DRUG INTERACTIONS WITH PROTEASE INHIBITORS
(NB: for additional interaction data involving amprenavir, indinavir, nelfinavir, unboosted saquinavir-soft gel capsules (Fortovase) and tipranavir, please refer to the chart "Drug Interactions with Secondary Protease Inhibitors")

	Atazanavir (Reyataz®)	Darunavir (Prezista®)	Fosamprenavir (Telzir®)	Lopinavir/ ritonavir (Kaletra®)	Ritonavir (Norvir®)	Saquinavir (Invirase®)
I) DOSING INFORMATION:						
Usual Dose	400 mg po QD or 300 mg/100 mg ritonavir QD	600 mg/100 mg ritonavir BID	PI-naïve subjects: • 1400 mg BID (US monograph only) • 1400 mg/ritonavir 100 mg QD PI-experienced: • **700 mg/100 mg ritonavir BID**	400 mg/100 mg po BID	Boosting doses: 100-200 mg QD-BID Single agent (rarely used): 600 mg po BID (titrate dose when initiating therapy; e.g., 300 mg po BID x 3/7, 400 mg po BID x 4/7, 500 mg po BID x 5/7, then full dose)	1000 mg/100 mg ritonavir BID
Kinetic Characteristics	Primarily metabolized by CYP3A4; also inhibits CYP3A and UGT1A1. Weak inhibitor of 2C8[1] Atazanavir alone does not induce glucuronidation, while atazanavir/ ritonavir does induce glucuronidation.[2]	Primarily metabolized by CYP3A4. Inhibits CYP3A4.[3]	Primarily metabolized by CYP3A4. Inhibitor of CYP3A4 (similar potency as indinavir and nelfinavir)[4]; also induces CYP3A4[5].	Lopinavir is primarily metabolized by CYP3A4. Kaletra inhibits CYP3A4, 2D6 (to lesser extent). Induces glucuronyl transferases and possibly CYP1A2, CYP2C19 and 2C9.[6]	Potent inhibitor of CYP enzymes in following order: 3A>2D6>2C9, 2C19>>2A6, 2E1. Induces glucuronyl transferases, CYP1A2, CYP2B6, CYP2C9 and CYP2C19.[6-8] Inhibits P-gp, OATP1B1/1B3, and MATE1.	Primarily metabolized by CYP3A4 and P-gp. Weak inhibitor of CYP3A4 and P-gp.[8, 9]
Food (NB: **garlic**: see entries for Atazanavir, Saquinavir and Ritonavir)	Take with a light meal for improved absorption (AUC ↑ 35% with a high fat meal, and ↑ 70% when given with a low fat meal, vs. taking on a fasted state).[10] In HIV-infected patients taking atazanavir 300/100 mg QD, atazanavir AUC ↓ 41%, Cmax ↓ 32% and Ctrough ↓ 53% when administered fasting versus with food.[11]	Bioavailability ↑ 42% when taken in fed conditions with ritonavir versus fasting conditions. Type of meal (standard breakfast, high-fat breakfast, nutritional protein drink, croissant + coffee) had very little impact on exposure.	<u>Amprenavir:</u> May be taken with or without food. Avoid taking with high-fat meal.[12] Administer amprenavir liquid solution at least 1 hour apart from other medications that contain sorbitol. <u>Fosamprenavir:</u> May be taken with or without food; high fat meal does not affect absorption.[13]	Take capsules with food (regular or high-fat meal ↑ AUC 12%, ↑ Cmin 44%, ↓ variability in drug concentrations).[14] Kaletra tablets may be taken with or without food.	Take with food. (15% ↑ AUC with food). OK with Advera, Ensure, & chocolate milk.	Take within 2 hours of meal (almost 7-fold ↑ AUC with food).
Cranberry Juice	Prospective, observational, cross-sectional study in HIV-positive patients (n=120) on ARVs for at least 12 weeks, and reporting		Prospective, observational, cross-sectional study in HIV-positive patients (n=120) on ARVs for at least 12 weeks, and reporting	Prospective, observational, cross-sectional study in HIV-positive patients (n=120) on ARVs for at least 12 weeks, and reporting		

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	current cranberry juice intake (median 237 mL once-twice daily for median 4.5 years) or no cranberry juice intake. No significant difference in ATV levels in patients on atazanavir 300/ritonavir 100 mg QD +/- cranberry juice. ATV Cmin: ATV alone group: 183 ng/ml, n=6; ATV + Cranberry juice group: 197ng/ml, n=7[15]		current cranberry juice intake (median 237 mL once-twice daily for median 4.5 years) or no cranberry juice intake. No significant difference in amprenavir levels in patients on fosamprenavir 700/ritonavir 100 mg BID +/- cranberry juice. APV Cmin: fosamprenavir alone group: 2132 ng/ml, n=4; FPV + Cranberry juice group: 1292ng/ml, n=2[15]	current cranberry juice intake (median 237 mL once-twice daily for median 4.5 years) or no cranberry juice intake. No significant difference in LPV levels in patients on lopinavir 400/ritonavir 100 mg BID +/- cranberry juice. LPV Cmin: LPV alone group: 4482 ng/ml, n=29; LPV + Cranberry juice group: 4175ng/ml, n=13[15]		
Garlic	Case report of subtherapeutic ATV levels and virologic failure with 6 cooked garlic cloves TID. Atazanavir concentrations remained subtherapeutic 10 days after garlic was discontinued.[16]				In a kinetic study of healthy volunteers, 4 days of **garlic** administration did not significantly affect the kinetics of single-dose ritonavir. Impact of chronic co-administration of both agents remains unclear.[17]	
Grapefruit juice *NB: in vitro data suggest **pomegranate juice** may also have CYP3A inhibiting activity similar to grapefruit juice, although no kinetic studies in humans.[18]	Not studied.		No significant changes in amprenavir concentrations when administered with 200 mL grapefruit juice.[19]	Not studied.	Not studied.	40-100% ↑ saquinavir AUC. Take 150 mL juice with each dose.[20]
II) ANTI-	**RETROVIRAL**	**INTERACTIONS**				
Atazanavir (ATV)		In healthy volunteers, ATV 300 mg QD plus darunavir/rtv 400/100 mg BID led to 50% ↑ Cmin, 11% ↓ Cmax and no change in AUC of ATV compared to ATV 300/rtv 100 mg alone. Ritonavir exposure ↑ 51-59%	Combination of ATV with amprenavir in HIV-infected peripheral blood mononuclear cells yielded additive to moderately synergistic antiviral effects.[22] In healthy subjects, **ATV 300 mg QD plus FPV**	In TDM case series, **ATV 300/ LPV 800/rtv 200 mg QD** yielded ATV Ctrough levels approx. 5-fold higher (mean 736 ng/mL) vs. ATV 400 mg QD (mean 122 ng/mL).[26] In a 2-phase kinetic study in HIV-infected	Additive-synergistic antiviral activity in vitro.[22] In healthy volunteer study, addition of **ritonavir 100-200 mg to ATV 200 or 400 mg daily** resulted in significantly ↑ ATV exposure.[32]	Additive-synergistic antiviral activity in vitro.[22] In 21 HIV+ subjects, **ATV 400 mg/SQV-hgc 1200 mg QD** led to higher proportion of patients with ATV Ctrough< IC90 vs. ATV 400 mg alone; SQV

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		when ATV added to darunavir/rtv. There were similar rates of hyperbilirubinemia and elevated lipase levels when subjects were given ATV/r alone and in combination with DRV/r.[21] ATV 300mg daily may be given with DRV/r BID without dose adjustment.	**700/100 mg BID** showed no significant change in amprenavir concentrations and ATV Ctrough, and 24% ↓ Cmax and 22% ↓ AUC of ATV. [23] In a healthy volunteer study, **ATV 400/FPV 1400 mg QD** for 14 days yielded APV Cmin comparable to FPV 1400 mg BID, while ATV AUC ↓ 33%, C_{24} ↓ 57% vs. ATV 400 mg QD alone.[24] In a case series of treatment-experienced patients, 14 subjects received **ATV 150 or 200/FPV 700/rtv 100 mg BID** (9 were on concomitant tenofovir/FTC); three patients received **ATV 400/FPV 700 mg BID**. All regimens produced ATV and APV C_{trough} well above the minimum acceptable concentrations. Mean ATV Ctrough was 0.96-1.66 ug/mL in ATV 150/FPV 700/rtv 100 mg BID, 0.77-2.4 ug/mL in ATV 200/FPV 700/rtv 100 mg BID and 0.53-1.38 ug/mL in ATV 400/FPV 700 mg BID arms. Mean APV Ctrough was 1.19-2.71 ug/mL in ATV 150/FPV 700/rtv 100 mg BID, 1.23-2.71 ug/mL in ATV 200/FPV 700/rtv 100 mg BID and 0.81-2.43 ug/mL in ATV 400/FPV 700 mg BID arms.[25]	men, this dosing combination yielded steady-state ATV Cmin of 541 ± 245 ng/mL and LPV Cmin 1424 ± 1423 ng/mL.[27] A small study in HIV-infected subjects on either stable **ATV 300/100 mg QD or LPV 400/100 mg BID** showed no changes in ATV concentrations and slight decreases in LPV exposure (16% ↓ AUC, 35% ↓ Cmin) when drugs were coadministered.[28] In HIV-negative subjects, **ATV 300 mg QD plus LPV/r 400/100 mg BID** led to 45% ↑ ATV Cmin (no change in AUC or Cmax) compared to ATV 300 mg/rtv 100 mg QD; LPV levels were not significantly different from historical controls.[29] A similar study in HIV-positive subjects yielded ATV AUC 38% ↓ similar Cmin vs. 300/100 mg (historical controls); LPV concentrations were not affected by ATV.[30] In a separate kinetic study in HIV-positive subjects, this combination resulted in significantly ↑ LPV levels compared to historical controls, while ATV levels were similar to historical controls taking ATV 300/rtv 100 mg QD. Combination was well tolerated.[31]	Separate steady-state study in healthy volunteers (n=30) of **ATV 300/ritonavir 100 mg QD** with a light meal resulted in 1.86-fold ↑ Cmax and 3.38-fold ↑ AUC of ATV; ritonavir kinetics not affected.[33] Current dosage recommendation: atazanavir 300 mg/ ritonavir 100 mg QD with food. In a cross-over, single-blind, two period study, healthy volunteers received **ATV 300 mg with either RTV 100 mg or 50 mg** for 10 days, 15 days apart. Ritonavir Cmax and AUC were lower with the 50 mg dose vs. 100 mg dose and all/most RTV Ctrough were below the level of detection. No differences in ATV exposures were noted between the 50 vs 100 mg RTV dose treatments and all ATV Ctrough were >0.15 mg/L (0.59 vs. 0.79 mg/L, respectively, p=0.132). The 50 mg ritonavir dose was associated with a lower impact on serum lipids.[34]	Ctrough <MEC in most patients. Additional dosage adjustment and/or RTV boosting may be required to optimize drug levels.[35] When ATV 300 mg added to **SQV 1600/r 100 mg QD** in 20 HIV+ subjects, SQV AUC ↑ 60%, Cmax ↑ 42%, Ctrough ↑ 112% (p <0.05) after 30 days. ATV levels were similar to those seen with ATV/r; total and indirect bilirubin ↑ by 5 times after 10 days of ATV therapy.[36] In TDM case series, **ATV 300/ SQV2000/rtv 100-200 mg QD** yielded ATV Ctrough levels approx. 6-fold higher (mean 749 and 899 ng/mL, respectively) vs. ATV 400 mg QD (mean 122 ng/mL).[26] In a healthy volunteer study, **ATV 200/SQV 1500 mg BID** led to ATV Cmin comparable to ATV 400 mg QD, while SQV Cmin was 0.129 ug/mL (75% were > 0.1 ug/mL).[37]

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				In a 2-phase kinetic study in HIV-infected men, **LPV/r 400/100mg BID and ATV 150mg BID** yielded mean LPV Cmin of 4644 ± 1965µg/L and AUC 87016 ± 27172µg/L.h, and ATV Cmin 1196 ± 433µg/L and AUC 21493 ± 6424µg/L.h.[27]		
Brecanavir (BCV)	In healthy adults, brecanavir 300 mg/rtv 100 mg BID plus atazanavir 300 mg QD led to 44% ↑ Cmin, 38% ↑ AUC and 48% ↑ Cmax of BCV, and 111%↑ Cmin, 44% ↑ AUC, 21% ↑ Cmax of ATV (compared to ATV 300/rtv 100 mg QD alone). Higher incidences of grade 4 bilirubin ↑ and premature study d/c with combination. Reduction in ATV dose may be considered (dose recommendation not available).[38]			In healthy adults, brecanavir 300 mg BID plus lopinavir 400/100 mg BID led to 16% ↓ Cmin and AUC of BCV vs. BCV 300/rtv 100 mg BID alone; lopinavir exposures were not affected. Combination was well-tolerated, may be co-administered without dosage reduction.[39]		
Capravirine				Capravirine 700 mg BID plus lopinavir/r resulted in 79% ↓ CPV clearance, and 63% ↑ LPV clearance; recommend ↑ LPV/r to 533/133 mg BID when dosing with CPV 700 mg BID.[40]		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.[41]
Cobicistat (GS-9350, a CYP3A4 inhibitor lacking anti-HIV activity)	In healthy subjects, co-administration of either ritonavir 100 mg or cobicistat 150 mg plus atazanavir led to equivalent atazanavir exposures.[42]	In healthy subjects, co-administration of either **cobicistat 150 mg or ritonavir 100 mg plus darunavir 800 mg QD** for 10 days resulted in equivalent darunavir Cmax and AUC.[43]				

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		In healthy subjects, the kinetics of two fixed-dose tablets of **darunavir 800 mg/ cobicistat 150 mg** were compared to darunavir 800/ritonavir 100 mg QD given as single agents. Comparable bioavailability was demonstrated for darunavir Cmax and AUC, while Cmin was 26-31% ↓ with darunavir/cobicistat vs. darunavir/ritonavir. This difference was not felt to be clinically relevant.[44] In a fixed-sequence crossover study, healthy volunteers received **darunavir 600 mg BID boosted with either cobicistat 150 mg BID or ritonavir 100 mg BID**. When darunavir was boosted with cobicistat, darunavir exposures were bioequivalent to darunavir/ritonavir, while cobicistat AUC was 47% ↓ vs. cobicistat 150 mg BID alone. Coadministration of elvitegravir 150 QD or etravirine 200 mg BID did not affect darunavir concentrations, while EVG and ETV exposures were comparable to historical data.[45]				
Darunavir (TMC114, *substrate of CYP3A4)*	In healthy volunteers, ATV 300 mg QD plus darunavir/rtv 400/100 mg BID led to 50% ↑ Cmin, 11% ↓ Cmax and no change in AUC of ATV			Combination of **lopinavir/ritonavir 400/100 mg BID plus darunavir 300 mg BID** (as oral solution) led to a	Kinetics of single-dose darunavir 800 mg increased in presence of ritonavir 600 mg BID; Cmax ↑ 2-fold, AUC ↑ 9-	Darunavir 400 mg BID plus saquinavir 1000/ritonavir 100 mg BID led to significant ↓ in darunavir exposure. darunavir Cmin ↓ 42%,

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	compared to ATV 300/rtv 100 mg alone. Ritonavir exposure ↑ 51-59% when ATV added to darunavir/rtv. There were similar rates of hyperbilirubinemia and elevated lipase levels when subjects were given ATV/r alone and in combination with DRV/r.[21, 46] ATV 300mg daily may be given with DRV/r BID without dose adjustment.			53% ↓ darunavir relative bioavailability and 19% ↓ in lopinavir exposure. Addition of extra ritonavir 100 mg BID did not impact reduction of darunavir exposure, while LPV bioavailability ↑ 37%. In a pk study of HIV-infected subjects, **darunavir 1200/rtv 100 mg BID plus LPV 400/100 mg BID** led to 9% ↑ AUC, 23% ↑ Cmin of LPV, but 38% ↓ AUC, 21% ↓ Cmax and 51% ↓ Cmin of darunavir. In the same study, **darunavir 1200 mg BID + LPV 533/rtv 133 mg BID** led to 9% ↑ LPV AUC but 41% ↓ darunavir AUC.[47] **Therefore, this combination is not recommended.**	fold, C12 ↑ 30-fold.	Cmax ↓ 17%, AUC ↓26% with combination, while no significant changes in SQV kinetics were observed. Therefore, not recommended to combine SQV and darunavir /ritonavir.[48]
Delavirdine	Potential for increased atazanavir concentrations. Appropriate doses have not yet been established.		Amprenavir 1200 mg +/- 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.[49] 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%.[50]	In a healthy volunteer study (n=26), DLV 600 mg BID plus lopinavir 400/100 mg BID resulted in higher lopinavir levels (Cmin ↑ 53%, AUC ↑ 24%, Cmax 13%); however, DLV exposure was ↓25-30%. Further studies are ongoing to establish optimal doses of both agents.[51]	70% ↑ RTV concentrations; kinetics of delavirdine and its metabolite unchanged with concomitant administration of full dose therapy.[52, 53] Similar effect (80% ↑ ritonavir AUC) seen in healthy volunteers given delavirdine 600 mg BID plus ritonavir 100 mg BID. No effect on delavirdine kinetic parameters[54]	Delavirdine 400 mg 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.[55]

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			Combination is contraindicated due to potential loss of virologic response and possible resistance to delavirdine.[4]			
Didanosine	Simultaneous administration of atazanavir, ***didanosine tablets*** and stavudine resulted in 89% ↓ Cmax and 87% ↓ AUC of atazanavir; kinetics of didanosine and stavudine were not affected. When atazanavir was administered 1 hour apart from didanosine, atazanavir concentrations were not affected. Recommend giving ddI-tablets 30 minutes before or 2 hours after atazanavir (which is taken with food).[10] ***ddI-EC*** should be given 1.5 hours before or 2 hours after atazanavir (which is taken with food).	In healthy volunteers, didanosine 400 mg QD on an empty stomach and darunavir 600 mg/ritonavir 100 mg BID with food (2 hours after ddI intake) did not significantly affect plasma levels of either drug. No dosage adjustment is required.[56]	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.[57]	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 lopinavir/r (given with food).	13% ↓ ddI AUC. Clinical significance unknown.[58]	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).
Dolutegravir (DTG)	In a randomized, open-label, two-period, crossover study, healthy adult subjects received dolutegravir 30 mg QD for 5 days, followed by the addition of either atazanavir 300/100 mg QD or atazanavir 400 mg QD for 14 days. Coadministration with ATV/RTV resulted in ↑ AUC 62%, ↑ Cmax 34% and ↑ Ctrough 121% of dolutegravir. Coadministration with	In an open-label, multiple dose, 2-period, 2-sequence crossover study, healthy subjects received dolutegravir 30 mg QD for 5 days followed by randomization to lopinavir/ritonavir 400/100 mg BID or darunavir/ritonavir 600/100 mg BID plus dolutegravir 30 mg QD for 14 days. In the presence of darunavir/ritonavir, dolutegravir AUC ↓ 22%, Cmax ↓ 11% and	Healthy volunteers received dolutegravir 50 mg daily for 5 days followed by the addition of fosamprenavir/r 700/100 mg BID for 10 days. In the presence of fosamprenavir/r, dolutegravir AUC ↓ 35%, Cmax ↓ 24% and C_T ↓ 49%, while amprenavir pharmacokinetics were similar to historical values. Despite the reductions, dolutegravir concentrations remained well above the protein-adjusted IC90 for wild-	In an open-label, multiple dose, 2-period, 2-sequence crossover study, healthy subjects received dolutegravir 30 mg QD for 5 days followed by randomization to lopinavir/ritonavir 400/100 mg BID or darunavir/ritonavir 600/100 mg BID plus dolutegravir 30 mg QD for 14 days. Steady-state dolutegravir kinetics were not altered in the presence of lopinavir/ritonavir.		

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	atazanavir 400 mg QD resulted in ↑ AUC 91%, ↑ Cmax 50% and ↑ Ctrough 90% of dolutegravir. The combinations were well tolerated. No dose adjustment is necessary when dolutegravir is coadministered with boosted or unboosted atazanavir.[59]	Ctrough ↓ 38%; these changes were considered not clinically significant. No dosage adjustment for dolutegravir is required when used with darunavir/ritonavir.[60]	type HIV.[61] 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.[62]	No dosage adjustment for dolutegravir is required when used with lopinavir/ritonavir.[60]		
Efavirenz	Study in healthy subjects of **ATV 400 QD** +/- efavirenz 600 mg QD with a light meal (n=27): ATV Cmax ↓ 59% and AUC ↓74% with concomitant EFV; EFV kinetics not significantly altered.[63] In a healthy volunteer study, coadministration of **atazanavir 300/ritonavir 100 mg QD** plus efavirenz x 2 weeks resulted in 39% ↑ atazanavir AUC vs. atazanavir 400 mg QD alone, while ATV 600 mg QD plus efavirenz resulted in 21% ↓ ATV AUC vs. ATV 400 mg QD alone.[64] In healthy subjects, **ATV 400/ ritonavir 100 mg QD** plus EFV results in ATV AUC and Cmax comparable to ATV/r	Multidose study of efavirenz 600 mg QD plus **darunavir (oral solution) 300 mg/ritonavir 100 mg BID** led to 31% ↓ Cmin and 13% ↓ AUC of darunavir, while EFV exposure ↑ 20%. Combination may be used without dose adjustments.[66] In a single sequence, 3-period PK study in healthy volunteers who received **DRV 900/r100 mg QD** x 10d, DRV/r + EFV 600 mg QD x 14d, then EFV x 14 d): • 57% ↓ Cmin, 14% ↓ AUC of darunavir • Mean 1138 vs. 2127 ng/mL, p=0.0003; all Cmin>55 ng/mL • No difference in EFV PK Clinical significance in HIV-positive patients not	In healthy volunteer study, **FPV 700/rtv 100 mg BID plus EFV** did not change APV levels vs. FPV/rtv alone. However, with **FPV 1395/rtv 200 mg QD**, addition of EFV led to 13% ↓ AUC, 36% ↓ Cmin of APV. Negative interaction corrected when rtv dose ↑ to 300 mg QD.[68] **Therefore, when coadministeringFPV/r and EFV: no change in FPV dose if BID regimen used; if QD, use FPV 1400 mg/rtv 300 mg QD.**	**<u>LPV/r capsules:</u>** Efavirenz 600 mg daily + lopinavir 400 mg/ritonavir 100 mg BID resulted in 25% ↓ AUC and 44% ↓ Cmin of lopinavir. Using lopinavir 533 mg/ritonavir 133 mg BID plus EFV resulted in similar lopinavir concentrations to those achieved in the absence of EFV.[69] **<u>LPV/r tablets:</u>** • Can use 400/100 mg BID with EFV in ARV-naïve subjects • ↑ to 600/150 mg (3 tablets) BID when co-administering in treatment-experienced subjects; this significantly ↑ lopinavir plasma concentrations ~35% and ritonavir concentrations ~56-92% compared to	Healthy volunteer study of EFV 600 mg/day + RTV 500 mg BID: 21% ↑ EFV AUC, 17% ↑ RTV AUC. Based on these data, may use RTV 500 mg BID with EFV 600 mg daily; if RTV intolerance occurs, may consider RTV dosage reduction.[73]	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. [74] 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[75]

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	300/100 alone, but ATV Cmin ↓ 42%. **ATV Cmin may not be optimal for treatment experienced patients.** RTV Cmax ↓ 15%, AUC ↓ 31%, Cmin ↓ 60% with combination, which may have contributed to lower ATV exposures.[65]	yet determined, combination may provide sufficient efficacy in naïve-patients with no pre-existing mutations.[67]		KALETRA tablets 400/100 mg twice-daily without efavirenz[70] • in 19 healthy volunteers, **LPV/r 500/125 mg BID** plus EFV 600 mg led to similar LPV levels as seen with LPV/r 400/100 mg BID alone (6% ↑ AUC, 10% ↓ Cmin)[71] • QD lopinavir/rtv in the presence of NNRTIs may not provide adequate lopinavir Ctrough[72]		
Elvitegravir (GS-9137, integrase inhibitor)	Randomized, crossover, multiple dose study in healthy subjects (n=14) assessed EVG/ATV 300mg/400mg daily vs. EVG/r 300mg/100g daily: ATV and RTV showed similar inhibition of CYP 3A activity using midazolam probe. ATV + EVG vs historical controls: ↓ ATV AUC 30%, ↓ ATV Cmin: 46% - ? potential of EVG to induce ATV metabolism. This requires further study. ATV 400mg daily has potential to boost EVG levels when RTV sparing regimen desired.[76] Two kinetic studies in healthy subjects: • **EVG 200/100mg QD** plus **ATV/r 300/100mg QD** led to ↑ EVG exposures vs. EVG 200/100mg QD alone, likely via inhibition of UGT1A1/3 metabolism by ATV/r. ATV	In a crossover study, healthy volunteers were randomized to receive either elvitegravir 125 mg/ritonavir 100 mg QD, darunavir 600 mg/ritonavir 100 mg BID, or **elvitegravir 125 mg QD plus darunavir 600 mg/ritonavir 100 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.[78] In a fixed-sequence crossover study assessing the kinetics of **darunavir 600/cobicistat 150 mg BID plus either elvitegravir 150 mg QD or etravirine 200 mg BID** vs. darunavir 600/ cobicistat 150 mg BID alone:	Healthy volunteers were randomized to receive either elvitegravir 125 mg/ritonavir 100 mg QD followed by elvitegravir 125 mg QD plus fosamprenavir 700 mg/ritonavir 100 mg BID, or fosamprenavir 700 mg/ritonavir 100 mg BID followed by elvitegravir 125 mg QD plus fosamprenavir 700 mg/ritonavir 100 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.[79]	Healthy volunteers (n=27) were randomized to receive either elvitegravir (EVG)/ritonavir 125/100mg QD for 2 weeks, then EVG/r 125/100 mg QD plus LPV/r 400/100mg BID for 2 weeks (group 1) or LPV/r 400/100mg BID for 2 weeks, then EVG/r 125/100 QD plus LPV/r 400/100mg BID for 2 weeks (group 2). EVG exposures were significantly increased in the presence of LPV/r: 75% ↑ $AUC_{tau,}$ 52% ↑ Cmax, 1382% ↑ Ctau, possibly via inhibition of UGT1A1/3 metabolism. LPV and RTV exposures were unchanged. Based on simulations, the authors recommend the dose of EVG be ↓ to 85mg daily when used with LPV/r.[80]	In healthy volunteers, ritonavir doses of 50, 100, and 200 mg plus elvitegravir 125 mg led to 41%, 54% and 56% ↓, respectively in apparent oral clearance of elvitegravir relative to 20 mg ritonavir. A ritonavir dose approaching 100 mg provided maximal inhibition of CYP activity. These data support a once-daily ritonavir dose of 100 mg when combined with elvitegravir.[81]	

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	exposure was modestly ↓ vs. ATV/r 300/100mg daily alone. • **EVG 85/100 mg daily + ATV/r 300/100mg QD** led to equivalent EVG exposures compared to the usual EVG 150mg daily dose; ATV exposure unchanged compared to ATV/r 300/100mg alone. Authors state an 85mg dose of EVG should be used when given with ATV/r.[77]	• darunavir exposures were not significantly affected by coadministration with either elvitegravir or etravirine • elvitegravir and etravirine exposures were comparable to historical reference data[45] Kinetics of **darunavir 800 mg and elvitegravir 150/cobicistat 150 mg once daily**: • elvitegravir Ctrough 52% ↓ and AUC ↓ 20% vs. elvitegravir/cobicistat/ TDF-FTC (Stribild®) • darunavir Ctrough ↓ 21% and AUC ↓ 3% vs. darunavir 800/cobicistat 150 mg QD[45] Clinical significance unclear.				
Enfuvirtide	No clinically significant interaction expected.	Analysis of PK data of 292 subjects in the POWER 3 trial showed no interaction between enfuvirtide and darunavir.[82] In 11 patients receiving darunavir 600/100 mg BID plus enfuvirtide, darunavir concentrations were measured before and 24 weeks after enfuvirtide was replaced by raltegravir. Following the switch to raltegravir, darunavir Cmin ↓ 33%, Cmax ↓ 32% and AUC ↓ 37%; no significant changes in ritonavir kinetics were noted.	No clinically significant interaction expected.	No clinically significant interaction expected. In the RESIST-1 and-2 studies, median lopinavir Cmin was 19% higher in the LPV/r plus enfuvirtide arm (n=60) compared to the LPV/r without enfuvirtide arm (n=240): i.e., 5.12 ug/mL vs. 3.84 ug/mL, respectively. Despite this, ALT elevation rates and investigator-reported rates of clinical hepatic events were lower in the comparator PI/r plus enfuvirtide arm compared to the comparator PI/r without enfuvirtide.[84]	No clinically relevant interaction noted with co-administration of enfuvirtide 90 mg SC BID and ritonavir 200 mg BID for 4 days in 12 HIV-infected subjects.[85]	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.[85] In the RESIST-1 and-2 studies, median saquinavir Cmin was 39% higher in the SQV/r plus enfuvirtide arm (n=27) compared to the SQV/r without enfuvirtide arm (n=110): i.e., 0.49 ug/mL vs. 0.38 ug/mL, respectively. Despite this, ALT elevation rates and investigator-reported rates of clinical hepatic

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		Mechanism and clinical significance of this interaction are not clear.[83]				events were lower in the comparator PI/r plus enfuvirtide arm compared to the comparator PI/r without enfuvirtide.[84]
Etravirine, TMC125, *(diaminopyrimidine NNRTI; inducer of CYP3A)*	In healthy subjects (n=14), **ATV 400 mg QD** administered with etravirine 800 mg BID (old formulation) for 7 days resulted in 47% ↑ Cmax , 50% ↑ AUC and 58% ↑ Cmin of TMC125, while atazanavir AUC ↓ 17% and Cmin ↓ 47%.[86] Combination of unboosted atazanavir and etravirine is not recommended.[87] In healthy subjects, **ATV 300/rtv 100 mg QD** plus TMC125 800 mg BID (old formulation) led to 100% ↑ AUC and 26% ↑ Cmin of etravirine, while atazanavir AUC ↓ 14% and Cmin ↓ 38%.[86] HIV-infected subjects on stable ATV 300/100 mg QD regimens (not including tenofovir) were randomized to receive either **ATV 300/100 mg QD or 400/100 mg QD with etravirine 200 mg BID**. In the presence of etravirine, ATV 300/100 mg dosing led to 4% ↓ AUC and 18% ↓ Cmin of atazanavir, and 1.24-fold ↑ etravirine AUC. In ATV 400/100 mg group, there was no change in AUC and 9% ↓ Cmin of atazanavir while	Pharmacokinetic interaction study of etravirine 200 mg BID added to **darunavir 600/100 mg BID** in HIV-infected subjects (n=10) led to ~30% ↓ AUC of etravirine compared to historical controls, not considered clinically significant. Kinetics of darunavir were unchanged.[89] Similar interaction observed in healthy subjects.[90] A pharmacokinetic substudy was conducted in 10 HIV-positive subjects participating in the ANRS TRIO study. Patients received raltegravir 400 mg BID and **darunavir 600/100 mg BID** on day 1, and etravirine 200 mg BID was added on day 7. PK parameters were measured on days 6 and 28. Raltegravir and darunavir PK (Cmax, Cmin and AUC) were not significantly different in the presence of etravirine.[91] In a phase II single arm study, ARV-naïve HIV-infected subjects received **etravirine 400 mg QD, darunavir 800/100 mg QD**, or the combination (plus tenofovir/FTC) each for	In an open-label interaction trial of HIV-infected subjects on stable FPV 700/rtv 100 mg BID, addition of etravirine 800 mg BID for 14 days (phase II formulation) led to 69% ↑ AUC, 62% ↑ Cmax and 77% ↑ Cmin of amprenavir compared to FPV/rtv alone. Etravirine parameters were similar to historical controls.[93] Etravirine should not be co-administered with fosamprenavir/ ritonavir.[87]	In healthy volunteers, coadministration of etravirine 200 mg BID and lopinavir/ritonavir tablets 400/100 mg BID for 8 days resulted in 45% ↓ Cmin, 30% ↓ Cmax and 35% ↓ AUC of ETV, and 20% ↓ Cmin, 11% ↓ Cmax and 13% ↓ AUC of LPV compared to each drug administered alone.[94] Because the ↓ in mean ETV exposures in the presence of LPVr is similar to the ↓ observed in the presence of darunavir/ ritonavir, ETV and LPVr may be co-administered without dose adjustment.[87] Etravirine 800 mg BID did not affect kinetics of **LPV 400/RTV 100/SQV 800-1000 mg BID** in 15 HIV-infected male subjects.[95]	Single dose etravirine 400 mg plus steady-state ritonavir 600 mg BID (n=11) resulted in 46% ↓ AUC and 32% ↓ Cmax of etravirine, likely due to induction of glucuronidation.[96] Ritonavir concentrations not measured. Etravirine should not be co-administered with ritonavir 600 mg BID.[87] In healthy volunteers, there was no evidence of a pharmacokinetic interaction between **single-dose etravirine 200 mg and single-dose ritonavir 100 mg** administered either simultaneously after breakfast, or when ritonavir was given 4 hours before or after etravirine. Simultaneous administration of ritonavir 400 mg plus etravirine 200 mg also had no effect on etravirine exposure relative to ritonavir 100 mg.[97]	Etravirine AUC ↓ 33% when co-administered with **saquinavir 1000/ritonavir 100 mg BID**. No dose adjustments required.[87] 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.[96] Etravirine concentrations not measured. Etravirine should not be administered with unboosted PIs. [87] Etravirine 800 mg BID did not affect kinetics of **LPV 400/RTV 100/SQV 800-1000 mg BID** in 15 HIV-infected male subjects.[95]

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	etravirine AUC was ↓ 16% with coadministration. These changes were smaller than interaction observed previously in healthy volunteers.[88] *NB: etravirine concentrations were compared to historical data from the DUET studies where etravirine was administered with darunavir/r BID. Coadministration is contraindicated in the US & Canadian Monographs,[87] but the European SPC says they can be coadministered without dose adjustment.	14 days. There was no change in ETV pk in the presence of DRV/r. Mean ETV Cmin was >50x higher than protein-adjusted EC50 for WT virus, with and without DRV/r. DRV pk was slightly higher and RTV was slightly lower vs. historical controls (ARTEMIS week 4 pk substudy).[92] Combination may be coadministered without dose adjustment.[87]				
Fosamprenavir (FPV)	Combination of ATV with amprenavir in HIV-infected peripheral blood mononuclear cells yielded additive to moderately synergistic antiviral effects.[22] In healthy subjects, **ATV 300 mg QD plus FPV 700/100 mg BID** showed no significant change in amprenavir concentrations and ATV Ctrough, and 24% ↓ Cmax and 22% ↓ AUC of ATV. [23] In a healthy volunteer study, ATV 400/FPV 1400 mg QD for 14 days yielded APV Cmin comparable to FPV 1400 mg BID, while ATV AUC ↓ 33%, C_{24} ↓ 57% vs. ATV 400 mg QD alone.[24]			**<u>LPV/r capsules:</u>** • 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%).[98] • Similar findings observed in cohort of HIV+ subjects with both APV and FPV formulations.[99] [100] **Optimal doses for co-administration not yet defined.** **Separating LPV and FPV doses by 4 or 12 hours did not improve APV conc.[101]** **Suggest TDM when using this**	In healthy volunteers, **FPV 1400mg/rtv 100 mg BID** led to 54% ↑ AUC, 26% ↑ Cmin of APV vs. FPV 700/rtv 100 mg BID regimen. **FPV 1400 mg/rtv 200 mg BID** led to 26% ↑ AUC, 32% ↑ Cmin of APV but ↑ incidence of ALT, AST elevations, and therefore is not recommended.[104] In a healthy volunteer pharmacokinetic study, **FPV 1400/rtv 100 mg QD** led to 10% ↓AUC, 38% ↓ Cmin of APV vs. FPV 1400/rtv 200 mg QD, although Cmin remained 5.9-fold higher than IC50 WT.[105] In both a retrospective cohort (n=51) of patients taking FPV 1400 mg/ritonavir 100-200 mg	In a group of 18 HIV+ subjects, **SQV-hgc 1000/FPV 700 mg BID plus either RTV 100-200 mg BID** resulted in: - non-sig. ↓ in SQV AUC_{0-12}, C_{trough} and C_{max} (14%, 24%, 9% respectively) with RTV 100 mg BID - non-sig. ↑ in SQV AUC_{0-12}, C_{trough} and C_{max} (12%, 3%, 20% respectively) with RTV 200 mg BID FPV levels not affected by SQV co-administration.[108] May wish to consider TDM if using RTV 100 mg BID dose with this combination.

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	In a case series of treatment-experienced patients, 14 subjects received **ATV 150 or 200/FPV 700/rtv 100 mg BID** (9 were on concomitant tenofovir/FTC); three patients received **ATV 400/FPV 700 mg BID**. All regimens produced ATV and APV C_{trough} well above the minimum acceptable concentrations. Mean ATV Ctrough was 0.96-1.66 ug/mL in ATV 150/FPV 700/rtv 100 mg BID, 0.77-2.4 ug/mL in ATV 200/FPV 700/rtv 100 mg BID and 0.53-1.38 ug/mL in ATV 400/FPV 700 mg BID arms. Mean APV Ctrough was 1.19-2.71 ug/mL in ATV 150/FPV 700/rtv 100 mg BID, 1.23-2.71 ug/mL in ATV 200/FPV 700/rtv 100 mg BID and 0.81-2.43 ug/mL in ATV 400/FPV 700 mg BID arms.[25]			**combination**.[102] In an open-label study of HIV-positive subjects stabilized on either **APV 750 mg BID + LPV/r 533/133 mg BID** or **FPV 1400 mg BID + LPV/r 533/133 mg BID**, switching from APV to FPV resulted in steady-state ↑ APV C_{max} 75%, C_{min} ↑58% and AUC_{tau} ↑ 76%. No change in tolerability was observed.[103] **<u>LPV/r tablets:</u>** • Can use 400/100 mg BID with FPV in ARV-naïve subjects • May ↑ to 600/150 mg (3 tablets) BID when co-administering in treatment-experienced subjects	QD,[106] and in a prospective, open-label study of 12 HIV-infected subjects stabilized on FPV 1400 mg/rtv 200 mg QD then switched to FPV 1400 mg/rtv 100 mg QD for 4 weeks,[107] median amprenavir exposures were not statistically different between the 100 mg and 200 mg ritonavir doses. Ritonavir ↑ plasma APV to similar extent with either APV or FPV. Therefore, FPV may replace APV, and metablic APV interactions are applicable to FPV.[104]	
Indinavir	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.[1]		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.[109] In HIV-infected subjects receiving indinavir 800/ritonavir 100 mg BID, addition of fosamprenavir 700 mg BID for 5 days resulted	**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.[111] **Indinavir 600 mg BID + LPV/r:** <u>Healthy volunteer study</u>: similar IDV AUC, ↓ Cmax, 3.5-fold ↑ Cmin vs. IDV 800 mg q8h alone; LPV kinetics not affected.[112, 113] <u>HIV+ subjects</u>: In an	***IDV/RTV 400/400 mg BID*** in healthy volunteers yielded indinavir AUC similar to those achieved with IDV 800 mg po q8h alone.[117] Also improved IDV PK profile: 62% ↓ Cmax, 3-fold ↑ Cmin, less impact of food on IDV absorption when given with RTV vs. alone,[118] ↓ nephrolithiasis in one case series.[119] ***IDV 800/RTV 100-200 mg BID*** also results in ↑ IDV trough levels compared to those with	Hgc: 5- to 8-fold ↑ SQV AUC;[130] in vitro study suggests synergy at low doses and antagonism at high doses.[131] Sgc: 620% ↑ SQV AUC (1200 mg SQV single dose + IDV 800 mg q8h x 2 days); no apparent clinically relevant changes to IDV.[132]

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			in 20% ↓ Cmax, 30% ↓ AUC and 20% ↓ C12 of indinavir, but these differences were not statistically significant. Median amprenavir levels (AUC 46.5 hr*mg/L, C12 2852 ng/mL) were comparable to historical controls. This dosage combination appears to be pharmacokinetically compatible.[110]	open-label PK study (n=11), both IDV & LPV PK parameters ↓ up to 64% vs. values seen with coadministration in healthy subjects.[114] **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.[115] A separate study showed no significant changes in LPV or IDV Cmin with combination.[116]	IDV 800 mg q8h alone;[120, 121] however, ↑ IDV peak levels[122], possible ↑ risk nephrolithiasis[123] or other adverse events.[124] IDV 600/RTV 200 mg BID may provide increased IDV Cmin without significantly increasing IDV Cmax.[125] ***IDV 400/RTV100 mg BID*** (open study, n=17): ↑ Cmin (~0.5 ug/mL), ↓ Cmax vs. IDV 800mg q8h.[126] Preliminary data on ***once daily dosing*** (1200/100-200 mg IDV/RTV) regimens show ↑ Cmax, and Cmin = those with 800 mg q8h.[127, 128] 1200/200mg QD regimen well-tolerated in naïve-subjects (n=40) up to 24 weeks; 1200/400 QD also under study.[129]	
Lersivirine (UK-453,061, a next-generation NNRTI. Primarily metabolized via CYP3A4 and UGT2B7, weak inducer of CYP3A).	In healthy subjects receiving either **atazanavir 400 mg QD or atazanavir 300/100 mg QD** plus lersivirine 500 mg BID or placebo for 12 days, atazanavir concentrations were not significantly affected by lersivirine. With unboosted atazanavir, AUC ↓ 2%, Cmax ↑ 3%, Cmin ↓ 18%, while with boosted atazanavir, AUC ↓ 0.6%, Cmax ↑ 2%, Cmin ↓ 7% in the presence of lersivirine.[133]	In healthy subjects receiving lersivirine 1000 mg QD with or without darunavir 600 mg/ritonavir 100 mg BID for 10 days, lersivirine AUC ↓ 22% and Cmax ↓ 17% in the presence of darunavir/rtv. A dose increase of lersivirine may be required if co-administering with darunavir/ ritonavir.[134]				
Lopinavir/ ritonavir (capsules)	In TDM case series, **ATV 300/ LPV 800/rtv 200 mg QD** yielded ATV Ctrough levels approx. 5-fold higher (mean 736	Combination of **lopinavir/ritonavir 400/100 mg BID plus darunavir 300 mg BID** (as oral solution) led to a	In a healthy volunteer multi-dose study, **LPV/r + APV 750 mg BID** gave similar APV AUC, and 4.6-fold ↑ Cmin vs. APV		In HIV+ subjects dosed for 24 weeks, lopinavir/ritonavir at 400/100 mg BID provides mean lopinavir	**Saquinavir-hgc 600-800 mg BID + lopinavir/r:** In 12 HIV-positive, ARV-naive subjects, both SQV doses resulted in SQV

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	ng/mL) vs. ATV 400 mg QD (mean 122 ng/mL).[26] In a 2-phase kinetic study in HIV-infected men, this dosing combination yielded steady-state ATV Cmin of 541 ± 245 ng/mL and LPV Cmin 1424 ± 1423 ng/mL.[27] A small study in HIV-infected subjects on either stable **ATV 300/100 mg QD or LPV 400/100 mg BID** showed no changes in ATV concentrations and slight decreases in LPV exposure (16% ↓ AUC, 35% ↓ Cmin) when drugs were coadministered.[28] In HIV-negative subjects, **ATV 300 mg QD plus LPV/r 400/100 mg BID** led to 45% ↑ ATV Cmin (no change in AUC or Cmax) compared to ATV 300 mg/rtv 100 mg QD; LPV levels were not significantly different from historical controls.[29] A similar study in HIV-positive subjects yielded ATV AUC 38% ↓ similar Cmin vs. 300/100 mg (historical controls); LPV concentrations were not affected by ATV.[30] In a separate kinetic study in HIV-positive subjects, this combination resulted in significantly ↑ LPV levels compared to historical controls, while ATV levels were similar to historical controls	53% ↓ darunavir relative bioavailability and 19% ↓ in lopinavir exposure. Addition of extra ritonavir 100 mg BID did not impact reduction of darunavir exposure, while LPV bioavailability ↑ 37%. In a pk study of HIV-infected subjects, **darunavir 1200/rtv 100 mg BID plus LPV 400/100 mg BID** led to 9% ↑ AUC, 23% ↑ Cmin of LPV, but 38% ↓ AUC, 21% ↓ Cmax and 51% ↓ Cmin of darunavir. In the same study, **darunavir 1200 mg BID + LPV 533/rtv 133 mg BID** led to 9% ↑ LPV AUC but 41% ↓ darunavir AUC.[47] **Therefore, this combination is not recommended.**	1200 mg BID alone. However, LPV and RTV conc. were ↓ in presence of APV (LPV AUC ↓ 38%, Cmin ↓57%).[98] Similar findings observed in cohort of HIV+ subjects with both APV and FPV formulations.[99] [100] **Optimal doses for co-administration not yet defined.** **Separating LPV and FPV doses by 4 or 12 hours did not improve APV conc.**[101] **Suggest TDM when using this combination**.[102] In an open-label study of HIV-positive subjects stabilized on either **APV 750 mg BID + LPV/r 533/133 mg BID** or **FPV 1400 mg BID + LPV/r 533/133 mg BID**, switching from APV to FPV resulted in steady-state ↑ APV C_{max} 75%, C_{min} ↑58% and AUC_{tau} ↑ 76%. No change in tolerability was observed.[103]		exposures at least 30-fold above the protein binding-adjusted IC50 for wild-type virus.[135] In a retrospective cohort of subjects (n=12) taking ritonavir 100 mg BID with various protease inhibitors, ritonavir Cmin was approx. 3-fold lower when combined with lopinavir vs. saquinavir or indinavr.[136] Clinical relevance of these data is unclear, since ritonavir is only used for kinetic-enhancing purposes, and lopinavir levels remained therapeutic. No additional dosage adjustments recommended at this time. Pilot study in ARV-experienced subjects (n=33) of higher dose LPV: - LPV/r 667/167 mg (i.e., five 133/33 mg LPV/r caps) BID, OR - 400/300 mg (i.e., three 133/33 mg LPV/r caps and two 100 mg ritonavir) BID: LPV C_{trough} values were similar for both regimens, 60 to 70% higher compared with LPV/r 400/100 mg twice weekly.[137]	PK parameters similar to historical data of SQV 1000/rtv 100 mg BID; LPV PK also not affected.[138]

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	taking ATV 300/rtv 100 mg QD. Combination was well tolerated.[31] In a 2-phase kinetic study in HIV-infected men, **LPV/r 400/100mg BID and ATV 150mg BID** yielded mean LPV Cmin of 4644 ± 1965µg/L and AUC 87016 ± 27172µg/L.h, and ATV Cmin 1196 ± 433µg/L and AUC 21493 ± 6424µg/L.h.[27]					
Lopinavir/ritonavir (tablets)			**<u>LPV/r tablets:</u>** • Can use 400/100 mg BID with FPV in ARV-naïve subjects May ↑ to 600/150 mg (3 tablets) BID when co-administering in treatment-experienced subjects			
Maraviroc	When maraviroc 300 mg BID was given with **atazanavir 400 mg QD,** maraviroc AUC ↑ 3.6-fold, Cmax ↑ 2.1-fold.[139] When maraviroc 300 mg BID was given with **atazanavir 300/ritonavir 100 mg QD**, maraviroc AUC ↑ 4.9-fold, Cmax ↑ 2.7-fold. Reduction of maraviroc dose by 50% in the presence of protease inhibitors/potent CYP3A4 inhibitors is recommended.[139] In 15 HIV-positive patients who received **maraviroc 150 mg plus atazanavir 300/100 mg daily** as part of a PK	In healthy subjects, **maraviroc 150 mg BID plus darunavir 600/ritonavir 100 mg BID** resulted in 2.3-fold ↑ Cmax, 4-fold ↑ AUC of maraviroc vs. maraviroc administered alone. Reduce maraviroc dose to 150 mg BID when coadministering with darunavir/ ritonavir.[143] In a retrospective review, peak and trough levels were compared in HIV-positive patients taking either **maraviroc 300 mg BID** plus tenofovir/FTC, **maraviroc 300 mg QD plus darunavir 800/100 mg QD** or **maraviroc 150 mg QD plus darunavir 800/100 mg**	In healthy volunteers, combination of maraviroc 300 mg BID plus **fosamprenavir 1400 mg BID** led to reduced concentrations of both drugs:[146] • 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:[146] • MVC AUC ↓2%, Cmax ↓ 7%, Cmin ↓23% • APV AUC ↓ 21%, Cmax ↓ 32%, Cmin ↓ 36% while maraviroc plus **fosamprenavir 700/ritonavir 100 mg**	When maraviroc 100 mg BID was given with lopinavir/ritonavir 400/100 mg BID, maraviroc AUC ↑ 3.8-fold, Cmax ↑ 1.8-fold. Reduction of maraviroc dose to 50 mg BID resulted in maraviroc AUC ↑ 1.6-fold. Maraviroc 50% dose reduction in the presence of protease inhibitors/potent CYP3A4 inhibitors is recommended.[139] When maraviroc was given as 150 mg QD with lopinavir/ritonavir 400/100 mg BID in HIV-infected subjects (n=10), median (IQR) maraviroc concentrations were as follows: AUC_{24h} 4694	When maraviroc 100 mg BID was given with ritonavir 100 mg BID, maraviroc AUC ↑ 2.6-fold, Cmax ↑ 1.3-fold. Reduction of maraviroc dose to 50 mg BID gave similar exposures as maraviroc 100 mg BID alone. Maraviroc 50% dose reduction in the presence of protease inhibitors/potent CYP3A4 inhibitors is recommended.[139]	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.[139]

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	substudy of a randomized 48 week trial comparing MVC/ATVr vs ATVr + TDF/FTC, adequate maraviroc exposures were achieved at week 2: AUC 4330 ng.h/mL, Cavg 180 ng/mL, Cmax 650 ng/mL, Cmin 37 ng/mL. All subjects achieved the targeted Cavg >75 ng/mL for near maximal virologic efficacy based upon exposure-response analysis from the MERIT study.[140] Week 24 interim analysis results of the randomized trial showed similar outcomes in both arms.[141] Modeling of maraviroc kinetics showed that **maraviroc 150 mg QD plus ATV 300/100 mg QD** in HIV-positive subjects yielded lower Cmax and Cavg but higher Cmin and effective constant concentrations compared to maraviroc 300 mg BID alone in healthy volunteers.[142]	**QD**. Maraviroc concentrations were comparable between the groups and all Ctrough >25 ng/mL. Cpeak did not exceed 1000 ng/mL and no cases of postural hypotension were noted. All darunavir concentrations were therapeutic.[144] Co-administration of **etravirine/darunavir/ritonavir with maraviroc** increased the exposure of maraviroc by 210% (AUC_{12}) and peak levels (C_{max}) by 77% compared to maraviroc alone. Thus, if maraviroc is being dosed alongside etravirine and darunavir together, a maraviroc dose reduction to 150mg twice daily is necessary. No dose adjustment of ETV is required.[145]	**BID** led to:[146] • 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 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.[147]	(3923-5516) hr*ng/ml, C_{avg} 179 (159 -221) ng/ml, C_{max} 601 (491-689) ng/ml, C_{min} 59 (39-64) ng/ml. All 10 subjects achieved the targeted C_{avg} (> 75 ng/ml).[148]		
Nelfinavir			Amprenavir 800 mg q8h + nelfinavir 750 mg po q8h: 2.89-fold ↑ Cmin of	**LPV/r capsules:** • Multi-dose study in healthy volunteers of	162% ↑ NFV AUC, 9% ↑ RTV AUC.[150]	SQV levels ↑, no significant changes in NFV concentrations with

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			APV (but no overall change in AUC) , 15%↑ NFV AUC. No dosage adjustment required for either drug.[109]	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%).[149] • 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	***RTV 400 mg BID plus NFV 500-750 mg BID***: NFV AUC similar to that seen with NFV 750 mg TID alone; M8 [ ] 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.[151] ***RTV 100-200 mg BID added to NFV 1250 mg BID*** resulted in 30%↑ NFV AUC; steady-state a.m. predose NFV concentrations ↑ 45-90%.[152] In healthy volunteers, nelfinavir 2000 mg/ritonavir 200 mg once daily provided ↑ AUC, Cmax and comparable Cmin compared to nelfinavir 1250 mg BID.[153]	combination of SQV-hgc plus NFV. [154-156] 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.[157]
Nevirapine	In an open-label cohort study of HIV+ subjects stable on 2-3 NRTIs and either NVP 200 mg BID or ATV 300/rtv 100 mg QD, the NVP group received NVP plus ATV 300/100 mg QD for 10 days, then NVP plus ATV 400/100 mg QD for 10 days. Compared to the group that continued ATV 300/100 mg QD alone: • **NVP plus ATV/r 300/100mg** daily led to ↓ Cmax 38%, ↓ AUC 42%, ↓ Cmin 72% of ATV • **NVP plus ATV/r**	In an open-label, randomized, crossover study, 19 HIV-positive subjects received nevirapine 200 mg BID plus NRTIs with or without darunavir (either 300/100 mg BID DRV oral solution or 400/100 mg BID DRV tablet) in two 14-day sessions. In the presence of DRV/r, NVP AUC ↑ 27%, while DRV and RTV exposures were similar to historical data.[160] In a population cohort analysis of 51 HIV-infected patients taking	In HIV+ subjects, **FPV 1400 mg BID + NVP** 200 mg BID for 14 days led to 33% ↓ AUC, 39% ↓ Cmin of APV, and 29% ↑ AUC and 34% ↑ Cmin of NVP.[39] When **FPV 700/rtv 100 mg BID** administered with NVP for 14 days, APV AUC ↓ 11%, Cmin ↓19%, NVP AUC ↑14%, Cmin ↑ 21% vs. controls.[39] Recommend **FPV 700/rtv 100 mg BID with NVP 200 mg BID.**	**LPV/r capsules:** • Nevirapine ↓ lopinavir AUC and Cmin. Using lopinavir 533 mg/ritonavir 133 mg BID plus nevirapine will result in similar lopinavir concentrations to those achieved in the absence of nevirapine.[162] **LPV/r tablets:** • Can use 400/100 mg BID with NVP in ARV-naïve subjects • ↑ to 600/150 mg (3 tablets) BID when co-	11% ↓ RTV AUC, no effect on NVP levels. Interaction considered clinically insignificant; no dosage adjustment suggested.[163] Preliminary data suggest that dosing nevirapine 400 mg once daily may have a more pronounced effect on decreasing ritonavir concentrations compared to nevirapine dosed 200 mg twice daily (median 31% decrease). These findings require further substantiation; may consider monitoring ritonavir levels/response	27%↓ SQV AUC; clinical significance unknown.[165] 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 dosage regimen.[164]

	Atazanavir (Reyataz®)	Darunavir (Prezista®)	Fosamprenavir (Telzir®)	Lopinavir/ ritonavir (Kaletra®)	Ritonavir (Norvir®)	Saquinavir (Invirase®)
	400/100mg daily led to 19% ↓ AUC and 59% ↓ Cmin of ATV. These ATV values were higher than historical ATV 400 mg QD alone. RTV AUC ↓ 40% in presence of NVP, which may have contributed to ↓ ATV levels, while ATV/r increased NVP AUC by 25%.[158] Open label, multiple dose study in HIV infected patients (n=11) to study the kinetics of **ATV/r 300mg/100mg** +/- NVP 200mg BID. Combination led to ↓ ATV levels: ↓ Ctrough 41% (631 vs 316ng/ml); ATV Ctrough remained higher than historical controls taking ATV 400mg daily; ↑ NVP Ctrough12 (GMR 1.46) compared to historical controls not taking ATV/r. Monitoring ATV Cmin is recommended, and a dose increase in ATV may be necessary.[159]	nevirapine (n=42 with other NRTIs, n=9 on concomitant darunavir/ritonavir), nevirapine Ctrough were 45% higher in the group taking darunavir/ritonavir vs. those on NRTIs only ($p<0.05$).[161] **No dose adjustment** is currently recommended, but literature indicates that changes in plasma NVP levels can lead to significant toxicity concerns, including hepatotoxicity. Monitor closely for dose-related nevirapine toxicity.[3]		administering in treatment-experienced subjects	if switching nevirapine dosage regimen.[164]	
Raltegravir, MK-0518 (integrase inhibitor)	In two healthy volunteer studies, raltegravir kinetics were measured in the presence of steady-state boosted or unboosted atazanavir. In the presence of chronic **atazanavir 400 mg QD**, single dose **raltegravir 100 mg** resulted in raltegravir AUC ↑ 72%, Cmax ↑ 53%, C12 ↑ 95% compared to raltegravir alone.	In an open-label, sequential 2-period study, 18 healthy subjects received raltegravir 400 mg BID for 4 days followed by raltegravir 400 mg BID plus darunavir 600/ritonavir 100 mg BID for 12 days. Eight subjects developed rash (7 mild-moderate, 1 serious) between days 8-12 of period 2, and only six subjects completed the study. Based on	In an open-label, 3-period study, subjects received raltegravir 400mg BID for 7days, then were randomized to 14 days of either fosamprenavir 1400mg BID, FPV/r 700mg/100mg BID, or FPV/r 1400mg/100mg QD alone or with RAL; subjects continued their randomized dose of FPV for 14 more days, adding or removing RAL based on receipt in Period 2.	Open label, 3 period, sequential, crossover, multiple dose study in healthy subjects (n=12) to investigate kinetics of RAL 400 mg BID +/- LPV/r 400 mg/100mg BID. LPV/r had no effect on RAL AUC (RAL alone VS combo: 5.3mg/L.h VS 5.4 mg/L.h) or Cmax (RAL alone vs combo: 1698ng/ml VS 1687 ng/ml). Concomitant use of LPV/r led to ↓ RAL C12h 30% (49.4ng/ml	In a placebo-controlled, 2 period study in 12 subjects, the combination of 400 mg raltegravir and 100 mg RTV BID did not affect raltegravir parameters compared to raltegravir 400 mg administered alone.[181]	

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	In an open-label, random order, crossover study, healthy volunteers received either RAL 400 mg BID or **RAL 400/ATV 400 mg QD** each for 7 days. In the presence of ATV, RAL Cmax ↑ 37% (p=0.4), Cmin ↓ 68% (P<0.001), AUC unchanged, and formation of RAL-glucuronide was significantly decreased. RAL pk showed high interindividual variability and significant intra-individual diurnal variation.[166] In an open-label, fixed sequence study, HIV-infected subjects received ATV 400 mg QD for 2 weeks, followed by **ATV 400/RAL 800 mg QD** for 10 days. Concomitant tenofovir, proton-pump inhibitors and other interacting drugs were not allowed. Compared to historical data of RAL 400 mg single dose, RAL Cmax ↑ 2.81-fold, AUC ↑ 18%, Ctrough ↓ 85%. 4/15 subjects had RAL Ctrough <33 nM. Atazanavir concentrations were not reported.[167] In an open-label, sequential, two-period study, 17 HIV-infected, virally suppressed subjects with no history of virologic failure received **ATV 600 mg daily** plus **RAL 400 mg**	limited data, raltegravir exposure appeared to be slightly decreased in the presence of darunavir/ritonavir (raltegravir AUC ↓ 29%, Cmax ↓ 33%, Cmin ↑ 38%), while darunavir parameters were similar to historical controls.[173] In 29 HIV-positive subjects receiving regimens including raltegravir, raltegravir/darunavir 600 mg/ritonavir 100 mg BID, or raltegravir/darunavir/ritonavir/ etravirine BID, no differences in raltegravir Ctrough were noted between the groups.[174] 14 HIV-positive patients on stable cART with VL<50 copies/mL participated in a 3 period, phase I pk study of TDF/FTC plus DRVr 800/100 mg QD (period 1), TDF/FTC/DRVr plus RAL 400 mg BID (period 2), and DRVr/RAL (period 3). Intensive PK were performed at steady-state in each period. No statistically significant differences in PK parameters were observed between period 2 versus 1. In period 3, darunavir Ctrough ↓ 36% and $t_{1/2}$ ↓ 31% compared to period 1, while DRV AUC, Cmax and RTV pk were not significantly changed. No difference in RAL pk was observed between periods 2 & 3.	With fosamprenavir, raltegravir PK decreased, especially at higher RTV doses, but RAL GM C_{min} were 3-9.4-fold >RAL IC_{95} for WT HIV (14.6ng/mL). With RAL, amprenavir PK decreased modestly; APV GM C_{min} for FPV/r 700/100 BID and FPV/r 1400/100 QD were 2.1-7.8-fold >APV EC_{90} documented for PI-naïve HIV+ pts (228ng/mL). The clinical implications of these results have yet to be determined.[179]	VS 34.4ng/ml). Raltegravir Cmin stayed above IC95 (15ng/ml). Dose adjustment not recommended.[180]		

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	BID for 2 weeks then **800 mg daily plus ATV 600 mg QD** for 4 weeks, concomitantly with 3TC or FTC. The AUC over 24 hours of QD RAL was not significantly different from that of BID RAL, while the Cmax was 33% higher and Cmin was 81% lower with QD vs. BID RAL. Atazanavir kinetics were similar with both RAL dosing regimens. All patients maintained an undetectable viral load and the regimens were well tolerated.[168] Six HIV-infected patients on **ATV 300/100 mg QD** were intensified **with RAL 400 mg QD** for 10 days. RAL exposure was adequate in most patients with only 1 Ctrough <15 ng/mL (IC95). Atazanavir concentrations were similar to historical controls and all Ctrough>150 ng/mL.[169] In 21 HIV-infected treatment-experienced subjects who switched to **ATV 200/RAL 400 mg BID** due to resistance or toxicity issues, mean ATV AUC was 6257 ng/mL.hr, Ctrough was 227 ng/mL (122-332), with 24% having ATV Ctrough <150 ng/mL. Mean RAL AUC was 9085 ng/mL.h and Ctrough 132 ng/mL. 62% subjects had VL<50 at study entry, all	Four subjects had DRV Ctrough < 550 ng/mL (IC50 for PI-resistant virus) in period 3 only, all levels were >55 ng/mL.[175] In 15 HIV-positive subjects receiving **DRV 800/100 mg QD plus RAL 400 mg BID**, favourable pharmacokinetics of both drugs were observed and all patients had VL<37 copies/mL at week 24.[176] In 24 HIV-positive subjects, no evidence of a pharmacokinetic interaction was found between **DRVr 800/100 mg QD plus RAL 400 mg BID or 800 mg QD**.[177] In 55 HIV-positive patients receiving darunavir-containing regimens with either NRTI or raltegravir, 117 darunavir Ctrough samples were measured. The mean (± sd) darunavir concentration was higher in the NRTI group as compared to the raltegravir group (4.20 ± 2.35 vs. 2.63 ± 1.84 mg/L, p=0.018). However, the proportion of subjects with VL<50 copies/mL was higher in the raltegravir vs. NRTI arm (76.5% vs. 44%, respectively, p=0.041). In a multivariate linear regression model, raltegravir was				

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	reached undetectable after 2 weeks.[170] In healthy subjects, coadministration of **atazanavir 300 mg BID and raltegravir 400 mg BID** resulted in 11% ↓ Cmax, 17% ↓ AUC and 29% ↓ Cmin of atazanavir compared to atazanavir 300 mg BID alone; mean ATV Cmin was 817 ng/mL. Raltegravir AUC ↑ 54%, Cmax ↑ 39% and Cmin ↑48% when given with atazanavir. Mean QRS and PR interval increases were observed with atazanavir alone, and remained when raltegravir was coadministered; the clinical relevance of these changes is unclear.[171] In 22 HIV-positive subjects who switched to **atazanavir 300 mg BID plus raltegravir 400 mg BID**, steady-state pharmacokinetics were assessed. Geometric mean atazanavir AUC, Cmax and C12h were 14454 ng.h/mL, 2275 ng/mL and 419 ng/mL, respectively. Raltegravir geometric mean AUC, Cmax and C12 were 7112 ng.h/mL, 1680 ng/mL and 62 ng/mL, respectively. Three subjects (14%) had atazanavir Ctrough <100 ng/mL. At the time of switch, 79% of patients had VL<50	independently related to lower darunavir levels. The mechanism for this unexpected interaction is unclear, but does not appear to be virologically significant.[178]				

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	copies/mL; by 24 weeks, all subjects had undetectable viral loads.[172]					
Rilpivirine	Potential for ↑ concentrations of rilpivirine. Rilpivirine is not expected to affect the plasma concentrations of co-administered PIs.[182]	In a randomized, crossover study in healthy volunteers, subjects received either rilpivirine 150mg daily for 22 days, or darunavir 800/100mg QD for 11 days followed by DRV 800/100mg QD plus rilpivirine 150mg QD from days 12-22. Co-administration of DRV/r increased exposures of rilpivirine: AUC24h ↑ 2.3 fold; Cmax ↑ 1.79 fold, Cmin ↑ 2.78 fold, likely a result of CYP3A4 inhibition. No clinically relevant changes in DRV exposure were observed in the presence of rilpivirine.[183] No dose adjustment is required with coadministration.[182]	Potential for ↑ concentrations of rilpivirine. Rilpivirine is not expected to affect the plasma concentrations of co-administered PIs.[182]	In healthy volunteers, rilpivirine 150 mg QD plus LPV/r 400/100 mg BID resulted in 52% ↑ AUC, 29% ↑ Cmax, 74% ↑ Cmin of rilpivirine; LPV kinetics not affected.[184] No dose adjustment is required with coadministration.[182]		Potential for ↑ concentrations of rilpivirine. Rilpivirine is not expected to affect the plasma concentrations of co-administered PIs.[182]
Ritonavir	Additive-synergistic antiviral activity in vitro.[22] In healthy volunteer study, addition of **ritonavir 100-200 mg to ATV 200 or 400 mg** daily resulted in significantly ↑ ATV exposure.[32] Separate steady-state study in healthy volunteers (n=30) of **ATV 300/ritonavir 100 mg QD** with a light meal resulted in 1.86-fold ↑ Cmax and 3.38-fold ↑ AUC of ATV; ritonavir kinetics not affected.[33]		In healthy volunteers, **FPV 1400mg/rtv 100 mg BID** led to 54% ↑ AUC, 26% ↑ Cmin of APV vs. FPV 700/rtv 100 mg BID regimen. **FPV 1400 mg/rtv 200 mg BID** led to 26% ↑ AUC, 32% ↑ Cmin of APV but ↑ incidence of ALT, AST elevations, and therefore is not recommended.[104] In a healthy volunteer pharmacokinetic study, **FPV 1400/rtv 100 mg QD** led to 10% ↓AUC, 38% ↓ Cmin of APV vs. FPV 1400/rtv 200 mg	In HIV+ subjects dosed for 24 weeks, lopinavir/ritonavir at 400/100 mg BID provides mean lopinavir exposures at least 30-fold above the protein binding-adjusted IC50 for wild-type virus.[135] In a retrospective cohort of subjects (n=12) taking ritonavir 100 mg BID with various protease inhibitors, ritonavir Cmin was approx. 3-fold lower when combined with lopinavir vs. saquinavir or indinavr. [136] Clinical relevance of these data	*Results from a cross-study analysis of ritonavir plus various protease inhibitors suggest that for a given PI dose, increasing the ritonavir dose will increase PI Cmin, while the PI Cmax remains relatively unchanged.[185] In other words, for dual protease inhibitor combinations involving ritonavir: • to increase PI Cmin, one should increase the ritonavir dose • to increase PI Cmax, AUC, one should increase the	***400 mg SQV/400 mg RTV BID:*** • 1587% ↑ SQV AUC[132, 186, 187]; well tolerated.[188] ***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.[189] • Kinetic substudy in 13 HIV+ subjects stabilized on combination showed equivalent SQV kinetic parameters (GMR of

	Atazanavir (Reyataz®)	Darunavir (Prezista®)	Fosamprenavir (Telzir®)	Lopinavir/ ritonavir (Kaletra®)	Ritonavir (Norvir®)	Saquinavir (Invirase®)
	Current dosage recommendation: atazanavir 300 mg/ ritonavir 100 mg QD with food. In a cross-over, single-blind, two period study, healthy volunteers received **ATV 300 mg with either RTV 100 mg or 50 mg** for 10 days, 15 days apart. Ritonavir Cmax and AUC were lower with the 50 mg dose vs. 100 mg dose and all/most RTV Ctrough were below the level of detection. No differences in ATV exposures were noted between the 50 vs 100 mg RTV dose treatments and all ATV Ctrough were >0.15 mg/L (0.59 vs. 0.79 mg/L, respectively, p=0.132). The 50 mg ritonavir dose was associated with a lower impact on serum lipids.[34]		QD, although Cmin remained 5.9-fold higher than IC50 WT.[105] In both a retrospective cohort (n=51) of patients taking FPV 1400 mg/ritonavir 100-200 mg QD,[106] and in a prospective, open-label study of 12 HIV-infected subjects stabilized on FPV 1400 mg/rtv 200 mg QD then switched to FPV 1400 mg/rtv 100 mg QD for 4 weeks,[107] median amprenavir exposures were not statistically different between the 100 mg and 200 mg ritonavir doses. Ritonavir ↑ plasma APV to similar extent with either APV or FPV. Therefore, FPV may replace APV, and metablic APV interactions are applicable to FPV.[104]	is unclear, since ritonavir is only used for kinetic-enhancing purposes, and lopinavir levels remained therapeutic. No additional dosage adjustments recommended at this time. Pilot study in ARV-experienced subjects (n=33) of higher dose LPV: - **LPV/r 667/167 mg** (i.e., five 133/33 mg LPV/r caps) **BID**, OR - **400/300 mg** (i.e., three 133/33 mg LPV/r caps and two 100 mg ritonavir) **BID**: LPV C_{trough} values were similar for both regimens, 60 to 70% higher compared with LPV/r 400/100 mg twice weekly.[137]	PI dose	hgc/sgc for AUC 1.40, Cmax 1.23, and Cmin 1.46) when SQV-sgc replaced by SQV-hgc[190] • 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)[191] ***1000 mg SQV/100 mg RTV BID*:** • SQV-hgc/r gave significantly ↑ 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.[192]
Saquinavir	Additive-synergistic antiviral activity in vitro.[22] In 21 HIV+ subjects, **ATV 400 mg/SQV-hgc 1200 mg QD** led to higher proportion of patients with ATV Ctrough< IC90 vs. ATV 400 mg alone; SQV Ctrough <MEC in most patients. Additional dosage adjustment and/or RTV boosting may be required to optimize drug levels.[35] When ATV 300 mg added to **SQV 1600/r**	Darunavir 400 mg BID plus saquinavir 1000/ritonavir 100 mg BID led to significant ↓ in darunavir exposure. darunavir Cmin ↓ 42%, Cmax ↓ 17%, AUC ↓26% with combination, while no significant changes in SQV kinetics were observed. Therefore, not recommended to combine SQV and darunavir /ritonavir.[48]	In a group of 18 HIV+ subjects, **SQV-hgc 1000/FPV 700 mg BID plus either RTV 100-200 mg BID** resulted in: - non-sig. ↓ in SQV AUC_{0-12}, C_{trough} and C_{max} (14%, 24%, 9% respectively) with RTV 100 mg BID - non-sig. ↑ in SQV AUC_{0-12}, C_{trough} and C_{max} (12%, 3%, 20% respectively) with RTV 200 mg BID FPV levels not affected by SQV co-administration.[108]	**Saquinavir-hgc 600-800 mg BID + lopinavir/r:** In 12 HIV-positive, ARV-naive subjects, both SQV doses resulted in SQV PK parameters similar to historical data of SQV 1000/rtv 100 mg BID; LPV PK also not affected.[138] **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	***400 mg SQV/400 mg RTV BID:*** • 1587% ↑ SQV AUC[132, 186, 187]; well tolerated.[188] ***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.[189] • Kinetic substudy in 13 HIV+ subjects stabilized on combination showed equivalent SQV kinetic	

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	100 mg QD in 20 HIV+ subjects, SQV AUC ↑ 60%, Cmax ↑ 42%, Ctrough ↑ 112% (*p* <0.05) after 30 days. ATV levels were similar to those seen with ATV/r; total and indirect bilirubin ↑ by 5 times after 10 days of ATV therapy.[36] In TDM case series, **ATV 300/ SQV2000/rtv 100-200 mg QD** yielded ATV Ctrough levels approx. 6-fold higher (mean 749 and 899 ng/mL, respectively) vs. ATV 400 mg QD (mean 122 ng/mL).[26] In a healthy volunteer study, ATV 200/SQV 1500 mg BID led to ATV Cmin comparable to ATV 400 mg QD, while SQV Cmin was 0.129 ug/mL (75% were > 0.1 ug/mL).[37]		May wish to consider TDM if using RTV 100 mg BID dose with this combination.	levels were not affected.[193]	parameters (GMR of hgc/sgc for AUC 1.40, Cmax 1.23, and Cmin 1.46) when SQV-sgc replaced by SQV-hgc[190] • 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)[191] ***1000 mg SQV/100 mg RTV BID*:** • SQV-hgc/r gave significantly ↑ 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.[192]	
Tenofovir	Combination of atazanavir and tenofovir (at standard doses) resulted in 25% ↓ AUC and 40% ↓ Cmin of atazanavir, while tenofovir AUC was ↑ by 24%.[194] With **atazanavir 300 mg/ ritonavir 100 mg QD** plus tenofovir**,** ATV AUC ↓ 11%, Cmin ↓ 20% while tenofovir AUC ↑ 37% and Cmin ↑ 29%.[195]		In healthy volunteers, tenofovir 300 mg daily plus **fosamprenavir 1400/ritonavir 100-200 mg QD** for 14 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.[196] Similarly, in an open-label study of 15 treatment-naïve subjects, **FPV 1400/rtv 200**/tenofovir	*Impact on tenofovir:* In healthy volunteers, tenofovir 300 mg daily plus lopinavir 400/ritonavir 100 mg BID resulted in slight ↑ AUC, Cmax of tenofovir; lopinavir AUC and Cmax were ↓ 15%, but Cmin unchanged and lopinavir IQ-wild type >90. These changes not likely clinically significant.[199] In a crossover study in healthy volunteers, TDF plus LPV/r with food led to ↑ 32% tenofovir AUC, while LPV and RTV kinetics were not affected. Clinical significance unclear.[200]	Retrospective data from a series of HIV subjects showed no effect of tenofovir on lopinavir and ritonavir Cmin at steady-state.[203] Ritonavir and tenofovir may be coadministered without dosage adjustment.	In cohort (n=14) of patients on **saquinavir-hgc 1600 mg/ ritonavir 100 mg QD**, no significant difference in saquinavir Cmin when NRTI backbone switched from ddI/d4T to tenofovir/3TC.[204] 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.[205] Similar effect observed in healthy volunteer study.[206]

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			300/emtricitabine 200 mg QD for 48 weeks yielded antiretroviral concentrations similar to historical controls.[107] 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.[197] In a healthy volunteer study, subjects received tenofovir 300 mg QD for 7 days (period 1), and then were randomized to receive fosamprenavir 1400 mg BID or fosamprenavir 700/rtv 100 mg BID alone and with tenofovir or vice versa (periods 2 & 3). Tenofovir Cmin, Cmax and AUC ↓ 12%, 25% and 15% with fosamprenavir and ↓ 9%, 18% and 7% with boosted fosamprenavir, respectively. In the presence of tenofovir, amprenavir Cmin, Cmax and AUC ↑ 31%, 3% and 7% (unboosted) and ↑ 31%, 4% and 16% (boosted). These changes are not likely clinically significant.[198]	In tenofovir compassionate access study, (median duration of 63 weeks), 94% of patients received TDF + LPV/r (n = 274/291), with no significant nephrotoxicity observed.[200] *Impact on lopinavir/ritonavir concentrations:* In patients taking LPV/r and TDF (n=14), mean lopinavir Ctrough was 5.6 ug/mL vs. 7 ug/mL in patients taking LPV/r plus other NRTIs (n=15).[201] In a kinetic interaction study in experienced patients (n=18), lopinavir Cmin ↓ by 34% (mean 4.61 vs. 3.06 ug/mL, p=0.04), while ritonavir Cmin ↓ by 44% (mean of 0.63 vs. 0.35 ug/mL, p=0.014) in the presence of tenofovir.[202] Recommendations on dosage adjustment not established. Monitor for tenofovir toxicity and possibly lopinavir efficacy, particularly in treatment-experienced patients. Consider TDM (if available) with possible dosage increase of lopinavir if suboptimal lopinavir concentrations and/or inadequate viral response.[202]		
Tipranavir *(inducer of CYP3A4, P-gp and glucuronyl transferase)*	Healthy volunteer study of steady-state atazanavir 300/100 mg, tipranavir 500/100 mg BID, or tipranavir		Pharmacokinetic analysis in treatment-experienced subjects taking TPV 500 mg/APV 600 mg/rtv 200 mg BID	Pharmacokinetic analysis in treatment-experienced subjects taking TPV 500 mg/LPV 400 mg/rtv 100 mg BID	Open-label, dose-ranging study in healthy subjects of TPV 250, 500, 750, 1000, or 1250 mg BID + 100/200 mg	Pharmacokinetic analysis in treatment-experienced subjects taking TPV 500 mg/SQV 1000 mg/rtv 200 mg BID

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	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. [207] Combination not recommended.		showed 45% ↓ AUC, 40% ↓ Cmax, 56% ↓ Cmin of APV compared to APV 600/rtv 200 mg BID alone.[208] 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.[209] Use combination with caution, and consider therapeutic drug monitoring if available.	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.[208] 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.[210] 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.[209] Use combination with caution, and consider therapeutic drug monitoring.	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.[211]	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.[208]
Vicriviroc (VVC)	The combination of vicriviroc 15 mg/ritonavir 100 mg QD plus atazanavir 300 mg QD in healthy volunteers did not lead to significant changes in vicriviroc plasma levels, compared	Open label, multidose study in healthy adult subjects (n=12) to investigate the PK effects of vicriviroc 30mg daily + RTV 100mg BID +/- DRV 600mg BID. Addition of darunavir led	The combination of vicriviroc 15 mg QD plus fosamprenavir 700 mg/ritonavir 100 mg BID in healthy volunteers did not lead to significant changes in vicriviroc plasma levels, compared	Vicriviroc exposure ↑ similarly by ritonavir or lopinavir/ritonavir: In healthy subjects, vicriviroc 10 mg QD was given alone or with ritonavir 100 mg QD or	Vicriviroc exposure ↑ similarly by ritonavir or lopinavir/ritonavir: In healthy subjects, vicriviroc 10 mg QD was given alone or with ritonavir 100 mg QD or	The combination of vicriviroc 15 mg QD plus saquinavir-sgc 1000 mg/ritonavir 100 mg BID in healthy volunteers did not lead to significant changes in vicriviroc plasma levels, compared

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	to vicriviroc 15 mg QD /ritonavir 100 mg BID alone. Vicriviroc may be added to a ritonavir-boosted PI regimen without dosage adjustment.[212]	to 7%↓ AUC, 17% ↓ Cmax, 3% ↑ Cmin of vicriviroc. Darunavir did not alter VCV levels to clinically important extent. No dose adjustment required.[213]	to vicriviroc 15 mg QD/ritonavir 100 mg BID alone. Vicriviroc may be added to a ritonavir-boosted PI regimen without dosage adjustment.[212]	lopinavir/ritonavir 400 mg QD for 14 days. In the presence of ritonavir, vicriviroc AUC ↑ 5.4-fold and Cmax ↑ 2.5-fold, while in the presence of lopinavir/rtv, vicriviroc AUC ↑ 4.2-fold and Cmax ↑ 2.3-fold. Both combinations were well tolerated.[214]	lopinavir/ritonavir 400 mg QD for 14 days. In the presence of ritonavir, vicriviroc AUC ↑ 5.4-fold and Cmax ↑ 2.5-fold, while in the presence of lopinavir/rtv, vicriviroc AUC ↑ 4.2-fold and Cmax ↑ 2.3-fold. Both combinations were well tolerated.[214]	to vicriviroc 15 mg QD/ritonavir 100 mg BID alone. Vicriviroc may be added to a ritonavir-boosted PI regimen without dosage adjustment.[212]
Zidovudine *(GT 60-75% > CYP3A, minor)*	In healthy volunteers (n=20), atazanavir 400 mg daily plus Combivr BID at steady-state did not result in any significant changes to PK parameters of any drug.[215] Atazanavir may be coadministered with zidovudine and lamivudine without dosage adjustment.		Amprenavir may inhibit ZDV glucuronidation to a small degree; no dosage adjustment necessary.[216]	Potential for ↓ zidovudine concentrations due to induction of glucuronyl transferases; clinical significance unknown, no dosage adjustments recommended.[162]	25% ↓ zidovudine AUC. May need to ↑ zidovudine dose.[7]	No interaction.
III)	**INTERACTIONS**	**WITH OTHER**	**MEDICATIONS**			
Albendazole					In healthy volunteers, single dose albendazole 400 mg was given alone or after 1 day or 8 days ritonavir 200 mg BID. Albendazole kinetics were unchanged by short-term ritonavir dosing, but AUC ↓ 27% and Cmax ↓ 26% in the presence of chronic ritonavir administration.[217]	
Antacids (NB: see separate entries for H2-blockers and Proton-pump inhibitors)	Atazanavir solubility decreases with increasing gastric pH. Administer atazanavir 2 hours before or 1 hour after antacids.[1]		In a single-dose healthy volunteer study, co-administration of 30 mL Maalox TC with 1400 mg fosamprenavir led to 18% ↓ in APV AUC_{last}, 35% ↓ C_{max}, and 14% ↑ C_{12}. **FPV may be coadministered with antacids without**	In a prospective observation of treatment-naïve subjects receiving LPV/r BID or QD, no significant differences in LPV levels were noted in the presence of either antacids, H2 blockers, or proton pump inhibitors.[219]	Effect of antacid coadministration on ritonavir absorption not studied.	

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			concern and without separation in dosing.[218]			
Anticoagulants • Dabigatran (Pradaxa®); *(P-gp)* • Rivaroxaban (Xarelto®); *(CYP3A4, P-gp)*	Potential for ↑ anticoagulant. Dabigatran monograph states that P-gp inhibitors including HIV protease inhibitors may be expected to increase systemic exposure to dabigatran, and should be used with caution.[220] Rivaroxaban monograph states that rivaroxaban is **contraindicated** in patients receiving concomitant systemic treatment with strong inhibitors of both CYP 3A4 and P-gp, such as **ritonavir.**[221]	Potential for ↑ anticoagulant. Dabigatran monograph states that P-gp inhibitors including HIV protease inhibitors may be expected to increase systemic exposure to dabigatran, and should be used with caution.[220] Rivaroxaban monograph states that rivaroxaban is **contraindicated** in patients receiving concomitant systemic treatment with strong inhibitors of both CYP 3A4 and P-gp, such as **ritonavir.**[221]	Potential for ↑ anticoagulant. Dabigatran monograph states that P-gp inhibitors including HIV protease inhibitors may be expected to increase systemic exposure to dabigatran, and should be used with caution.[220] Rivaroxaban monograph states that rivaroxaban is **contraindicated** in patients receiving concomitant systemic treatment with strong inhibitors of both CYP 3A4 and P-gp, such as **ritonavir.**[221]	Potential for ↑ anticoagulant. Dabigatran monograph states that P-gp inhibitors including HIV protease inhibitors may be expected to increase systemic exposure to dabigatran, and should be used with caution.[220] Lopinavir/ritonavir monograph recommends avoiding concomitant use of rivaroxaban and lopinavir/ritonavir, as coadministration is expected to result in ↑ exposure of rivaroxaban which may lead to risk of increased bleeding.[162] Rivaroxaban monograph states that rivaroxaban is **contraindicated** in patients receiving concomitant systemic treatment with strong inhibitors of both CYP 3A4 and P-gp, such as **ritonavir.**[221]	Potential for ↑ anticoagulant. Dabigatran monograph states that P-gp inhibitors including HIV protease inhibitors may be expected to increase systemic exposure to dabigatran, and should be used with caution.[220] Rivaroxaban monograph states that rivaroxaban is **contraindicated** in patients receiving concomitant systemic treatment with strong inhibitors of both CYP 3A4 and P-gp, such as **ritonavir.**[221]	Potential for ↑ anticoagulant. Dabigatran monograph states that P-gp inhibitors including HIV protease inhibitors may be expected to increase systemic exposure to dabigatran, and should be used with caution.[220] Rivaroxaban monograph states that rivaroxaban is **contraindicated** in patients receiving concomitant systemic treatment with strong inhibitors of both CYP 3A4 and P-gp, such as **ritonavir.**[221]
Antihistamines, non-sedating (i.e., astemizole, terfenadine) *(CYP3A4)*	Possible ↑ antihistamine AUC and cardiotoxicity. **Avoid combination.**		Possible ↑ antihistamine AUC and cardiotoxicity. **Avoid combination.**[4]	Possible ↑ antihistamine AUC and cardiotoxicity. **Avoid combination.**[162]	Possible ↑ antihistamine AUC and cardiotoxicity. **Avoid combination**.[7]	368% ↑ terfenadine AUC; **avoid combination**.[132] Potential for similar interaction with astemizole.
Atovaquone/ proguanil (Malarone®) Atovaquone: GT Proguanil: CYP2C19 to active metabolite, cycloguanil, 40-	In 19 HIV-positive patients on atazanavir/rtv, single dose atovaquone 250/ proguanil 100 mg resulted in atovaquone AUC ↓ 46% and proguanil AUC ↓ 70% (only in those who had			In 19 HIV-positive patients on LPV/r, single dose atovaquone 250/ proguanil 100 mg resulted in atovaquone AUC ↓ 74% and proguanil AUC ↓ 68% (only in those who had no CYP2C19*2 or -*3		

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60% Clr	no CYP2C19*2 or -*3 alleles) compared to healthy volunteers.[222]			alleles) compared to healthy volunteers.[222]		
Benzodiazepines • 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).		Risk of prolonged sedation. **Avoid combination**, or use agents which are glucuronidated (e.g., lorazepam, oxazepam, temazepam).[4]	Risk of prolonged sedation. Midazolam, triazolam are contraindicated with lopinavir/ ritonavir.[162]	Risk of prolonged sedation. **Avoid combination**, or use agents which are glucuronidated (e.g., lorazepam, temazepam).[7] Recent single-dose PK study suggests that alprazolam may also be safe to use with ritonavir.	Possible risk of prolonged sedation. Use with caution.[9]
Cisapride *(CYP3A4)*	Possible ↑ cisapride AUC and cardiotoxicity. **Avoid combination.**		Possible ↑ cisapride AUC and cardiotoxicity. **Avoid combination.**[4]	Possible ↑ cisapride AUC and cardiotoxicity. **Avoid combination.**[162]	Possible ↑ cisapride AUC and cardiotoxicity. **Avoid combination**.[7]	Possible ↑ cisapride AUC and cardiotoxicity. **Avoid combination**.[9]
Calcium channel blockers, e.g. • amlodipine, diltiazem, felodipine, nifedipine, nimodipine, verapamil (CYP3A substrates)	Potential for ↑ calcium channel blocker concentrations with concomitant protease inhibitor therapy. In healthy subjects on indinavir 800/ritonavir 100 mg BID, steady-state amlodipine AUC ↑ 90% and diltiazem AUC ↑ 27% (NB: 2/13 subjects (15%) had >4-fold ↑ diltiazem AUC).[223] If coadministration is necessary, initiate calcium blocker therapy at low doses, with careful titration to response and side effects.	Potential for ↑ calcium channel blocker concentrations with concomitant protease inhibitor therapy. In healthy subjects on indinavir 800/ritonavir 100 mg BID, steady-state amlodipine AUC ↑ 90% and diltiazem AUC ↑ 27% (NB: 2/13 subjects (15%) had >4-fold ↑ diltiazem AUC).[223] If coadministration is necessary, initiate calcium blocker therapy at low doses, with careful titration to response and side effects.	Potential for ↑ calcium channel blocker concentrations with concomitant protease inhibitor therapy. In healthy subjects on indinavir 800/ritonavir 100 mg BID, steady-state amlodipine AUC ↑ 90% and diltiazem AUC ↑ 27% (NB: 2/13 subjects (15%) had >4-fold ↑ diltiazem AUC).[223] If coadministration is necessary, initiate calcium blocker therapy at low doses, with careful titration to response and side effects.	Potential for ↑ calcium channel blocker concentrations with concomitant protease inhibitor therapy. In healthy subjects on indinavir 800/ritonavir 100 mg BID, steady-state amlodipine AUC ↑ 90% and diltiazem AUC ↑ 27% (NB: 2/13 subjects (15%) had >4-fold ↑ diltiazem AUC).[223] Extreme bradycardia with complete AV block and hypotension occurred in a patient on stable therapy including lacidipine, ramipril, levothyroxine, rosuvastatin, metoprolol and ASA; symptoms developed 48 hours after starting tenofovir, emtricitabine, and lopinavir/ritonavir for post-exposure prophylaxis. An interaction between lopinavir/ritonavir and	Potential for ↑ calcium channel blocker concentrations with concomitant protease inhibitor therapy. In healthy subjects on indinavir 800/ritonavir 100 mg BID, steady-state amlodipine AUC ↑ 90% and diltiazem AUC ↑ 27% (NB: 2/13 subjects (15%) had >4-fold ↑ diltiazem AUC).[223] If coadministration is necessary, initiate calcium blocker therapy at low doses, with careful titration to response and side effects.	Potential for ↑ calcium channel blocker concentrations with concomitant protease inhibitor therapy. In healthy subjects on indinavir 800/ritonavir 100 mg BID, steady-state amlodipine AUC ↑ 90% and diltiazem AUC ↑ 27% (NB: 2/13 subjects (15%) had >4-fold ↑ diltiazem AUC).[223] If coadministration is necessary, initiate calcium blocker therapy at low doses, with careful titration to response and side effects.

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				metoprolol and lacidipine was hypothesized to be the cause of this adverse event.[224] If coadministration is necessary, initiate calcium blocker therapy at low doses, with careful titration to response and side effects.		
Clarithromycin *(parent: CYP3A4; inhibits CYP3A4, 1A2?) (CLA-14 OH: renal, CYP3A4)*	In healthy subjects, clarithromycin 500 mg BID plus atazanavir 400 mg QD resulted in 28% ↑ ATV AUC, and 50%↑ Cmax, 94% ↑ AUC clarithromycin and 70% ↓ CLA-14 OH metabolite.[225] Recommend 50% dosage reduction of clarithromycin since QTC prolongations have been reported with elevated clarithromycin levels. Consider alternate agent for infections other than M. avium complex since clarithromycin metabolite levels reduced.[1]	Combination of darunavir 400/100 mg BID and clarithromycin 500 mg BID led to a 57% ↑ in clarithromycin exposure, while darunavir exposure was not affected. For patients with renal impairment, clarithromycin dosage should be adjusted as follows: • Clcr 30-60 mL/min: 50%↓ clarithromycin dose • Clcr <30 mL/min: 75%↓ clarithromycin dose	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.[226]	Potential for ↑ clarithromycin exposure. Reduce clarithromycin dosage if renal failure:[162] • ↓ dose 50% if Clcr 30-60 mL/min • ↓ dose 75% if Clcr <30 mL/min	77% ↑ AUC of clarithromycin. Reduce dose only if renal failure. Inhibition of CLA-OH metabolite (i.e., ↓ Gram-neg. activity, such as H. influenzae).[227]	177% ↑ SQV-sgc AUC; 45% ↑ clarithromycin AUC.[132]
Colchicine *(biliary, renal excretion; p-glycoprotein substrate)*	Potential for significant ↑ colchicine AUC due to P-gp inhibition and ↓ biliary excretion. For treatment of gout flares: 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. For prophylaxis of gout flares: use colchicine 0.3 mg once daily or every other day. For treatment of familial Mediterranean fever: Do not exceed colchicine 0.6	Potential for significant ↑ colchicine AUC due to P-gp inhibition and ↓ biliary excretion. For treatment of gout flares: 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. For prophylaxis of gout flares: use colchicine 0.3 mg once daily or every other day. For treatment of familial Mediterranean fever: Do not exceed colchicine 0.6	Potential for significant ↑ colchicine AUC due to P-gp inhibition and ↓ biliary excretion. **For fosamprenavir/ ritonavir:** For treatment of gout flares: 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. For prophylaxis of gout flares: use colchicine 0.3 mg once daily or every other day. For treatment of familial	Potential for significant ↑ colchicine AUC due to P-gp inhibition and ↓ biliary excretion. For treatment of gout flares: 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. For prophylaxis of gout flares: use colchicine 0.3 mg once daily or every other day. For treatment of familial Mediterranean fever: Do not exceed colchicine 0.6	In an open-label, nonrandomized, one-sequence, two-period study, 24 healthy volunteers received a single 0.6-mg dose of colchicine alone and in the presence of steady-state ritonavir 100 mg BID. In the presence of ritonavir, colchicine Cmax ↑ 170%, AUCo-t ↑ 245% compared with colchicine alone.[229] In the presence of ritonavir 100 mg BID, colchicine AUC ↑ 296%,	Potential for significant ↑ colchicine AUC due to P-gp inhibition and ↓ biliary excretion. For treatment of gout flares: 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. For prophylaxis of gout flares: use colchicine 0.3 mg once daily or every other day. For treatment of familial Mediterranean fever: Do not exceed colchicine 0.6

	Atazanavir (Reyataz®)	Darunavir (Prezista®)	Fosamprenavir (Telzir®)	Lopinavir/ ritonavir (Kaletra®)	Ritonavir (Norvir®)	Saquinavir (Invirase®)
	mg once daily or 0.3 mg BID.[228] Monitor for colchicine toxicity.	mg once daily or 0.3 mg BID.[228] Monitor for colchicine toxicity.	Mediterranean fever: Do not exceed colchicine 0.6 mg once daily or 0.3 mg BID.[228] **For unboosted fosamprenavir:** For treatment of gout flares: use 1.2 mg x 1 dose and no repeat dose for at least 3 days. For prophylaxis of gout flares: use 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 1.2 mg once daily or 0.6 mg BID.[228] Monitor for colchicine toxicity.	mg once daily or 0.3 mg BID.[228] Monitor for colchicine toxicity.	Cmax ↑ 184%.[228] For treatment of gout flares: 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. For prophylaxis of gout flares: use colchicine 0.3 mg once daily or every other day. For treatment of familial Mediterranean fever: Do not exceed colchicine 0.6 mg once daily or 0.3 mg BID.[228] Monitor for colchicine toxicity.	mg once daily or 0.3 mg BID.[228] Monitor for colchicine toxicity.
Corticosteroids (oral/inhaled, injectable or topical) e.g., betamethasone, budesonide, dexamethasone, fluticasone, prednisone, triamcinolone *Note: see also Salmeterol*	An HIV-positive patient on **inhaled fluticasone-salmeterol** for asthma developed Cushing's syndrome within three months of switching from an efavirenz-based regimen to an atazanavir-ritonavir based regimen. All symptoms resolved completely within 4 months after discontinuation of fluticasone.[230] One case report of Cushing's syndrome and adrenal suppression in a patient on atazanavir/ritonavir and **dexamethasone 0.1% eye drops six times daily, and betamethasone 0.1% eye ointment** at night, in both eyes for over 8	In an open-label, prospective, randomized study, healthy volunteers received **inhaled beclomethasone** 160 mcg twice a day alone, or with either ritonavir 100 mg BID or darunavir 600/ritonavir 100 mg BID, each for 14 days. The AUC of 17-BMP (the active metabolite of beclomethasone) was not significantly increased by DRVr, whereas in the presence of ritonavir 100 mg BID, the AUC of 17-BMP ↑ 2-fold, which is considered clinically inconsequential. ACTH stimulation tests were conducted on days 1, 14, 28, and 42. Combined use of BDP and RTV or DRV/r for 28 days did not cause significant adrenal	**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.[232] In a retrospective cohort study, 9 cases of confirmed HPA-axis suppression (including 5 with clinical evidence of Cushing's syndrome) were diagnosed in subjects who had	Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported during postmarketing use in patients when certain ritonavir-containing products have been coadministered with **fluticasone propionate** or **budesonide**.[162] A drug interaction study in healthy subjects has shown that ritonavir significantly ↑ plasma **fluticasone propionate** exposures, resulting in significantly ↓ serum cortisol concentrations. Similar effects may be expected with the combination of lopinavir/rtv and fluticasone. Therefore, **coadministration of**	Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported during postmarketing use in patients when certain ritonavir-containing products have been coadministered with **fluticasone propionate** or **budesonide**.[162] In healthy subjects, ritonavir 100 mg BID plus **fluticasone propionate aqueous nasal spray** for 7 days led to 350-fold ↑ AUC and 25-fold ↑ Cmax of fluticasone, resulting in an 86% ↓ in plasma cortisol AUC.[7] Several reports of Cushing's syndrome with combination of inhaled **fluticasone** and ritonavir. Therefore,	**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.[232]

	Atazanavir (Reyataz®)	Darunavir (Prezista®)	Fosamprenavir (Telzir®)	Lopinavir/ ritonavir (Kaletra®)	Ritonavir (Norvir®)	Saquinavir (Invirase®)
	months. ATVr was replaced with efavirenz while continuing the steroid eye drops, and oral hydrocortisone 15 mg daily was added to avoid precipitating crisis due to adrenal insufficiency. Over the following year, the patient's weight declined, with marked improvement in her adrenal function.[231] **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.[232] Case report of **budesonide**-related adrenal suppression and Cushing's syndrome secondary to an interaction with atazanavir/ritonavir.[233] In a retrospective cohort study, 9 cases of confirmed HPA-axis suppression (including 5 with clinical evidence of Cushing's syndrome) were diagnosed in subjects who had	suppression.[237] **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.[232] Case report of a 48-year-old woman with HIV who developed Cushing's syndrome with adrenal suppression secondary to an interaction between **inhaled budesonide** and darunavir/ritonavir.[238] In a retrospective cohort study, 9 cases of confirmed HPA-axis suppression (including 5 with clinical evidence of Cushing's syndrome) were diagnosed in subjects who had received **corticosteroid injection therapy (n=8 triamcinolone, n=1 methylprednisone)** on concomitant PI therapy (n=4 atazanavir, n=2 atazanavir/r, n=2 darunavir/r, n=1 fosamprenavir/lopinavir). The median time between the first	received **corticosteroid injection therapy (n=8 triamcinolone, n=1 methylprednisone)** on concomitant PI therapy (n=4 atazanavir, n=2 atazanavir/r, n=2 darunavir/r, n=1 fosamprenavir/lopinavir). The median time between the first injection and development of HPA-axis dysfunction was 31 days. All subjects were treated with prednisone replacement therapy.[234]	**fluticasone and lopinavir/rtv is not recommended** unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.[7] Four cases of **budesonide**-related adrenal suppression and Cushing's syndrome secondary to an interaction with lopinavir/ritonavir (n=1) or ritonavir (n=3 pediatric patients) have been reported.[240, 241] Seven cases of Cushing's syndrome have been reported with the use of **intra-articular triamcinolone injections** in patients on ritonavir-boosted regimens (100-200 mg daily of ritonavir).[242-245] In most cases, cushingoid symptoms and profound adrenal suppression appeared about 2 weeks after a single injection of triamcinolone acetonide 40-80 mg. Three cases required supplemental hydrocortisone 10-30 mg po daily for up to 8 months.[242, 243] Most cases resolved after several months, however there were two reports of avascular necrosis of the hip[242, 245] at 2 and 11 months post-steroid exposure, respectively. Inhaled beclomethasone or ciclesonide, or	**combination is not recommended**. Of note, use of **Advair® (fluticasone/salmeterol)** should be avoided with ritonavir, due to the additional interaction risk between ritonavir and salmeterol.[7] In healthy volunteers, **prednisone** 20 mg in the presence of ritonavir 200 mg BID led to 28-37% ↑ prednisolone AUC.[246] Seven cases of **budesonide**-related adrenal suppression and Cushing's syndrome secondary to an interaction with lopinavir/ritonavir (n=1), ritonavir (n=4), atazanavir/ritonavir (n=1) and darunavir/ritonavir (n=1) have been reported.[233, 238, 240, 241, 247] Seven cases of Cushing's syndrome have been reported with the use of **intra-articular triamcinolone injections** in patients on ritonavir-boosted regimens (100-200 mg daily of ritonavir).[242-245] In most cases, cushingoid symptoms and profound adrenal suppression appeared about 2 weeks after a single injection of triamcinolone acetonide 40-80 mg. Three cases required supplemental hydrocortisone 10-30 mg po daily for up to 8 months.[242, 243] Most	

	Atazanavir (Reyataz®)	Darunavir (Prezista®)	Fosamprenavir (Telzir®)	Lopinavir/ ritonavir (Kaletra®)	Ritonavir (Norvir®)	Saquinavir (Invirase®)
	received **corticosteroid injection therapy (n=8 triamcinolone, n=1 methylprednisone)** on concomitant PI therapy (n=4 atazanavir, n=2 atazanavir/r, n=2 darunavir/r, n=1 fosamprenavir/lopinavir). The median time between the first injection and development of HPA-axis dysfunction was 31 days. All subjects were treated with prednisone replacement therapy.[234] Case report of pulmonary embolism and Cushing's in a 51-year old male on **atazanavir/ ritonavir,** etravirine and didanosine after 2 **injections of triamcinolone**.[235] Case report of a 48-year-old woman on **atazanavir/ritonavir** and tenofovir/emtricitabine who developed Iatrogenic Cushing syndrome and relative adrenal insufficiency manifested by headache, dizziness, and candida and herpes simplex virus ulcerative esophagitis 7 days after receiving an **epidural triamcinolone injection** for cervical radicular pain. Atazanavir/ritonavir was replaced with raltegravir and the patient's symptoms improved.[236]	injection and development of HPA-axis dysfunction was 31 days. All subjects were treated with prednisone replacement therapy.[234] Case report of an HIV-infected patient treated with ritonavir-boosted darunavir who developed cushingoid features following an intra-articular injection of triamcinolone acetate.[239]		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.[232]	cases resolved after several months, however there were two reports of avascular necrosis of the hip[242, 245] at 2 and 11 months post-steroid exposure, respectively. In a retrospective cohort study, 9 cases of confirmed HPA-axis suppression (including 5 with clinical evidence of Cushing's syndrome) were diagnosed in subjects who had received **corticosteroid injection therapy (n=8 triamcinolone, n=1 methylprednisone)** on concomitant PI therapy (n=4 atazanavir, n=2 atazanavir/r, n=2 darunavir/r, n=1 fosamprenavir/lopinavir). The median time between the first injection and development of HPA-axis dysfunction was 31 days. All subjects were treated with prednisone replacement therapy.[234] One case report of Cushing's syndrome and adrenal suppression in a patient on atazanavir/ritonavir and **dexamethasone 0.1% eye drops six times daily, and betamethasone 0.1% eye ointment** at night, in both eyes for over 8 months. ATVr was replaced with efavirenz while continuing the steroid eye	

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					drops, and oral hydrocortisone 15 mg daily was added to avoid precipitating crisis due to adrenal insufficiency. Over the following year, the patient's weight declined, with marked improvement in her adrenal function.[231] 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.[232]	
Crofelemer	Clinically significant Interaction not expected.	Clinically significant Interaction not expected.	Clinically significant Interaction not expected.	Population PK of ART and crofelemer were assessed in HIV+ subjects receiving placebo or crofelemer 125, 250, or 500 mg BID in a phase 3 trial. At all doses, crofelemer had no statistically significant effect on the kinetics of of ritonavir (p=1.0), tenofovir (p=0.09), FTC (p=1.00), 3TC (p=0.33), lopinavir/ritonavir (p=1.00), or efavirenz (p=1.00).[248]	Population PK of ART and crofelemer were assessed in HIV+ subjects receiving placebo or crofelemer 125, 250, or 500 mg BID in a phase 3 trial. At all doses, crofelemer had no statistically significant effect on the kinetics of of ritonavir (p=1.0), tenofovir (p=0.09), FTC (p=1.00), 3TC (p=0.33), lopinavir/ritonavir (p=1.00), or efavirenz (p=1.00).[248]	Clinically significant Interaction not expected.
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.	An interaction trial with darunavir 600/ritonavir 100 mg BID plus single dose digoxin 0.4 mg showed 77% ↑ AUC digoxin. Recommend using lowest dose of digoxin, monitor digoxin levels and titrate dose to clinical effect.[3]	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.	In healthy volunteers, ritonavir 300 mg BID plus digoxin 0.5 mg ↑ digoxin AUC by 86%, likely via inhibition of renal p-gp.[249] Case report of woman maintained on indinavir, 3TC, d4T and digoxin 0.25 mg/d who experienced acute	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.

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					digoxin toxicity 3 days after ritonavir 200 mg BID added to regimen. Symptoms resolved after ritonavir discontinued, and patient resumed original HAART without incident.[250]	
Ergot alkaloids *(CYP3A>others)*	**Coadministration is contraindicated.**[1] 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 not: ulcer/persistent numbness (n=1), gangrene (n=1), amputation (n=2), death (n=1).[251]	**Coadministration is contraindicated.**[3] 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 not: ulcer/persistent numbness (n=1), gangrene (n=1), amputation (n=2), death (n=1).[251]	**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 but 5 patients did not: ulcer/persistent numbness (n=1), gangrene (n=1), amputation (n=2), death (n=1).[251]	**Ergot derivatives are contraindicated with Kaletra.**[162] Postmarketing reports of acute ergot toxicity with combination.[252, 253] 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 not: ulcer/persistent numbness (n=1), gangrene (n=1), amputation (n=2), death (n=1).[251]	**Combination contraindicated.**[7] Postmarketing reports of acute ergot toxicity with combination.[254-256] 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 not: ulcer/persistent numbness (n=1), gangrene (n=1), amputation (n=2), death (n=1).[251]	**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 not: ulcer/persistent numbness (n=1), gangrene (n=1), amputation (n=2), death (n=1).[251]
Fluconazole *(~80% Clrenal, 11% metabolized via CYP3A4; inhibits 3A4 (weak), 2C9, 2C19)*	In healthy subjects, coadministration of atazanavir 300/rtv 100 mg QD plus fluconazole 200 mg QD for 10 days did not result in changes to pharmacokinetic parameters of either ATV, rtv or fluconazole. Combination may be given without dosage adjustment.[257]			Clinically significant interaction not expected.[162]	12% ↑ RTV AUC. Clinical significance unclear.[7]	
Ginko biloba *(CYP3A inducer)*	Potential for ↓ atazanavir concentrations due to CYP3A induction by ginko biloba.[258] Case report of viral breakthrough and resistance to efavirenz after introduction of ginko biloba.[259] **Avoid concomitant use with**	Plasma exposure of boosted protease inhibitors unlikely to be affected by ginko biloba;[258] however, concentrations of unboosted PIs may be decreased.	Potential for ↓ amprenavir concentrations due to CYP3A induction by ginko biloba.[258] Case report of viral breakthrough and resistance to efavirenz after introduction of ginko biloba.[259] **Avoid**	In healthy subjects, chronic administration of ginko biloba 120 mg BID reduced midazolam AUC by 33% (presumably via CYP3A induction), while steady-state LPV/r exposure was not affected.[258]	Plasma exposure of boosted protease inhibitors unlikely to be affected by ginko biloba;[258] however, concentrations of unboosted PIs may be decreased.	Plasma exposure of boosted protease inhibitors unlikely to be affected by ginko biloba;[258] however, concentrations of unboosted PIs may be decreased.

	Atazanavir (Reyataz®)	Darunavir (Prezista®)	Fosamprenavir (Telzir®)	Lopinavir/ ritonavir (Kaletra®)	Ritonavir (Norvir®)	Saquinavir (Invirase®)
	unboosted atazanavir.		**concomitant use with unboosted fosamprenavir.**			
H2 blockers (including cimetidine, famotidine, nizatidine, ranitidine, etc.) **equivalent doses:* *<u>H2RAs (treatment)</u>: Famotidine 20 mg BID or 40 mg qhs Nizatidine 150 mg BID or 300 mg qhs Ranitidine 150 mg BID or 300 mg qhs* *<u>H2RAs (maintenance qhs dosing)</u>: Famotidine 20 mg Nizatidine 150 mg Ranitidine 150 mg*	In healthy volunteers, **40 mg famotidine BID plus atazanavir 400 mg QD** led to 47%↓ Cmax, 41% ↓ AUC and 42% ↓ Cmin of atazanavir; coadministration of cola did not mitigate this effect.[260] In a 2-cohort, 3-period, multi-dose sequential interaction study, HIV-infected subjects received **atazanavir 300/ ritonavir 100 mg QD** ± **tenofovir** with **famotidine 20 mg or 40 mg BID**. When FAM 20 mg BID was administered simultaneously with ATV/r, ATV AUC ↓ 13% while Cmin was unchanged. When FAM 20 mg BID was temporally separated from ATV/r plus tenofovir, ATV AUC ↓ 21% and Cmin ↓ 19%. With FAM 40 mg BID, ATV AUC and Cmin ↓ 20-23% in those not on tenofovir and 23-25% in those on tenfovir.[261] In an open-label, 3 period, multi-dose sequential cross-over study in 24 HIV-infected subjects on stable ATV 300/100 mg, tenofovir 300 mg + ≥1 NRTI, subjects increased to **ATV 400/100 mg QD (+ TDF**/NRTIs) and took	No significant change in darunavir kinetic parameters when coadministered with ranitidine 150 mg BID.[263] Combination may be coadministered.	In a single-dose healthy volunteer study, co-administration of ranitidine 300 mg with 1400 mg fosamprenavir led to 30% ↓ in APV AUC_{last} and 51% ↓ C_{max}, C12 unchanged. **Use caution when FPV is coadministered with H2-blockers**.[218]	<u>Lopinavir capsules:</u> In a prospective observation of treatment-naïve subjects receiving LPV/r BID or QD, no significant differences in LPV levels were noted in the presence of either antacids, H2 blockers, or proton pump inhibitors.[219] <u>Lopinavir tablets:</u> In a randomized, healthy volunteer study, subjects received LPV/r BID or QD at standard doses plus ranitidine 150 mg 1 hour before breakfast. LPV exposure was not affected by the presence of ranitidine.[264]		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.[265]

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	famotidine 20 mg BID for 7 days, then **famotidine 40 mg BID** for 7 days, both simultaneously with ATV in the morning after a meal. Famotidine 40 mg BID with ATV 400/100 mg QD resulted in similar ATV exposures compared to ATV 300/100 mg without famotidine (ATV Cmax ↓ 5%, AUC ↓ 2%, Ctrough ↑ 1%). Famotidine 20 mg BID with ATV 400/100 mg QD resulted in 18% ↑ AUC & Cmax, 24% ↑ Ctrough of ATV relative to ATV 300/100 mg QD without famotidine.[262] Management options: • Give **ATV 300/100 rtv QD with famotidine simultaneously or 10 hours after H2RA.** Maximum 40 mg BID (treatment-naïve) or 20 mg BID (treatment-experienced) of famotidine. • If also on tenofovir, increase to ATV 400/100 mg QD in experienced patients.[1]					
Hmg-CoA Reductase inhibitors • atorvastatin *(CYP3A)* • fluvastatin *(2C9>>3A)* • lovastatin *(CYP3A)*	Potential for ↑ concentrations of statins due to enzyme inhibition by atazanavir. **Pitavastatin** may be used without dose limitations with boosted and unboosted	Combination of **atorvastatin** 10 mg daily plus darunavir 300/ritonavir 100 mg BID led to 15% ↓ atorvastatin AUC vs. atorvastatin 40 mg QD alone. **Do not exceed 20 mg**	In healthy volunteers, FPV 1400 mg BID or FPV 700 mg/ ritonavir 100 mg BID plus **atorvastatin 10 mg** led to significant ↑ in atorvastatin Cmax (404% and 284%, respectively) and AUC (230% and	**Atorvastatin**: potential for ↑ atorvastatin concentrations. Use combination with caution, use lowest atorvastatin dose necessary.[266] In an open-label, 3-phase pharmacokinetic	Pharmacokinetic study in HIV-negative subjects taking saquinavir 400 mg/ritonavir 400 mg BID plus 40 mg of **atorvastatin, pravastatin, or simvastatin** revealed	Pharmacokinetic study in HIV-negative subjects taking saquinavir 400 mg/ritonavir 400 mg BID plus 40 mg of atorvastatin, pravastatin, or simvastatin revealed the

	Atazanavir (Reyataz®)	Darunavir (Prezista®)	Fosamprenavir (Telzir®)	Lopinavir/ ritonavir (Kaletra®)	Ritonavir (Norvir®)	Saquinavir (Invirase®)
• pitavastatin *(UGT1A3,UGT 2B7>> CYP2C9, 2C8)* • pravastatin *(40-50% Clr, > 3A4)* • rosuvastatin *(10% via 2C9, 2C19)* • simvastatin *(CYP3A)*	atazanavir.[266] **Limit rosuvastatin dose to 10 mg once daily** with boosted or unboosted atazanavir.[266] **Lovastatin and simvastatin** are contraindicated with all HIV protease inhibitors.[266]	**atorvastatin daily**.[266] In healthy volunteers, coadministration of **pitavastatin 4 mg** and darunavir 800/100 mg QD resulted in 26% ↓ AUC of pitavastatin, and no significant changes in darunavir exposures compared to either drug administered alone.[267] In healthy volunteers, coadministration of **pitavastatin 2 mg** daily with darunavir/ritonavir 800/100 mg daily did not result in significant interactions. Pitavastatin AUC ↓ 9% and Cmax ↓ 7% in the presence of darunavir/r, while darunavir AUC ↑ 8% and Cmax ↑ 3%.[268] **Pravastatin** and **pitavastatin** may be used without dose limitations.[266] **Lovastatin and simvastatin** are contraindicated with all HIV protease inhibitors.[266]	253%, respectively); APV levels were not affected.[269] **Do not exceed 20 mg atorvastatin daily** with either boosted or unboosted fosamprenavir.[266] **Lovastatin and simvastatin** are contraindicated with all HIV protease inhibitors.[266]	study in healthy volunteers, the combination of **rosuvastatin** 20 mg/day plus LPV/r 400/100 mg BID for 7 days led to a 2.1-fold ↑ AUC and 4.7-fold ↑ Cmax of rosuvastatin, compared to rosuvastatin alone ($p<0.0001$). LPV levels were not changed in the presence of rosuvastatin.[270] **Limit rosuvastatin dose to 10 mg once daily** with lopinavir/ritonavir.[266] In healthy volunteers, administration of **pitavastatin 4 mg daily** in the presence of steady-state lopinavir/ritonavir 400/100 mg BID did not result in clinically significant changes in pharmacokinetic exposures of either drug.[271] **Pravastatin** and **pitavastatin** may be used without dose limitations.[266] **Lovastatin and simvastatin** are contraindicated with all HIV protease inhibitors.[266]	the following effects: • 35% ↓ AUC pravastatin • 31.6 fold ↑ AUC simvastatin • 4.5-fold ↑ AUC atorvastatin[272] **Lovastatin and simvastatin** are contraindicated with all HIV protease inhibitors.[266]	following effects: • 35% ↓ AUC pravastatin • 31.6 fold ↑ AUC simvastatin • 4.5-fold ↑ AUC atorvastatin[272] **Pravastatin** may be administered without dosage adjustment. **Do not exceed 20 mg atorvastatin daily.** **Lovastatin and simvastatin** are contraindicated with all HIV protease inhibitors.[266]
Itraconazole *(CYP3A4; inhibits 3A, 2C9)*	Potential for increased itraconazole and/or atazanavir concentrations. Clinical significance unclear, monitor for dose-related toxicities.	Coadministration of darunavir 400/100 mg BID and ketoconazole 200 mg BID led to 212% ↑ ketoconazole exposure and 42% ↑ darunavir exposure.[273] Do not exceed 200 mg ketoconazole or itraconazole per day while on darunavir.	Potential for increased itraconazole and/or amprenavir concentrations. Clinical significance unclear, monitor for dose-related toxicities.	In a case report of an HIV-positive patient on itraconazole 200 mg QD and lopinavir/r, itraconazole levels were significantly ↑ (similar to itraconazole 400 mg QD alone) and hydroxy-itraconazole levels were significantly ↓. Lopinavir/r levels not	In a case report, itraconazole blood levels in a patient taking ritonavir and saquinavir showed more than five-fold ↑ increase half-life, and therapeutic levels of itraconazole were still detectable even 27 days after discontinuation of the drug.[276] Use	5-fold increase in saquinavir exposure when hard-gel capsules coadministered with itraconazole 200 mg;[277] In a prospective randomized study in 17 HIV-infected subjects, saquinavir-sgc 800 or 1200 mg BID plus itraconazole 100 mg

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				affected.[274] Similarly, in another case report of an HIV-positive patient with disseminated histoplasmosis infection, lopinavir concentrations remained stable after initiation of itraconazole 200 mg daily, and therapeutic antifungal levels (itraconazole + hydroxy-itraconazole) were achieved along with clinical response.[275] Itraconazole doses >200 mg/day not recommended.[162]	combination with caution.	daily resulted in SQV concentrations equivalent to SQV-sgc 1400 mg BID alone.[278]
Ketoconazole *(CYP3A4; inhibits 3A, 2C9)*	In a healthy volunteer study, coadministration of 400 mg atazanavir plus 200 mg ketoconazole daily did not result in significant changes in atazanavir concentrations. Combination may be administered without dosage adjustment.[279]	Coadministration **of darunavir 400 mg BID and ketoconazole 200 mg BID** in healthy volunteers (n=6) led to 155% ↑ AUC, 179% ↑ Cmin of darunavir, and no significant change in ketoconazole levels. Coadministration **of darunavir 400/100 mg BID and ketoconazole 200 mg BID** in healthy volunteers (n=17) led to 212% ↑ ketoconazole exposure and 42% ↑ darunavir exposure. Do not exceed 200 mg ketoconazole per day while on darunavir/ritonavir.[273]	32% ↑ amprenavir AUC, 44% ↑ ketoconazole AUC. Clinical significance unclear.[280]	Single 200 mg ketoconazole dose had no significant effect on lopinavir/r concentrations.[162] Lopinavir/r AUC increased 3-fold. Ketoconazole doses >200 mg/day not recommended. Monitor for dose-related toxicities.	Coadministration of ketoconazole 200 mg daily ritonavir 500 mg BID (n=12) resulted in an 18% ↑ ritonavir AUC, and 3.4 fold ↑ ketoconazole AUC and 55% ↑ Cmax. Manufacturer suggests using no more than 200 mg daily ketoconazole with concomitant ritonavir.[7]	**Saquinavir 1200 mg TID** plus ketoconazole 400 mg QD: 1.5-fold ↑ saquinavir AUC. Dosage adjustment not necessary.[9] Multiple dose study of **SQV/r 1000/100mg BID** and ketoconazole 200mg daily in healthy subjects resulted in: • Ketoconazole ↑ AUC 168%, ↑ Cmax 45%. • No substantial change in saquinavir and ritonavir exposures [281] In 25 patients stable on SQV/r 2000/100 mg QD, switching to SQV 2000 mg plus ketoconazole 400 mg QD for 2 weeks led to 80% lower SQV exposures. Mean SQV AUC and Cmin were 57.93 mg/h/L and 0.35 mg/L when boosted with ritonavir, versus 12 mg/h/L and 0.03 mg/L, respectively when boosted with ketoconazole. Boosting

	Atazanavir (Reyataz®)	Darunavir (Prezista®)	Fosamprenavir (Telzir®)	Lopinavir/ ritonavir (Kaletra®)	Ritonavir (Norvir®)	Saquinavir (Invirase®)
						of saquinavir by ketoconazole is not recommended.[282]
Levothyroxine *(GT)*	Ritonavir induces glucuronyl 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.	Ritonavir induces glucuronyl 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.	Ritonavir induces glucuronyl 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.	Case report of 58-year old woman on stable Combivir/Kaletra therapy with persistent hypothyroidism following thyroidectomy despite daily levothyroxine up to 225 ug/day and introduction of liothyronine. TSH and T4 parameters normalized when HAART was withdrawn, but hypothyroidism recurred 1 month after lopinavir therapy was reinitatiated. Replacing lopinavir/ritonavir with nelfinavir did not improve TSH and T4. Normalization of thyroid tests only occurred when patient was switched to a triple nucleoside regimen. Mechanism of interaction postulated to be ritonavir-mediated induction of glucuronyl transferases.[283]	Case report of a 29-year old male stabilized on levothyroxine 125 ug/day for an auto-immune thyroiditis induced by interferon therapy. One month starting ritonavir 600 mg BID, his TSH serum level increased to 18 mIU/l and the patient became lethargic. Doubling his levothyroxine dose to 0.25 mg daily reduced his TSH to 7.35 mIU/l. After ritonavir was discontinued, the patient was able to return to his original dose of levothyroxine. Subsequent administration of indinavir 800 mg q8h did not affect the patient's thyroid indices, and no further levothyroxine dosage alterations were required.[284]	Ritonavir induces glucuronyl 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.
Mebendazole					In healthy volunteers, single dose mebendazole 1000 mg was given alone or after 1 or 8 days ritonavir 200 mg BID. Mebendazole kinetics were unchanged by short-term ritonavir dosing, but AUC ↓ 43% and Cmax ↓ 41% in the presence of chronic ritonavir administration.[217]	
Mefloquine *(CYP3A?, GT)*					In a healthy volunteer study, ritonavir had no effect on mefloquine kinetics; ritonavir AUC ↓	

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					35%, Cmax ↓ 38%, Cmin ↓ 54% in presence of mefloquine.[285]	
Methadone *(CYP3A4, 2C19, 2B6>>GT; weak inhibitor of CYP2D6)* **See also "Antiretroviral-Methadone Interaction Chart" for additional information*	Prospective, open-label study of atazanavir 400 mg QD for 14 days in 16 HIV-negative subjects on chronic methadone. In the presence of atazanavir, no significant changes were observed in the pharmacokinetic parameters of the active (R)-isomer of methadone; exposure to the inactive (S)-isomer was modestly reduced but changes were not deemed significant. No clinical symptoms of opiate withdrawal were observed. Kinetic parameters of atazanavir were comparable to previously reported data.[286] Atazanavir and methadone may be co-adnimistered without dosage adjustment.	Monitor for methadone withdrawal when initiating darunavir/ritonavir in subjects stabilized on methadone, as reductions in methadone exposures have been noted with ritonavir administration.[287, 288, 289] Adjustment of methadone dosage may be necessary. Formal drug-drug interaction study underway.	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 methadone dosage may need to be increased when these drugs are coadministered.[4, 290]	Approximately 55%↓ methadone concentrations.[162] Monitor for symptoms of methadone withdrawal; adjustment of methadone dosage may be necessary.	In vitro study showed 2-fold ↑ methadone conc., but healthy volunteer study showed 36% ↓ methadone AUC, no change in $t_{1/2}$ when given with ritonavir.[287] Similar observations in HIV-infected subjects.[288, 289] Monitor for methadone withdrawal when initiating ritonavir in subjects stabilized on methadone.	Likelihood of interaction low, since saquinavir is a weak CYP3A4 inhibitor.
Minocycline	Twelve adult HIV-infected subjects on stable ATV/r 300/100 mg QD received minocycline 100 mg BID for 14 days, and then minocycline plus valproid acid 250 mg BID for 14 days. Atazanavir AUC ↓ 33%, Cmin ↓ 50% and Cmax ↓ 25% in the presence of minocycline; the addition of valproic acid did not mediate this effect. Ritonavir concentrations were not significantly altered by concomitant minocycline with or without valproic acid,					

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	suggesting that decreased absorption may be the most likely reason for ↓ atazanavir concentrations. Clinical significance is unclear and it is not known whether minocycline affects concentrations of other protease inhibitors.[291]					
Oral Contraceptives *(GT, sulphatase (primary)> CYP3A (~30%); inhibits 1A2, 3A)*	Twenty-two healthy women stabilized on an OC regimen (ethinyl estradiol/ norethindrone) received **atazanavir 400 mg/d** for 2 weeks. Vs. OC alone, ethinyl estradiol AUC ↑48% and norethindrone AUC ↑110% in presence of ATV.[64] Use lowest effect dose of each contraceptive component and monitor for side effects (incl. ↓ HDL and ↑ insulin resistance, esp. in diabetic women).[1] Healthy women stabilized on Ortho Tricyclen (ethinyl estradiol 35 ug plus norgestimate/NGM 0.18/0.215/ 0.25) received Ortho Tricylen LO (EE 25 ug + NGM 0.18/ 0.215/0.25) plus **ATV/r 300/100mg QD** for 14 days. In the presence of ATV/r, EE AUC ↓ 20%, while 17-deacetyl NGM AUC ↑ 85%. Thus, an oral contraceptive with 35ug EE plus ATV/r is expected to produce EE exposures similar to EE 25ug alone.[292]	Eighteen healthy women stabilized on an OC regimen (ethinyl estradiol/ norethindrone) received darunavir 600/rtv 100 mg BID for 2 weeks. Ethinyl estradiol AUC ↓44% and Cmin ↓ 62%, and norethindrone AUC ↓14% and Cmin ↓30% in presence of darunavir/rtv. Alternative or additional contraceptive measures should to be used when estrogen-based contraceptives are co-administered with darunavir/rtv.[293]	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. Furthermore, co-administration of fosamprenavir/ ritonavir and Brevinor resulted in clinically significant hepatic transaminase elevations in some healthy subjects.[4] Therefore, oral contraceptives should not be taken with fosamprenavir. Use alternate non-hormonal methods of contraception.[4]	42% ↓ ethinyl estradiol AUC, 17% ↓ norethindrone AUC; use additional/alternate methods of contraception.[162] The pharmacokinetic interaction between lopinavir/ritonavir and **transdermally delivered ethinyl estradiol (EE) and norelgestromin (NGMN)** was investigated in 8 HIV-positive women on stable LPV/r and compared to a control group of 24 women not on HAART. Also, EE AUC after a single dose of a combination oral contraceptive pill including EE and norethindrone was measured before patch placement and was compared with patch EE AUC in both groups. Patch EE median AUC was 45% ↓ and pill EE AUC was 55% ↓ in women on LPVr vs. controls (p=0.064 and p=0.003, respectively). Patch NGMN AUC was 83% ↑ in LPVr group vs. controls (p=0.036). The	40% ↓ ethinyl estradiol AUC. Use alternate methods of contraception.[295]	In a pharmacokinetic study in healthy women, oral contraceptives did not affect the kinetics of single 600 mg saquinavir-hgc.[296]

	Atazanavir (Reyataz®)	Darunavir (Prezista®)	Fosamprenavir (Telzir®)	Lopinavir/ ritonavir (Kaletra®)	Ritonavir (Norvir®)	Saquinavir (Invirase®)
				investigators concluded that although the kinetics of EE and NGMN were significantly altered in the presence of LPVr, the contraceptive efficacy of the patch was likely to be maintained.[294]		
Phosphodiester-ase Type 5 (PDE5) Inhibitors • avanafil (Stendra®); *(CYP3A4>> CYP2C substrate)* • sildenafil (Viagra®, Revatio®); *(CYP3A4>>2C 9 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. **Tadalafil:**[297] • on demand dosing while on PIs or other CYP3A4 inhibitors: 10-20 mg q48h, max 3 times per week • daily dosing for erectile dysfunction/BPH: 5 mg/day (no dose adjustment needed if on PIs) **Vardenafil is contraindicated** with ritonavir.[298]	Administration of single-dose **sildenafil 25 mg** mg in the presence of darunavir 400/ritonavir 100 mg BID yielded sildenafil concentrations similar to 100 mg sildenafil alone. The pharmacokinetics of darunavir were not significantly affected by sildenafil. Use no more than 25 mg **sildenafil** in a 48-hour period in the presence of darunavir/ ritonavir.[299] **Tadalafil:**[297] • on demand dosing while on PIs or other CYP3A4 inhibitors: 10-20 mg q48h, max 3 times per week • daily dosing for erectile dysfunction/BPH: 5 mg/day (no dose adjustment needed if on PIs) **Vardenafil is contraindicated** with ritonavir.[298]	No information on combination. Consider starting with an initial sildenafil dose of 25 mg q24-48 hours and titrating up based on patient response and tolerability.[300] 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.[301] **Tadalafil:**[297] • on demand dosing while on PIs or other CYP3A4 inhibitors: 10-20 mg q48h, max 3 times per week • daily dosing for erectile dysfunction/BPH: 5 mg/day (no dose adjustment needed if on PIs) **Vardenafil is contraindicated** with ritonavir.[298]	Potential for increased sildenafil concentrations. Case report of a 44yr old HIV+ male patient on LPV/r 666/166mg/day and indinavir 1200mg/day who started **sildenafil** 25 mg q8h for treatment of pulmonary arterial hypertension; sildenafil AUC and t1/2 of were approximately doubled vs. healthy controls. Authors postulated that effect of RTV on CYP3A activity may be different after single dose vs. chronic therapy. Coexistence of immediate competitive and irreversible mechanism-based inhibition of CYP3A with delayed PXR induction (receptor plays a central role in regulating hepatic and intestinal CYP3A4 and also MDR1 transcription) may explain the different effects of RTV (and possibly PIs) on PK of sildenafil. Authors recommend combined monitoring of the sildenafil plasma concentration, pulmonary function, and physical performance.[302]	Coadministration of ritonavir (500 mg bid at steady state) with sildenafil (100 mg single dose) resulted in a 300% (4-fold) increase in sildenafil Cmax and a 1,000% (11-fold) increase in sildenafil plasma AUC. At 24 hours the plasma levels of sildenafil were still ~200 ng/mL, compared to approximately 5 ng/mL when sildenafil was dosed alone. Sildenafil had no effect on ritonavir pharmacokinetics. **Avoid combination if possible**. If coadministration is absolutely necessary, do not take more than 25 mg of sildenafil within a 48-hour period. [303] **Tadalafil:**[297] • AUC of tadalafil ↑ 124% with ritonavir 200 mg BID. • on demand dosing while on PIs or other CYP3A4 inhibitors: 10-20 mg q48h, max 3 times per week • daily dosing for erectile dysfunction/BPH: 5 mg/day (no dose adjustment needed if	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. [303] **Tadalafil:**[297] • on demand dosing while on PIs or other CYP3A4 inhibitors: 10-20 mg q48h, max 3 times per week • daily dosing for erectile dysfunction/BPH: 5 mg/day (no dose adjustment needed if on PIs) **Vardenafil is contraindicated** with ritonavir.[298]

	Atazanavir (Reyataz®)	Darunavir (Prezista®)	Fosamprenavir (Telzir®)	Lopinavir/ ritonavir (Kaletra®)	Ritonavir (Norvir®)	Saquinavir (Invirase®)
				Use with caution at a dose of 25 mg every 48 hours, and monitor for adverse effects.[162] **Tadalafil:**[297] • <u>on demand dosing while on PIs or other CYP3A4 inhibitors</u>: 10-20 mg q48h, max 3 times per week • <u>daily dosing for erectile dysfunction/BPH</u>: 5 mg/day (no dose adjustment needed if on PIs) **Vardenafil is contraindicated** with ritonavir.[298] **Do not use lopinavir/ritonavir with avanafil** because a safe and effective avanafil dosage regimen has not been established.[162]	on PIs) 49-fold ↑vardenafil AUC in presence of ritonavir 600 mg BID; **vardenafil is contraindicated with ritonavir**.[298]	
	<u>For treatment of pulmonary arterial hypertension (PAH):</u> • **Sildenafil use for PAH is contraindicated with all PIs.**[228] • 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.[228]					
Posaconazole *(UGT1A4; inhibits CYP3A4)*	In healthy subjects randomized to receive **ATV 300 mg QD or ATV 300/r 100 mg QD** alone or with posaconazole 400 mg BID each for 7 days: ATV AUC ↑ 3.7-fold and Cmax ↑ 2.6-fold with ATV and posaconazole co-administration ATV AUC ↑ 2.5-fold and Cmax ↑ 1.5-fold with ATV/r and posaconazole	Potential for ↑ concentrations of protease inhibitor. Monitor for PI dose-related toxicity when agents are co-administered.	In a 3 period, cross-over, open-label multi-dose study, healthy volunteers received either posaconazole 400 mg BID, fosamprenavir 700/ritonavir 100 mg BID, or posaconazole plus fosamprenavir 700 mg BID for 10 days separated by 17 day washout periods. When posaconazole and fosamprenavir were coadministered,	Potential for ↑ concentrations of protease inhibitor. Monitor for PI dose-related toxicity when agents are co-administered.	In HIV infected patients on stable doses of AZT, 3TC and ritonavir 600 mg BID or indinavir 800 mg every 8 h, Cmax and AUC of these antiretrovirals was not affected by posaconazole 200 mg daily for 10 days. Posaconazole exposures were unchanged in the presence of ritonavir 600 mg BID. No dosage adjustments	Potential for ↑ concentrations of protease inhibitor. Monitor for PI dose-related toxicity when agents are co-administered.

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	co-administration Posaconazole concentrations were not affected by the presence of ATV or ATV/r. Frequent monitoring for PI dose-related toxicity is recommended when posaconazole is coadministered with boosted or unboosted ATV.[304]		posaconazole AUC ↓ 23% and Cmax ↓ 21% vs. posaconazole alone, and amprenavir AUC ↓ 65% and Cmax ↓ 36% compared to fosamprenavir-ritonavir. Avoid posaconazole and unboosted fosamprenavir; optimal dosing of posaconazole and boosted fosamprenavir has not yet been determined. If concomitant therapy is required, use boosted fosamprenavir and consider TDM of both fosamprenavir and posaconazole.[305]		required.(Posanol® prescribing information, Schering-Plough, 2008). 80% ↑ AUC RTV with RTV 100mg daily x 14 days and posaconazole 400mg twice daily x 7 days.[306] When RTV is used in lower boosting doses of 100mg twice daily, empiric dosage adjustments are likely not required. However if used in larger doses, ↓ RTV dose may be warranted. Monitor for RTV-related toxicity. In cases of suspected toxicity, TDM may be useful to dose-adjust.	
Prasugrel *(converted to active metabolite via 3A4, 2B6>2C9, 2C19)*	Ketoconazole 400 mg daily did not affect prasugrel-mediated inhibition of platelet aggregation or the active metabolite's AUC and T_{max}, but decreased the C_{max} by 34 to 46%. Therefore, CYP3A inhibitors are not anticipated to have a significant effect on the pharmacokinetics of the active metabolite.[307]				In vitro, ritonavir inhibited dose-dependent inhibition of prasugrel metabolism via inhibition of CYP3A4 and 2B6.[308] Clinical significance unclear, as ritonavir may induce 2B6 in vivo.	Ketoconazole 400 mg daily did not affect prasugrel-mediated inhibition of platelet aggregation or the active metabolite's AUC and T_{max}, but decreased the C_{max} by 34 to 46%. Therefore, CYP3A inhibitors are not anticipated to have a significant effect on the pharmacokinetics of the active metabolite.[307]
Proton-pump inhibitors (PPIs), including esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, etc. **equivalent doses:* *PPIs (daily standard dose):*	Pharmacokinetic studies: When **omeprazole 40 mg** was given 2 hours before **ATV 400 mg QD**, ATV AUC, Cmax and Cmin ↓ by >93% vs. ATV 400 mg alone.[309] In a randomized, open-label, multi-dose study, administration of **omeprazole 40 mg** QD 2 hours before **atazanavir 300/rtv 100**	No significant change in darunavir kinetic parameters when coadministered with **omeprazole 20 mg QD**.[263] Combination may be coadministered. Open label randomized crossover study in 12 healthy volunteers of darunavir 600 mg/ritonavir 100mg BID	In a randomized, open-label, multi-dose study in healthy subjects, coadministration of **esomeprazole 20 mg QD** with either FPV 1400 mg BID or FPV 700/rtv 100 mg BID for 14 days did not affect steady-state amprenavir kinetics. Esomeprazole AUC ↑ 55% when coadministered with	Lopinavir capsules: In a prospective observation of treatment-naïve subjects receiving LPV/r BID or QD, no significant differences in LPV levels were noted in the presence of either antacids, H2 blockers, or proton pump inhibitors.[219] In a separate healthy		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.[322]

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Esomeprazole 20 mg *Lansoprazole 30 mg* *Omeprazole 20 mg* *Pantoprazole 40 mg* *Rabeprazole 20 mg*	**mg QD** led to 76% ↓ AUC and 78% ↓ Cmin of ATV. This interaction was not overcome with either ↑ ATV to 400 mg/rtv 100 mg QD or co-administering with 8 oz cola[310]. In a healthy volunteer study, administration of **atazanavir 400 mg QD plus lansoprazole 60 mg QD** led to a 94% ↓ in ATV AUC.[311] In healthy volunteers**, 20 mg omeprazole qpm** plus **atazanavir 300/rtv 100 mg qam** resulted in: • 27% ↓ ATV AUC and Cmin with steady-state omeprazole • no change in ATV after single-dose omeprazole[312, 313] In a separate healthy volunteer study, **ATV 400/rtv 100 mg QD** plus **omeprazole 20 mg QD** either 1 hour before or 12 hours apart led to ~30% ↓ ATV exposures, relative to ATV 300/rtv 100 mg QD alone.[314] <u>Case reports/series:</u> Case series of 14 treatment-experienced subjects on atazanavir +/- rtv and gastric modifying agents; virologic suppression maintained or achieved in 12/14 subjects.[315] Separate case report of therapeutic ATV levels and viral suppression in treatment-experienced	plus single dose **omeprazole 40 mg** led to ↓ omeprazole to 5-OH-omeprazole AUC ratio by 31% suggesting induction of CYP2C19 enzyme activity. May be attributed to coadministration of RTV.[318]	FPV, but did not change when given with FPV/r.[319] FPV and FPV/r may be coadministered with PPIs. Prospective, open-label, crossover study with healthy volunteers to assess the kinetics of **FPV/r 1400mg/200mg once daily** (morning) alone and in combination with **omeprazole 20mg daily** (evening): when coadministered with omeprazole (multidose phase): APV AUC24h ↓ 4%, APV Cmin ↓ 2%. This effect is not clinically important. As well, <u>single dose omeprazole</u> did NOT significantly affect APV trough concentrations. FPV and PPIs may be safely coadministered.[313]	volunteer study, LPV/r increased CYP2C19 activity and ↑ omeprazole metabolism. Higher doses of omeprazole may be needed.[320] <u>Lopinavir tablets:</u> In a randomized, healthy volunteer study, subjects received LPV/r BID or QD at standard doses plus **omeprazole 40 mg** 1 hour before breakfast. LPV exposure was not affected by the presence of omeprazole.[264] Similarly in HIV-infected subjects stabilized on LPV/r BID, the addition of **omeprazole 40 mg QD** for 7 days did not significantly alter lopinavir or ritonavir concentrations.[321]		In HIV-positive subjects on SQV 1 g/rtv 100 mg BID, addition of **omeprazole 40 mg QD** led to 54% ↑ AUC, 73% ↑ Cmin and 55% ↑ Cmax of SQV when administered simultaneously, and 67% ↑ AUC, 97% ↑ Cmin and 65% ↑ Cmax of SQV when administered 2 hours apart. No short-term SQV toxicities were noted.[323]

	Atazanavir (Reyataz®)	Darunavir (Prezista®)	Fosamprenavir (Telzir®)	Lopinavir/ ritonavir (Kaletra®)	Ritonavir (Norvir®)	Saquinavir (Invirase®)
	subject on lansoprazole 30 mg BID and ATV/r.[316] In a prospective, open-label study of HIV-infected subjects on ATV 300/rtv 100 mg QD, ATV Cmin were not significantly different in those taking ATV/r alone (n=107) or with a PPI (n=17) (median 500 and 551 ng/mL, respectively). ATV Cmin in both groups were lower than historical controls in healthy subjects, possibly due to reduced gastric acid secretion in HIV.[317] **Coadministration of atazanavir with proton pump inhibitors is not recommended. If coadministration is unavoidable, ↑ atazanavir to 400 mg with 100 mg of ritonavir; doses of proton pump inhibitors comparable to omeprazole 20 mg should not be exceeded.**[1] Recommend close monitoring and TDM if available.					
Rifabutin *(CYP3A > deacetylase; moderate inducer of CYP3A)*	**ATV 400 mg + rifabutin 150 mg QD** in healthy subjects did not result in any significant changes in ATV kinetics (vs. ATV 400 mg alone); 2.5-fold ↑ rifabutin & metabolite exposure vs. standard 300 mg dose. Reduce rifabutin dosage by at least 75% (i.e., max. 150 mg q2d or 3 times/week); monitor for	Reports of lymphopenia and influenza-like illness in subjects participating in a study of darunavir 400/100 mg BID plus rifabutin 150 mg QD; limited PK (n=1) suggest ↑ exposure to rifabutin and metabolite. Healthy volunteers who received darunavir 600/rtv 100 mg BID plus	In healthy volunteers, fosamprenavir 700 mg/ritonavir 100 mg BID plus rifabutin 150 mg Q2D for 14 days yielded similar RFB exposures compared to rifabutin 300 mg QD alone. **RFB 150mg Q2D is recommended when co-administered with FPV/RTV 700mg/100mg BID.**[328]	303% ↑ rifabutin AUC and 47.5-fold ↑+ metabolite AUC; **rifabutin 150 mg daily** had no significant effect on lopinavir/r concentrations.[162] Reduce rifabutin dosage by at least 75% (i.e., max. 150 mg q2d or 3 times/week);[329] monitor for adverse events and further decrease rifabutin	400% ↑ rifabutin AUC, risk of toxicity.[7] Recommend reducing rifabutin dose to 150 mg 2-3 times per week.[333] For combination ritonavir 400 mg BID + saquinavir 400 mg BID, may be possible to administer RFB 150 mg q3days.[334] Case report of 3 HIV patients with low CD4	40% ↓ saquinavir AUC. **Avoid combination** if using saquinavir as sole protease inhibitor.[335] For combination **ritonavir 400 mg BID + saquinavir 400 mg BID,** may be possible to administer RFB 150 mg q3days.[334] Case report of 3 HIV

	Atazanavir (Reyataz®)	Darunavir (Prezista®)	Fosamprenavir (Telzir®)	Lopinavir/ ritonavir (Kaletra®)	Ritonavir (Norvir®)	Saquinavir (Invirase®)
	adverse events and further decrease rifabutin dose if necessary.[324] In healthy subjects, **ATV 300/rtv 100 mg plus rifabutin 150 mg twice weekly** resulted in rifabutin Cmax ↑ 149%, Cavg ↑ 48% and Cmin ↑ 40% and 25-*O*-desacetylrifabutin Cmax ↑ 7.8-fold, Cavg ↑ 10.9-fold and Cmin ↑ 11.5-fold. Total activity was estimated to have ↑ 119% and be similar to that of rifabutin 300 mg QD. 13/18 subjects in the combination arm discontinued due to mild-moderate neutropenia or pyrexia, versus 1/15 subjects (for cough) on rifabutin 150 mg QD alone. Monitoring for neutropenia is recommended with this combination.[325] 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.[326] **When co-administering with boosted protease inhibitors, rifabutin 150 mg once daily or 300**	**rifabutin 150 mg q2d** had 881% ↑ AUC of 25-*O*-desacetylrifabutin, 57% ↑ darunavir AUC and 66% ↑ ritonavir AUC compared to levels observed with standard doses of each drug alone. Half the ubjects discontinued the study prematurely due to safety reasons, primarily headache, diarrhea, back pain, dizziness and vomiting. Therefore, increased monitoring for rifabutin-related adverse events is warranted in patients receiving the combination with darunavir/r.[327] 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.[326] **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.**[228]	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.[326] **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.**[228]	dose if necessary. In healthy subjects, **LPV 400/rtv 100 mg BID mg plus rifabutin 150 mg 3 times weekly** resulted 3-fold ↑ in sum exposures of rifabutin and 25-*O*-desacetylrifabutin compared to rifabutin 150 mg QD alone. 13/14 subjects in the combination arm experienced at least 1 ADR including fever, rash, neutropenia or lymphopenia. Future studies of this combination in healthy subjects is not recommended.[330] Kinetics of rifabutin and 25-*O*-desacetylrifabutin were measured in 10 HIV-patients with active TB **with RFB dosed 300 mg 3x/week, RFB 150 mg 3x/week plus LPVr 400/100 mg BID, and RFB 300 mg 3x/week plus LPVr** if RFB plasma concentrations were below target. Rifabutin at 300 mg without LPVr yielded low *C*max in 5/10 patients. After LPVr was added and RFB was reduced to 150 mg, 9/10 had low *C*max values. Eight patients had RFB dose ↑ to 300 mg with LPVr. Most RFB *C*max values were below the tuberculosis MIC and most AUC values were lower than those associated with treatment failure or relapse and with	(<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.[326] **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.**[228]	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.[326] In healthy volunteers, coadministration of rifabutin 150 mg q3d plus **SQV 1000/rtv 100 mg BID** showed no significant impact on protease inhibitor levels. In contrast, AUC of RFB + active metabolite ↑ 134% and 60% when **RFB was dosed 150 mg every 3 or 4 days**, respectively with SQV/rtv BID compared to RFB 150 mg daily alone. Monitor for neutropenia and elevated LFTs while on combination.[336] **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.**[228]

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	mg three times a week is recommended, along with close monitoring for antimycobacterial activity and therapeutic drug monitoring if available.[228]			acquired rifamycin resistance. One of the 10 patients experienced relapse with acquired rifamycin resistance. 8/18 LPV Cmin measurements were also lower than target of 4 mg/L.[331] 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.[326] In 16 TB/HIV co-infected patients, the kinetics of rifabutin were measured alone (300 mg QD) and in conjunction with LPVr 400/100 mg BID either as RFB 150 mg daily or 3 times weekly. Median rifabutin AUC and Cmax were 3026 ng/mL.h and 297 ng/mL (RFB alone), 2307 and 168 (150 mg 3x/wk with LPVr) and 5010 and 311 (150 mg QD with LPVr). **Rifabutin 150 mg daily** combined with LPV/r produces C_{max} concentrations within the recommended target range of 300 to 900 ng/mL.[332] **When co-administering**		

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				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.[228]		
Rifampin *(Deacetylase> hydrolysis, GT?, CYP?; potent inducer of CYP3A and GT)*	In an open-label, randomized study of healthy subjects, coadministration of rifampin 600 mg QD plus **atatazanavir/r at 300/100 or 300/200 mg QD** led to significant ↓ in ATV AUC (57 and 31%, respectively) and Cmin (93 and 80%, respectively) vs. ATV 400 mg QD alone. **ATV/r 400/200 mg** plus rifampin led to comparable ATV AUC but 60% ↓ Cmin vs. ATV alone.[337] In a separate study in HIV-infected individuals receiving active TB therapy (n=3), ATV Cmin was undetectable and AUC was significantly reduced in the presence of rifampin.[338] In healthy subjects, steady-state atazanavir C12 was 811 ng/mL with ATV 300 mg BID alone, 44 ng/mL with **ATV 300 mg BID plus rifampin 600 mg QD**, and 113 ng/mL with **ATV 400 mg BID plus rifampin 600 mg QD**.[339]		81% ↓ AUC and 91% ↓ Cmin of amprenavir. **Avoid combination**.[340]	75% ↓ LPV AUC. **Avoid combination**.[162] In a healthy volunteer study, subjects received LPV/r 400/100 mg BID (days 1-15), plus RIF 600 mg/d (days 11-24), and then were randomized to receive either LPV/rtv 800/200 or 400/400 mg BID (days 16-24) with RIF: • no change in rifampin Cmax vs. historical data • 56% ↓ lopinavir Cmin with 800/200 mg BID dose, vs. 400/100 mg BID dose • overall, no statistically sig. change in LPV Cmin with 400/400 mg BID dose, although ↓ seen in some subjects[341] In a healthy volunteer study of RIF 600 mg plus **LPV 600/rtv 150 mg BID or LPV 800/200 mg BID**, an **unexpected high incidence of nausea and vomiting** (10/11 subjects) and **elevated AST/ALT levels** (11/11 subjects) was observed after LPV/rtv was added	35% ↓ ritonavir AUC. May need to ↑ ritonavir dose.[7] 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%. **Avoid concurrent rifampin administration until further study**.[344]	80% ↓ saquinavir AUC. **Avoid combination**.[9] Addition of ritonavir (e.g., **saquinavir/ritonavir 400/400 mg BID, or 1000/100 mg BID**) may provide therapeutic concentrations in presence of rifampin.[345, 346] However, in a Phase I, randomized, open-label, multi-dose study in healthy volunteers, 11/28 (39.3%) of subjects 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).

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	Avoid concurrent rifampin administration until further study.			to RIF therapy; the study was prematurely discontinued.[342] In a cohort of HIV-infected patients suppressed on a lopinavir/ritonavir 400/100 mg BID regimen, rifampin 600 mg daily was initiated and LPVr dose was sequentially increased to 600/150 mg BID and then 800/200 mg BID at weekly intervals. Lopinavir exposures achieved with 800/200 mg BID in the presence of rifampin were similar to baseline values prior to starting rifampin. Two patients developed grade 3-4 ALT elevations. **Doubling the dose of LPVr overcomes the induction effect of rifampin**.[343]		
Rifapentine	**Reducted exposures of protease inhibitors expected with combination. Do not coadminister rifapentine and PIs.**[228]					
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.**[7]. 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.[7] Symbicort® (budesonide/formoterol) Turbuhaler may be a suitable alternative to Advair®.[232]					
Sulfamethoxazole (SMX) *(primarily N-acetylase> GT > CYP2C9 (minor)*				Clinically significant interaction not expected.[162]	20% ↓ SMX AUC. May need to ↑ SMX dose.[7]	
Theophylline *(CYP1A2 (>70%) >2E1>3A4 (minor)*					43% ↓ theophylline AUC. May need to ↑ theophylline dose.[7]	
Trimethoprim *(10-20%*				Clinically significant interaction not	20% ↑ TMP AUC. Clinical significance	

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metabolized, via CYP?)				expected.[162]	unknown.[7]	
Voriconazole *(CYP2C19, 2C9, 3A; inhibits CYP3A4, 2C9, 2C19)*	Case report of positive immunologic and virologic response in a patient with multidrug-resistant HIV on **atazanavir 300 mg QD,** raltegravir 400 mg BID and tenofovir/emtricitabine concurrently with **voriconazole 200 mg twice daily**.[347] An open-label nonrandomized study assessed the impact of atazanavir/ritonavir 300/100-mg QD on the kinetics of voriconazole in CYP2C19 extensive metabolizers (EMs) and poor metabolizers (PMs). Among EMs, coadministration resulted in 33% ↓ AUC and ↓ 39% Cmin of voriconazole, and 12% ↓ AUC and 20% ↓ Cmin of atazanavir. Among PMs, coadministration resulted in ↑ voriconazole Cmax, AUC and Cmin by 4.4-, 5.6-, and 7.7-fold, while atazanavir AUC ↓ 20%, Cmax ↓ 19% and Cmin ↓ 31%. Ritonavir AUC and Cmax did not change substantially with voriconazole codosing in either study group.[348] **Avoid combination** unless the benefits outweigh the risks of antifungal failure.	Combination has not been studied. Administration of voriconazole with ritonavir 100 mg BID led to 39% ↓ AUC of voriconazole. Case report of a patient on **darunavir 900/100 mg QD, etravirine 200 mg BID, 2 NRTIs and voriconazole 400 mg BID** for 6 weeks. Drug levels were obtained during voriconazole co-administration and 3 weeks after voriconazole discontinuation. Therapeutic voriconazole levels were achieved, while etravirine Ctrough ↑ 134%, ritonavir Ctrough was undetectable and darunavir Ctrough was well below historical reference data. After voriconazole was discontinued, ritonavir Ctrough increased to the same range as the historical control and darunavir Ctrough increased by four-fold. The combination of etravirine/darunavir/ritonavir with voriconazole should be undertaken with caution and BID dosing of darunavir/ritonavir should be considered in this setting. Therapeutic drug monitoring should be utilized when available.[349]	A dual inhibition interaction is possible via CYP 3A4 inhibition by unboosted PI and voriconazole. CYP2C19 poor metabolizers may be at increased risk of higher voriconazole concentrations due to preferential CYP3A4 inhibition. Potential for ↑ concentrations of unboosted PIs and voriconazole. Monitor for both PI and voriconazole toxicity. Consider TDM of both drugs.	<u>With RTV 100 mg twice daily:</u> 39% ↓ voriconazole AUC; 14% ↓ RTV AUC[350, 351] Use of low boosting doses of RTV (i.e. 100mg twice daily) combined with any of the other PIs should be **avoided** unless the benefits outweigh the risks of antifungal failure.[162, 352] Consider voriconazole TDM or use other antifungals that do not interact significantly with RTV.	Coadministration of voriconazole 200 mg BID with **ritonavir 400 mg Q12h is contraindicated** because of 82% ↓ AUC, ↓ Cmax 66% of voriconazole healthy subjects after 9 days of coadministration; ritonavir concentrations were unaffected.[350] **Ritonavir 100 mg BID** plus voriconazole 200 mg BID led to significant decrease Voriconazole levels: 39% ↓ $AUC_{0\text{-}12Hr}$, 24% ↓ Cmax of voriconazole, and slight reduction in ritonavir levels (14% ↓ $AUC_{0\text{-}12Hr}$, 24% ↓ Cmax). Try to avoid low dose RTV and voriconazole combination.[350] In a study in healthy individuals stratified by CYP2C19 genotype, a 42% ↓ in voriconazole clearance was observed in all phenotypes after coadministration of **ritonavir 300 mg BID** plus single-dose voriconazole. [353] Therefore, combination should be avoided; risk of short-term voriconazole toxicity particularly in CYP2C19 poor metabolizers, and potential long-term loss of voriconazole efficacy.	

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		Avoid co-administration with darunavir/ ritonavir unless potential benefits outweigh possible risks.				
Warfarin, Acenocoumarol/ nicoumalone *(racemic mixture; R: CYP1A2, 3A, 2C19; S: 2C9 primarily)* *NB:* The S-enantiomer of warfarin exhibits 2 to 5 times more anticoagulant activity than the R-enantiomer in humans, but generally has a more rapid clearance. The R(+) and S(−) enantiomers of acenocoumarol have comparable anticoagulant effects, but the S-enantiomer has a very short half-life; thus only the R-enantiomer provides a pharmacologic effect in vivo. **See also entry for "Anticoagulants"*	May potentially inhibit anticoagulant metabolism; monitor for ↑ INR and adjust anticoagulant dose accordingly when starting and discontinuing therapy.[1] Case report of a patient who required doubling of acenocoumarol dose to maintain therapeutic INR while on atazanavir 300/100 mg daily. When atazanavir/ritonavir was replaced with raltegravir, the acenocoumarol dose was reduced and therapeutic INR was maintained.[354]	May induce anticoagulant metabolism. Monitor for ↓ INR and adjust anticoagulant dose accordingly when starting and discontinuing therapy.[3] Open label randomized crossover study in 12 healthy volunteers of darunavir 600 mg/ritonavir 100mg BID plus single dose **warfarin 10 mg** led to ↓ S-Warfarin AUC 21% suggesting induction of CYP2C9 enzyme activity. May be attributed to co administration of RTV.[318] In a 50 year old HIV-positive patient stabilized on warfarin and emtricitabine monotherapy, initiation of the TRIO regimen (etravirine, darunavir/ritonavir and raltegravir) required a 45% increase in mean warfarin dose.[355]	May potentially inhibit anticoagulant metabolism; monitor for ↑ INR and adjust anticoagulant dose accordingly when starting and discontinuing therapy.	Three case reports where INR declined significantly and warfarin dosage was increased 40-140% in order to achieve therapeutic INR following initiation of lopinavir/ritonavir therapy.[356-358] Monitor for changes in INR and adjust anticoagulant dose accordingly when starting and discontinuing therapy.	May induce anticoagulant metabolism. Case reports where warfarin dosage was almost doubled to maintain INR with ritonavir[359, 360] and a 3-fold increase in acenocoumarol dose was noted.[361] However, another case report documented the opposite effect (increased INR requiring vitamin K and decrease in warfarin dose).[362] Monitor for changes in INR and adjust anticoagulant dose accordingly when starting and discontinuing therapy.	May inhibit anticoagulant metabolism; case report of hypo-prothrombinemia which required 20% ↓ warfarin dose with concomitant saquinavir.[363] Monitor for ↑ INR and adjust anticoagulant dose accordingly when starting and discontinuing therapy.

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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