

DRUG INTERACTIONS WITH SECONDARY PROTEASE INHIBITORS

	Amprenavir (Agenerase®)	Indinavir (Crixivan®)	Nelfinavir (Viracept®)	Saquinavir hgc-(Invirase®) sgc-(Fortovase®)
I) DOSING INFORMATION				
Usual Dose	Amprenavir: 1200 mg po BID <i>NB: Amprenavir is 14% less bioavailable from liquid vs. capsules; therefore not interchangeable on a mg-per-mg basis.</i>	800 mg po q8h	Adults: 750 mg po TID or 1250 mg po BID Children (2-13 years old): 20-30 mg/kg/dose TID	hgc: 600 mg po q8h sgc: 1200 mg TID or 1600 mg BID
Kinetic Characteristics	Primarily metabolized by CYP3A4. Inhibitor of CYP3A4 (similar potency as indinavir and nelfinavir) ¹ ; also induces CYP3A4 ² .	Primarily metabolized by CYP3A4. Inhibitor of CYP3A4; may also be weak inhibitor of CYP2D6. ³ ⁴ Requires acidic pH for optimal absorption.	Metabolized by CYP3A4 and CYP2C19. Inhibitor of CYP3A4. ^{5,6} Induces CYP2B6, 2C8 and 2C9. ⁷	Primarily metabolized by CYP3A4. Weak inhibitor of CYP3A4. ³
Food (NB: garlic: see entries for Saquinavir and Ritonavir)	May be taken with or without food. Avoid taking with high-fat meal. ¹ Administer amprenavir liquid solution at least 1 hour apart from other medications that contain sorbitol.	Take on empty stomach or with light meal. (77% ↓ AUC with full meal) ⁸	Take with meal or light snack (2-5 fold ↑ in Cmax, AUC). Highest nelfinavir levels observed with greater food intake, i.e., 500-1000 kCal and 20-50% fat. ⁹	Take within 2 hours of meal (almost 7-fold ↑ AUC with food). In a kinetic study of healthy volunteers, chronic garlic administration plus saquinavir-sgc 1200 mg TID led to a 51% ↓ saquinavir AUC. Use caution when combining garlic supplements with saquinavir used as a sole protease inhibitor. ¹⁰
Grapefruit juice	No significant changes in amprenavir concentrations when administered with 200 mL grapefruit juice. ¹¹	No change in indinavir concentrations when administered with 6 oz. Double-strength grapefruit juice. ¹²	Not studied.	40-100% ↑ saquinavir AUC. Take 150 mL juice with each dose. ¹³
Vitamins	Vitamin E: Each amprenavir capsule contains 109 IU vitamin E ∴ avoid additional vit. E supplements.	Vitamin C: In a study of healthy volunteers, Vit C 1 g daily resulted in a significant ↓ in IDV C _{max} (-20%, p = 0.04) and steady-state AUC _{8hr} (-14%, p <0.05); IDV C _{min} was 32% lower with Vit C (265 vs. 181 ng/mL, p = 0.09). Clinical significance unclear, use combination with caution. ¹⁴		
II) ANTI-RETROVIRAL INTERACTIONS				
Amprenavir (APV), fos-amprenavir (FPV)		Single dose study: 31% ↑ Cmax and 18% ↑ AUC of amprenavir, 35% ↓ AUC and 23% ↓ Cmax of indinavir. Multiple-dose study: 33% ↑ APV AUC, 38% ↓ IDV AUC, 27% ↓ Cmin. No dosage adjustments recommended for either drug. ¹⁵	Amprenavir 800 mg q8h + nelfinavir 750 mg po q8h: 2.89-fold ↑ Cmin of APV (but no overall change in AUC), 15% ↑ NFV AUC. No dosage adjustment required for either drug. ¹⁵	Amprenavir: In a randomized, prospective study of 11 HIV+ subjects, SQV AUC ↓ 81% and C ₁₂ ↓ 61% when given in a regimen of SQV 1000/rtv 100/APV 600 mg BID vs. SQV 1000/rtv 100 mg BID in the absence of APV. APV exposure was not affected. When doses were adjusted to SQV

	Amprenavir (Agenerase®)	Indinavir (Crixivan®)	Nelfinavir (Viracept®)	Saquinavir hgc-(Invirase®) sgc-(Fortovase®)
				<p>1400/rtv 200/APV 600 mg BID, SQV exposure returned to baseline.¹⁶</p> <p>May wish to consider TDM if using RTV 100 mg BID dose with this combination.</p>
Atazanavir (ATV)	<p>Combination of ATV with amprenavir in HIV-infected peripheral blood mononuclear cells yielded additive to moderately synergistic antiviral effects.¹⁷</p> <p>In a series of expanded access subjects (n=30), combination of ATV 400 mg QD, APV 1200 mg/d, and tenofovir 300 mg/d led to lower ATV C_{trough} (0.073 ug/mL) vs. either ATV/APV or ATV alone (0.11 and 0.251 ug/mL, respectively).¹⁸</p>	<p>Combination ATV with indinavir in HIV-infected peripheral blood mononuclear cells yielded additive to moderately synergistic antiviral effects.¹⁷</p> <p>However, combination not recommended due to the risk for additive hyperbilirubinemia.¹⁹</p>	Combination of ATV with nelfinavir in HIV-infected peripheral blood mononuclear cells yielded additive to moderately synergistic antiviral effects. ¹⁷	Additive-synergistic antiviral activity in vitro. ¹⁷ In healthy volunteers, ATV 400 mg QD plus saquinavir-sgc 800, 1200, or 1600 mg QD resulted in 5.4- to 7.1-fold ↑ AUC and 6.6- to 17.6-fold ↑ C _{min} of saquinavir; ATV kinetics not affected. ²⁰
Capravirine			Healthy volunteer, multi-dose study of CPV 1400 mg BID + nelfinavir 1250 mg BID with food: ↑ CPV C _{max} 84%, AUC ↑ 138%, C _{min} ↑ 263%, NFV kinetics unchanged. ²¹	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. ²²
Darunavir, TMC114 (substrate of CYP3A4)				Saquinavir-sgc: Single dose SQV-sgc 1200 mg plus 1200 mg TMC-114 BID led to 5-fold ↑ SQV AUC and C _{max} and 1.4-fold ↑ TMC AUC.
Delavirdine	<p>Amprenavir 1200 mg +/- delavirdine 600 mg BID (healthy volunteer study) significantly increased amprenavir concentrations (4-fold ↑ AUC, 6-fold ↑ C_{min}, 1.3 fold ↑ C_{max}); no change in delavirdine concentrations.²³</p> <p>In a separate healthy volunteer multi-dose study, administration of APV 600 mg BID +/- DLV 600 mg BID resulted in ↑ APV C_{min} 133% & AUC 117%; however, median DLV C_{min} ↓ 88%. Suggest avoiding this dosage combination until further</p>	<p>IDV 600 mg q8h + DLV: ↑ IDV AUC, C_{min} vs. IDV 800 mg q8h alone.^{25, 26}</p> <p>Thus, ↓ IDV to 600 mg q8h with delavirdine.</p> <p>Healthy volunteer study of IDV/DLV BID regimens:</p> <p>a) 800/600 mg BID: similar AUC, C_{max}, but C_{min} IDV ↓ 35-40% (vs. IDV 800 mg q8h)</p> <p>b) 1200/600 mg BID: similar C_{min}, ↑ AUC (50-70%), ↑ C_{max} (20-50%)</p> <p>Thus, 1200/600 mg BID may be preferable (NB: risk nephrolithiasis?); may take +/- food.²⁷</p>	Interaction data in HIV subjects taking DLV 600 mg TID + standard NFV: approx. 2-fold ↑ NFV AUC, and DLV C _{min} similar to that with DLV 400 mg TID alone. ²⁸	<p>Delavirdine 400 mg TID + saquinavir-hgc 600 mg TID in healthy volunteers: 5-fold ↑ SQV AUC, C_{min}, C_{max}; monitor LFTs during initial weeks of combination therapy. Dosage adjustments not necessary.²⁹</p> <p>In a randomized study in HIV-subjects (n=10), these regimens were compared:</p> <ul style="list-style-type: none"> • SQV-sgc 1200 mg TID • SQV-sgc 1400 mg + delavirdine 600 mg BID • SQV-sgc 1000 mg + delavirdine 400 mg TID <p>When combined with DLV, SQV exposure was ↑ vs.</p>

	Amprenavir (Agenerase®)	Indinavir (Crixivan®)	Nelfinavir (Viracept®)	Saquinavir hgc-(Invirase®) sgc-(Fortovase®)
	data available. ²⁴			SQV alone; SQV Cmin was higher in the TID vs. BID arm, both were greater than Cmin SQV alone. ³⁰
Didanosine	No significant changes in amprenavir AUC or Cmin observed when administered: <ul style="list-style-type: none"> concurrently with ddl-EC (in fasting state) concurrently with ddl tablets (in fasting state) 1 hour prior to ddl tablets (fasting) compared to amprenavir alone in the fasting state. Authors suggest amprenavir may be dosed concurrently with both ddl tablets and enteric-coated capsules in the fasting state. ³¹	Indinavir requires acidic pH for best absorption. Separate doses by 1 hour. ^{32, 33} No difference in pharmacokinetics of indinavir observed when coadministered with 400 mg enteric-coated didanosine in healthy volunteers. ³⁴	Dosage adjustment not required. However, since didanosine needs to be administered on an empty stomach, it should be given 1 hour before or 2 hours after nelfinavir (given with food/snack).	Dosage adjustment not required. However, since didanosine needs to be administered on an empty stomach, it should be given 1 hour before or 2 hours after saquinavir (given with a full meal).
Efavirenz	APV 1200 mg BID + EFV 600 mg: 36% ↓ AUC, 39% ↓ Cmax, 43% ↓ Cmin APV; 15% ↑ EFV AUC ³⁵ . Avoid negative interaction by adding either: <ul style="list-style-type: none"> 200/500 mg RTV BID, or 1250 mg nelfinavir BID to APV 1200 mg BID plus EFV 600 mg qhs.³⁶ Other dosage combinations that yielded stable APV conc.: <ul style="list-style-type: none"> APV 600 mg/ rtv 200 mg BID + EFV³⁷ APV 1200 mg/ rtv 300 mg QD plus EFV³⁸ APV/EFV + NFV 1250 mg BID³⁹ APV/EFV + IDV 1200 mg BID³⁹ APV/EFV + RTV 100 mg BID³⁹ 	IDV alone: 30-35% ↓ indinavir levels; no change in efavirenz levels. Increase IDV dosage to 1000 mg q8h. ⁴⁰ Indinavir/rtv BID When efavirenz was added to IDV 800 mg/RTV 100 mg BID regimen, IDV exposure was significantly reduced (19% ↓ AUC, 48% ↓ Cmin). May wish to consider ↑ to indinavir 800 mg/ritonavir 200 mg BID. ⁴¹ indinavir/rtv QD: When efavirenz was added to IDV/RTV once daily regimens (800/100, 800/200, 1200/100), significant ↓ in IDV and RTV concentrations (esp. C24) were observed. Avoid using EFV with once daily IDV/RTV regimens. ⁴²	Healthy volunteer study: efavirenz 600 mg + nelfinavir 750 mg q8h x 7 days: 20% ↑ NFV levels, 37% ↓ M8 levels; no change in efavirenz levels. ⁴³ However, subsequent kinetic study in HIV+ subjects of efavirenz 600 mg qhs and nelfinavir 1250 mg BID showed ↓ 65% nelfinavir Cmin (p=0.04), ↓ 38% AUC and ↓ 21% Cmax at 32 weeks. ⁴⁴ Therefore, monitor for antiretroviral efficacy when using this combination. Nelfinavir dosage adjustment may be necessary, consider therapeutic drug monitoring where available.	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. ⁴⁵ Can avoid this negative interaction by adding ritonavir to combination at the following doses: <ul style="list-style-type: none"> saquinavir-sgc 400 mg BID ritonavir 400 mg BID efavirenz 600 mg qhs⁴⁶
Enfuvirtide	No clinically significant interaction expected.	No clinically significant interaction expected.	No clinically significant interaction expected.	No clinically relevant interaction noted with co-administration of enfuvirtide 90 mg SC BID and saquinavir 1000 mg/ ritonavir 100 mg BID for 4 days in 12 HIV-infected subjects. ⁴⁷
Etravirine, TMC125, (diaminopyrimidine NNRTI; inducer of	Potential for decreased amprenavir concentrations secondary to enzyme induction by etravirine. Optimal dosages for co-	Steady-state study of etravirine 1600 mg BID plus indinavir 800 mg TID (n=10) resulted in 51% ↑ AUC and Cmax of	Potential for decreased nelfinavir concentrations secondary to enzyme induction by etravirine.	Etravirine 900 mg BID at steady state plus single-dose saquinavir 1200 mg (n=12) resulted in 52% ↓ AUC and 46% ↓ Cmax of

	Amprenavir (Agenerase®)	Indinavir (Crixivan®)	Nelfinavir (Viracept®)	Saquinavir hgc-(Invirase®) sgc-(Fortovase®)
CYP3A)	administration have not yet been established.	etravirine, likely due to CYP3A inhibition; indinavir AUC ↓ 46%, Cmax ↓ 28%. ⁴⁸ Guidelines for dosage adjustment not available; avoid combination if possible, until further information available.	Etravirine should not be co-administered with PIs without low-dose ritonavir. ⁴⁹	saquinavir, likely due to CYP3A induction. ⁴⁸ Etravirine concentrations not measured. Guidelines for dosage adjustment not available; avoid combination if possible, until further information available. Etravirine 800 mg BID did not affect pharmacokinetics of LPV 400/RTV 100/SQV 800-1000 mg BID in 15 HIV-infected male subjects. ⁵⁰
Indinavir	Single dose study: 31% ↑ Cmax and 18% ↑ AUC of amprenavir, 35% ↓ AUC and 23% ↓ Cmax of indinavir. Multiple-dose study: 33% ↑ APV AUC, 38% ↓ IDV AUC, 27% ↓ Cmin. No dosage adjustments recommended for either drug. ¹⁵		In a single dose study, 83% ↑ NFV AUC, 51% ↑ IDV AUC observed. ⁵¹ In multi-dose trial of HIV-infected subjects (n=20), IDV 1200 mg and NFV 1250 mg BID provided IDV kinetics similar to IDV 800 mg q8h alone; indinavir had no effect on nelfinavir kinetics, and NFV Cmin was similar to values seen with 750 mg TID. ⁵²	Hgc: 5- to 8-fold ↑ SQV AUC; ⁵³ in vitro study suggests synergy at low doses and antagonism at high doses. ⁵⁴ Sgc: 620% ↑ SQV AUC (1200 mg SQV single dose + IDV 800 mg q8h x 2 days); no apparent clinically relevant changes to IDV. ⁵⁵
Lopinavir/ ritonavir	LPV/r capsules: <ul style="list-style-type: none"> 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%).⁵⁶ Similar findings observed in cohort of HIV+ subjects with both APV and FPV formulations.^{57 58} In a prospective cohort (n=27) of experienced patients, combination of LPV/r 400/100 mg BID and APV 600 mg BID led to a 54% ↓ APV exposure vs. APV/r 600/100mg BID. Addition of additional RTV 100 mg BID to combination did not improve APV levels.⁵⁹ In cohort of experienced 	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. ⁶² 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. ^{63, 64} <u>HIV+ subjects:</u> In an open-label PK study (n=11), both IDV & LPV PK parameters ↓ up to 64% vs. values seen with coadministration in healthy subjects. ⁶⁵ 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. ⁶⁶ A separate	LPV/r capsules: Multi-dose study in healthy volunteers of LPV/r 400/100 mg BID and NFV 1000 mg BID resulted in NFV concentrations similar to those with NFV 1250 mg BID alone; LPV levels significantly ↓ in the presence of nelfinavir (LPV Cmax ↓ 21%, AUC ↓ 27%, Cmin ↓ 33%). ⁶⁸ LPV dosage may need to be adjusted if coadministered with nelfinavir. LPV/r tablets: <ul style="list-style-type: none"> Can use 400/100 mg BID with NFV in ARV-naïve subjects May ↑ to 600/150 mg (3 tablets) BID when co-administering in treatment-experienced subjects	Saquinavir-sgc 800-1200 mg BID + lopinavir/r: Healthy volunteer study showed 6.3-fold ↑ AUC, 9.6-fold ↑ Cmax, 16.7-fold ↑ Cmin compared to saquinavir 1200 mg TID alone. Similar SQV concentrations were observed with 1200 mg BID plus lopinavir/r. Single and steady-state saquinavir-sgc 800 mg BID had no effect on lopinavir/r kinetics. ^{63, 64} Saquinavir-sgc 1000 mg BID + lopinavir/r: In a cohort of ARV-experienced subjects (n=27), combination gave therapeutic SQV levels (median trough 1.25 ug/mL); lopinavir levels were not affected. ⁶⁹

	Amprenavir (Agenerase®)	Indinavir (Crixivan®)	Nelfinavir (Viracept®)	Saquinavir hgc-(Invirase®) sgc-(Fortovase®)
	<p>HIV-subjects (n=46), APV 600-750 mg + LPV/r 400/100 mg BID retrospectively compared to APV 600-750 mg/RTV 100 mg BID:</p> <ul style="list-style-type: none"> • with APV 600 mg dose, APV Cmin ↓ 51% with LPV/r vs. RTV alone (p=0.004) • with APV 750 mg, Cmin ↓ 33 % with LPV/r vs. RTV alone (not statistically sig.) • median LPV Cmin not affected by APV dose • Clinical significance unclear, since 85% of APV/LPV/r subjects had APV Cmin ≤3-fold Cmin with APV 1200 mg BID alone. <p>In a prospective cohort of 12 HIV+, treatment-exp. subjects starting LPV/r plus APV 600 mg BID, 50% req. LPV/r dose ↑ to 533/133 mg or 666/166 mg BID to achieve target LPV Cmin.⁶⁰</p> <p>Optimal doses for co-administration not yet defined.</p> <p>Suggest TDM when using this combination.⁶¹</p>	<p>study showed no significant changes in LPV or IDV Cmin with combination.⁶⁷</p>		
Maraviroc				<p>When maraviroc 100 mg BID was given with saquinavir-sgc 1200 mg TID, maraviroc AUC ↑ 4.3-fold, Cmax ↑ 3.3-fold.⁷⁰</p> <p>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.</p> <p>Maraviroc 50% dose reduction in the presence of protease inhibitors/potent CYP3A4 inhibitors is</p>

	Amprenavir (Agenerase®)	Indinavir (Crixivan®)	Nelfinavir (Viracept®)	Saquinavir hgc-(Invirase®) sgc-(Fortovase®)
				recommended. ⁷⁰
Nelfinavir	Amprenavir 800 mg q8h + nelfinavir 750 mg po q8h: 2.89-fold ↑ C _{min} of APV (but no overall change in AUC), 15% ↑ NFV AUC. No dosage adjustment required for either drug. ¹⁵	In a single dose study, 83% ↑ NFV AUC, 51% ↑ IDV AUC observed. ⁵¹ In multi-dose trial of HIV-infected subjects (n=20), IDV 1200 mg and NFV 1250 mg BID provided IDV kinetics similar to IDV 800 mg q8h alone; indinavir had no effect on nelfinavir kinetics, and NFV C _{min} was similar to values seen with 750 mg TID. ⁵²		At steady-state, 169% ↑ SQV-soft gel capsules AUC, no significant changes in NFV concentrations ⁴⁵ ; may use lower dose of SQV-SGC (i.e., 800 mg vs. 1200 mg TID + NFV 750 mg TID, or SQV-sgc 1200 mg BID + NFV 1250 mg BID). ^{55, 71, 72}
Nevirapine	With APV 600/RTV 100 mg BID/NVP 400 mg QD , APV C _{min} and C _{max} ↓ 80%, AUC ↓ 77%. APV plasma levels stable with APV 450/RTV 200 mg BID plus NVP 400 mg daily . ⁷³ Therefore, recommend APV 450/RTV 200 mg BID with NNRTIs.	28% ↓ IDV AUC, <10% ↓ NVP AUC (non-significant). Suggest ↑ IDV dose to 1000 mg q8h when using with NVP 200 mg BID. ⁷⁴ Preliminary data suggest that dosing nevirapine 400 mg once daily may have a more pronounced effect on decreasing indinavir concentrations compared to nevirapine dosed 200 mg twice daily (median 31% decrease). These findings require further substantiation; may consider monitoring indinavir levels/response if switching nevirapine dosage regimen. ⁷⁵	No statistically significant changes in NFV levels after the addition of NVP (AUC +8%, C _{max} +14%, and C _{min} +2%). Compared to historical controls, NVP levels appear to be unchanged. ⁷⁶ Similar results were demonstrated in a separate study, and NFV C _{min} remained above minimum effective concentration during nevirapine coadministration. ⁷⁷ Thus, dosage adjustments not required.	27% ↓ SQV AUC; clinical significance unknown. ⁷⁸ 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. ⁷⁵
Rilpivirine	Potential for ↑ concentrations of rilpivirine. Rilpivirine is not expected to affect the plasma concentrations of co-administered PIs. ⁷⁹	Potential for ↑ concentrations of rilpivirine. Rilpivirine is not expected to affect the plasma concentrations of co-administered PIs. ⁷⁹	Potential for ↑ concentrations of rilpivirine. Rilpivirine is not expected to affect the plasma concentrations of co-administered PIs. ⁷⁹	Potential for ↑ concentrations of rilpivirine. Rilpivirine is not expected to affect the plasma concentrations of co-administered PIs. ⁷⁹
Ritonavir	Amprenavir AUC, C _{min} and C _{max} were ↑ by 131%, 484% and 33%, respectively, when ritonavir 200mg BID was given with amprenavir 1200mg BID. ⁸⁰ Amprenavir AUC, C _{min} significantly ↑, ↓ C _{max} when combined with ritonavir in the following dosages: ⁸¹⁻⁸³ <ul style="list-style-type: none"> • 450/300 mg BID • 600/100 mg BID • 1200/200 mg once daily. Preliminary clinical data (12 weeks) promising for 600/100 mg BID and 1200/200 mg QD. ⁸⁴ Ritonavir ↑ plasma APV to	IDV/RTV 400/400 mg BID in healthy volunteers yielded indinavir AUC similar to those achieved with IDV 800 mg po q8h alone. ⁸⁶ Also improved IDV PK profile: 62% ↓ C _{max} , 3-fold ↑ C _{min} , less impact of food on IDV absorption when given with RTV vs. alone, ⁸⁷ ↓ nephrolithiasis in one case series. ⁸⁸ IDV 800/RTV 100-200 mg BID also results in ↑ IDV trough levels compared to those with IDV 800 mg q8h alone; ^{89, 90} however, ↑ IDV peak levels ⁹¹ , possible ↑	162% ↑ NFV AUC, 9% ↑ RTV AUC. ⁹⁹ RTV 400 mg BID plus NFV 500-750 mg BID: NFV AUC similar to that seen with NFV 750 mg TID alone; M8 levels higher with NFV 750 mg BID regimen. Higher RTV AUC, C _{min} values when combined with NFV 500 mg vs. 750 mg BID. Overall, PK benefits similar with 2 regimens. ¹⁰⁰ RTV 100-200 mg BID added to NFV 1250 mg BID resulted in 30% ↑ NFV AUC; steady-state a.m. predose NFV	400 mg SQV-sgc /400 mg RTV BID: <ul style="list-style-type: none"> • 121% ↑ SQV AUC¹⁰³ 800 mg SQV-sgc/200-400 mg RTV BID: <ul style="list-style-type: none"> • 1589-2158% ↑ SQV AUC⁴⁵ 1600 mg SQV-sgc/RTV 100 mg QD: <ul style="list-style-type: none"> • Preliminary data in healthy volunteers: 300-800% ↑ SQV AUC, C_{min} > than with SQV-sgc 1200 mg TID.¹⁰⁴ • Kinetic substudy in 13 HIV+ subjects stabilized on combination showed equivalent SQV kinetic

	Amprenavir (Agenerase®)	Indinavir (Crixivan®)	Nelfinavir (Viracept®)	Saquinavir hgc-(Invirase®) sgc-(Fortovase®)
	similar extent with either APV or FPV. Therefore, FPV may replace APV, and metabolic APV interactions are applicable to FPV. ⁸⁵	risk nephrolithiasis ⁹² or other adverse events. ⁹³ IDV 600/RTV 200 mg BID may provide increased IDV Cmin without significantly increasing IDV Cmax. ⁹⁴ IDV 400/RTV100 mg BID (open study, n=17): ↑ Cmin (~0.5 ug/mL), ↓ Cmax vs. IDV 800mg q8h. ⁹⁵ Preliminary data on once daily dosing (1200/100-200 mg IDV/RTV) regimens show ↑ Cmax, and Cmin = those with 800 mg q8h. ^{96, 97} 1200/200mg QD regimen well-tolerated in naïve-subjects (n=40) up to 24 weeks; 1200/400 QD also under study. ⁹⁸	concentrations ↑ 45-90%. ¹⁰¹ In healthy volunteers, nelfinavir 2000 mg/ritonavir 200 mg once daily provided ↑ AUC, Cmax and comparable Cmin compared to nelfinavir 1250 mg BID. ¹⁰²	parameters (GMR of hgc/sgc for AUC 1.40, Cmax 1.23, and Cmin 1.46) when SQV-sgc replaced by SQV-hgc ¹⁰⁵ <ul style="list-style-type: none"> 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)¹⁰⁶ 1000 mg SQV/100 mg RTV BID: <ul style="list-style-type: none"> Compared SQV-sgc vs. SQV-hgc plus RTV in healthy subjects SQV-hgc/r gave significantly higher SQV levels vs. SQV-sgc/r (Cmin: 217 vs 153 ng/mL, p=0.0147, AUC 15798 ng.h/mL vs. 11655 ng.h/mL, p=0.0043); also significantly less GI side effects with SQV-hgc/r vs. SQV-sgc/r, possibly due to capmul content of SQV-sgc.¹⁰⁷
Saquinavir	In a randomized, prospective study of 11 HIV+ subjects, SQV AUC ↓ 81% and C ₁₂ ↓ 61% when given in a regimen of SQV 1000/rtv 100/APV 600 mg BID vs. SQV 1000/rtv 100 mg BID in the absence of APV. APV exposure was not affected. When doses were adjusted to SQV 1400/rtv 200/APV 600 mg BID , SQV exposure returned to baseline. ¹⁶	Hgc: 5- to 8-fold ↑ SQV AUC; ⁵³ in vitro study suggests synergy at low doses and antagonism at high doses. ⁵⁴ Sgc: 620% ↑ SQV AUC; no apparent clinically relevant changes to IDV. ⁵⁵	SQV levels ↑, no significant changes in NFV concentrations with combination of SQV-hgc plus NFV. ¹⁰⁸⁻¹¹⁰ 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. ¹¹¹	
Tenofovir	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. ¹¹² In a cohort of 21 HIV-infected subjects taking fosamprenavir 700/ritonavir 100 mg BID plus tenofovir and an NRTI, steady-state	In healthy volunteers, tenofovir 300 mg daily plus indinavir 800 mg q8h resulted in slightly delayed Tmax and ↓ Cmax of indinavir, but overall AUC was unchanged; tenofovir Cmax was slightly ↑ but AUC unchanged. These changes not likely to be clinically significant; indinavir and tenofovir may be coadministered without dosage adjustment. ¹¹⁴	In 18 patients stabilized on nelfinavir 1250 mg BID, addition of tenofovir 300 mg QD for 7 days did not affect the AUC of nelfinavir. Combination may be coadministered without dosage adjustment. ¹¹⁵	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 ddl/d4T to tenofovir/3TC. ¹¹⁶ 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. ¹¹⁷ Similar effect observed in healthy volunteer study. ¹¹⁸

	Amprenavir (Agenerase®)	Indinavir (Crixivan®)	Nelfinavir (Viracept®)	Saquinavir hgc-(Invirase®) sgc-(Fortovase®)
	Cmin concentrations of amprenavir, ritonavir and tenofovir were within the therapeutic range and comparable to historical controls. ¹¹³			
Tipranavir (<i>inducer of CYP3A4 and glucuronyl transferase</i>)	Pharmacokinetic analysis in treatment-experienced subjects taking TPV 500 mg/APV 600 mg/rtv 200 mg BID showed 45% ↓ AUC, 40% ↓ Cmax, 56% ↓ Cmin of APV compared to APV 600/rtv 200 mg BID alone. Clinical significance not established, no current dosage recommendations available. Use combination with caution. ¹¹⁹	Potential for decreased indinavir concentrations secondary to enzyme induction by tipranavir. Optimal dosages for co-administration have not yet been established.	Potential for decreased nelfinavir concentrations secondary to enzyme induction by tipranavir. Optimal dosages for co-administration have not yet been established.	Pharmacokinetic analysis in treatment-experienced subjects taking TPV 500 mg/SQV 1000 mg/rtv 200 mg BID showed 70% ↓ AUC, 66% ↓ Cmax, 81% ↓ Cmin of SQV compared to boosted SQV alone. Clinical significance not established, no current dosage recommendations available. Use combination with caution. ¹¹⁹
Vicriviroc			The combination of vicriviroc 15 mg QD /ritonavir 100 mg BID plus nelfinavir 1250 mg BID in healthy volunteers did not lead to significant changes in vicriviroc plasma levels, compared to vicriviroc 15 mg QD /ritonavir 100 mg BID alone. Vicriviroc may be added to a ritonavir-boosted PI regimen without dosage adjustment. ¹²⁰	
Zidovudine (<i>GT 60-75% > CYP3A, minor</i>)	Amprenavir may inhibit ZDV glucuronidation to a small degree; no dosage adjustment necessary. ¹²¹	Slight ↑ in AUCs of both drugs. No dosage modification necessary. ³²	Nelfinavir dosage adjustment not required with zidovudine, lamivudine, or stavudine. ¹²²	No interaction.
III)	INTERACTIONS WITH OTHER MEDICATIONS:			
Antacids (NB: see separate entries for H2-blockers and Proton-pump inhibitors)	Separate doses by at least an hour to avoid potential interference with absorption. ⁸⁰	Indinavir requires acidic pH for best absorption. Separate indinavir and antacid doses by 1 hour. ³²		
Antihistamines, non-sedating (i.e., astemizole, terfenadine) (CYP3A4)	Possible ↑ antihistamine AUC and cardiotoxicity. Avoid combination. ⁸⁰	Possible ↑ antihistamine AUC and cardiotoxicity. Avoid combination. ³²	↑ terfenadine AUC; avoid combination. ⁵¹ Potential for similar interaction with astemizole.	368% ↑ terfenadine AUC; avoid combination. ⁵⁵ Potential for similar interaction with astemizole.
Benzodiazepine • alprazolam, midazolam, triazolam, zolpidem (CYP3A4) • diazepam (2C19>3A4)	Risk of prolonged sedation. Avoid combination, or use agents which are glucuronidated (e.g., lorazepam, oxazepam, temazepam). ⁸⁰	Risk of prolonged sedation. Use with caution. ³²	Risk of prolonged sedation. Avoid combination, or use agents which are glucuronidated (e.g., lorazepam, oxazepam, temazepam). ¹²²	Possible risk of prolonged sedation. Use with caution. ¹²³
Calcium channel blockers, e.g.	Potential for ↑ calcium channel blocker concentrations with	Healthy subjects on steady-state indinavir 800/ritonavir 100 mg BID	Potential for ↑ calcium channel blocker concentrations with	Potential for ↑ calcium channel blocker concentrations with

	Amprenavir (Agenerase®)	Indinavir (Crixivan®)	Nelfinavir (Viracept®)	Saquinavir hgc-(Invirase®) sgc-(Fortovase®)
<ul style="list-style-type: none"> amlodipine, bepredil, diltiazem, felodipine, nicardipine, nimodipine, verapamil (CYP3A substrates) 	concomitant protease inhibitor therapy. If coadministration is necessary, initiate calcium blocker therapy at low doses, with careful titration to response and side effects	received either either diltiazem 120 mg daily or amlodipine 5 mg daily for 7 days. In the presence of indinavir/ritonavir, amlodipine AUC ↑ 90% and diltiazem AUC ↑ 27%. 2/13 subjects (15%) had >4-fold ↑ diltiazem AUC. Desacetyldiltiazem AUC ↑ by 102% and desmethyl diltiazem AUC ↓ by 27%. Steady-state AUCs of indinavir and ritonavir were not affected by either amlodipine or diltiazem. If coadministration is necessary, initiate calcium blocker therapy at low doses, with careful titration to response and side effects. ¹²⁴	concomitant protease inhibitor therapy. If coadministration is necessary, initiate calcium blocker therapy at low doses, with careful titration to response and side effects	concomitant protease inhibitor therapy. If coadministration is necessary, initiate calcium blocker therapy at low doses, with careful titration to response and side effects
Caspofungin			Open-label study in 9 healthy male subjects, who received a 14 day course of caspofungin 50 mg intravenously along with nelfinavir 1250 mg twice daily. Steady-state caspofungin levels were unaltered in the presence of nelfinavir. No dosage adjustments necessary. ¹²⁵	
Cisapride (CYP3A4)	Possible ↑ cisapride AUC and cardiotoxicity. Avoid combination. ⁸⁰	Possible ↑ cisapride AUC and cardiotoxicity. Avoid combination. ³²	Possible ↑ cisapride AUC and cardiotoxicity. Avoid combination. ¹²²	Possible ↑ cisapride AUC and cardiotoxicity. Avoid combination. ¹²³
Clarithromycin (parent: CYP3A4; inhibits CYP3A4, 1A2?) (CLA-14 OH: renal, CYP3A4)	Multi-dose trial in healthy volunteers, using 1200 mg APV BID + 500 mg CLA BID: 18% ↑ APV AUC, 10% ↓ CLA Cmax, 35% ↓ AUC of CLA-14 OH metabolite. No dosage adjustment necessary for either drug. ¹²⁶	29% ↑ indinavir AUC, 53% ↑ clarithromycin AUC. No dose modification necessary. ³²	Nelfinavir may be administered with macrolides (including azithromycin, clarithromycin, erythromycin) without dosage adjustment. ⁵ In healthy volunteers, coadministration of NFV 750mg TID plus 1200 mg azithromycin resulted in 28% ↓ NFV and 23% ↓ M8 AUC (not clin. significant), and >100% ↑ azithromycin AUC. ¹²⁷	177% ↑ SQV-sgc AUC; 45% ↑ clarithromycin AUC. ⁵⁵
Colchicine (biliary, renal excretion; p-glycoprotein substrate)	Potential for ↑ colchicine concentrations due to P-gp inhibition and ↓ biliary excretion. Monitor for colchicine toxicity.	Potential for ↑ colchicine concentrations due to P-gp inhibition and ↓ biliary excretion. Monitor for colchicine toxicity.	Potential for ↑ colchicine concentrations due to P-gp inhibition and ↓ biliary excretion. Monitor for colchicine toxicity.	Potential for ↑ colchicine concentrations due to P-gp inhibition and ↓ biliary excretion. Monitor for colchicine toxicity.
Digoxin (p-glycoprotein substrate, 57-	Potential for ↑ digoxin concentrations via PI-mediated inhibition of renal	Case report of woman maintained on indinavir, 3TC, d4T and digoxin 0.25	Potential for ↑ digoxin concentrations via PI-mediated inhibition of renal	Potential for ↑ digoxin concentrations via PI-mediated inhibition of renal

	Amprenavir (Agenerase®)	Indinavir (Crixivan®)	Nelfinavir (Viracept®)	Saquinavir hgc-(Invirase®) sgc-(Fortovase®)
80% <i>Clr</i>)	p-glycoprotein. Use combination with caution. Monitor digoxin levels and response, and adjust dose if necessary.	mg/d who experienced acute digoxin toxicity 3 days after ritonavir 200 mg BID added to regimen. Symptoms resolved after ritonavir discontinued, and patient resumed original HAART without incident. ¹²⁸	p-glycoprotein. Use combination with caution. Monitor digoxin levels and response, and adjust dose if necessary.	p-glycoprotein. Use combination with caution. Monitor digoxin levels and response, and adjust dose if necessary.
Ergot alkaloids (<i>CYP3A>others</i>)	Concurrent administration is contraindicated. ⁸⁰			
Fluconazole (~80% <i>Clrenal</i> , 11% metabolized via <i>CYP3A4</i> ; inhibits 3A4 (weak), 2C9, 2C19)		No clinically significant effect on indinavir AUC. OK to use combination. ³²	Nelfinavir may be administered with azoles (including fluconazole, itraconazole, and ketoconazole) without dosage adjustment. ¹²⁹	
H2 blockers (including cimetidine, famotidine, nizatidine, ranitidine, etc.)		Coadministration of cimetidine (600 mg twice daily for 6 days) and indinavir (400 mg single dose) to 12 subjects led to a 7% ↑ in C _{max} , 2% ↓ AUC, and 18% ↓ C _{min} of IDV. ¹³⁰ Combination may be coadministered.		Healthy volunteer study of SQV-sgc 1200 mg TID vs. SQV 1200 mg BID plus cimetidine 400 mg BID: SQV AUC ↑ 120%, C _{max} ↑ 179%, C _{min} stable in presence of cimetidine. ¹³¹
Ginko biloba (<i>CYP3A inducer</i>)	Potential for ↓ amprenavir concentrations due to <i>CYP3A</i> induction by ginko biloba. ¹³² Case report of viral breakthrough and resistance to efavirenz after introduction of ginko biloba. ¹³³ Avoid concomitant use with unboosted amprenavir.	Potential for ↓ indinavir concentrations due to <i>CYP3A</i> induction by ginko biloba. ¹³² Case report of viral breakthrough and resistance to efavirenz after introduction of ginko biloba. ¹³³ Avoid concomitant use.	Potential for ↓ nelfinavir concentrations due to <i>CYP3A</i> induction by ginko biloba. ¹³² Case report of viral breakthrough and resistance to efavirenz after introduction of ginko biloba. ¹³³ Avoid concomitant use.	Potential for ↓ saquinavir concentrations due to <i>CYP3A</i> induction by ginko biloba. ¹³² Case report of viral breakthrough and resistance to efavirenz after introduction of ginko biloba. ¹³³ Avoid concomitant use with unboosted saquinavir.
Hmg-CoA Reductase inhibitors <ul style="list-style-type: none"> atorvastatin (<i>CYP3A</i>) fluvastatin (<i>2C9>>3A</i>) lovastatin (<i>CYP3A</i>) pravastatin (<i>40-50% Clr</i>, > 3A4) simvastatin (<i>CYP3A</i>) 	Potential for ↑ concentrations of atorvastatin, lovastatin, and simvastatin, possibly fluvastatin due to enzyme inhibition by amprenavir. Consider using rosuvastatin or pravastatin if Hmg-CoA reductase inhibitor necessary, or use a fibric acid derivative for hypertriglyceridemia.	Potential for ↑ concentrations of atorvastatin, lovastatin, and simvastatin, possibly fluvastatin due to enzyme inhibition by indinavir. Consider using rosuvastatin or pravastatin if treatment with an Hmg-CoA reductase inhibitor is desired, or use a fibric acid derivative for hypertriglyceridemia.	Pharmacokinetic study in HIV-negative subjects taking nelfinavir 1250 mg BID plus either 10 mg atorvastatin or 20 mg simvastatin resulted in ¹³⁴ : <ul style="list-style-type: none"> 506% ↑ AUC simvastatin 74% ↑ AUC atorvastatin Avoid concurrent use of simvastatin and nelfinavir. Consider using pravastatin if treatment with an Hmg-CoA reductase inhibitor is desired, or use a fibric acid derivative for hypertriglyceridemia.	Pharmacokinetic study in HIV-negative subjects taking saquinavir 400 mg/ritonavir 400 mg BID plus 40 mg of atorvastatin, pravastatin, or simvastatin revealed the following effects: <ul style="list-style-type: none"> 35% ↓ AUC pravastatin 31.6 fold ↑ AUC simvastatin 4.5-fold ↑ AUC atorvastatin Therefore, atorvastatin and simvastatin should be avoided if possible in patients receiving ritonavir/saquinavir. Consider using rosuvastatin or pravastatin if treatment with an Hmg-CoA reductase inhibitor is

	Amprenavir (Agenerase®)	Indinavir (Crixivan®)	Nelfinavir (Viracept®)	Saquinavir hgc-(Invirase®) sgc-(Fortovase®)
				desired, or use a fibric acid derivative for hypertriglyceridemia. Pravastatin may be administered without dosage adjustment. ¹³⁵
Itraconazole (CYP3A4; inhibits 3A, 2C9)	Potential for increased itraconazole and/or amprenavir concentrations. Clinical significance unclear, monitor for dose-related toxicities.	In a multiple-dose study, administration of itraconazole 200 mg BID with indinavir 600 mg every 8 hours resulted in indinavir AUC similar to what would be expected from indinavir 800 mg every eight hours alone. ¹³⁶ Consider reducing indinavir dose to 600 mg q8h.	Potential for increased itraconazole and/or nelfinavir concentrations. Clinical significance unclear, monitor for dose-related toxicities.	In a prospective randomized study in 17 HIV-infected subjects, saquinavir-sgc 800 or 1200 mg BID plus itraconazole 100 mg daily resulted in SQV concentrations equivalent to SQV-sgc 1400 mg BID alone. ¹³⁷
Ketoconazole (CYP3A4; inhibits 3A, 2C9)	32% ↑ amprenavir AUC, 44% ↑ ketoconazole AUC. Clinical significance unclear. ¹³⁸	Single-dose study of indinavir 400 mg and ketoconazole 400 mg: 68% ↑ indinavir AUC. Reduce indinavir dose to 600 mg q8h. ¹³⁶	35% ↑ NFV AUC. No dosage adjustment required. ⁵¹	1.5-fold ↑ saquinavir AUC. Dosage adjustment not necessary. ¹²³
Levothyroxine (GT)		Case report of a 36 year old woman receiving chronic levothyroxine 0.75 mg/day, who developed a pharmacological hyperthyroidism within 1 month after starting an indinavir-containing regimen. Her symptoms resolved and thyroid hormone parameters returned to baseline after her levothyroxine dose was reduced to 0.12 mg/day. The authors hypothesized that indinavir may have inhibited glucuronidation of levothyroxine. ¹³⁹	Nelfinavir induces glucuronyl transferase, and may potentially ↑ clearance of levothyroxine. See case report described under "Lopinavir-ritonavir and levothyroxine".	
Mefloquine (CYP3A?, GT)		Case report of patient on indinavir 800 mg q8h and mefloquine 250 mg/week for 16 weeks: therapeutic levels of both drugs observed; no side effects reported. ¹⁴⁰	Case report of patient on nelfinavir 1250 mg BID and mefloquine 250 mg/week for 6 weeks: therapeutic levels of both drugs observed; no side effects reported. ¹⁴⁰	
Methadone (CYP3A4>>GT; weak inhibitor of CYP2D6)	In HIV-negative subjects (n=16) maintained on methadone for at least 30 days, addition of amprenavir 1200 mg BID for 10 days resulted in delayed APV absorption, 13% ↓ AUC of active methadone enantiomer. No clinical evidence of methadone withdrawal was observed. Compared to a non-	In vitro study: 30% ↑ methadone concentrations. However, no significant changes in concentrations of either drug were observed with coadministration in blinded, randomized, crossover study in 12 HIV-negative methadone maintenance subjects, ¹⁴² as well as a case series (n=6) of HIV-positive subjects. ¹⁴³	29-50% ↓ methadone concentrations when nelfinavir given to patients on stable methadone dosages. ^{143,144} Monitor for symptoms of methadone withdrawal; adjustment of methadone dosage may be necessary. In an open study of healthy volunteers (n=16) stable on methadone 40-120 mg/day, coadministration of NFV	Likelihood of interaction low, since saquinavir is a weak CYP3A4 inhibitor.

	Amprenavir (Agenerase®)	Indinavir (Crixivan®)	Nelfinavir (Viracept®)	Saquinavir hgc-(Invirase®) sgc-(Fortovase®)
	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. ^{80, 141}		1250 mg BID for 5 days resulted in ↑ NFV parent and ↓ M8 exposure vs. controls. ¹⁴⁵ Clinical significance unclear.	
Milk thistle		Interaction study in healthy volunteers (n=10) who took milk thistle 175 mg (= silymarin 153 mg) TID for 3 weeks, and indinavir 800 mg q8h at baseline, end of week 3, and after an 11-day washout period. After 3 weeks of milk thistle, indinavir AUC ↓ by 9% and Ctrough ↓ 25%. Authors concluded that these changes were not significant, and that these two products may be coadministered. ¹⁴⁶		
Mycophenolate mofetil (MMF) (active metabolite, mycophenolic acid: GT)		In a small case series (n=6) of HIV+ subjects receiving ddl, 3TC, abacavir, indinavir 800/ ritonavir 100 mg BID and nevirapine 200 mg BID, there was no significant change in indinavir concentrations in the presence of chronic MMF administration. ¹⁴⁷		
Oral Contraceptives (GT, sulphatase (primary)> CYP3A (~30%); inhibits 1A2, 3A)	Ethinyl estradiol 0.035 mg/ norethindrone 1 mg daily for one cycle plus amprenavir 1200 mg BID resulted in a 22% ↓ AUC and 20% ↓ Cmin of amprenavir; Cmin of oral contraceptives ↑ 32-45%, no significant change in AUC. Oral contraceptives should not be taken with amprenavir. Use alternate non-hormonal methods of contraception. ⁸⁰	Slight ↑ in oral contraceptive AUC. No dose modification necessary. ³²	47% ↓ ethinyl estradiol AUC; use alternate methods of contraception. ⁵¹ Depo-medroxy-progesterone acetate, DMPA (Depo-Provera®): In a prospective, open-label study of 20 HIV-infected women on stable NFV therapy, NFV AUC was not significantly altered in the presence of DMPA. Efficacy of DMPA did not appear to be altered, with no evidence of ovulation occurring based on progesterone levels through week 12. ¹⁴⁸	In a pharmacokinetic study in healthy women, oral contraceptives did not affect the kinetics of single 600 mg saquinavir-hgc. ¹⁴⁹
Phosphodiester-	Potential for increased	Potential for increased	Potential for increased	Potential for increased

	Amprenavir (Agenerase®)	Indinavir (Crixivan®)	Nelfinavir (Viracept®)	Saquinavir hgc-(Invirase®) sgc-(Fortovase®)
ase Type 5 (PDE5) Inhibitors • sildenafil (Viagra®, Revatio®); (CYP3A4>>2 C9 substrate; weak inhibitor of CYP1A2, 2C9, 2C19, 2D6, 2E1, 3A4 - unlikely to cause significant interactions) • tadalafil (Cialis®, Adcirca®); CYP3A4 substrate • vardenafil (Levitra®); substrate of CYP3A4>3A5, 2C	sildenafil concentrations. Use with caution at a dose of 25 mg every 48 hours, and monitor for adverse effects. Case report of a 36-year old man on fosamprenavir 700/100 mg BID who experienced recurrent priapism after taking tadalafil 10 mg for recreational purposes. ¹⁵⁰ Tadalafil: ¹⁵¹ • <u>on demand dosing while on PIs or other CYP3A4 inhibitors:</u> 10-20 mg q48h, max 3 times per week • <u>daily dosing:</u> 5 mg/day (no dose adjustment needed if on PIs) Vardenafil is contraindicated with ritonavir. ¹⁵²	sildenafil concentrations. Use with caution at a dose of 25 mg every 48 hours, and monitor for adverse effects. Tadalafil: ¹⁵¹ • <u>on demand dosing while on PIs or other CYP3A4 inhibitors:</u> 10-20 mg q48h, max 3 times per week • <u>daily dosing:</u> 5 mg/day (no dose adjustment needed if on PIs) Vardenafil is contraindicated with indinavir and ritonavir. ¹⁵²	sildenafil concentrations. Use with caution at a dose of 25 mg every 48 hours, and monitor for adverse effects. Tadalafil: ¹⁵¹ • <u>on demand dosing while on PIs or other CYP3A4 inhibitors:</u> 10-20 mg q48h, max 3 times per week • <u>daily dosing:</u> 5 mg/day (no dose adjustment needed if on PIs) Vardenafil is contraindicated with ritonavir. ¹⁵²	sildenafil concentrations. Use with caution at a dose of 25 mg every 48 hours, and monitor for adverse effects. Tadalafil: ¹⁵¹ • <u>on demand dosing while on PIs or other CYP3A4 inhibitors:</u> 10-20 mg q48h, max 3 times per week • <u>daily dosing:</u> 5 mg/day (no dose adjustment needed if on PIs) Vardenafil is contraindicated with ritonavir. ¹⁵²
Posaconazole (UGT1A4, Pgp substrate, inhibits CYP3A4, possibly Pgp)	Possible ↑ PI concentrations due to CYP3A4 inhibition by posaconazole. Monitor for PI toxicity.	Possible ↑ PI concentrations due to CYP3A4 inhibition by posaconazole. Monitor for PI toxicity.	Possible ↑ PI concentrations due to CYP3A4 inhibition by posaconazole. Monitor for PI toxicity.	Possible ↑ PI concentrations due to CYP3A4 inhibition by posaconazole. Monitor for PI toxicity.
Proton-pump inhibitors (PPIs), including esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, etc.		Coadministration of single-dose omeprazole 40 mg and IDV 800 mg in healthy subjects (n=14) led to 47% ↓ AUC and 55% ↓ Cmin of IDV. This effect was reversed when ritonavir 200 mg was coadministered. Avoid combining unboosted IDV with omeprazole and other PPIs. ¹⁵³	In an open-label, healthy volunteer study, coadministration of nelfinavir 1250 mg BID plus omeprazole 40 mg QD for 4 days resulted in significant reductions in NFV (↓ 36% AUC, 37% ↓ Cmax, 39% ↓ Cmin) and M8 (↓ 92% AUC, 89% ↓ Cmax, 75% ↓ Cmin). Co-administration of omeprazole and nelfinavir is not recommended. ¹⁵⁴	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. ¹⁵⁵
Ravuconazole (may act as CYP3A4 inhibitor after single dose, and as CYP3A2B inducer with chronic dosing)			32% ↑ NFV AUC (day 2) and 16% ↓ NFV AUC (day 29) after ravuconazole 400 mg daily and nelfinavir 750 mg given as two single doses in healthy male subjects. Standard doses of both drugs may be given. ¹⁵⁶	
Rifabutin (CYP3A >	14% ↓ amprenavir, 3-6 fold ↑ rifabutin Cmin. Decrease	Interaction study of half-dose RFB + indinavir:	32% ↓ NFV AUC, 3-fold ↑ RFB AUC. Reduce	40% ↓ saquinavir AUC. Avoid combination if

	Amprenavir (Agenerase®)	Indinavir (Crixivan®)	Nelfinavir (Viracept®)	Saquinavir hgc-(Invirase®) sgc-(Fortovase®)
<i>deacetylase; moderate inducer of CYP3A)</i>	<p>dose of rifabutin to 150 mg daily or 300 mg 3 times weekly to avoid toxicity.^{157, 158}</p> <p>Case report of 3 HIV patients with low CD4 (<50 cells/mm³) and prior episodes of drug-sensitive TB who relapsed with rifamycin-resistant <i>M. tuberculosis</i> infection despite receiving fully supervised directly observed therapy including rifabutin 150 mg q2d or 3x/week, plus either atazanavir/rtv or lopinavir/rtv-based HAART. Higher doses of rifabutin and a ritonavir-boosted HIV protease inhibitor as treatment for tuberculosis should be studied further.¹⁵⁹</p>	<p>155% ↑ rifabutin AUC, 33% ↓ indinavir AUC. Thus, ↑ indinavir to 1000 mg q8h and ↓ rifabutin to 150 mg daily or 300 mg three times weekly.^{32, 160 158} This dosing regimen results in ↑ AUC of RFB and its metabolite by 60% and 125% vs. RFB 300 mg alone.¹⁶¹</p> <p>Case report of 3 HIV patients with low CD4 (<50 cells/mm³) and prior episodes of drug-sensitive TB who relapsed with rifamycin-resistant <i>M. tuberculosis</i> infection despite receiving fully supervised directly observed therapy including rifabutin 150 mg q2d or 3x/week, plus either atazanavir/rtv or lopinavir/rtv-based HAART. Higher doses of rifabutin and a ritonavir-boosted HIV protease inhibitor as treatment for tuberculosis should be studied further.¹⁵⁹</p>	<p>rifabutin dose to 150 mg/day or 300 mg three times per week.⁵¹ Increase nelfinavir to 1000 mg q8h.¹⁵⁸ May have more consistent NFV concentrations with 1250 mg BID plus 150 mg RFB daily (or 300 mg 3 times weekly).^{160, 162}</p>	<p>using saquinavir as sole protease inhibitor.¹⁶³ For combination ritonavir 400 mg BID + saquinavir 400 mg BID, may be possible to administer RFB 150 mg q3days.¹⁶⁴</p> <p>Case report of 3 HIV patients with low CD4 (<50 cells/mm³) and prior episodes of drug-sensitive TB who relapsed with rifamycin-resistant <i>M. tuberculosis</i> infection despite receiving fully supervised directly observed therapy including rifabutin 150 mg q2d or 3x/week, plus either atazanavir/rtv or lopinavir/rtv-based HAART. Higher doses of rifabutin and a ritonavir-boosted HIV protease inhibitor as treatment for tuberculosis should be studied further.¹⁵⁹</p>
Rifampin (<i>Deacetylase</i> > hydrolysis, <i>GT?</i> , <i>CYP?</i> ; potent inducer of <i>CYP3A</i> and <i>GT</i>)	<p>81% ↓ AUC and 91% ↓ Cmin of amprenavir. Avoid combination.¹⁵⁷</p>	<p>Indinavir AUC ↓ 89% after 1 week rifampin 600 mg/day administration. Avoid combination.¹³⁶</p> <p>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%.¹⁶⁵</p> <p>Similarly, in 6 HIV-infected individuals on stable indinavir 800/ritonavir 100 mg BID, 4 days of rifampin 300 mg/day resulted in 87% ↓ indinavir Cmin.¹⁶⁶</p> <p>Eighteen Thai HIV+ patients receiving rifampin for active TB were given indinavir 600/100 mg BID plus 2 NRTIs; IDV pk was measured at 2 weeks, and</p>	<p>82% ↓ NFV AUC. Avoid combination.⁵¹</p> <p>NB: In a 7-month old infant with HIV/TB co-infection, addition of ritonavir improved nelfinavir kinetic parameters in the presence of rifampin therapy.¹⁶⁸ However, optimal dosages have not yet been determined.</p>	<p>80% ↓ saquinavir AUC. Avoid combination.¹²³</p> <p>Addition of ritonavir (e.g., saquinavir/ritonavir 400/400 mg BID, or 1000/100 mg BID) may provide therapeutic concentrations in presence of rifampin.^{169, 170}</p> <p>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</p>

	Amprenavir (Agenerase®)	Indinavir (Crixivan®)	Nelfinavir (Viracept®)	Saquinavir hgc-(Invirase®) sgc-(Fortovase®)
		<p>Trough at 4, 8 and 12 weeks, as well as at least 4 weeks after RIF discontinuation (whereby IDV ↓ to standard Thai dose of 400/100 mg BID). Mean IDV Trough was significantly reduced in the presence of RIF (0.03 vs. 0.68 mg/L, p=0.004).¹⁶⁷</p> <p>Avoid concurrent rifampin administration.</p>		saquinavir therapy (Dear Healthcare Provider Letter, Roche Laboratories, USA, February 2005).
<p>Sildenafil/Viagra®, Tadalafil/Cialis®, vardenafil/Levitra® (CYP3A4>>2C9; weak inhibitor of CYP1A2, 2C9, 2C19, 2D6, 2E1, 3A4 - unlikely to cause significant interactions)</p>	<p>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.¹⁷¹</p> <p>Use tadalafil with caution at reduced doses of 10 mg every 72 hours with increased monitoring for adverse events.</p> <p>Use vardenafil with caution at reduced doses of no more than 2.5 mg every 24 hours with increased monitoring for adverse events.¹⁹</p>	<p>Coadministration of indinavir 800 mg q8h at steady state with sildenafil 25 mg in HIV-infected subjects resulted in 4.4 fold ↑ sildenafil concentrations; sildenafil had no significant effects on indinavir pharmacokinetics.¹⁷² Pharmacologic effects of sildenafil persisted up to 72 hours post-ingestion in some subjects. Thus, a starting dose of 12.5 mg sildenafil may be considered in order to minimize dose-related toxicity.</p> <p>Use tadalafil with caution at reduced doses of 10 mg every 72 hours with increased monitoring for adverse events.</p> <p>16-fold ↑ vardenafil AUC, 30% ↓ indinavir AUC with combination; use vardenafil 2.5 mg every 24 hours.¹⁹</p>	<p>Nelfinavir concentrations not significantly changed in presence of sildenafil (n=5); sildenafil levels not measured.¹⁷³ Potential for increased sildenafil concentrations. Consider starting with an initial sildenafil dose of 25 mg q24-48 hours and titrating up based on patient response and tolerability.¹⁷¹</p> <p>Use tadalafil with caution at reduced doses of 10 mg every 72 hours with increased monitoring for adverse events.</p>	<p>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.¹⁷⁴</p> <p>Use tadalafil with caution at reduced doses of 10 mg every 72 hours with increased monitoring for adverse events.</p> <p>Use vardenafil with caution at reduced doses of no more than 2.5 mg every 72 hours with increased monitoring for adverse events.¹⁹</p>
Sulfamethoxazole (SMX) (primarily N-acetylase > GT > CYP2C9 (minor))		No interaction. ³²		
Trimethoprim (10-20% metabolized, via CYP?)		19% ↑ trimethoprim AUC. No dose modification necessary. ³²		
Voriconazole (CYP2C19, 2C9, 3A; inhibits CYP3A, 2C9, 2C19)	Potential for ↑ concentrations of unboosted PIs and voriconazole. Monitor for both PI and voriconazole toxicity. Consider TDM of both drugs.	In healthy volunteers, coadministration of voriconazole 200 mg BID and indinavir 800 mg q8h for 7 days did not affect the pharmacokinetics of either drug. ¹⁷⁵	Potential for ↑ concentrations of unboosted PIs and voriconazole. Monitor for both PI and voriconazole toxicity. Consider TDM of both drugs.	Potential for ↑ concentrations of unboosted PIs and voriconazole. Monitor for both PI and voriconazole toxicity. Consider TDM of both drugs.
Warfarin (racemic)	May potentially inhibit warfarin metabolism;	May potentially inhibit warfarin metabolism;	May potentially inhibit or induce warfarin	May inhibit warfarin metabolism; case report of

	Amprenavir (Agenerase®)	Indinavir (Crixivan®)	Nelfinavir (Viracept®)	Saquinavir hgc-(Invirase®) sgc-(Fortovase®)
<i>mixture; R: CYP1A2, 3A, 2C19; S: 2C9 primarily)</i>	monitor for ↑ INR and adjust warfarin dose accordingly when starting and discontinuing therapy.	however, paradoxical effect observed in 1 case report, where warfarin dosage needed to be increased to maintain INR with indinavir. ¹⁷⁶ Monitor for changes in INR and adjust warfarin dose accordingly when starting and discontinuing therapy.	metabolism; one case report where warfarin dosage was tripled to maintain INR with nelfinavir. ¹⁷⁷ Monitor for changes in INR and adjust warfarin dose accordingly when starting and discontinuing therapy.	hypo-prothrombinemia which required 20% ↓ warfarin dose with concomitant saquinavir. ¹⁷⁸ Monitor for ↑ INR and adjust warfarin 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.

References:

1. GlaxoSmithKline. Agenerase (amprenavir) Prescribing Information. Research Triangle Park, NC 2002.
2. GlaxoSmithKline. Lexiva (fosamprenavir) Prescribing Information. Research Triangle Park, NC 2003.
3. Eagling VA, Back DJ, Barry MG. Differential inhibition of cytochrome P450 isoforms by the protease inhibitors, ritonavir, saquinavir and indinavir. *British Journal of Clinical Pharmacology* 1997;44(2):190-4.
4. Merck Frosst Canada Ltd. Crixivan (indinavir) Prescribing Information. Kirkland, QC 2009.
5. Lee CA, Liang BH, Wu EY, et al. Prediction of nelfinavir mesylate (VIRACEPT) clinical drug interactions based on in vitro human P450 metabolism studies. 4th National Conference on Retroviruses and Opportunistic Infections, January 22-26, 1997, Washington DC.
6. Pfizer Canada Inc. Viracept (nelfinavir) Prescribing Information. Kirkland, QC 2008.
7. Dixit V, Hariparsad N, Li F, et al. Cytochrome P450 enzymes and transporters induced by anti-human immunodeficiency virus protease inhibitors in human hepatocytes: implications for predicting clinical drug interactions. *Drug Metab Dispos* 2007;35(10):1853-9.
8. Yeh KC, Deutsch PJ, Haddix H, et al. Single-dose pharmacokinetics of indinavir and the effect of food. *Antimicrobial Agents and Chemotherapy* 1998;42:332-8.
9. Petersen C, Pun E, Strada R, et al. Pharmacokinetics of nelfinavir (Viracept 250 mg tablet): effect of food intake on single-dose PK parameters [abstract 544]. 10th Conference on Retroviruses and Opportunistic Infections, February 10-14, 2003, Boston, MA.
10. Piscitelli SC, Burstein AH, Welden N, et al. The effect of garlic supplements on the pharmacokinetics of saquinavir. *Clinical Infectious Diseases* 2002 February 4-8;34:234-38.
11. Demarles D, Gillotin C, Bonaventure-Paci S, et al. Single-dose pharmacokinetics of amprenavir coadministered with grapefruit juice. *Antimicrob Agents Chemother* 2002;46:1589-90.
12. Wynn H, Shelton MJ, Bartosi L, et al. Grapefruit juice increases gastric pH, but does not affect indinavir exposure, in HIV patients [abstract 660]. 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, September 26-28, 1999, San Francisco, CA.
13. Kupferschmidt HHT, Fattinger KE, Ha HR, et al. Grapefruit juice enhances the bioavailability of the HIV protease inhibitor saquinavir in man. *British Journal of Clinical Pharmacology* 1998;45(4):355-9.
14. Slain D, Amsden JR, Khakoo RA, et al. Effect of high-dose vitamin C on the steady-state pharmacokinetics of the protease inhibitor indinavir in healthy volunteers. *Pharmacother* 2005;25(2):165-70.

15. Sadler BM, Gillotin C, Lou Y, et al. Pharmacokinetic study of human immunodeficiency virus protease inhibitors used in combination with amprenavir. *Antimicrobial Agents and Chemotherapy* 2001;45:3663-68.
16. Corbett AH, Eron J, Fiscus SA, et al. The pharmacokinetics, safety, and initial virologic response of a triple-protease inhibitor salvage regimen containing amprenavir, saquinavir, and ritonavir. *JAIDS* 2004;36:921-8.
17. Robinson BS, Riccardi KA, Gong YF, et al. BMS-232632, a highly potent human immunodeficiency virus protease inhibitor that can be used in combination with other available antiretroviral agents. *Antimicrobial Agents and Chemotherapy* 2000;44(8):2093-9.
18. Guffanti M, Villani P, Seminari E, et al. Atazanavir pharmacokinetics when combined with amprenavir in highly experienced HIV-positive patients [abstract]. 5th International Workshop on Clinical Pharmacology of HIV Therapy, April 1-3, 2004, Rome, Italy.
19. Bristol-Myers Squibb Company. Reyataz (atazanavir) Prescribing Information. Princeton, NJ 2003.
20. O'Mara E, Mummaneni V, Randall D, et al. BMS-232632: a summary of multiple-dose pharmacokinetic, food effect, and drug interaction studies in healthy subjects [abstract 504]. 7th Conference on Retroviruses and Opportunistic Infections, January 30-February 2, 2000, San Francisco.
21. Raber S, Reynolds R, Hee B, et al. Evaluation of the pharmacokinetic drug interaction between capravirine and nelfinavir in healthy volunteers and HIV-infected patients [abstract 8.8]. 4th International Workshop on Clinical Pharmacology of HIV Therapy, March 27-29, 2003, Cannes, France.
22. Raber S, Amantea M, Zhou J, et al. Addition of saquinavir (SQV) to a regimen of capravirine (CPV) plus lopinavir/ritonavir (LPV/r) does not alter systemic exposure of the antiretrovirals in healthy volunteers [abstract TuPeB4631]. XV International AIDS Conference, July 11-16, 2004, Bangkok, Thailand.
23. Tran JQ, Petersen C, Garrett M, et al. Delavirdine significantly increases plasma concentrations of amprenavir in healthy volunteers. *AIDS* 2000;14 (supplement 4):S92.
24. Justesen U, Klitgaard N, Brosen K, et al. Amprenavir is an effective inducer of delavirdine metabolism: a steady-state pharmacokinetic interaction study between amprenavir and delavirdine in healthy volunteers [abstract 442-W]. 9th Conference on Retroviruses and Opportunistic Infections, February 24-28, 2002, Seattle, WA.
25. Cox S, Sargent S, Para M, et al. Plasma viral load reduction in an open-label randomized study of Rescriptor in combination with zidovudine and two dose levels of indinavir compared to zidovudine, lamivudine, and indinavir in HIV-1 infected individuals [abstract 427]. 7th Annual Canadian Conference on HIV/AIDS Research, April 30-May 3, 1998, Quebec City, PQ.
26. Ferry J, Herman B, Cox S, et al. Delavirdine (DLV) and indinavir (IDV): a pharmacokinetic drug-drug interaction study in healthy adult volunteers. 4th National Conference on Retroviruses and Opportunistic Infections, 1997, Washington DC.
27. Tran JQ, Petersen C, Garrett M, et al. The pharmacokinetics and tolerability of indinavir and delavirdine administered twice-daily in the absence and presence of food in healthy volunteers [abstract 1634]. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, September 17-20, 2000, Toronto, Canada.
28. Freimuth W, Peaks S, Slater L, et al. An open-label randomized study of Rescriptor (delavirdine mesylate) plus nelfinavir, didanosine, and stavudine in quadruple treatment regimens in HIV-1 infected individuals [abstract 426]. 7th Annual Canadian Conference on HIV/AIDS Research, April 30-May 3, 1998, Quebec City, PQ.
29. Cox S, Batts D, Stewart F, et al. Evaluation of the pharmacokinetic interaction between saquinavir and delavirdine in healthy volunteers. 4th National Conference on Retroviruses and Opportunistic Infections, 1997, Washington DC.
30. Cox S, Conway B, Freimuth W, et al. Pilot study of BID and TID combinations of saquinavir-SGC, delavirdine, zidovudine and lamivudine as initial therapy: pharmacokinetic interaction between saquinavir & delavirdine [abstract 82]. 7th Conference on Retroviruses and Opportunistic Infections, January 30-February 2, 2000, San Francisco.
31. Shelton MJ, Giovanniello AA, Cloen D, et al. Effects of didanosine formulations on the pharmacokinetics of amprenavir. *Pharmacotherapy* 2003;23(7):835-42.
32. Merck Frosst Canada & Co. Crixivan Product Monograph. 2001.
33. Shelton MJ, Mei JH, Hewitt RG, et al. If taken 1 hour before indinavir, didanosine does not affect indinavir exposure, despite persistent buffering effects. *Antimicrobial Agents and Chemotherapy* 2001;45:298-300.

34. Damle BD, Mummaneni V, Kaul S, et al. Lack of effect of simultaneously administered didanosine encapsulated enteric bead formulation (Videx EC) on oral absorption of indinavir, ketoconazole, or ciprofloxacin. *Antimicrobial Agents and Chemotherapy* 2002;46:385-91.
35. Falloon J, Piscitelli S, Vogel S, et al. Combination therapy with amprenavir, abacavir, and efavirenz in human immunodeficiency virus (HIV)-infected patients failing a protease-inhibitor regimen: pharmacokinetic drug interactions and antiviral activity. *Clinical Infectious Diseases* 2000;30:313-8.
36. Piscitelli S, Bechtel C, Sadler B, et al. The addition of a second protease inhibitor eliminates amprenavir-efavirenz drug interactions and increases plasma amprenavir concentrations [abstract 78]. 7th Conference on Retroviruses and Opportunistic Infections, January 30-February 2, 2000, San Francisco.
37. Alvarez-Amao D, Pace W, Gold M. Switch from high to low dose amprenavir in combination with efavirenz and ritonavir [abstract 2.7]. 3rd International Workshop on Clinical Pharmacology of HIV Therapy, April 11-13, 2002, Washington DC.
38. Wood R, Wire MB, Lancaster T, et al. An assessment of plasma amprenavir pharmacokinetics following administration of Agenerase and low dose ritonavir QD in combination with efavirenz in HIV-infected adult subjects (COL30500) [abstract 2.2]. 3rd International Workshop on Clinical Pharmacology of HIV Therapy, April 11-13, 2002, Washington DC.
39. Morse GD, Rosenkranz S, Para MF, et al. 3-way pharmacokinetic interaction among amprenavir, efavirenz, and a second protease inhibitor [abstract 614]. 11th Conference on Retroviruses and Opportunistic Infections, February 8-11, 2004, San Francisco CA.
40. Fiske WD, Mayers D, Wagner K, et al. Pharmacokinetics of DMP 266 and indinavir multiple oral doses in HIV-1 infected individuals [abstract]. 4th Conference on Retroviruses and Opportunistic Infections, January 22-26, 1997, Washington DC.
41. Aarnoutse RE, Burger DM, Hugen PWH, et al. A pharmacokinetic study to investigate the influence of efavirenz on a BID indinavir 800 mg/ritonavir 100 mg in healthy volunteers [abstract 423]. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, September 17-20, 2000, Toronto, Canada.
42. Saah A, Winchell G, Rhodes R, et al. Multiple-dose pharmacokinetics and tolerability of indinavir with ritonavir and efavirenz combinations in a once-daily regimen in healthy volunteers (Merck 093) [P284]. 5th International Congress on Drug Therapy in HIV Infection, October 22-26, 2000, Glasgow, Scotland: AIDS.
43. Fiske WD, Benedek IH, White SJ, et al. Pharmacokinetic interaction between efavirenz and nelfinavir mesylate in healthy volunteers [abstr. 349]. 5th Conference on Retroviruses and Opportunistic Infections, February 1-5, 1998, Chicago, IL.
44. Smith PF, Robbins GK, Shafer RW, et al. Pharmacokinetics of nelfinavir and efavirenz in antiretroviral-naïve, human immunodeficiency virus-infected subjects when administered alone or in combination with nucleoside analog reverse transcriptase inhibitors *Antimicrob Agents Chemother* 2005;49(8):3558-61.
45. Jorga K, Buss NE. Pharmacokinetic drug interaction with saquinavir soft gelatin capsule [abstract 339]. 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, September 26-28, 1999, San Francisco, CA.
46. Hendrix CW, Fiske WD, Fuchs EJ, et al. Pharmacokinetics of the triple combination of saquinavir, ritonavir, and efavirenz in HIV-positive patients [abstract 79]. 7th Conference on Retroviruses and Opportunistic Infections, January 30-February 2, 2000, San Francisco.
47. Ruxrungtham K, Boyd M, Bellibas SE, et al. Lack of interaction between enfuvirtide and ritonavir or ritonavir-boosted saquinavir in HIV-1-infected patients. *Journal of Clinical Pharmacology* 2004;44(7):793-803.
48. Baede P, Piscitelli S, Graham N, et al. Drug interactions with TMC125, a potent next generation NNRTI [abstract A1827]. 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy, September 27-30, 2002, San Diego, CA.
49. Tibotec I. Intelence (etravirine) Product Monograph. USA 2008.
50. Harris M, Zala C, Ramirez S, et al. Pharmacokinetics and safety of adding TMC125 to stable regimens of saquinavir, lopinavir, ritonavir and NRTI in HIV+ adults [abstract 575b]. 13th Conference on Retroviruses and Opportunistic Infections February 5-8, 2006, Denver, CO

51. Kerr B, Lee C, Yuen G, et al. Overview of in-vitro and in-vivo drug interaction studies of nelfinavir mesylate, a new HIV-1 protease inhibitor [abstract 373]. 4th Conference on Retroviruses and Opportunistic Infections, January 22-26, 1997, Washington DC.
52. Riddler S, Havlir D, Squires KE, et al. Coadministration of indinavir and nelfinavir in human immunodeficiency virus type 1-infected adults: safety, pharmacokinetics, and antiretroviral activity. *Antimicrobial Agents and Chemotherapy* 2002;46(12):3877-82.
53. McCrea J, Buss N, Stone J, et al. Indinavir-saquinavir single dose pharmacokinetic study [abstr]. 4th National Conference on Retroviruses and Opportunistic Infections, 1997, Washington DC.
54. Manion D, Merrill DP, Hirsch MS. Combination drug regimens against multidrug resistant Hiv-1 in vitro. 4th National Conference on Retroviruses and Opportunistic Infections, 1997, Washington DC.
55. Buss N. Saquinavir soft gel capsule (Fortovase): pharmacokinetics and drug interactions [abstr. 354]. 5th Conference on Retroviruses and Opportunistic Infections, February 1-5, 1998, Chicago, IL.
56. Bertz R, Foit C, Burt D, et al. Assessment of the multiple-dose pharmacokinetic interaction between Kaletra (lopinavir/ritonavir) and amprenavir in healthy volunteers [abstract 7.6]. 3rd International Workshop on Clinical Pharmacology of HIV Therapy, April 11-13, 2002, Washington DC.
57. Bertz RJ, Foit C, Ashbrenner E, et al. Effect of amprenavir on the steady-state pharmacokinetics of lopinavir/ritonavir in HIV+ and healthy subjects [abstract A1823]. 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy, September 27-30, 2002, San Diego, CA.
58. Wire MB, Naderer OJ, Masterman AL, et al. The pharmacokinetic interaction between GW433908 and lopinavir/ritonavir (APV10011 and APV10012) [abstract 612]. 11th Conference on Retroviruses and Opportunistic Infections, February 8-11, 2004, San Francisco CA.
59. Taburet AM, Raguin G, Le Tiec C, et al. Interactions between amprenavir and the lopinavir-ritonavir combination in heavily pretreated patients infected with human immunodeficiency virus. *Clinical Pharmacology and Therapeutics* 2004;75:310-23.
60. Wynn Vezina HE, Brundage RC, Bushman L, et al. Pharmacologic management of the drug-drug interaction between lopinavir/ritonavir and amprenavir [abstract 609]. 11th Conference on Retroviruses and Opportunistic Infections, February 8-11, 2004, San Francisco CA.
61. Solas C, Quinson AM, Couprie C, et al. Pharmacokinetic interaction between lopinavir/r and amprenavir in salvage therapy [abstract 440-W]. 9th Conference on Retroviruses and Opportunistic Infections, February 24-28, 2002, Seattle, WA.
62. Tseng A, Phillips E, Antoniou A, et al. Steady-state pharmacokinetics and tolerability of indinavir when co-administered with lopinavir/r in antiretroviral-experienced subjects [abstract 8.10]. 4th International Workshop on Clinical Pharmacology of HIV Therapy, March 27-29, 2003, Cannes, France.
63. Hsu A, Bertz R, Ashbrenner E, et al. Interaction of ABT-378/ritonavir with protease inhibitors in healthy volunteers [abstract 2.4]. First International Workshop on Clinical Pharmacology of HIV Therapy, March 30-31, 2000, Noordwijk, the Netherlands.
64. Bertz R, Foit C, Ashbrenner E, et al. Assessment of the steady-state pharmacokinetic interaction of lopinavir/ritonavir with either indinavir or saquinavir in healthy subjects [abstract A1822]. 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy, September 27-30, 2002, San Diego, CA.
65. Burger DM, Schmitz K, Schneider K, et al. Pharmacokinetics of lopinavir and reduced-dose indinavir as part of a salvage therapy regimen [abstract 8.2]. 4th International Workshop on Clinical Pharmacology of HIV Therapy, March 27-29, 2003, Cannes, France.
66. Isaac A, Taylor S, Cane P, et al. Lopinavir/ritonavir combined with twice-daily 400 mg indinavir: pharmacokinetics and pharmacodynamics in blood, CSF and semen. *Antimicrobial Agents and Chemotherapy* 2004;54(2):498-502.
67. Poirier J, Meynard J, Zouai O, et al. Lack of alteration of lopinavir and indinavir trough plasma concentrations in HIV-experienced patients treated with Kaletra and Crixivan [abstract]. 5th International Workshop on Clinical Pharmacology of HIV Therapy, April 1-3, 2004, Rome, Italy.

68. Klein C, Bertz R, Ashbrenner E, et al. Assessment of the multiple-dose pharmacokinetic interaction of lopinavir/ritonavir with nelfinavir [abstract 536]. 10th Conference on Retroviruses and Opportunistic Infections, February 10-14, 2003, Boston, MA.
69. Staszewski S, Dauer B, Stephan C, et al. Pharmacokinetic profile monitoring as an augmentation to therapy evaluation in patients taking a simple boosted double protease inhibitor regimen of lopinavir/r plus saquinavir without reverse transcriptase inhibitors [abstract 2.4]. 3rd International Workshop on Clinical Pharmacology of HIV Therapy, April 11-13, 2002, Washington DC.
70. Abel S, Russell D, Ridgway C, et al. Overview of the drug-drug interaction data for maraviroc (UK-427,857) [abstract 76]. 6th International Workshop on Clinical Pharmacology of HIV Therapy April 28-30, 2005, Quebec.
71. Kravcik S, Sahai J, Kerr B, et al. Nelfinavir mesylate (NFV) increases saquinavir-soft gel capsule (SQV-SGC) exposure in HIV+ patients. 4th National Conference on Retroviruses and Opportunistic Infections, 1997, Washington DC.
72. Slater L, Sension M, Feinberg J, et al. Fortovase BID regimens in HIV-1 infected patients: combination with 2 nucleoside analogs or with nelfinavir plus 1 nucleoside analogue [abstract 390]. 6th Conference on Retroviruses and Opportunistic Infections, January 31-February 4, 1999, Chicago IL.
73. Degen O, Kurowski M, Van Lunzen J, et al. Amprenavir and ritonavir: intraindividual comparison of different doses and influence of concomitant NNRTI on steady-state pharmacokinetics in HIV-infected patients [abstract 739]. 8th Conference on Retroviruses and Opportunistic Infections, February 4-8, 2001, Chicago IL.
74. Murphy R, Gagnier P, Lamson M, et al. Effect of nevirapine on pharmacokinetics of indinavir and ritonavir in HIV-1 patients [abstract 374]. 4th Conference on Retroviruses and Opportunistic Infections, January 22-26, 1997, Washington DC.
75. Crommentuyn KML, van Heeswijk RPG, Veldkamp AI, et al. Nevirapine once daily versus twice daily: implications for drug-drug interactions [abstract 1.11]. 2nd International Workshop on Clinical Pharmacology of HIV Therapy, April 2-4, 2001, Noordwijk, the Netherlands.
76. Skowron G, Leoung G, Kerr B, et al. Lack of pharmacokinetic interaction between nelfinavir and nevirapine. *AIDS* 1998;12(10):1243-4.
77. Vilaro J, Mascaro J, Colomer J, et al. The pharmacokinetics of combination therapy with nelfinavir plus nevirapine in HIV-positive patients [abstract A497]. 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, December 16-19, 2001, Chicago, IL.
78. Sahai J, Cameron W, Salgo M, et al. Drug interaction study between saquinavir (SQV) and nevirapine (NVP). 4th National Conference on Retroviruses and Opportunistic Infections, 1997, Washington DC.
79. Tibotec Inc. Edurant (rilpivirine) Product Monograph. Raritan, NJ 2011.
80. Glaxo Wellcome Inc. Agenerase Product Monograph. Mississauga, Ontario 2001.
81. Sadler BM, Piliero PJ, Preston SL, et al. Pharmacokinetic drug-interaction between amprenavir and ritonavir in HIV-seronegative subjects after multiple, oral dosing [abstract 77]. 7th Conference on Retroviruses and Opportunistic Infections, January 30-February 2, 2000, San Francisco.
82. Wood R, Trepo C, Livrozet JM, et al. Enhancement of pharmacokinetic parameters of amprenavir when combined with low dose ritonavir (APV 600 mg/RTV 100 mg BID) and preliminary efficacy results [P283]. 5th International Congress on Drug Therapy in HIV Infection October 22-26, 2000, Glasgow, Scotland: AIDS.
83. Garraffo R, Demarles D, Durant J, et al. Amprenavir plasma and intracellular concentrations when coadministered with ritonavir in twice and once daily regimen in HIV-infected patients [abstract A-489]. 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, December 16-19, 2001, Chicago, IL.
84. Wood R, Trepo C, Livrozet JM, et al. Amprenavir 600 mg/ritonavir 100 mg BID or APV 1200 mg/RTV 200 mg QD given in combination with abacavir and lamivudine maintains efficacy in ART- naive HIV-1-infected adults over 12 weeks (APV20001) [abstract 332]. 8th Conference on Retroviruses and Opportunistic Infections, February 4-8, 2001, Chicago IL.
85. Wire MB, Shelton MJ, Lou Y, et al. Ritonavir increases plasma amprenavir exposure to a similar extent when co-administered with either fosamprenavir or amprenavir (APV10022) [abstract A-450]. 44th Interscience Conference on Antimicrobial Agents and Chemotherapy, October 30-November 2, 2004, Washington, DC.

86. Hsu A, Granneman GR, Cao G, et al. Pharmacokinetic interaction between ritonavir and indinavir in healthy volunteers. *Antimicrobial Agents and Chemotherapy* 1998;42(11):2784-91.
87. Hsu A, Granneman GR, Heath-Chiozzi M, et al. Indinavir can be taken with regular meals when administered with ritonavir [abstract 22361]. 12th World AIDS Conference, June 28-July 3, 1998, Geneva, Switzerland.
88. Workman C, Whittaker W, Dyer W, et al. Combining ritonavir and indinavir decreases indinavir-associated nephrolithiasis [abstract 677]. 6th Conference on Retroviruses and Opportunistic Infections, January 31-February 4, 1999, Chicago IL.
89. Burger DM, Hugen PWH, Prins JM, et al. Pharmacokinetics of an indinavir/ritonavir 800/100mg BID regimen [abstract 363]. 6th Conference on Retroviruses and Opportunistic Infections, January 31-February 4, 1999, Chicago IL.
90. Van Heeswijk RPG, Veldkamp AI, Hoetelmans RMW, et al. The steady-state plasma pharmacokinetics of indinavir alone or in combination with ritonavir in twice daily dosing regimens in HIV-1 infected patients [abstract P55]. 4th International Congress of Drug Therapy in HIV Infection, November 7-12, 1998, Glasgow, Scotland.
91. Saah AJ, Winchell G, Seniuk M, et al. Multiple-dose pharmacokinetics and tolerability of indinavir ritonavir combinations in healthy volunteers [abstract 362]. 6th Conference on Retroviruses and Opportunistic Infections, January 31-February 4, 1999, Chicago IL.
92. O'Brien WA, Atkinson TA, Han X, et al. Combination therapy with indinavir and ritonavir in antiretroviral-experienced patients [abstract 2209]. 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, September 26-28, 1999, San Francisco, CA.
93. Lamotte C, Peytavin G, Perre P, et al. Increasing adverse events with indinavir dosages and plasma concentrations in four different ritonavir-indinavir containing regimens in HIV-infected patients [abstract 738]. 8th Conference on Retroviruses and Opportunistic Infections, February 4-8, 2001, Chicago IL.
94. Taylor S, Reynolds H, Drake SM, et al. A pharmacokinetic study of ritonavir 200 mg BID and indinavir 600 mg BID in plasma and semen of HIV-1 infected men [P278]. 5th International Congress on Drug Therapy in HIV Infection, October 22-26, 2000, Glasgow, Scotland: AIDS.
95. Peytavin G, Lamotte C, Ait-Mohand H, et al. Ritonavir-indinavir 100/400 mg BID: pharmacokinetic, efficacy and tolerance of a simple regimen in a prospective study in HIV-infected patients [abstract 3.15]. 2nd International Workshop on Clinical Pharmacology of HIV Therapy, April 2-4, 2001, Noordwijk, the Netherlands.
96. Saah AJ, Winchell G, Seniuk M, et al. Multiple-dose pharmacokinetics and tolerability of indinavir and ritonavir combinations in a once-daily regimen in healthy volunteers (Merck 089) [abstract 329]. 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, September 26-28, 1999, San Francisco, CA.
97. Burger DM, Hugen PWH, TerHofstede HJM, et al. Dose-finding study of a once daily indinavir/ritonavir regimen in healthy volunteers [abstract 321]. 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, September 26-28, 1999, San Francisco, CA.
98. Suleiman J, Rhodes R, Campo R, et al. Preliminary results from indinavir and ritonavir in a once-daily regimen (Merck 103/104) [abstract 336]. 8th Conference on Retroviruses and Opportunistic Infections, February 4-8, 2001, Chicago IL.
99. Yuen G, Anderson R, Daniels R, et al. Investigations of nelfinavir mesylate pharmacokinetic interactions with indinavir and ritonavir. 4th National Conference on Retroviruses and Opportunistic Infections, 1997, Washington DC.
100. Flexner C, Hsu A, Kerr B, et al. Steady-state pharmacokinetic interactions between ritonavir, nelfinavir, and the nelfinavir active metabolite M8 [abstract 42265]. 12th World AIDS Conference, June 28-July 3, 1998, Geneva, Switzerland.
101. Kurowski M, Kaeser B, Mroziekiewicz A, et al. The influence of low doses of ritonavir on the pharmacokinetics of nelfinavir 1250 mg BID [abstract 1639]. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, September 17-20, 2000, Toronto, Canada.
102. Aarnoutse RE, Droste JAH, van Oosterhout JGG, et al. Pharmacokinetics, food intake requirements and tolerability of once daily combinations of nelfinavir and low-dose ritonavir in healthy volunteers. *British Journal of Clinical Pharmacology* 2003;55:115-25.
103. Hoffmann-LaRoche Limited. Fortovase Product Monograph. Mississauga, Ontario 2001.

104. Kilby JM, Sfakianos G, Gizzi NA, et al. Safety and pharmacokinetics of once-daily regimens of soft-gel capsule saquinavir plus minidose ritonavir in human immunodeficiency virus-negative patients. *Antimicrobial Agents and Chemotherapy* 2000;44(10):2672-8.
105. Cardiello P, Monhaphol T, Mahanontharit A, et al. Pharmacokinetics of once daily saquinavir-hard gel caps and saquinavir-soft gel caps boosted with ritonavir in HIV-1+ Thai patients: HIV NAT001.4 substudy [abstract 1.2]. 3rd International Workshop on Clinical Pharmacology of HIV Therapy, April 11-13, 2002, Washington DC.
106. Ford J, Boffito M, Wildfire A, et al. Intracellular and plasma pharmacokinetics of saquinavir/ritonavir administered once daily in HIV-infected patients [abstract 601]. 11th Conference on Retroviruses and Opportunistic Infections, February 8-11, 2004, San Francisco CA.
107. Kurowski M, Sternfeld T, Hill A, et al. Comparative pharmacokinetics and short-term safety of twice daily Fortovase/ritonavir and Invirase/ritonavir [abstract 423-W]. 9th Conference on Retroviruses and Opportunistic Infections, February 24-28, 2002, Seattle, WA.
108. Merry C, Barry MG, Mulcahy FM, et al. Saquinavir pharmacokinetics alone and in combination with nelfinavir in HIV infected patients [abstr. 352]. 5th Conference on Retroviruses and Opportunistic Infections, February 1-5, 1998, Chicago, IL.
109. Merry C, Barry MG, Mulcahy F, et al. Saquinavir pharmacokinetics alone and in combination with nelfinavir in HIV-infected patients. *AIDS* 1997;11:F117-F20.
110. Gallicano K, Sahai J, Kravcik S, et al. Nelfinavir increases plasma exposure of saquinavir in hard gel capsule in HIV+ patients [abstr. 353]. 5th Conference on Retroviruses and Opportunistic Infections, February 1-5, 1998, Chicago, IL.
111. Squires K, Currier J, Clark R, et al. Final 48-week results of a phase II, randomized study of the safety, efficacy, and pharmacokinetics of BID vsTID nelfinavir and saquinavir in combination with lamivudine and stavudine in HIV-positive women (Women First Trial) [abstract 330]. 8th Conference on Retroviruses and Opportunistic Infections, February 4-8, 2001, Chicago IL.
112. Kurowski M, Walli R, Breske A, et al. Coadministration of tenofovir 300 mg QD with fosamprenavir/ritonavir 1400/100 mg QD or 1400/200 mg QD does not affect amprenavir pharmacokinetics [abstract 10]. 6th International Workshop on Clinical Pharmacology of HIV Therapy April 28-30, 2005, Quebec.
113. Peytavin G, Marcelin AG, Rouault a, et al. Plasma concentrations of amprenavir, ritonavir and tenofovir in HIV-infected patients treated with fosamprenavir/ritonavir (700/100 mg BID) and tenofovir 300 mg QD containing regimens [abstract 32]. 6th International Workshop on Clinical Pharmacology of HIV Therapy April 28-30, 2005, Quebec.
114. Kearney BP, Flaherty J, Wolf J, et al. Lack of clinically relevant drug-drug interactions between tenofovir DF and efavirenz, indinavir, lamivudine, and lopinavir/ritonavir in healthy subjects [abstract P171]. 8th European Conference on Clinical Aspects and Treatment of HIV Infection, October 28-31, 2001, Athens.
115. Kruse G, Esser S, Stocker H, et al. Tenofovir does not Impair the pharmacokinetics of nelfinavir in HIV-infected patients [A-446]. 44th Interscience Conference on Antimicrobial Agents and Chemotherapy, October 30-November 2, 2004, Washington, DC.
116. Ananworanich J, Siangphoe U, Mahanontharit A, et al. Saquinavir Cmin before and after switching NRT to tenofovir in patients treated with once daily saquinavir-hard gel capsule/ritonavir 1600/100 mg [abstract]. 5th International Workshop on Clinical Pharmacology of HIV Therapy, April 1-3, 2004, Rome, Italy.
117. Boffito M, D'Avolio A, Di Perri G, et al. Repeated pharmacokinetics of tenofovir disoproxil fumarate in HIV-infected adults receiving saquinavir hard gel/ritonavir 1000/100 mg BID [abstract]. 5th International Workshop on Clinical Pharmacology of HIV Therapy, April 1-3, 2004, Rome, Italy.
118. Zong J, Chittick G, Blum MR, et al. Pharmacokinetic assessment of tenofovir DF and ritonavir-boosted saquinavir in healthy subjects [A-444]. 44th Interscience Conference on Antimicrobial Agents and Chemotherapy, October 30-November 2, 2004, Washington, DC.
119. Leith J, Walmsley S, Katlama C, et al. Pharmacokinetics and safety of tipranavir/ritonavir alone or in combination with saquinavir, amprenavir, or lopinavir: interim analysis of BI1182.51 [abstract]. 5th International Workshop on Clinical Pharmacology of HIV Therapy, April 1-3, 2004, Rome, Italy.

120. Sansone A, Keung A, Tetteh E, et al. Pharmacokinetics of vicriviroc are not affected in combination with five different protease inhibitors boosted by ritonavir [abstract 582]. 13th Conference on Retroviruses and Opportunistic Infections, February 5-8, 2006, Denver, CO.
121. Sadler BM, Gillotin C, Chittick GE, et al. Pharmacokinetic drug interactions with amprenavir [abstract 12389]. 12th World AIDS Conference, June 28-July 3, 1998, Geneva, Switzerland.
122. Agouron Pharmaceuticals Canada Ltd. Viracept Product Monograph. 2000.
123. Hoffmann-LaRoche Limited. Invirase Product Monograph. Mississauga, Ontario, Canada 1997.
124. Glesby MJ, Aberg JA, Kendall MA, et al. Pharmacokinetic interactions between indinavir plus ritonavir and calcium channel blockers. *Clin Pharmacol Ther* 2005;78(2):143-53.
125. Stone JA, Migoya EM, Hickey L, et al. Potential for interactions between caspofungin and nelfinavir or rifampin. *Antimicrob Agents Chemother* 2004;48:4306-14.
126. Brophy DF, Israel DS, Pastor A, et al. Pharmacokinetic interaction between amprenavir and clarithromycin in healthy male volunteers. *Antimicrobial Agents and Chemotherapy* 2000;44(4):978-84.
127. Amsden GW, Foulds G. The pharmacokinetics of azithromycin and nelfinavir when co-administered in healthy volunteers [abstract 1651]. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, September 17-20, 2000, Toronto, Canada.
128. Phillips EJ, Rachlis AR, Ito S. Digoxin toxicity and ritonavir: a drug interaction mediated through p-glycoprotein? *AIDS* 2003;17(10):1577-8.
129. Kerr B, Yuen G, Daniels R, et al. Strategic approach to nelfinavir mesylate (NFV) drug interactions involving CYP3A metabolism. 4th National Conference on Retroviruses and Opportunistic Infections, 1997, Washington DC.
130. Merck Frosst Canada Ltd. Crixivan (indinavir) Prescribing Information. Kirkland, QC 2004.
131. Boffito M, Trentini L, Raiteri R, et al. Pharmacokinetic enhancement of saquinavir by cimetidine: an alternative booster to ritonavir? [abstract 2.8]. 3rd International Workshop on Clinical Pharmacology of HIV Therapy, April 11-13, 2002, Washington DC.
132. Robertson S, Davey RT, Voell J, et al. Effect of Ginkgo biloba extract on lopinavir, midazolam and fexofenadine pharmacokinetics in healthy subjects. *Curr Med Res Opin* 2008 Feb;24(2):591-9.
133. Wiegman D-J, Brinkman K, Franssen E.J.F. Interaction of Ginkgo biloba with efavirenz. *AIDS* 2009;23:1184-5.
134. Hsyu PH, Schultz-Smith MD, Lillibridge JH, et al. Pharmacokinetic interactions between nelfinavir and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors atorvastatin and simvastatin. *Antimicrobial Agents and Chemotherapy* 2001;45:3445-50.
135. Fichtenbaum C, Gerber J, Rosenkranz S, et al. Pharmacokinetic interactions between protease inhibitors and statins in HIV-seronegative volunteers: ACTG Study A5047. *AIDS* 2002;16(4):569-77.
136. Merck & Co. Inc. Crixivan (indinavir) Prescribing Information. Whitehouse Station, NJ 2003.
137. Cardiello P, Samor T, Burger D, et al. Pharmacokinetics of lower doses of saquinavir soft gel caps (800- and 1200-mg BID) with itraconazole compared to 1400 mg SQV BID without itra in HIV-1+ Thai patients [abstract 447-W]. 9th Conference on Retroviruses and Opportunistic Infections, February 24-28, 2002, Seattle, WA.
138. Polk RE, Crouch M, Israel DS, et al. Pharmacokinetic interaction between ketoconazole and amprenavir after single doses in healthy men. *Pharmacotherapy* 1999;19(12):1378-84.
139. Lanzafame M, Trevenzoli M, Faggian F, et al. Interaction between levothyroxine and indinavir in a patient with HIV infection. *Infection* 2002;30:54-5.
140. Schippers EF, Hugen PW, den Hartigh J, et al. No drug-drug interaction between nelfinavir or indinavir and mefloquine in HIV-1-infected patients. *AIDS* 2000;14(17):2794-5.

141. Hendrix C, Wakeford J, Wire MB, et al. Pharmacokinetic and pharmacodynamic evaluation of methadone enantiomers following co-administration with amprenavir in opioid-dependent subjects [abstract 1649]. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, September 17-20, 2000, Toronto, Canada.
142. Cantilena L, et al. Lack of a pharmacokinetic interaction between indinavir and methadone [abstract PI-74]. *Clinical Pharmacology and Therapeutics* 1999;65(2):135.
143. Beauverie P, Taburet AM, Dessalles MC, et al. Therapeutic drug monitoring of methadone in HIV-infected patients receiving protease inhibitors. *AIDS* 1998;12(18):2510-1.
144. Hsyu PH, Lillibridge JH, Maroldo L, et al. Pharmacokinetic and pharmacodynamic interactions between nelfinavir and methadone [abstract 87]. 7th Conference on Retroviruses and Opportunistic Infections, January 30-February 2, 2000, San Francisco.
145. Smith PF, Booker BM, Difrancesco R, et al. Effect of methadone or LAAM on the pharmacokinetics of nelfinavir & M8 [abstract A-491]. 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, December 16-19, 2001, Chicago, IL.
146. Piscitelli S, Formentini E, Burstein AH, et al. Effect of milk thistle on the pharmacokinetics of indinavir in healthy volunteers. *Pharmacotherapy* 2002;22(5):551-6.
147. Martorell J, Brunet M, García F, et al. Mycophenolate mofetil lowers plasma nevirapine concentrations but has no effect on intracellular triphosphate concentrations [abstract 539]. 10th Conference on Retroviruses and Opportunistic Infections, February 10-14, 2003, Boston, MA.
148. Cohn SE, Park JG, Watts DH, et al. Depo-medroxyprogesterone in women on antiretroviral therapy: effective contraception and lack of clinically significant interactions. *Clin Pharmacol Ther* 2007;81(2):222-7.
149. Frohlich M, Burhenne J, Martin-Facklam M, et al. Oral contraception does not alter single dose saquinavir pharmacokinetics in women. *British Journal of Clinical Pharmacology* 2004;57(3):244-52.
150. Loulergue P, Gaillard R, Mir O. Interaction involving tadalafil and CYP3A4 inhibition by ritonavir. *Scand J Infect Dis* 2011;43(3):239-40.
151. Eli Lilly Canada Inc. Cialis (tadalafil) Product Monograph. Toronto, ON 2009.
152. Bayer Inc. Levitra (vardenafil) Product Monograph. Toronto, ON 2011.
153. Rublein JC, Donovan BJ, Hollowell SB, et al. Effect of omeprazole on the plasma concentrations of indinavir in HIV-negative subjects [abstract A-1611]. 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, September, 2003, Chicago.
154. Fang A, Damle BD, Labadie R, et al. Omeprazole significantly decreases nelfinavir systemic exposure in healthy subjects [abstract A-0384]. 46th Interscience Conference on Antimicrobial Agents and Chemotherapy September 27-30 2006, San Francisco, CA.
155. Winston A, et al. E. Effect of omeprazole on the pharmacokinetics of saquinavir 500 mg formulation with ritonavir in healthy male and female volunteers [abstract 4.3/16]. 10th European AIDS Conference, November 17-20, 2005, Dublin.
156. Yan J, Marino MR, Smith RA, et al. The effect of ravuconazole on the pharmacokinetics of nelfinavir in healthy male volunteers. *J Clin Pharmacol* 2006;46:193-200.
157. Polk RE, Brophy DF, Israel DS, et al. Pharmacokinetic Interaction between amprenavir and rifabutin or rifampin in healthy males. *Antimicrobial Agents and Chemotherapy* 2001;45(2):502-8.
158. Centers for Disease Control and Prevention. Updated guidelines for the use of rifamycins for the treatment of tuberculosis among HIV-infected patients taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors [version 1.20.04]. *Morbidity and Mortality Weekly Report* 2004 January 23;53(2):37.
159. Jenny-Avital ER, Joseph K. Rifamycin-resistant Mycobacterium tuberculosis in the highly active antiretroviral therapy era: a report of 3 relapses with acquired rifampin resistance following alternate-day rifabutin and boosted protease inhibitor therapy. *Clin Infect Dis* 2009;48:1471-4.

160. Centers for Disease Control and Prevention. Updated guidelines for the use of rifabutin or rifampin for the treatment and prevention of tuberculosis among HIV-infected patients taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors. *Morbidity and Mortality Weekly Report* 2000;49(9):185-9.
161. Hamzeh FM, Benson CA, Gerber JG, et al. Steady-state pharmacokinetic interaction of modified-dose indinavir and rifabutin. *Clinical Pharmacology and Therapeutics* 2003;73(3):159-69.
162. Kerr BM, Daniels R, Clendeninn N. Pharmacokinetic interaction of nelfinavir with half-dose rifabutin [abstract B203]. 8th Annual Canadian Conference on HIV/AIDS Research, May 1-4, 1999, Victoria, BC.
163. Sahai J, Stewart F, Swick L, et al. Rifabutin reduces saquinavir plasma levels in HIV-infected patients [abstract A027]. 36th Interscience Conference on Antimicrobial Agents and Chemotherapy, 1996, New Orleans.
164. Gallicano K, Khaliq Y, Seguin I, et al. A pharmacokinetic study of intermittent rifabutin dosing with a combination of ritonavir and saquinavir in HIV patients [abstract B204]. 8th Annual Canadian Conference on HIV/AIDS Research, May 1-4, 1999, Victoria, BC.
165. de Gast M, Burger D, van Crevel R, et al. Double trouble: a pharmacokinetic study of indinavir/ritonavir (800 +100 mg BID) and rifampin for patients co-infected with TB and HIV [abstract 1.10]. 2nd International Workshop on Clinical Pharmacology of HIV Therapy, April 2-4, 2001, Noordwijk, the Netherlands.
166. Justesen U, Andersen A, Klitgaard N, et al. Pharmacokinetic interaction between rifampin and the twice-daily combination of indinavir and low-dose ritonavir in HIV-infected patients [abstract 542]. 10th Conference on Retroviruses and Opportunistic Infections, February 10-14, 2003, Boston, MA.
167. Avihingsanon A, van der Lugt J, Singphore U, et al. Pharmacokinetics Safety and 24 weeks efficacy of ritonavir-boosted indinavir (600/100 mg BID) in HIV/TB co-infected Thai patients receiving rifampin [abstract TUPEB144]. 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention, July 19-22, 2009, Capetown, South Africa.
168. Bergshoeff AS, Wolfs TFW, Geelen SPM, et al. Favourable nelfinavir pharmacokinetics during rifampin use by coadministration of ritonavir: case report [abstract 1.13]. 2nd International Workshop on Clinical Pharmacology of HIV Therapy, April 2-4, 2001, Noordwijk, the Netherlands.
169. Veldkamp AI, Hoetelmans RMW, Beijnen JH, et al. Ritonavir enables continued therapy with rifampin and saquinavir. *Clinical Infectious Diseases* 1999;29:1586.
170. Ribera E, Azuaje C, Montero F, et al. Saquinavir, ritonavir, didanosine, and lamivudine in a once daily regimen for HIV infection in patients with rifampin-containing antituberculosis treatment [abstract ThPeB7280]. XIV International AIDS Conference, July 7-12, 2002, Barcelona, Spain.
171. Nandwani R, Gourlay Y. Possible interaction between sildenafil and HIV combination therapy [letter]. *Lancet* 1999;353:840.
172. Merry C, Barry MG, Ryan M, et al. Interaction of sildenafil and indinavir when co-administered to HIV-positive patients. *AIDS* 1999;13(15):101-07.
173. Bratt G, Stahle L. Sildenafil does not alter nelfinavir pharmacokinetics. *Therapeutic Drug Monitoring* 2003;25(2):240-2.
174. Muirhead GJ, Wulff MB, Fielding A, et al. Pharmacokinetic interactions between sildenafil and saquinavir/ritonavir. *British Journal of Clinical Pharmacology* 2000;50:99-107.
175. Purkins L, Wood N, Kleinermans D, et al. No clinically significant pharmacokinetic interactions between voriconazole and indinavir in healthy volunteers. *British Journal of Clinical Pharmacology* 2003;56(Suppl 1):62-8.
176. Gatti G, Alessandrini A, Camera M, et al. Influence of indinavir and ritonavir on warfarin anticoagulant activity [letter]. *Aids* 1998;12(7):825-6.
177. Garcia B, De Juana P, Bermejo T, et al. Sequential interaction of ritonavir and nelfinavir with acenocoumarol [abstract 1069]. 7th European Conference on Clinical Aspects and Treatment of HIV Infection, October 23-27, 1999, Lisbon, Portugal.
178. Darlington MR. Hypoprothrombinemia during concomitant therapy with warfarin and saquinavir [letter]. *Annals of Pharmacotherapy* 1997;31(5):647.

