosine	No significant changes in amprenavir AUC or Cmin observed when administered: • concurrently with ddI-EC (in fasting state) • concurrently with ddI tablets (in fasting state) • 1 hour prior to ddI tablets (fasting) compared to amprenavir alone in the fasting state. Authors suggest amprenavir may be dosed concurrently with both ddI tablets and enteric-coated capsules in the fasting state.[39]	Indinavir requires acidic pH for best absorption. Separate doses by 1 hour.[4, 40] No difference in pharmacokinetics of indinavir observed when coadministered with 400 mg enteric-coated didanosine in healthy volunteers.[41]	Dosage adjustment not required. However, since didanosine needs to be administered on an empty stomach, it should be given 1 hour before or 2 hours after nelfinavir (given with food/snack).	Dosage adjustment not required. However, since didanosine needs to be administered on an empty stomach, it should be given 1 hour before or 2 hours after saquinavir (given with a full meal).	Healthy volunteer, randomized, parallel group study (n=23) of either **TPV/r 500 mg/100 mg or TPV/r 750 mg/200 mg** plus **ddI EC** 400 mg daily. At steady state, 32% ↑ Cmax and 34%↓ C12h of TPV, although overall TPV AUC unchanged; no change in ddI PK observed. [42] **Suggest giving ddI EC 2 hours apart from TPV/r.**
Dolutegravir (DTG; S/GSK1349572, integrase inhibitor)					In an open-label, single sequence crossover study, healthy volunteers received dolutegravir

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					50 mg once daily for 5 days, then tipranavir/ritonavir 500/200 mg BID for 7 days, followed by dolutegravir 50 mg QD and tipranavir/ritonavir 500/200 mg BID for 5 days. In the presence of tipranavir/ritonavir, dolutegravir AUC ↓ 59%, Cmax ↓ 46% and Ctrough ↓ 76%, likely via enzyme induction of UGT1A1 and CYP3A4. Four of 18 subjects discontinued the study due to increases in ALT during the TPV/r dosing alone. Dolutegravir concentrations remained 4-5 fold higher than the protein-adjusted IC90 for WT virus.[43] A dose adjustment of dolutegravir to 50 mg twice daily is recommended in treatment-naïve or treatment-experienced, INSTI-naïve patients. Alternative combinations that do not include metabolic inducers should be considered where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.[44]
Efavirenz	**APV 1200 mg BID + EFV 600** mg: 36% ↓ AUC, 39% ↓ Cmax, 43% ↓ Cmin APV; 15% ↑ EFV AUC[45]. Avoid negative interaction by adding either: • 200/500 mg RTV	**IDV alone:** 30-35% ↓ indinavir levels; no change in efavirenz levels. Increase IDV dosage to 1000 mg q8h.[50] **Indinavir/rtv BID** When efavirenz was added to IDV 800	Healthy volunteer study: efavirenz 600 mg + nelfinavir 750 mg q8h x 7 days: 20% ↑ NFV levels, 37% ↓ M8 levels; no change in efavirenz levels.[53]	Multiple dose healthy volunteer study of efavirenz 600 mg/day + SQV-sgc 1200 mg q8h: 12% ↓ efavirenz AUC (not clinically significant), and 62% ↓ SQV AUC. [55]	Healthy volunteer open-label, randomized, parallel group study (n=68) of either **TPV/r 500 mg/100 mg or TPV/r 750 mg/200 mg** plus EFV 600 mg daily. PK

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	BID, or • 1250 mg nelfinavir BID to APV 1200 mg BID plus EFV 600 mg qhs.[46] Other dosage combinations that yielded stable APV conc.: • **APV 600 mg/ rtv 200 mg BID** + EFV[47] • **APV 1200 mg/ rtv 300 mg QD** plus EFV[48] • APV/EFV + **NFV 1250 mg BID**[49] • APV/EFV **+ IDV 1200 mg BID**[49] • APV/EFV + **RTV 100 mg BID**[49]	mg/RTV 100 mg BID regimen, IDV exposure was significantly reduced (19% ↓ AUC, 48% ↓ Cmin). May wish to consider ↑ to indinavir 800 mg/ritonavir 200 mg BID.[51] **indinavir/rtv QD:** When efavirenz was added to IDV/RTV once daily regimens (800/100, 800/200, 1200/100), significant ↓ in IDV and RTV concentrations (esp. C24) were observed. Avoid using EFV with once daily IDV/RTV regimens.[52]	However, subsequent kinetic study in HIV+ subjects of efavirenz 600 mg qhs and nelfinavir 1250 mg BID showed ↓ 65% nelfinavir Cmin (p=0.04), ↓ 38% AUC and ↓ 21% Cmax at 32 weeks.[54] Therefore, monitor for antiretroviral efficacy when using this combination. Nelfinavir dosage adjustment may be necessary, consider therapeutic drug monitoring where available.	Can avoid this negative interaction by adding ritonavir to combination at the following doses: • saquinavir-sgc 400 mg BID • ritonavir 400 mg BID • efavirenz 600 mg qhs[56]	sampling done after single dose and at steady state. At steady state, ↑ in TPV AUC, Cmax and C12h observed with EFV.[42] In a separate healthy subject study (n=16), EFV 600 mg QD plus **TPV/r 500/200mg BID** for 14 days did not result in clinically important changes on the steady state PK of TPV or RTV, and EFV AUC levels were comparable to historical controls.[57] May consider using TPV/RTV plus EFV without further dosage adjustment.
Elvitegravir (GS-9137, integrase inhibitor)					In a crossover study, healthy volunteers were randomized to receive either elvitegravir 200 mg/ritonavir 100 mg QD, **tipranavir 500 mg/ritonavir 200 mg BID, or elvitegravir 200 mg QD plus tipranavir 500 mg/ritonavir 200 mg BID**, each for 14 days. Treatment was well tolerated, and there were no clinically relevant effects on PK parameters for either drug suggesting that this combination can be co-administered without dose adjustment.[58] In a fixed-sequence crossover study, the pharmacokinetics of **tipranavir 500 mg BID with either cobicistat 150 mg BID or ritonavir 200 mg BID** were assessed. When

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					boosted with cobicistat, tipranavir concentrations were significantly lower (Ctau ↓ 85.6%, AUC ↓ 53.8%, Cmax ↓ 37.8%) compared to those achieved when boosted with ritonavir. Avoid combination until further information is available.[30]
Enfuvirtide	No clinically significant interaction expected.	No clinically significant interaction expected.	No clinically significant interaction expected.	No clinically relevant interaction noted with co-administration of enfuvirtide 90 mg SC BID and saquinavir 1000 mg/ ritonavir 100 mg BID for 4 days in 12 HIV-infected subjects.[59]	In a series of 39 subjects taking TPV/r with or without concomitant enfuvirtide, serial TPV Ctroughs were obtained (average 3.4/pt). In subjects receiving both TPV/r and ENF, TPV Ctrough ↑ 53% and RTV Ctrough ↑ 55% compared to those on TPV/r without ENF. In 3 cases, the addition or removal of ENF led to changes in TPV levels that reflected this trend. Mechanism and clinical significance unclear.[60] Similarly, in 7 patients receiving tipranavir/ritonavir plus enfuvirtide, tipranavir concentrations were measured before and 24 weeks after enfuvirtide was replaced by raltegravir. Following the switch to raltegravir, tipranavir Cmin ↓ 31%, Cmax ↓ 57% and AUC ↓ 43%; no significant changes in ritonavir kinetics were noted. Mechanism and clinical significance of this interaction are not clear.[61]

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					A separate kinetic study conducted in 12 HIV-positive patients (8 with and 4 without ENF) did not show a significant difference in TPV levels between the 2 groups.[62] In the RESIST-1 and-2 studies, median tipranavir Cmin was 31% higher in the TPV/r plus enfuvirtide arm (n=154) compared to the TPV/r without enfuvirtide arm (n=507): i.e., 41.34 umol/L vs. 27.53 umol/L, respectively. Despite this, rates of grade 3-4 transaminase elevations were significantly lower in the TPV/r plus enfuvirtide arm compared to the TPV/r without enfuvirtide ($p<0.05$).[63]
Etravirine, TMC125, *(diaminopyrimi-dine NNRTI; inducer of CYP3A)*	Potential for decreased amprenavir concentrations secondary to enzyme induction by etravirine. Optimal dosages for co-administration have not yet been established.	Steady-state study of etravirine 1600 mg BID plus indinavir 800 mg TID (n=10) resulted in 51% ↑ AUC and Cmax of etravirine, likely due to CYP3A inhibition; indinavir AUC ↓ 46%, Cmax ↓28%.[64] Guidelines for dosage adjustment not available; avoid combination if possible, until further information available.	Potential for decreased nelfinavir concentrations secondary to enzyme induction by etravirine. Etravirine should not be co-administered with PIs without low-dose ritonavir. [65]	Etravirine 900 mg BID at steady state plus single-dose saquinavir 1200 mg (n=12) resulted in 52% ↓ AUC and 46% ↓ Cmax of saquinavir, likely due to CYP3A induction.[64] Etravirine concentrations not measured. Guidelines for dosage adjustment not available; avoid combination if possible, until further information available. Etravirine 800 mg BID did not affect pharmacokinetics of **LPV 400/RTV 100/SQV 800-1000 mg BID** in 15 HIV-	In randomized, cross-over study in healthy subjects, etravirine 800 mg BID plus TPV 500/rtv 200 mg BID led to significant reductions in etravirine concentrations (71% ↓ Cmax, 76% ↓ AUC, 82% ↓ Cmin), while TPV exposure was slightly increased (18% ↑ AUC, 14% ↑ Cmax, 24% ↑ Cmin).[67] Do not co-administer tipranavir/ritonavir and etravirine. [65]

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				infected male subjects.[66]	
Indinavir	Single dose study: 31%↑ Cmax and 18% ↑ AUC of amprenavir, 35% ↓ AUC and 23% ↓ Cmax of indinavir. Multiple-dose study: 33% ↑ APV AUC, 38% ↓ IDV AUC, 27% ↓ Cmin. No dosage adjustments recommended for either drug.[18]		In a single dose study, 83% ↑ NFV AUC, 51% ↑ IDV AUC observed.[68] In multi-dose trial of HIV-infected subjects (n=20), IDV 1200 mg and NFV 1250 mg BID provided IDV kinetics similar to IDV 800 mg q8h alone; indinavir had no effect on nelfinavir kinetics, and NFV Cmin was similar to values seen with 750 mg TID.[69]	Hgc: 5- to 8-fold ↑ SQV AUC;[70] in vitro study suggests synergy at low doses and antagonism at high doses.[71] Sgc: 620% ↑ SQV AUC (1200 mg SQV single dose + IDV 800 mg q8h x 2 days); no apparent clinically relevant changes to IDV.[72]	Potential for decreased indinavir concentrations secondary to enzyme induction by tipranavir. Optimal dosages for co-administration have not yet been established.
Lopinavir/ ritonavir	**LPV/r capsules:** • In a healthy volunteer multi-dose study, **LPV/r + APV 750 mg BID** gave similar APV AUC, and 4.6-fold ↑ Cmin vs. APV 1200 mg BID alone. However, LPV and RTV conc. were ↓ in presence of APV (LPV AUC ↓ 38%, Cmin ↓57%).[73] • Similar findings observed in cohort of HIV+ subjects with both APV and FPV formulations.[74] [75] • In a prospective cohort (n=27) of experienced patients, combination of **LPV/r 400/100 mg BID and APV 600 mg BID** led to a 54% ↓ APV exposure vs. APV/r 600/100mg BID. Addition of additional RTV 100 mg BID to combination did not improve APV levels.[76]	**Indinavir 800 mg BID + LPV/r:** In HIV+ subjects (n=5), steady-state PK of combination yielded IDV PK similar to IDV 800/r 100 mg BID; median LPV PK slightly ↓ than expected.[79] **Indinavir 600 mg BID + LPV/r:** Healthy volunteer study: similar IDV AUC, ↓ Cmax, 3.5-fold ↑ Cmin vs. IDV 800 mg q8h alone; LPV kinetics not affected.[80, 81] HIV+ subjects: In an open-label PK study (n=11), both IDV & LPV PK parameters ↓ up to 64% vs. values seen with coadministration in healthy subjects.[82] **Indinavir 400 mg BID + LPV/r:** In a case series of HIV+ men taking lopinavir/r, addition of indinavir 400 mg BID did not significantly alter median lopinavir kinetics; indinavir Cmin were above target in 5/8 subjects.[83] A	**LPV/r capsules:** Multi-dose study in healthy volunteers of LPV/r 400/100 mg BID and NFV 1000 mg BID resulted in NFV concentrations similar to those with NFV 1250 mg BID alone; LPV levels significantly ↓ in the presence of nelfinavir (LPV Cmax ↓ 21%, AUC ↓ 27%, Cmin ↓ 33%).[85] LPV dosage may need to be adjusted if coadministered with nelfinavir. **LPV/r tablets:** • Can use 400/100 mg BID with NFV in ARV-naïve subjects May ↑ to 600/150 mg (3 tablets) BID when co-administering in treatment-experienced subjects	**Saquinavir-sgc 800-1200 mg BID + lopinavir/r:** Healthy volunteer study showed 6.3-fold ↑ AUC, 9.6-fold ↑ Cmax, 16.7-fold ↑ Cmin compared to saquinavir 1200 mg TID alone. Similar SQV concentrations were observed with 1200 mg BID plus lopinavir/r. Single and steady-state saquinavir-sgc 800 mg BID had no effect on lopinavir/r kinetics.[80, 81] **Saquinavir-sgc 1000 mg BID + lopinavir/r:** In a cohort of ARV-experienced subjects (n=27), combination gave therapeutic SQV levels (median trough 1.25 ug/mL); lopinavir levels were not affected.[86]	**LPV/r capsules:** Pharmacokinetic analysis in treatment-experienced subjects taking TPV 500 mg/LPV 400 mg/rtv 100 mg BID showed 49% ↓ AUC, 43% ↓ Cmax, 55% ↓ Cmin of LPV compared to LPV/r 400/100 mg BID alone. Clinical significance not established, no current dosage recommendations available.[20] In an open-label pilot study of 12 HIV-infected subjects on stable LPV/r, two dosing regimens were studied: a) TPV 500/LPV 400/rtv 300 mg BID b) TPV 500/LPV 533/rtv 233 mg BID LPV Ctrough were generally higher compared to LPV/r alone (7.05 ug/mL group A, 5.2 ug/mL group B vs. ~4 ug/mL), but greater interpatient variability was also observed.[87]

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	• In cohort of experienced HIV-subjects (n=46), **APV 600-750 mg + LPV/r 400/100 mg BID** retrospectively compared to APV 600-750 mg/RTV 100 mg BID:
	  • with APV 600 mg dose, APV Cmin ↓ 51% with LPV/r vs. RTV alone (p=0.004)
	  • with APV 750 mg, Cmin ↓ 33 % with LPV/r vs. RTV alone (not statistically sig.)
	  • median LPV Cmin not affected by APV dose
	• Clinical significance unclear, since 85% of APV/LPV/r subjects had APV Cmin ≤3-fold Cmin with APV 1200 mg BID alone.
	
	In a prospective cohort of 12 HIV+, treatment-exp. subjects starting LPV/r plus APV 600 mg BID, 50% req. LPV/r dose ↑ to **533/133 mg or 666/166 mg BID** to achieve target LPV Cmin.[77]
	
	Optimal doses for co-administration not yet defined.
	
	Suggest TDM when using this combination.[78]
		separate study showed no significant changes in LPV or IDV Cmin with combination.[84]			In a series of HIV-positive patients receiving TPV 500/LPV 533/rtv233 mg BID, therapeutic LPV levels (>3 ug/mL) were observed in 74% of subjects.[21]
					
					Use combination with caution, and consider therapeutic drug monitoring.

Maraviroc	Maraviroc 50% dose reduction in the presence of protease inhibitors/potent CYP3A4 inhibitors is recommended.[88]	In healthy volunteers, combination of maraviroc 300 mg BID plus **fosamprenavir 1400 mg BID** led to reduced	Maraviroc 50% dose reduction in the presence of protease inhibitors/potent CYP3A4 inhibitors is recommended.[88]	When maraviroc 100 mg BID was given with **saquinavir-sgc 1200 mg TID**, maraviroc AUC ↑ 4.3-fold, Cmax ↑ 3.3-fold.[88]	Combination of maraviroc 150 mg BID plus tipranavir 500/200 mg BID in healthy subjects did not lead to any significant changes in maraviroc

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		concentrations of both drugs:[89] • MVC AUC ↓13%, Cmax ↓ 11%, Cmin ↓28% • APV AUC ↓ 44%, Cmax ↓ 51%, Cmin ↓ 1% In same study, maraviroc plus **fosamprenavir 1400/ritonavir 100 mg QD** led to:[89] • MVC AUC ↓2%, Cmax ↓ 7%, Cmin ↓23% • APV AUC ↓ 21%, Cmax ↓ 32%, Cmin ↓ 36% while maraviroc plus **fosamprenavir 700/ritonavir 100 mg BID** led to:[89] • MVC AUC ↓66%, Cmax ↓ 70%, Cmin ↓54% • APV AUC ↓ 26%, Cmax ↓ 31%, Cmin ↓ 24% These data suggest that standard dose maraviroc may be used with fosamprenavir. In an open-label, fixed sequence study in healthy volunteers, cohort 1 received **maraviroc 300 mg BID** alone, **fosamprenavir 700/100 mg BID** alone, then the combination. With coadministration, maraviroc AUC ↑ 2.49 fold, Cmax ↑ 52% and Ctau ↑ 4.74-fold, while amprenavir AUC ↓ 35%, Cmax ↓ 34% and Ctau ↓ 36%. In cohort 2, volunteers received **maraviroc 300 mg QD** alone, **fosamprenavir 1400/100 mg QD** alone, then the		When maraviroc 100 mg BID was given with **saquinavir-sgc/ritonavir 1000/100 mg BID**, maraviroc AUC ↑ 8.3-fold, Cmax ↑ 4.2-fold. Reduction of maraviroc dose to 25 mg BID resulted in maraviroc AUC ↑ 1.4-fold. Maraviroc 50% dose reduction in the presence of protease inhibitors/potent CYP3A4 inhibitors is recommended.[88]	exposure.[91] Regular dosing of maraviroc (i.e., 300 mg BID) may be used with tipranavir/ritonavir.

	Amprenavir (Agenerase®)	Indinavir (Crixivan®)	Nelfinavir (Viracept®)	Saquinavir hgc-(Invirase®) sgc-(Fortovase®)	Tipranavir (Aptivus®)
		combination. With coadministration, maraviroc AUC ↑ 2.26 fold, Cmax ↑ 45% and Ctau ↑ 1.8-fold, while amprenavir AUC ↓ 30%, Cmax ↓ 29% and Ctau ↓ 15%. The combination was well tolerated. Further investigation of maraviroc 300 mg QD with fosamprenavir 1400/100 mg QD is suggested.[90]			
Nelfinavir	Amprenavir 800 mg q8h + nelfinavir 750 mg po q8h: 2.89-fold ↑ Cmin of APV (but no overall change in AUC) , 15%↑ NFV AUC. No dosage adjustment required for either drug.[18]	In a single dose study, 83% ↑ NFV AUC, 51% ↑ IDV AUC observed.[68] In multi-dose trial of HIV-infected subjects (n=20), IDV 1200 mg and NFV 1250 mg BID provided IDV kinetics similar to IDV 800 mg q8h alone; indinavir had no effect on nelfinavir kinetics, and NFV Cmin was similar to values seen with 750 mg TID.[69]		At steady-state, 169% ↑ SQV-soft gel capsules AUC, no significant changes in NFV concentrations[55]; may use lower dose of SQV-SGC (i.e., 800 mg vs. 1200 mg TID + NFV 750 mg TID, or SQV-sgc 1200 mg BID + NFV 1250 mg BID).[72, 92, 93]	Potential for decreased nelfinavir concentrations secondary to enzyme induction by tipranavir. Optimal dosages for co-administration have not yet been established.
Nevirapine	With **APV 600/RTV 100 mg BID/NVP 400 mg QD**, APV Cmin and Cmax ↓ 80%, AUC ↓ 77%. APV plasma levels stable with **APV 450/RTV 200 mg BID plus NVP 400 mg daily.**[94] Therefore, recommend APV 450/RTV 200 mg BID with NNRTIs.	28% ↓ IDV AUC, <10%↓ NVP AUC (non-significant). Suggest ↑ IDV dose to 1000 mg q8h when using with NVP 200 mg BID.[95] Preliminary data suggest that dosing nevirapine 400 mg once daily may have a more pronounced effect on decreasing indinavir concentrations compared to nevirapine dosed 200 mg twice daily (median 31% decrease). These findings require further substantiation; may	No statistically significant changes in NFV levels after the addition of NVP (AUC +8%, Cmax +14%, and Cmin +2%). Compared to historical controls, NVP levels appear to be unchanged.[97] Similar results were demonstrated in a separate study, and NFV Cmin remained above minimum effective concentration during nevirapine coadministration.[98] Thus, dosage adjustments not required.	27%↓ SQV AUC; clinical significance unknown.[99] Preliminary data suggest that dosing nevirapine 400 mg once daily may have a more pronounced effect on decreasing saquinavir concentrations compared to nevirapine dosed 200 mg twice daily (median 31% decrease). These findings require further substantiation; may consider monitoring saquinavir levels/response if switching nevirapine	Healthy volunteer study of 1250 mg TPV BID plus 200 mg BID NVP +/- 200 mg RTV BID:[100] • no sig. impact on TPV levels • NVP AUC ↓37% by TPV (stat. sig),; levels improved with addition of RTV • RTV clearance sig. ↑ in presence of TPV and NVP, but still higher than historical controls May consider using TPV/RTV plus NVP without further

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		consider monitoring indinavir levels/response if switching nevirapine dosage regimen.[96]		dosage regimen.[96]	dosage adjustment.
Raltegravir, MK-0518 (integrase inhibitor)					In an open-label, 3 period study in 15 healthy subjects, addition of 400 mg raltegravir BID to steady-state TPV 500/rtv 200 mg BID for 4 days led to a 55% ↓ in raltegravir Cmin, while AUC ↓ 24% and Cmax ↓ 18%. The combination was generally well tolerated.[101] Although this result is borderline for clinical significance for C12 hr, there are considerable safety and efficacy data available for the concomitant use of tipranavir and raltegravir from the Phase III studies, which support the efficacy of this combination. There was no clinically meaningful difference in the efficacy profile of raltegravir with or without coadministration of tipranavir. Based on these data, tipranavir may be coadministered with raltegravir without dose adjustment. In an open-label study of 7 treatment-experienced patients initiating salvage therapy, optimized background therapy (OBT) and raltegravir 400 mg BID were initiated, with tipranavir 500/ritonavir 200 mg BID added on 4 days later; intensive 12-

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					hour PK was performed at days 4 and 19. In the presence of steady-state tipranavir/ritonavir, raltegravir AUC ↓ 28%, Cmax ↑ 5% and C12 ↑ 7% compared to raltegravir without TPV/r. At week 24, viral load was <50 in all patients (n=6) who completed the study; 1 patient discontinued at week 3 due to GI intolerance. Two subjects developed grade 3 transaminase elevations which resolved (1 spontaneously, one upon dose reduction to tipranavir 500/100 mg BID).[102]
Rilpivirine	Potential for ↑ concentrations of rilpivirine. Rilpivirine is not expected to affect the plasma concentrations of co-administered PIs.[103]	Potential for ↑ concentrations of rilpivirine. Rilpivirine is not expected to affect the plasma concentrations of co-administered PIs.[103]	Potential for ↑ concentrations of rilpivirine. Rilpivirine is not expected to affect the plasma concentrations of co-administered PIs.[103]	Potential for ↑ concentrations of rilpivirine. Rilpivirine is not expected to affect the plasma concentrations of co-administered PIs.[103]	Potential for ↑ or ↓ concentrations of rilpivirine. Rilpivirine is not expected to affect the plasma concentrations of co-administered PIs.[104]
Ritonavir	Amprenavir AUC, C_{min} and C_{max} were ↑ by 131%, 484% and 33%, respectively, when ritonavir 200mg BID was given with amprenavir 1200mg BID.[105] Amprenavir AUC, Cmin significantly ↑, ↓ Cmax when combined with ritonavir in the following dosages:[106-108] • 450/300 mg BID • 600/100 mg BID • 1200/200 mg once daily. Preliminary clinical data (12 weeks) promising for 600/100 mg BID and 1200/200 mg QD.[109]	***IDV/RTV 400/400 mg BID*** in healthy volunteers yielded indinavir AUC similar to those achieved with IDV 800 mg po q8h alone.[111] Also improved IDV PK profile: 62% ↓ Cmax, 3-fold ↑ Cmin, less impact of food on IDV absorption when given with RTV vs. alone,[112] ↓ nephrolithiasis in one case series.[113] ***IDV 800/RTV 100-200 mg BID*** also results in ↑ IDV trough levels compared to those with IDV 800 mg q8h alone;[114, 115] however, ↑ IDV peak	162% ↑ NFV AUC, 9% ↑ RTV AUC.[124] ***RTV 400 mg BID plus NFV 500-750 mg BID***: NFV AUC similar to that seen with NFV 750 mg TID alone; M8 levels higher with NFV 750 BID regimen. Higher RTV AUC, Cmin values when combined with NFV 500 mg vs. 750 mg BID. Overall, PK benefits similar with 2 regimens.[125] ***RTV 100-200 mg BID added to NFV 1250 mg BID*** resulted in 30%↑ NFV AUC; steady-state a.m. predose	***400 mg SQV-sgc /400 mg RTV BID:*** • 121% ↑ SQV AUC[128] ***800 mg SQV-sgc/200-400 mg RTV BID:*** • 1589-2158% ↑ SQV AUC[55] ***1600 mg SQV-sgc/RTV 100 mg QD:*** • Preliminary data in healthy volunteers: 300-800% ↑ SQV AUC, Cmin > than with SQV-sgc 1200 mg TID.[129] • Kinetic substudy in 13 HIV+ subjects stabilized on combination showed equivalent SQV kinetic parameters (GMR	Open-label, dose-ranging study in healthy subjects of TPV 250, 500, 750, 1000, or 1250 mg BID + 100/200 mg RTV BID: TPV Cmax, AUC ↑ at least 4-fold and TPV Cmin ↑ at least 20-fold when combined with RTV. More consistent inhibition of CYP3A4 activity with RTV 200 mg vs. 100 mg dose.[133]

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	Ritonavir ↑ plasma APV to similar extent with either APV or FPV. Therefore, FPV may replace APV, and metablic APV interactions are applicable to FPV.[110]	levels[116], possible ↑ risk nephrolithiasis[117] or other adverse events.[118] IDV 600/RTV 200 mg BID may provide increased IDV Cmin without significantly increasing IDV Cmax.[119] ***IDV 400/RTV100 mg BID*** (open study, n=17): ↑ Cmin (~0.5 ug/mL), ↓ Cmax vs. IDV 800mg q8h.[120] Preliminary data on ***once daily dosing*** (1200/100-200 mg IDV/RTV) regimens show ↑ Cmax, and Cmin = those with 800 mg q8h.[121, 122] 1200/200mg QD regimen well-tolerated in naïve-subjects (n=40) up to 24 weeks; 1200/400 QD also under study.[123]	NFV concentrations ↑ 45-90%.[126] In healthy volunteers, nelfinavir 2000 mg/ritonavir 200 mg once daily provided ↑ AUC, Cmax and comparable Cmin compared to nelfinavir 1250 mg BID.[127]	of hgc/sgc for AUC 1.40, Cmax 1.23, and Cmin 1.46) when SQV-sgc replaced by SQV-hgc[130] • Intracellular t1/2 of SQV & RTV longer than plasma (median 4.5 & 5.9 hrs, p=0.034, and 4.1 & 6.2 hrs, p=0.033, respectively)[131] ***1000 mg SQV/100 mg RTV BID*:** • Compared SQV-sgc vs. SQV-hgc plus RTV in healthy subjects • SQV-hgc/r gave significantly higher SQV levels vs. SQV-sgc/r (Cmin: 217 vs 153 ng/mL, p=0.0147, AUC 15798 ng.h/mL vs. 11655 ng.h/mL, p=0.0043); also significantly less GI side effects with SQV-hgc/r vs. SQV-sgc/r, possibly due to capmul content of SQV-sgc.[132]	
Saquinavir	In a randomized, prospective study of 11 HIV+ subjects, SQV AUC ↓ 81% and C_{12} ↓ 61% when given in a regimen of SQV 1000/rtv 100/APV 600 mg BID vs. SQV 1000/rtv 100 mg BID in the absence of APV. APV exposure was not affected. When doses were adjusted to **SQV 1400/rtv 200/APV 600 mg BID**, SQV exposure returned to baseline.[19]	Hgc: 5- to 8-fold ↑ SQV AUC;[70] in vitro study suggests synergy at low doses and antagonism at high doses.[71] Sgc: 620% ↑ SQV AUC; no apparent clinically relevant changes to IDV.[72]	SQV levels ↑, no significant changes in NFV concentrations with combination of SQV-hgc plus NFV. [134-136] Final 48-week analysis showed durable viral suppression with either SQV-hgc 600/NFV 750 mg TID or 1 g SQV/1250 mg NFV BID.[137]		Pharmacokinetic analysis in treatment-experienced subjects taking TPV 500 mg/SQV 1000 mg/rtv 200 mg BID showed 70% ↓ AUC, 66% ↓ Cmax, 81% ↓ Cmin of SQV compared to boosted SQV alone. Clinical significance not established, no current dosage recommendations available. Use combination with caution.[20]
Tenofovir	In healthy volunteers, tenofovir 300 mg daily plus fosamprenavir 1400/ritonavir 100-200 mg QD for 14	In healthy volunteers, tenofovir 300 mg daily plus indinavir 800 mg q8h resulted in slightly delayed Tmax and ↓	In 18 patients stabilized on nelfinavir 1250 mg BID, addition of tenofovir 300 mg QD for 7 days did not	In cohort (n=14) of patients on **saquinavir-hgc 1600 mg/ ritonavir 100 mg QD**, no significant difference	Healthy volunteer, randomized, parallel group study (n=49) of either **TPV/r 500 mg/100 mg or TPV/r 750 mg/200 mg** plus

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	days showed no change in amprenavir AUC and a non-significant ↑ in Cmin. A non-significant ↑ in ritonavir AUC and Cmax were observed in the FPV 1400/rtv 200 mg arm in the presence of tenofovir.[138] In a cohort of 21 HIV-infected subjects taking fosamprenavir 700/ritonavir 100 mg BID plus tenofovir and an NRTI, steady-state Cmin concentrations of amprenavir, ritonavir and tenofovir were within the therapeutic range and comparable to historical controls.[139]	Cmax of indinavir, but overall AUC was unchanged; tenofovir Cmax was slightly ↑ but AUC unchanged. These changes not likely to be clinically significant; indinavir and tenofovir may be coadministered without dosage adjustment.[140]	affect the AUC of nelfinavir. Combination may be coadministered without dosage adjustment.[141]	in saquinavir Cmin when NRTI backbone switched from ddI/d4T to tenofovir/3TC.[142] Separate study of **saquinavir-hgc 1000 mg/ritonavir 100 mg BID** and tenofovir (n=18 HIV+ adults) showed no change in tenofovir PK parameters with coadministration.[143] Similar effect observed in healthy volunteer study.[144]	tenofovir 300 mg daily. At steady state, a dose-dependent ↓ in TDF Cmax of 23%–38% was shown, and 17% and 11% ↓ in TPV at the 500/100 and 750/200 doses, respectively.[42] May consider using TPV/r plus tenofovir without further dosage adjustment.
Tipranavir *(inducer of CYP3A4 and glucuronyl transferase)*	Pharmacokinetic analysis in treatment-experienced subjects taking TPV 500 mg/APV 600 mg/rtv 200 mg BID showed 45% ↓ AUC, 40% ↓ Cmax, 56% ↓ Cmin of APV compared to APV 600/rtv 200 mg BID alone. Clinical significance not established, no current dosage recommendations available. Use combination with caution.[20]	Potential for decreased indinavir concentrations secondary to enzyme induction by tipranavir. Optimal dosages for co-administration have not yet been established.	Potential for decreased nelfinavir concentrations secondary to enzyme induction by tipranavir. Optimal dosages for co-administration have not yet been established.	Pharmacokinetic analysis in treatment-experienced subjects taking TPV 500 mg/SQV 1000 mg/rtv 200 mg BID showed 70% ↓ AUC, 66% ↓ Cmax, 81% ↓ Cmin of SQV compared to boosted SQV alone. Clinical significance not established, no current dosage recommendations available. Use combination with caution.[20]	
Vicroviroc			The combination of vicriviroc 15 mg QD /ritonavir 100 mg BID plus nelfinavir 1250 mg BID in healthy volunteers did not lead to significant changes in vicriviroc plasma levels, compared to vicriviroc 15 mg QD /ritonavir 100 mg BID alone. Vicriviroc may be added to a		

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			ritonavir-boosted PI regimen without dosage adjustment.[145]		
Zidovudine *(GT 60-75% > CYP3A, minor)*	Amprenavir may inhibit ZDV glucuronidation to a small degree; no dosage adjustment necessary.[146]	Slight ↑ in AUCs of both drugs. No dosage modification necessary.[4]	Nelfinavir dosage adjustment not required with zidovudine, lamivudine, or stavudine.[6]	No interaction.	Healthy volunteer, randomized, parallel group study (n=60) of either **TPV/r 500 mg/100 mg or TPV/r 750 mg/200 mg** plus AZT 300 mg BID. At steady state, TPV/r caused a 56%–61% ↓ in ZDV Cmax and a 33%–43% ↓ in AUC. ZDV did not affect the PK of TPV/r.[42] May consider using TPV/r plus AZT at usual doses.
III)	**INTERACTIONS WITH OTHER**	**MEDICATIONS:**			
Antacids (NB: see separate entries for H2-blockers and Proton-pump inhibitors)	Separate doses by at least an hour to avoid potential interference with absorption.[105]	Indinavir requires acidic pH for best absorption. Separate indinavir and antacid doses by 1 hour.[4]			In healthy volunteers, coadministration of single-dose Maalox on tipranavir 500 mg/ritonavir 200 mg BID resulted in 25-29% ↓ in tipranavir AUC, Cmax and C12 ($p<0.01$). May consider separating tipranavir/rtv and antacid doses by at least 1 hour.[147]
Antihistamines, non-sedating (i.e., astemizole, terfenadine) *(CYP3A4)*	Possible ↑ antihistamine AUC and cardiotoxicity. **Avoid combination.**[105]	Possible ↑ antihistamine AUC and cardiotoxicity. **Avoid combination**.[4]	↑ terfenadine AUC; **avoid combination**.[68] Potential for similar interaction with astemizole.	368% ↑ terfenadine AUC; **avoid combination**.[72] Potential for similar interaction with astemizole.	
Benzodiazepine • alprazolam, midazolam, triazolam, zolpidem (CYP3A4) • diazepam (2C19>3A4)	Risk of prolonged sedation. **Avoid combination**, or use agents which are glucuronidated (e.g., lorazepam, oxazepam, temazepam).[105]	Risk of prolonged sedation. Use with caution.[4]	Risk of prolonged sedation. **Avoid combination**, or use agents which are glucuronidated (e.g., lorazepam, oxazepam, temazepam).[6]	Possible risk of prolonged sedation. Use with caution.[148]	
Calcium channel blockers, e.g. • amlodipine, bepredil, diltiazem, felodipine, nicardipine,	Potential for ↑ calcium channel blocker concentrations with concomitant protease inhibitor therapy. If coadministration is	Healthy subjects on steady-state indinavir 800/ritonavir 100 mg BID received either either diltiazem 120 mg daily or amlodipine 5 mg	Potential for ↑ calcium channel blocker concentrations with concomitant protease inhibitor therapy. If coadministration is	Potential for ↑ calcium channel blocker concentrations with concomitant protease inhibitor therapy. If coadministration is	Potential for ↑ calcium channel blocker concentrations with concomitant protease inhibitor therapy. In healthy subjects on indinavir

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nimodipine, verapamil (CYP3A substrates)	necessary, initiate calcium blocker therapy at low doses, with careful titration to response and side effects	daily for 7 days. In the presence of indinavir/ritonavir, amlodipine AUC ↑ 90% and diltiazem AUC ↑ 27%. 2/13 subjects (15%) had >4-fold ↑ diltiazem AUC. Desacetyldiltiazem AUC ↑ by 102% and desmethyldiltiazem AUC ↓ by 27%. Steady-state AUCs of indinavir and ritonavir were not affected by either amlodipine or diltiazem. If coadministration is necessary, initiate calcium blocker therapy at low doses, with careful titration to response and side effects.[149]	necessary, initiate calcium blocker therapy at low doses, with careful titration to response and side effects	necessary, initiate calcium blocker therapy at low doses, with careful titration to response and side effects	800/ritonavir 100 mg BID, steady-state amlodipine AUC ↑ 90% and diltiazem AUC ↑ 27% (NB: 2/13 subjects (15%) had >4-fold ↑ diltiazem AUC).[149] If coadministration is necessary, initiate calcium blocker therapy at low doses, with careful titration to response and side effects.
Caspofungin			Open-label study in 9 healthy male subjects, who received a 14 day course of caspofungin 50 mg intravenously along with nelfinavir 1250 mg twice daily. Steady-state caspofungin levels were unaltered in the presence of nelfinavir. No dosage adjustments necessary.[150]		
Cisapride *(CYP3A4)*	Possible ↑ cisapride AUC and cardiotoxicity. **Avoid combination.**[105]	Possible ↑ cisapride AUC and cardiotoxicity. **Avoid combination**.[4]	Possible ↑ cisapride AUC and cardiotoxicity. **Avoid combination**.[6]	Possible ↑ cisapride AUC and cardiotoxicity. **Avoid combination**.[148]	
Clarithromycin *(parent: CYP3A4; inhibits CYP3A4, 1A2?) (CLA-14 OH: renal, CYP3A4)*	Multi-dose trial in healthy volunteers, using 1200 mg APV BID + 500 mg CLA BID: 18% ↑ APV AUC, 10% ↓ CLA Cmax, 35% ↓ AUC of CLA-14 OH metabolite. No dosage adjustment necessary for either drug.[151]	29% ↑ indinavir AUC, 53% ↑ clarithromycin AUC. No dose modification necessary.[4]	Nelfinavir may be administered with macrolides (including azithromycin, clarithromycin, erythromycin) without dosage adjustment.[5] In healthy volunteers, coadminstration of NFV 750mg TID plus 1200 mg azithromycin resulted in 28% ↓	177% ↑ SQV-sgc AUC; 45% ↑ clarithromycin AUC.[72]	In healthy volunteers, coadministration of tipranavir 500/rtv 200 mg BID plus clarithromycin 500 mg BID led to 68% ↑ clarithromycin Cminss and almost full inhibition of CLA-14OH metabolite, while steady-state TPV AUC ↑ 59%, Cmax ↑ 43%, and

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			NFV and 23% ↓ M8 AUC (not clin. significant), and >100% ↑ azithromycin AUC.[152]		Cmin ↑ 112%. **No dosage adjustment needed for clarithromycin in subjects with normal renal function.**[153] However, inhibition of CLA-OH metabolite will ↓ Gram-neg. activity, such as H. influenzae. In patients with Clcr 30-60 mL/min, ↓ clarithromycin dose 50%; if Clcr<30 mL/min, ↓ clarithromycin dose 75%.
Colchicine *(biliary, renal excretion; p-glycoprotein substrate)*	Potential for significant ↑ colchicine AUC due to P-gp inhibition and ↓ biliary excretion. **For fosamprenavir/ ritonavir:** <u>For treatment of gout flares</u>: use 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>For prophylaxis of gout flares:</u> use colchicine 0.3 mg once daily or every other day. <u>For treatment of familial Mediterranean fever:</u> Do not exceed colchicine 0.6 mg once daily or 0.3 mg BID.[154] **For unboosted fosamprenavir:** <u>For treatment of gout flares</u>: use 1.2 mg x 1 dose and no repeat dose for at least 3 days. <u>For prophylaxis of gout flares:</u> use colchicine 0.3 mg BID or 0.6 mg once daily or 0.3 mg once	Potential for significant ↑ colchicine AUC due to P-gp inhibition and ↓ biliary excretion. <u>For treatment of gout flares</u>: use 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>For prophylaxis of gout flares:</u> use colchicine 0.3 mg once daily or every other day. <u>For treatment of familial Mediterranean fever:</u> Do not exceed colchicine 0.6 mg once daily or 0.3 mg BID.[154] Monitor for colchicine toxicity.	Potential for significant ↑ colchicine AUC due to P-gp inhibition and ↓ biliary excretion. <u>For treatment of gout flares</u>: use 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>For prophylaxis of gout flares:</u> use colchicine 0.3 mg once daily or every other day. <u>For treatment of familial Mediterranean fever:</u> Do not exceed colchicine 0.6 mg once daily or 0.3 mg BID.[154] Monitor for colchicine toxicity.	Potential for significant ↑ colchicine AUC due to P-gp inhibition and ↓ biliary excretion. <u>For treatment of gout flares</u>: use 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>For prophylaxis of gout flares:</u> use colchicine 0.3 mg once daily or every other day. <u>For treatment of familial Mediterranean fever:</u> Do not exceed colchicine 0.6 mg once daily or 0.3 mg BID.[154] Monitor for colchicine toxicity.	Potential for significant ↑ colchicine AUC due to P-gp inhibition and ↓ biliary excretion. <u>For treatment of gout flares</u>: use 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>For prophylaxis of gout flares:</u> use colchicine 0.3 mg once daily or every other day. <u>For treatment of familial Mediterranean fever:</u> Do not exceed colchicine 0.6 mg once daily or 0.3 mg BID.[154] Monitor for colchicine toxicity.

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	daily. For treatment of familial Mediterranean fever: Do not exceed 1.2 mg once daily or 0.6 mg BID.[154] Monitor for colchicine toxicity.				
Corticosteroids (oral/inhaled, injectable or topical) e.g., betamethasone, budesonide, dexamethasone, fluticasone, prednisone, triamcinolone *Note: see also Salmeterol*	**Avoid coadministration of fluticasone** and boosted protease inhibitors. Inhaled beclomethasone or ciclesonide, or intranasal beclomethasone or triamcinolone may be safer alternatives, but caution is still warranted. Use lowest possible corticosteroid dose and monitor closely for systemic corticosteroid side effects.[155]	**Avoid coadministration of fluticasone** and boosted protease inhibitors. Inhaled beclomethasone or ciclesonide, or intranasal beclomethasone or triamcinolone may be safer alternatives, but caution is still warranted. Use lowest possible corticosteroid dose and monitor closely for systemic corticosteroid side effects.[155]	**Avoid coadministration of fluticasone** and boosted protease inhibitors. Inhaled beclomethasone or ciclesonide, or intranasal beclomethasone or triamcinolone may be safer alternatives, but caution is still warranted. Use lowest possible corticosteroid dose and monitor closely for systemic corticosteroid side effects.[155]	**Avoid coadministration of fluticasone** and boosted protease inhibitors. Inhaled beclomethasone or ciclesonide, or intranasal beclomethasone or triamcinolone may be safer alternatives, but caution is still warranted. Use lowest possible corticosteroid dose and monitor closely for systemic corticosteroid side effects.[155]	**Avoid coadministration of fluticasone** and boosted protease inhibitors. Inhaled beclomethasone or ciclesonide, or intranasal beclomethasone or triamcinolone may be safer alternatives, but caution is still warranted. Use lowest possible corticosteroid dose and monitor closely for systemic corticosteroid side effects.[155]
Digoxin *(p-glycoprotein substrate, 57-80% Clr)*	Potential for ↑ digoxin concentrations via PI-mediated inhibition of renal p-glycoprotein. Use combination with caution. Monitor digoxin levels and response, and adjust dose if necessary.	Case report of woman maintained on indinavir, 3TC, d4T and digoxin 0.25 mg/d who experienced acute digoxin toxicity 3 days after ritonavir 200 mg BID added to regimen. Symptoms resolved after ritonavir discontinued, and patient resumed original HAART without incident.[156]	Potential for ↑ digoxin concentrations via PI-mediated inhibition of renal p-glycoprotein. Use combination with caution. Monitor digoxin levels and response, and adjust dose if necessary.	Potential for ↑ digoxin concentrations via PI-mediated inhibition of renal p-glycoprotein. Use combination with caution. Monitor digoxin levels and response, and adjust dose if necessary.	Potential for ↑ digoxin concentrations via PI-mediated inhibition of renal p-glycoprotein. Use combination with caution. Monitor digoxin levels and response, and adjust dose if necessary.
Ergot alkaloids *(CYP3A>others)*	**Concurrent administration is contraindicated.**[105] Clinical ergotism reported in 23 Thai patients on boosted PIs (n=22) or efavirenz (n=1) after median 1 day (range 1-14) of ergotamine use. 78% experienced complete recovery	**Concurrent administration is contraindicated.**[4] Clinical ergotism reported in 23 Thai patients on boosted PIs (n=22) or efavirenz (n=1) after median 1 day (range 1-14) of ergotamine use. 78% experienced complete recovery	**Concurrent administration is contraindicated.**[6] Clinical ergotism reported in 23 Thai patients on boosted PIs (n=22) or efavirenz (n=1) after median 1 day (range 1-14) of ergotamine use. 78% experienced complete recovery	**Coadministration is contraindicated.**[148] Clinical ergotism reported in 23 Thai patients on boosted PIs (n=22) or efavirenz (n=1) after median 1 day (range 1-14) of ergotamine use. 78% experienced complete recovery but 5 patients did	**Coadministration is contraindicated.**[9] Clinical ergotism reported in 23 Thai patients on boosted PIs (n=22) or efavirenz (n=1) after median 1 day (range 1-14) of ergotamine use. 78% experienced complete recovery but 5 patients did

	Amprenavir (Agenerase®)	Indinavir (Crixivan®)	Nelfinavir (Viracept®)	Saquinavir hgc-(Invirase®) sgc-(Fortovase®)	Tipranavir (Aptivus®)
	but 5 patients did not: ulcer/persistent numbness (n=1), gangrene (n=1), amputation (n=2), death (n=1).[157]	but 5 patients did not: ulcer/persistent numbness (n=1), gangrene (n=1), amputation (n=2), death (n=1).[157]	but 5 patients did not: ulcer/persistent numbness (n=1), gangrene (n=1), amputation (n=2), death (n=1).[157]	not: ulcer/persistent numbness (n=1), gangrene (n=1), amputation (n=2), death (n=1).[157]	not: ulcer/persistent numbness (n=1), gangrene (n=1), amputation (n=2), death (n=1).[157]
Fluconazole *(~80% Clrenal, 11% metabolized via CYP3A4; inhibits 3A4 (weak), 2C9, 2C19)*		No clinically significant effect on indinavir AUC. OK to use combination.[4]	Nelfinavir may be administered with azoles (including fluconazole, itraconazole, and ketoconazole) without dosage adjustment.[158]		In healthy volunteers, coadministration of TPV 500/rtv 200 mg BID with fluconazole 100 mg QD resulted in 56%↑ AUC, 46% ↑ Cmax, 104% ↑ C12 of TPV; fluconazole PK parameters not significantly changed.[153] Fluconazole doses >200 mg/day are not recommended.
Ginko biloba *(CYP3A inducer)*	Potential for ↓ amprenavir concentrations due to CYP3A induction by ginko biloba.[159] Case report of viral breakthrough and resistance to efavirenz after introduction of ginko biloba.[160] **Avoid concomitant use with unboosted amprenavir.**	Potential for ↓ indinavir concentrations due to CYP3A induction by ginko biloba.[159] Case report of viral breakthrough and resistance to efavirenz after introduction of ginko biloba.[160] **Avoid concomitant use.**	Potential for ↓ nelfinavir concentrations due to CYP3A induction by ginko biloba.[159] Case report of viral breakthrough and resistance to efavirenz after introduction of ginko biloba.[160] **Avoid concomitant use.**	Potential for ↓ saquinavir concentrations due to CYP3A induction by ginko biloba.[159] Case report of viral breakthrough and resistance to efavirenz after introduction of ginko biloba.[160] **Avoid concomitant use with unboosted saquinavir.**	Plasma exposure of boosted protease inhibitors unlikely to be affected by ginko biloba;[159] however, concentrations of unboosted PIs may be decreased.
H2 blockers (including cimetidine, famotidine, nizatidine, ranitidine, etc.)		Coadministration of cimetidine (600 mg twice daily for 6 days) and indinavir (400 mg single dose) to 12 subjects led to a 7% ↑ in Cmax, 2% ↓ AUC, and 18% ↓ Cmin of IDV.[4] Combination may be coadministered.		Healthy volunteer study of SQV-sgc 1200 mg TID vs. SQV 1200 mg BID plus cimetidine 400 mg BID: SQV AUC ↑ 120%, Cmax ↑ 179%, Cmin stable in presence of cimetidine.[161]	
Hmg-CoA Reductase inhibitors • atorvastatin *(CYP3A)* • fluvastatin *(2C9>>3A)* • lovastatin *(CYP3A)* • pitavastatin *(UGT1A3,UGT2B7>>*	Potential for ↑ concentrations of statins due to enzyme inhibition by amprenavir. Use combination with caution, use lowest atorvastatin or rosuvastatin dose necessary, or use a fibric acid derivative for	Potential for ↑ concentrations of statins due to enzyme inhibition by by indinavir. Use combination with caution, use lowest atorvastatin or rosuvastatin dose necessary, or use a fibric acid derivative for	Pharmacokinetic study in HIV-negative subjects taking nelfinavir 1250 mg BID plus either 10 mg **atorvastatin** or 20 mg **simvastatin** resulted in[163]: • 506% ↑ AUC simvastatin • 74% ↑ AUC	Pharmacokinetic study in HIV-negative subjects taking saquinavir 400 mg/ritonavir 400 mg BID plus 40 mg of atorvastatin, pravastatin, or simvastatin revealed the following effects:	Potential for ↓ /↑ concentrations of **lovastatin, and simvastatin**, possibly **fluvastatin** due to enzyme induction by tipranavir or enzyme inhibition by ritonavir. In healthy volunteers,

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CYP2C9, 2C8) • pravastatin *(40-50% Clr, > 3A4)* • rosuvastatin *(10% via 2C9, 2C19)* • simvastatin *(CYP3A)*	hypertriglyceridemia. **Lovastatin and simvastatin** are contraindicated with all HIV protease inhibitors.[162]	hypertriglyceridemia. **Lovastatin and simvastatin** are contraindicated with all HIV protease inhibitors.[162]	atorvastatin Do not exceed **40 mg atorvastatin** daily with nelfinavir. **Lovastatin and simvastatin** are contraindicated with all HIV protease inhibitors.[162]	• 35% ↓ AUC pravastatin • 31.6 fold ↑ AUC simvastatin • 4.5-fold ↑ AUC atorvastatin[164] **Pravastatin** may be administered without dosage adjustment. **Do not exceed 20 mg atorvastatin daily.** **Lovastatin and simvastatin** are contraindicated with all HIV protease inhibitors.[162]	coadministration of **atorvastatin 10 mg** with tipranavir 500 mg/ritonavir 200 mg BID resulted in 9-fold ↑ in atorvastatin AUC compared to atorvastatin alone.[147] **Avoid using atorvastatin and tipranavir**.[162] In 16 healthy volunteers, **tipranavir 500/ritonavir 200 mg BID** plus single dose rosuvastatin 10 mg led to 37% ↑ AUC and 123% ↑ Cmax of rosuvastatin; TPV and RTV levels were not changed in the presence of rosuvastatin. Use lowest dose of rosuvastatin (5 mg/day) and titrate slowly to treatment response.[165] **Lovastatin and simvastatin** are contraindicated with all HIV protease inhibitors.[162]
Itraconazole *(CYP3A4; inhibits 3A, 2C9)*	Potential for increased itraconazole and/or amprenavir concentrations. Clinical significance unclear, monitor for dose-related toxicities.	In a multiple-dose study, administration of itraconazole 200 mg BID with indinavir 600 mg every 8 hours resulted indinavir AUC similar to what would be expected from indinavir 800 mg every eight hours alone.[4] Consider reducing indinavir dose to 600 mg q8h.	Potential for increased itraconazole and/or nelfinavir concentrations. Clinical significance unclear, monitor for dose-related toxicities.	In a prospective randomized study in 17 HIV-infected subjects, saquinavir-sgc 800 or 1200 mg BID plus itraconazole 100 mg daily resulted in SQV concentrations equivalent to SQV-sgc 1400 mg BID alone.[166]	No data, use with caution. Do not exceed itraconazole 200 mg daily.
Ketoconazole *(CYP3A4; inhibits 3A, 2C9)*	32% ↑ amprenavir AUC, 44% ↑ ketoconazole AUC. Clinical significance unclear.[167]	Single-dose study of indinavir 400 mg and ketoconazole 400 mg: 68% ↑ indinavir AUC. Reduce indinavir dose to 600 mg q8h.[4]	35% ↑ NFV AUC. No dosage adjustment required.[68]	1.5-fold ↑ saquinavir AUC. Dosage adjustment not necessary.[148]	No data, use with caution. Do not exceed ketoconazole 200 mg daily.
Levothyroxine *(GT)*		Case report of a 36 year old woman	Nelfinavir induces glucuronyl		Ritonavir induces glucuronyl

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		receiving chronic levothyroxine 0.75 mg/day, who developed a pharmacological hyperthyroidism within 1 month after starting an indinavir-containing regimen. Her symptoms resolved and thyroid hormone parameters returned to baseline after her levothyroxine dose was reduced to 0.12 mg/day. The authors hypothesized that indinavir may have inhibited glucuronidation of levothyroxine.[168]	transferase, and may potentially ↑ clearance of levothyroxine. See case report described under "Lopinavir-ritonavir and levothyroxine".		transferase, and may potentially ↑ clearance of levothyroxine. Close monitoring of thyroid hormone indices is recommended when levothyroxine is co-administered with ritonavir-boosted protease inhibitor regimens. Adjustment of levothyroxine dosage may be necessary.
Mefloquine *(CYP3A?, GT)*		Case report of patient on indinavir 800 mg q8h and mefloquine 250 mg/week for 16 weeks: therapeutic levels of both drugs observed; no side effects reported.[169]	Case report of patient on nelfinavir 1250 mg BID and mefloquine 250 mg/week for 6 weeks: therapeutic levels of both drugs observed; no side effects reported.[169]		
Methadone *(CYP3A4>>GT; weak inhibitor of CYP2D6)*	In HIV-negative subjects (n=16) maintained on methadone for at least 30 days, addition of amprenavir 1200 mg BID for 10 days resulted in delayed APV absorption, 13% ↓ AUC of active methadone enantiomer. No clinical evidence of methadone withdrawal was observed. Compared to a non-matched historical control group, 30%, 27%, and 25% ↓ in AUC, Cmax, and Cmin of amprenavir was observed. May wish to consider alternative antiretroviral therapy, as amprenavir may be less effective and	In vitro study: 30% ↑ methadone concentrations. However, no significant changes in concentrations of either drug were observed with coadministration in blinded, randomized, crossover study in 12 HIV-negative methadone maintenance subjects,[171] as well as a case series (n=6) of HIV-positive subjects.[172]	29-50% ↓ methadone concentrations when nelfinavir given to patients on stable methadone dosages.[172, 173] Monitor for symptoms of methadone withdrawal; adjustment of methadone dosage may be necessary. In an open study of healthy volunteers (n=16) stable on methadone 40-120 mg/day, coadministration of NFV 1250 mg BID for 5 days resulted in ↑ NFV parent and ↓ M8 exposure vs. controls.[174] Clinical significance unclear.	Likelihood of interaction low, since saquinavir is a weak CYP3A4 inhibitor.	Pharmacokinetic study in 15 adult healthy volunteers on steady-state tipranavir 500/ritonavir 100 mg BID plus single-dose methadone 5 mg resulted in 53% ↓ methadone levels; large ↓ in both R- and S-enantiomers. Dosage of methadone may need to be increased when co-administered with tipranavir and 200 mg of ritonavir.[175]

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	methadone dosage may need to be increased when these drugs are coadministered.[105, 170]				
Milk thistle		Interaction study in healthy volunteers (n=10) who took milk thistle 175 mg (= silymarin 153 mg) TID for 3 weeks, and indinavir 800 mg q8h at baseline, end of week 3, and after an 11-day washout period. After 3 weeks of milk thistle, indinavir AUC ↓ by 9% and Ctrough ↓ 25%. Authors concluded that these changes were not significant, and that these two products may be coadministered.[176]			
Mycophenolate mofetil (MMF) *(active metabolite, mycophenolic acid: GT)*		In a small case series (n=6) of HIV+ subjects receiving ddI, 3TC, abacavir, indinavir 800/ ritonavir 100 mg BID and nevirapine 200 mg BID, there was no significant change in indinavir concentrations in the presence of chronic MMF administration.[177]			
Oral Contraceptives *(GT, sulphatase (primary)> CYP3A (~30%); inhibits 1A2, 3A)*	Ethinyl estradiol 0.035 mg/ norethindrone 1 mg daily for one cycle plus amprenavir 1200 mg BID resulted in a 22% ↓ AUC and 20% ↓ Cmin of amprenavir; Cmin of oral contraceptives ↑ 32-45%, no significant change in AUC. Oral contraceptives should not be taken with amprenavir. Use alternate non-hormonal methods of contraception.[105]	Slight ↑ in oral contraceptive AUC. No dose modification necessary.[4]	47% ↓ ethinyl estradiol AUC; use alternate methods of contraception.[68] **Depo-medroxy-progesterone acetate, DMPA (Depo-Provera®):** In a prospective, open-label study of 20 HIV-infected women on stable NFV therapy, NFV AUC was not significantly altered in the presence of DMPA. Efficacy of DMPA did not appear to be altered,	In a pharmacokinetic study in healthy women, oral contraceptives did not affect the kinetics of single 600 mg saquinavir-hgc.[179]	50% ↓ ethinyl estradiol AUC and Cmax. Use alternate methods of contraception Women using estrogen may have an increased risk of non-serious rash. Women using estrogens for hormone replacement therapy should be monitored clinically for signs of estrogen deficiency.

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			with no evidence of ovulation occurring based on progesterone levels through week 12.[178]		
Phosphodiesterase Type 5 (PDE5) Inhibitors • sildenafil (Viagra®, Revatio®); *(CYP3A4>>2 C9 substrate; weak inhibitor of CYP1A2, 2C9, 2C19, 2D6, 2E1, 3A4 - unlikely to cause significant interactions)* • tadalafil (Cialis®, Adcirca®); *CYP3A4 substrate* • vardenafil (Levitra®); substrate of *CYP3A4>3A5, 2C*	**For treatment of erectile dysfunction:** Potential for increased **sildenafil** concentrations. Use with caution at a dose of 25 mg every 48 hours, and monitor for adverse effects. Case report of a 36-year old man on fosamprenavir 700/100 mg BID who experienced recurrent priapism after taking **tadalafil** 10 mg for recreational purposes.[180] **Tadalafil:**[181] • on demand dosing while on PIs or other CYP3A4 inhibitors: 10-20 mg q48h, max 3 times per week • daily dosing: 5 mg/day (no dose adjustment needed if on PIs) **Vardenafil is contraindicated** with ritonavir.[182]	Coadministration of indinavir 800 mg q8h at steady state with sildenafil 25 mg in HIV-infected subjects resulted in 4.4 fold ↑ sildenafil concentrations; sildenafil had no significant effects on indinavir pharmacokinetics.[183] Pharmacologic effects of sildenafil persisted up to 72 hours post-ingestion in some subjects. Thus, a starting dose of 12.5 mg sildenafil may be considered in order to minimize dose-related toxicity. **Tadalafil:**[181] • on demand dosing while on PIs or other CYP3A4 inhibitors: 10-20 mg q48h, max 3 times per week • daily dosing: 5 mg/day (no dose adjustment needed if on PIs) 16-fold ↑ **vardenafil** AUC, 30% ↓ indinavir AUC with combination.[24] **Vardenafil is contraindicated** with indinavir and ritonavir.[182]	Nelfinavir concentrations not significantly changed in presence of sildenafil (n=5); sildenafil levels not measured.[184] Potential for increased sildenafil concentrations. Consider starting with an initial sildenafil dose of 25 mg q24-48 hours and titrating up based on patient response and tolerability.[185] **Tadalafil:**[181] • on demand dosing while on PIs or other CYP3A4 inhibitors: 10-20 mg q48h, max 3 times per week • daily dosing: 5 mg/day (no dose adjustment needed if on PIs) **Vardenafil is contraindicated** with ritonavir.[182]	Coadministration of Fortovase at steady state (1200 mg tid) with sildenafil (100 mg single dose) resulted in a 140% increase in sildenafil Cmax and a 210% increase in sildenafil AUC; sildenafil had no effect on saquinavir pharmacokinetics. Consider a 25mg q24-48 hours starting dose of Viagra when administered to patients also taking Fortovase. [186] **Tadalafil:**[181] • on demand dosing while on PIs or other CYP3A4 inhibitors: 10-20 mg q48h, max 3 times per week • daily dosing: 5 mg/day (no dose adjustment needed if on PIs) **Vardenafil is contraindicated** with ritonavir.[182]	In healthy subjects, **tadalafil 10 mg** was administered after single dose tipranavir 500/ritonavir 200 mg and steady-state TPV/rtv BID. After the first dose of TPV/rtv, tadalafil AUC ↑ 133%, Cmax ↓ 22% and Cmin ↑ 44% relative to tadalafil 10 mg alone. At TPV/rtv steady state, tadalafil AUC and Cmin were unaltered and Cmax ↓ 30% relative to tadalafil alone. Administer tadalafil at lowest possible dose if using within first days of TPV/rtv therapy; if TPV/rtv steady state has been achieved (i.e., after 7-10 days), no dose adjustment of tadalafil is required.[187] Combination not studied. Use with caution. Start with **sildenafil** dose of 25 mg q48 hours. **Tadalafil:**[181] • on demand dosing while on PIs or other CYP3A4 inhibitors: 10-20 mg q48h, max 3 times per week • daily dosing: 5 mg/day (no dose adjustment needed if on PIs) **Vardenafil is contraindicated** with ritonavir.[182]

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	<u>For treatment of pulmonary arterial hypertension (PAH):</u> • **Sildenafil use for PAH is contraindicated with all PIs.**[154] • Tadalafil: ○ For patients on stable (i.e,. greater than 7 days) PI treatment who require therapy for PAH: tadalafil may be initiated at a dose of 20 mg once daily and increased to 40 mg once daily based on tolerability. For patients already stabilized on tadalafil who require PI-based treatment: tadalafil should be discontinued at least 24 hours prior to initiating the PI, and restarted 7 days after PI initiation at a dose of 20 mg once daily, increasing to 40 mg once daily based on tolerability.[154]				
Posaconazole *(UGT1A4, Pgp substrate, inhibits CYP3A4, possibly Pgp)*	Possible ↑ PI concentrations due to CYP3A4 inhibition by posaconazole. Monitor for PI toxicity.	Possible ↑ PI concentrations due to CYP3A4 inhibition by posaconazole. Monitor for PI toxicity.	Possible ↑ PI concentrations due to CYP3A4 inhibition by posaconazole. Monitor for PI toxicity.	Possible ↑ PI concentrations due to CYP3A4 inhibition by posaconazole. Monitor for PI toxicity.	Potential for ↑ concentrations of protease inhibitor. Monitor for PI dose-related toxicity when agents are co-administered.
Proton-pump inhibitors (PPIs), including esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, etc.		Coadministration of single-dose **omeprazole 40 mg** and IDV 800 mg in healthy subjects (n=14) led to 47% ↓ AUC and 55% ↓ Cmin of IDV. This effect was reversed when ritonavir 200 mg was coadministered. Avoid combining unboosted IDV with omeprazole and other PPIs.[188].	In an open-label, healthy volunteer study, coadministration of nelfinavir 1250 mg BID plus **omeprazole 40 mg QD** for 4 days resulted in significant reductions in NFV (↓ 36% AUC, 37% ↓ Cmax, 39% ↓ Cmin) and M8 (↓ 92% AUC, 89% ↓ Cmax, 75% ↓ Cmin). Co-administration of omeprazole and nelfinavir is not recommended.[189]	In healthy subjects taking SQV tablets 1 g/100 mg rtv BID with or without **omeprazole 40 mg**, saquinavir exposure was significantly increased (Cmin ↑ 2-fold, Cmax ↑ 75%, AUC ↑ 82%) in the presence of omeprazole. No short-term saquinavir toxicity was observed. Mechanism of interaction unknown.[190]	In an open-label study of healthy subjects, the effect of **omeprazole 40 mg** QD for 5 days on single-dose tipranavir 500/ ritonavir 200 mg was studied. No significant effect of omeprazole on tipranavir pharmacokinetics was observed.[13]
Ravuconazole *(may act as CYP3A4 inhibitor after single dose, and as CYP3A/2B inducer with chronic dosing)*			32% ↑ NFV AUC (day 2) and 16% ↓ NFV AUC (day 29) after ravuconazole 400 mg daily and nelfinavir 750 mg given as two single doses in healthy male subjects. Standard doses of both drugs may be given.[191]		
Rifabutin *(CYP3A > deacetylase; moderate inducer of CYP3A)*	14% ↓ amprenavir, 3-6 fold ↑ rifabutin Cmin. Decrease dose of rifabutin to 150 mg daily or 300 mg 3 times weekly to avoid toxicity.[192, 193] Case report of 3 HIV patients with low CD4 (<50 cells/mm^3) and prior episodes of drug-sensitive TB	Interaction study of half-dose RFB + indinavir: 155% ↑ rifabutin AUC, 33% ↓ indinavir AUC. **Thus, ↑ indinavir to 1000 mg q8h and ↓ rifabutin to 150 mg daily or 300 mg three times weekly**.[4, 195 193] This dosing regimen	32% ↓ NFV AUC, 3-fold ↑ RFB AUC. Reduce rifabutin dose to 150 mg/day or 300 mg three times per week.[68] Increase nelfinavir to 1000 mg q8h.[193] May have more consistent NFV concentrations with 1250 mg BID plus 150 mg RFB daily	40% ↓ saquinavir AUC. **Avoid combination** if using saquinavir as sole protease inhibitor.[198] For combination ritonavir 400 mg BID + saquinavir 400 mg BID, may be possible to administer RFB 150 mg q3days.[199]	In healthy volunteers, administration of single dose rifabutin 150 mg to steady-state tipranavir 500/rtv 200 mg BID led to significant ↑ in exposure to rifabutin and its metabolite. Single-dose rifabutin did not affect the kinetics of

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	who relapsed with rifamycin-resistant *M. tuberculosis* infection despite receiving fully supervised directly observed therapy including rifabutin 150 mg q2d or 3x/week, plus either atazanavir/rtv or lopinavir/rtv-based HAART. **Higher doses of rifabutin and a ritonavir-boosted HIV protease inhibitor as treatment for tuberculosis should be studied further.**[194]	results in ↑ AUC of RFB and its metabolite by 60% and 125% vs. RFB 300 mg alone.[196] Case report of 3 HIV patients with low CD4 (<50 cells/mm^3) and prior episodes of drug-sensitive TB who relapsed with rifamycin-resistant *M. tuberculosis* infection despite receiving fully supervised directly observed therapy including rifabutin 150 mg q2d or 3x/week, plus either atazanavir/rtv or lopinavir/rtv-based HAART. **Higher doses of rifabutin and a ritonavir-boosted HIV protease inhibitor as treatment for tuberculosis should be studied further.**[194]	(or 300 mg 3 times weekly).[195, 197]	Case report of 3 HIV patients with low CD4 (<50 cells/mm^3) and prior episodes of drug-sensitive TB who relapsed with rifamycin-resistant *M. tuberculosis* infection despite receiving fully supervised directly observed therapy including rifabutin 150 mg q2d or 3x/week, plus either atazanavir/rtv or lopinavir/rtv-based HAART. **Higher doses of rifabutin and a ritonavir-boosted HIV protease inhibitor as treatment for tuberculosis should be studied further.**[194]	tipranavir/rtv. Recommend rifabutin 150 mg 3 times/week with this combination.[153] Case report of 3 HIV patients with low CD4 (<50 cells/mm^3) and prior episodes of drug-sensitive TB who relapsed with rifamycin-resistant *M. tuberculosis* infection despite receiving fully supervised directly observed therapy including rifabutin 150 mg q2d or 3x/week, plus either atazanavir/rtv or lopinavir/rtv-based HAART.[194] **When co-administering with boosted protease inhibitors, rifabutin 150 mg once daily or 300 mg three times a week is recommended, along with close monitoring for antimycobacterial activity and therapeutic drug monitoring if available.**[154]
Rifampin *(Deacetylase> hydrolysis, GT?, CYP?; potent inducer of CYP3A and GT)*	81% ↓ AUC and 91% ↓ Cmin of amprenavir. **Avoid combination**.[192]	Indinavir AUC ↓ 89% after 1 week rifampin 600 mg/day administration. **Avoid combination**.[4] NB: In HIV-negative subjects taking rifampin >2 weeks, administration of ***indinavir 800/ritonavir 100 mg*** resulted in 81% ↓ indinavir AUC and 89% ↓ ritonavir AUC compared to controls, while rifampin AUC was ↑ 25%.[200]	82% ↓ NFV AUC. **Avoid combination.**[68] NB: In a 7-month old infant with HIV/TB co-infection, addition of ritonavir improved nelfinavir kinetic parameters in the presence of rifampin therapy.[203] However, optimal dosages have not yet been determined.	80% ↓ saquinavir AUC. **Avoid combination**.[148] Addition of ritonavir (e.g., **saquinavir/ritonavir 400/400 mg BID, or 1000/100 mg BID**) may provide therapeutic concentrations in presence of rifampin.[204, 205] However, in a Phase I, randomized, open-label, multi-dose study in healthy volunteers, 11/28 (39.3%) of subjects	Combination not studied. Coadministration not recommended.

	Amprenavir (Agenerase®)	Indinavir (Crixivan®)	Nelfinavir (Viracept®)	Saquinavir hgc-(Invirase®) sgc-(Fortovase®)	Tipranavir (Aptivus®)
		Similarly, in 6 HIV-infected individuals on stable ***indinavir 800/ritonavir 100 mg BID***, 4 days of rifampin 300 mg/day resulted in 87%↓ indinavir Cmin.[201] Eighteen Thai HIV+ patients receiving rifampin for active TB were given **indinavir 600/100 mg BID** plus 2 NRTIs; IDV pk was measured at 2 weeks, and Ctrough at 4, 8 and 12 weeks, as well as at least 4 weeks after RIF discontinuation (whereby IDV ↓ to standard Thai dose of 400/100 mg BID). Mean IDV Ctrough was significantly reduced in the presence of RIF (0.03 vs. 0.68 mg/L, p=0.004).[202] **Avoid concurrent rifampin administration.**		who received **rifampin 600 mg QD plus SQV 1000/rtv 100 mg BID** developed **significant hepatocellular toxicity**, including transaminase elevations of up to > 20X upper limit of normal values. LFTs returned to normal upon drug discontinuation. Therefore, **rifampin should not be given to patients receiving boosted saquinavir therapy** (Dear Healthcare Provider Letter, Roche Laboratories, USA, February 2005).	
Salmeterol/ Serevent®, Advair® (with fluticasone) *(CYP3A4)* *See also entry for Corticosteroids, Oral/inhaled.*	**Potential for ↑ salmeterol exposure with CYP3A inhibitors.** Coadministration of ketoconazole, a strong CYP3A4 inhibitor, at a dose of 400 mg/day with salmeterol at a dose of 50 mcg twice daily for 7 days led to a significant 16-fold ↑ in salmeterol AUC and a significant 1.4-fold ↑ in salmeterol Cmax versus salmeterol plus placebo. The mean QTc was not significantly affected by coadministration of ketoconazole and salmeterol; however, concomitant use was associated with a higher rate of increases in QTc duration compared with salmeterol and placebo. Although not studied with ritonavir, also a strong CYP3A4 inhibitor, the risk of cardiovascular adverse events may be increased**. The concomitant use of ritonavir and salmeterol is contraindicated.**[206]. If concurrent use is required, consider monitoring the patient for increased salmeterol plasma levels and cardiovascular adverse events including QT prolongation, palpitations and sinus tachycardia. Other beta-agonists such as salbutamol, formoterol, fenoterol, terbutaline may be safter options. Of note, use of Advair® (fluticasone/salmeterol) should be avoided with ritonavir, due to the additional interaction risk between ritonavir and fluticasone.[206] Symbicort® (budesonide/formoterol) Turbuhaler may be a suitable alternative to Advair®.[155]				
Trimethoprim *(10-20% metabolized, via CYP?)*		19% ↑ trimethoprim AUC. No dose modification necessary.[4]			
Voriconazole *(CYP2C19, 2C9, 3A; inhibits CYP3A, 2C9, 2C19)*	Potential for ↑ concentrations of unboosted PIs and voriconazole. Monitor for both PI and voriconazole toxicity. Consider TDM of both drugs.	In healthy volunteers, coadministration of voriconazole 200 mg BID and indinavir 800 mg q8h for 7 days did not affect the pharmacokinetics of	Potential for ↑ concentrations of unboosted PIs and voriconazole. Monitor for both PI and voriconazole toxicity. Consider TDM of both drugs.	Potential for ↑ concentrations of unboosted PIs and voriconazole. Monitor for both PI and voriconazole toxicity. Consider TDM of both drugs.	No data, but potential for bi-directional inhibition between voriconazole and PIs exists. RTV 400 mg BID ↓ voriconazole AUC by 82%. Effect of low dose RTV

	Amprenavir (Agenerase®)	Indinavir (Crixivan®)	Nelfinavir (Viracept®)	Saquinavir hgc-(Invirase®) sgc-(Fortovase®)	Tipranavir (Aptivus®)
		either drug.[207]			(100-400 mg/day) has not been studied. Some suggest not to co-administer until data become available.
Warfarin *(racemic mixture; R: CYP1A2, 3A, 2C19; S: 2C9 primarily)*	May potentially inhibit warfarin metabolism; monitor for ↑ INR and adjust warfarin dose accordingly when starting and discontinuing therapy.	May potentially inhibit warfarin metabolism; however, paradoxical effect observed in 1 case report, where warfarin dosage needed to be increased to maintain INR with indinavir.[208] Monitor for changes in INR and adjust warfarin dose accordingly when starting and discontinuing therapy.	May potentially inhibit or induce warfarin metabolism; one case report where warfarin dosage was tripled to maintain INR with nelfinavir.[209] Monitor for changes in INR and adjust warfarin dose accordingly when starting and discontinuing therapy.	May inhibit warfarin metabolism; case report of hypo-prothrombinemia which required 20% ↓ warfarin dose with concomitant saquinavir. [210] Monitor for ↑ INR and adjust warfarin dose accordingly when starting and discontinuing therapy.	May induce anticoagulant metabolism. Monitor for ↓ INR and adjust anticoagulant dose accordingly when starting and discontinuing therapy. Use combination with caution as tipranavir has been associated with increased risk of intracranial hemorrhage.[9]

Please note: This chart summarizes some of the major drug interactions identified to date, based on current available data; other drug interactions may exist. Please use caution whenever adding/modifying therapy. The information in this table is intended for use by experienced physicians and pharmacists. It is not intended to replace sound professional judgment in individual situations, and should be used in conjunction with other reliable sources of information. Due to the rapidly changing nature of information about HIV treatment and therapies, users are advised to recheck the information contained herein with the original source before applying it to patient care.

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