

DRUG INTERACTIONS WITH NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

	Delavirdine (Rescriptor®)	Efavirenz (Sustiva®)	Etravirine (Intence®)	Nevirapine (Viramune®)	Rilpivirine (Edurant®)
Usual Dose	400 mg po TID; 600 mg BID under study	600 mg po daily at bedtime.	200 mg BID following a meal	200 mg po BID (lead-in dosing of 200 mg daily for first 14 days)	25 mg QD following a meal
Kinetic Characteristics	pH-dependent oral absorption; highly protein bound; metabolized via CYP3A4; also inhibits 3A4, as well as 2C9, 2C19. ¹	In vitro is a potent inducer and inhibitor of CYP3A4. Efavirenz induces 2B6 ² and UGT1A1. ³ Also inhibits CYP2C9, 2C19. Substrates of CYP3A4 should be monitored carefully for effect and toxicity when used in combination with efavirenz. ³	Etravirine is a substrate of CYP3A4, CYP2C9, and CYP2C19. Etravirine is a weak inducer of CYP3A4, weak inhibitor of CYP2C9 and a moderate inhibitor of CYP2C19. Etravirine also inhibits p- glycoprotein. Etravirine has no clinically relevant effect on CYP1A2 or CYP2D6. ^{4,5}	Substrate and potent inducer of CYP3A4 and 2B6 enzymes. ²	Metabolized primarily by CYP3A4, as well as CYP2C19, 1A2, 2C8/9/10 (minor). Moderate inducer of CYP2C19, slight inducer of CYP1A2, 2B6 and 3A4. A clinically relevant effect on CYP enzyme activity is considered unlikely with 25 mg dose. ^{6,7} No effect on CYP2E1 activity. ⁸
Food	May take with or without a meal (based on steady state studies). ¹	May be administered with or without food. ³	The effect of different types of food on the bioavailability of single dose etravirine 100 mg was examined in 24 healthy volunteers. Fasted State: etravirine AUC ↓ 51% compared to a standard breakfast. Light Breakfast (Croissant): AUC ↓ 20% compared to a standard breakfast. Enhanced Fiber Breakfast: AUC ↓ 25% compared to a standard breakfast. High Fat Breakfast (70g): AUC ↑ 9% compared to a standard breakfast. Recommendations: Give etravirine following a meal; the type of meal is not important. ⁹	May be administered with or without food or antacids. ²	The effect of different types of food on the bioavailability of single dose rilpivirine 75 mg tablet was examined in 20 healthy subjects. Fasting conditions: rilpivirine Cmax ↓ 46%, AUC ↓ 43% compared to standard breakfast (21 g fat, 533 kcal). Protein rich nutritional drink (8 g fat, 300 kcal): similar exposures to fasting conditions (Cmax & AUC ↓ 50% compared to standard breakfast). High Fat Breakfast (56 g fat, 928 kcal): rilpivirine Cmax ↓ 8%, AUC ↓ 8% compared to standard breakfast. Recommendations : Give rilpivirine with food (standard or high fat meal). Do not give rilpivirine on an empty stomach or with a protein rich

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Cranberry juice		<p>Prospective, observational, cross-sectional study in HIV-positive patients (n=120) on ARVs for at least 12 weeks, and reporting current cranberry juice intake (median 237 mL once-twice daily for median 4.5 years) or no cranberry juice intake.</p> <p>No significant difference in efavirenz levels in patients on efavirenz +/- cranberry juice. EFV Cmin: EFV alone group: 2099 ng/ml, n=3; EFV + Cranberry juice group: 3948ng/ml, n=3¹¹</p>			nutritional drink. ¹⁰

INTERACTIONS WITH ANTIRETROVIRALS:

Amprenavir (see separate entry for Fosamprenavir)	<p>Amprenavir 1200 mg +/- delavirdine 600 mg BID (healthy volunteer study) significantly increased amprenavir concentrations (4-fold ↑ AUC, 6-fold ↑ Cmin, 1.3 fold ↑ Cmax); no change in delavirdine concentrations.¹</p> <p>In a separate healthy volunteer multi-dose study, administration of APV 600 mg BID +/- DLV 600 mg BID resulted in ↑ APV Cmin 133% & AUC 117%; however, median DLV Cmin ↓ 88%. Suggest avoiding this dosage combination until further data available.¹²</p>	<p>APV 1200 mg BID + EFV 600 mg: 36% ↓ AUC, 39% ↓ Cmax, 43% ↓ Cmin APV; 15% ↑ EFV AUC¹³. Avoid negative interaction by adding either:</p> <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.¹⁴ <p>Other dosage combinations that yielded stable APV conc.:</p> <ul style="list-style-type: none"> • APV 600 mg/ rtv 200 mg BID + EFV¹⁵ • APV 1200 mg/ rtv 300 mg QD plus EFV¹⁶ • APV/EFV + NFV 1250 mg BID¹⁷ • APV/EFV + IDV 		<p>With APV 600/RTV 100 mg BID/NVP 400 mg QD, APV Cmin and Cmax ↓ 80%, AUC ↓ 77%. APV plasma levels stable with APV 450/RTV 200 mg BID plus NVP 400 mg daily.¹⁸ Therefore, recommend APV 450/RTV 200 mg BID with NNRTIs.</p>	
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		1200 mg BID¹⁷ • APV/EFV + RTV 100 mg BID¹⁷			
Atazanavir (ATV) Take with a light meal for improved absorption.		<p>Study in healthy subjects of ATV 400 QD +/- efavirenz 600 mg QD with a light meal (n=27): ATV Cmax ↓ 59% and AUC ↓ 74% with concomitant EFV; EFV kinetics not significantly altered.¹⁹</p> <p>In a healthy volunteer study, coadministration of atazanavir 300/ritonavir 100 mg QD plus efavirenz x 2 weeks resulted in 39% ↑ atazanavir AUC vs. atazanavir 400 mg QD alone, while ATV 600 mg QD plus efavirenz resulted in 21% ↓ ATV AUC vs. ATV 400 mg QD alone.²⁰</p> <p>In healthy subjects, ATV 400/ ritonavir 100 mg QD plus EFV results in ATV AUC and Cmax comparable to ATV/r 300/100 alone, but ATV Cmin ↓ 42%. ATV Cmin may not be optimal for treatment experienced patients. RTV Cmax ↓ 15%, AUC ↓ 31%, Cmin ↓ 60% with combination, which may have contributed to lower ATV exposures.²¹</p> <p>Manufacturer recommends using atazanavir 400 mg/ritonavir 100 mg with efavirenz for treatment-naïve patients. This combination should</p>	<p><u>Atazanavir/cobicistat:</u> Coadministration is not recommended due to potential for reductions in atazanavir and cobicistat exposures and possible loss of therapeutic effect.²³</p> <p><u>Atazanavir/ritonavir:</u> May coadminister without dose adjustments. Unboosted atazanavir should not be given with etravirine.⁴</p> <p>In healthy subjects (n=14), ATV 400 mg QD administered with etravirine 800 mg BID (old formulation) for 7 days resulted in 47% ↑ Cmax, 50% ↑ AUC and 58% ↑ Cmin of TMC125, while atazanavir AUC ↓ 17% and Cmin ↓ 47%.²⁴ Combination of unboosted atazanavir and etravirine is not recommended.⁴</p> <p>In healthy subjects, ATV 300/rtv 100 mg QD plus TMC125 800 mg BID (old formulation) led to 100% ↑ AUC and 26% ↑ Cmin of etravirine, while atazanavir AUC ↓ 14% and Cmin ↓ 38%.²⁴</p> <p>HIV-infected subjects on stable ATV 300/100 mg</p>	<p><u>Atazanavir/cobicistat:</u> Coadministration is contraindicated due to potential for substantial reductions in atazanavir exposures and possible loss of therapeutic effect. Potential risk for nevirapine-associated adverse reactions due to increased nevirapine exposures.²³</p> <p><u>Atazanavir/ritonavir:</u> In an open-label cohort study of HIV+ subjects stable on 2-3 NRTIs and either NVP 200 mg BID or ATV 300/rtv 100 mg QD, the NVP group received NVP plus ATV 300/100 mg QD for 10 days, then NVP plus ATV 400/100 mg QD for 10 days. Compared to the group that continued ATV 300/100 mg QD alone (mean ATV Cmin 533 ng/mL):</p> <ul style="list-style-type: none"> • NVP plus ATV/r 300/100mg daily led to ↓ Cmax 38%, ↓ AUC 42%, ↓ Cmin 72% of ATV (mean Cmin 150 ng/mL). • NVP plus ATV/r 400/100mg daily led to 19% ↓ AUC and 59% ↓ Cmin of ATV (mean Cmin 216 ng/mL). These ATV 	<p>Potential for ↑ concentrations of rilpivirine. Rilpivirine is not expected to affect the plasma concentrations of co-administered PIs.⁷</p>

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		be avoided in treatment-experienced patients. ²²	QD regimens (not including tenofovir) were randomized to receive either ATV 300/100 mg QD or 400/100 mg QD with etravirine 200 mg BID. In the presence of etravirine, ATV 300/100 mg dosing led to 4% ↓ AUC and 18% ↓ Cmin of atazanavir, and 1.24-fold ↑ etravirine AUC*. In ATV 400/100 mg group, there was no change in AUC and 9% ↓ Cmin of atazanavir while etravirine AUC* was ↓ 16% with coadministration. These changes were smaller than interaction observed previously in healthy volunteers. ²⁵ *NB: etravirine concentrations were compared to historical data from the DUET studies where etravirine was administered with darunavir/r BID.	values were higher than historical ATV 400 mg QD alone. RTV AUC ↓ 40% in presence of NVP, which may have contributed to ↓ ATV levels, while ATV/r increased NVP AUC by 25%. ²⁶ Open label, multiple dose study in HIV infected patients (n=11) to study the kinetics of ATV/r 300mg/100mg +/- NVP 200mg BID. Combination led to: • ↓ ATV levels: ↓ Ctrough 41% (631 vs 316ng/ml); ATV Ctrough remained higher than historical controls taking ATV 400mg daily • ↑ NVP Ctrough 12 (GMR 1.46) compared to historical controls not taking ATV/r. Monitoring ATV Cmin is recommended, and a dose increase in ATV may be necessary. ²⁷	
Darunavir		Multidose study of efavirenz 600 mg QD plus darunavir (oral solution) 300 mg/ritonavir 100 mg BID led to 31% ↓ Cmin and 13% ↓ AUC of darunavir, while EFV exposure ↑ 20%. Combination may be used without dose adjustments. ²⁸ In a single sequence, 3-period PK study in healthy volunteers who received DRV 900/r100 mg QD x 10d, DRV/r + EFV	<u>Darunavir/cobicistat</u> : coadministration is not recommended. ³⁰ <u>Darunavir/ritonavir</u> : Combination may be coadministered without dose adjustment. ⁴ Pharmacokinetic interaction study of etravirine 200 mg BID added to darunavir 600/100 mg BID in HIV-infected subjects (n=10) led to ~30% ↓ AUC of etravirine compared to	<u>Darunavir/cobicistat</u> : coadministration is not recommended. ³⁰ <u>Darunavir/ritonavir</u> : No dose adjustment is currently recommended, but literature indicates that changes in plasma NVP levels can lead to significant toxicity concerns, including hepatotoxicity. Monitor closely for dose-related nevirapine toxicity. ³⁵	In a randomized, crossover study in healthy volunteers, subjects received either rilpivirine 150mg daily for 22 days, or darunavir 800/100mg QD for 11 days followed by DRV 800/100mg QD plus rilpivirine 150mg QD from days 12-22. Co-administration of DRV/r increased exposures of rilpivirine: AUC _{24h} ↑ 2.3 fold; C _{max} ↑ 1.79 fold, C _{min} ↑ 2.78 fold, likely a result of CYP3A4

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		<p>600 mg QD x 14d, then EFV x 14 d):</p> <ul style="list-style-type: none"> • 57% ↓ Cmin, 14% ↓ AUC of darunavir • Mean 1138 vs. 2127 ng/mL, p=0.0003; all Cmin>55 ng/mL • No difference in EFV PK <p>Clinical significance in HIV-positive patients not yet determined, combination may provide sufficient efficacy in naïve-patients with no pre-existing mutations.²⁹</p>	<p>historical controls, not considered clinically significant. Kinetics of darunavir were unchanged.³¹ Similar interaction observed in healthy subjects.³²</p> <p>A pharmacokinetic substudy was conducted in 10 HIV-positive subjects participating in the ANRS TRIO study. Patients received raltegravir 400 mg BID and darunavir 600/100 mg BID on day 1, and etravirine 200 mg BID was added on day 7. PK parameters were measured on days 6 and 28. Raltegravir and darunavir PK (Cmax, Cmin and AUC) were not significantly different in the presence of etravirine.³³</p> <p>In a phase II single arm study, ARV-naïve HIV-infected subjects received etravirine 400 mg QD, darunavir 800/100 mg QD, or the combination (plus tenofovir/FTC) each for 14 days. There was no change in ETV pk in the presence of DRV/r. Mean ETV Cmin was >50x higher than protein-adjusted EC50 for WT virus, with and without DRV/r. DRV pk was slightly higher and RTV was slightly lower vs. historical controls (ARTEMIS week 4 pk</p>	<p>In an open-label, randomized, crossover study, 19 HIV-positive subjects received nevirapine 200 mg BID plus NRTIs with or without darunavir (either 300/100 mg BID DRV oral solution or 400/100 mg BID DRV tablet) in two 14-day sessions. In the presence of DRV/r, NVP AUC ↑ 27%, while DRV and RTV exposures were similar to historical data.³⁶</p> <p>In a population cohort analysis of 51 HIV-infected patients taking nevirapine (n=42 with other NRTIs, n=9 on concomitant darunavir/ritonavir), nevirapine Ctrough were 45% higher in the group taking darunavir/ritonavir vs. those on NRTIs only (p<0.05).³⁷</p>	<p>inhibition. No clinically relevant changes in DRV exposure were observed in the presence of rilpivirine.³⁸</p> <p>No dose adjustment is required with coadministration.⁷</p>

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Darunavir/rtv + maraviroc			<p>substudy).³⁴</p> <p>Co-administration of etravirine/darunavir/ritonavir with maraviroc increased the exposure of maraviroc by 210% (AUC₁₂) and peak levels (C_{max}) by 77% compared to maraviroc alone.</p> <p>Thus, if maraviroc is being dosed alongside etravirine and darunavir together, a maraviroc dose reduction to 150mg twice daily is necessary. No dose adjustment of ETV is necessary.</p>		
Didanosine	37% ↓ DLV Cmax, 22% ↓ ddl concentration; thus, administer 1 hour before ddl if possible. ⁶	No effect on EFV concentrations when administered with 30 mL Mylanta DS (AlOH, MgOH, simethicone); ⁷ therefore, ddl buffer should not affect EFV concentrations.	In a crossover study of healthy volunteers, no clinically relevant interaction was observed between etravirine 800 mg BID with food and ddl-EC 400 mg QD (given 2 hours before etravirine on an empty stomach). No dosage adjustments required for combination. ³⁹	May be administered together. ²	No dose adjustment is required. However, didanosine should be administered on an empty stomach at least 2 hours before or 4 hours after rilpivirine, which should be administered after a meal. ⁷
Dolutegravir (DTG)		In an open-label, single sequence crossover study, healthy volunteers received dolutegravir 50 mg once daily for 5 days followed by DTG 50 mg and efavirenz 600 mg QD for 14 days. In the presence of efavirenz, DTG AUC ↓ 57%, Cmax ↓ 39% and Ctrough ↓ 75%, likely via enzyme induction of UGT1A1 and CYP3A4. Dolutegravir concentrations remained 4-5 fold higher than the	<p>In an open-label, two-period, crossover study, healthy adult subjects received dolutegravir 50 mg QD for 5 days, then added etravirine 200 mg BID with food for 14 days. In the presence of etravirine, dolutegravir AUC ↓ 70%, Cmax ↓ 52% and Ctrough ↓ 88%.</p> <p>In a second randomized, open-label crossover study, healthy subjects began with dolutegravir 50 mg QD for 5 days, then</p>	In 10 adult HIV-infected subjects on stable abacavir/3TC and nevirapine 400 mg daily, dolutegravir 50 mg daily was added for 5 days; nevirapine was then discontinued while dolutegravir continued to be administered with abacavir/3TC for 2 weeks. Dolutegravir exposures were significantly reduced (19% ↓ AUC, 34% ↓ Ctrough) with coadministration of nevirapine. No	In an open-label, two-cohort, single sequence crossover study, healthy subjects, received either DTG 50mg daily for 5days or S/GSK1265744 30mg daily for 12 days (Period 1), rilpivirine 25 mg daily for 11-12 days (Period 2) and rilpivirine 25 mg daily plus DTG 50 mg daily or S/GSK1265744 30 mg daily for 12 days (Period 3); all doses were administered following a moderate fat meal. The combinations of

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		<p>protein-adjusted IC90 for WT virus.⁴⁰</p> <p>A dose adjustment to dolutegravir 50 mg BID is recommended in treatment-naïve or treatment-experienced, INSTI-naïve patients. Alternative combinations that do not include metabolic inducers should be considered where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.⁴¹</p> <p>In pharmacokinetic simulation models, dolutegravir and efavirenz concentrations were predicted following a switch from efavirenz 600 mg daily to dolutegravir 50 mg daily. Following the switch, efavirenz concentrations stayed above the MEC up to 3 days and dolutegravir Ctrough achieved MEC 3 days post switch. Since dolutegravir Ctrough achieved MEC before efavirenz concentrations fell below MEC, dolutegravir 50 mg QD may be initiated immediately following efavirenz discontinuation.⁴²</p>	<p>added etravirine 200 mg BID plus either lopinavir/ritonavir 400/100 mg BID or darunavir 600/100 mg BID for 14 days. Dolutegravir kinetics were not significantly altered when given with etravirine plus lopinavir/ritonavir. When coadministered with etravirine plus darunavir/ritonavir, dolutegravir AUC ↓ 25%, Cmax ↓ 12% and Ctrough ↓ 37%. These changes were considered not clinically significant.⁴³</p> <p>Dolutegravir may be coadministered with etravirine without a dosage adjustment if atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir is concurrently administered.⁴¹</p>	<p>dosing recommendations were provided by the investigators, but dolutegravir 50 mg BID could be considered.⁴⁴</p> <p>NB: currently, the dolutegravir product monograph states that coadministration with nevirapine should be avoided because there are insufficient data to make dosing recommendations.⁴¹</p>	<p>RPV + DTG and RPV + S/GSK1265744 were well-tolerated and no significant changes in the PK parameters of any drug were observed.⁴⁵</p>
Efavirenz			Steady-state efavirenz 600 mg QD plus single-dose etravirine 900 mg resulted in 41% ↓	Combination of nevirapine 400 mg daily plus efavirenz 600 mg daily in HIV-infected individuals	In HIV infected patients on steady state efavirenz, administration of a single dose of

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			<p>AUC and 18% ↓ Cmax of etravirine.⁴⁶ Etravirine and other NNRTIs should not be co-administered.⁴</p> <p>In a healthy volunteer study, etravirine was administered 400 mg QD or 200 mg BID for 14 days at baseline and then again after 14 days of efavirenz treatment to assess for any continued effects of efavirenz enzyme induction on etravirine metabolism. Steady-state ETV parameters were significantly reduced after EFV intake in both QD and BID dosing arms: ETV AUC ↓ 28-29%, Cmax ↓ 21-22%, Ctrough ↓ 33-37%. These changes are likely not clinically significant as all subjects had ETV levels well above 4 ng/mL (protein binding-adjusted EC50) and ETV concentrations are comparable to those observed in clinical trials where ETV was co-administered with darunavir/ritonavir. Therefore, authors suggest that switching from EFV to ETV QD or BID may be done without dose adjustment.⁴⁷</p>	<p>resulted in reduced efavirenz concentrations (22% ↓ AUC, 36% ↓ Cmin); nevirapine levels were not changed. Thus, may need to administer higher doses of efavirenz (e.g., 800 mg daily) in conjunction with nevirapine.⁴⁸</p>	<p>rilpivirine 75 mg resulted in 70% ↓ AUC and 30% ↓ Cmax of rilpivirine compared to rilpivirine alone (historical controls). Do not coadminister rilpivirine and efavirenz.⁷</p> <p>In healthy volunteers, subjects received rilpivirine 25 mg QD for 14 days (period A) followed by a 14-21 day washout, then efavirenz 600 mg QD for 14 days (period B), followed immediately by rilpivirine 25 mg QD for 28 days (period C). At days 1, 14 and 21 of period C, rilpivirine AUC and Cmax were lower than in period A: day 1 - AUC ↓ 46%, Cmax ↓ 36%, day 14 - AUC ↓ 18%, Cmax ↓ 19%, Cmin ↓ 28%, day 21 - AUC ↓ 16%, Cmax ↓ 13%, Cmin ↓ 28%. By day 28 of period C, rilpivirine AUC and Cmin were similar to period A, while Cmin ↓ 25%. Plasma EFV was undetectable by 7 days after period B.⁴⁹</p>
Elvitegravir		Three-period study in healthy subjects of EVG/COBI/FTC/TDF (Quad) for 1 week followed by washout, efavirenz/FTC/TDF (Atripla®) for 2	In healthy subjects, no clinically relevant PK changes were observed for elvitegravir/ritonavir 150/100mg daily and etravirine 200mg BID		

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		<p>weeks, then Quad for 5 weeks. Following the switch from Atripla® to the Quad, elvitegravir exposures were lower:</p> <ul style="list-style-type: none"> Day 35: AUC ↓ 37%, Cmax ↓ 19%, Ctau ↓ 67% Day 42: AUC ↓ 29%, Cmax ↓ 11%, Ctau ↓ 54% <p>Cobicistat Ctau was ↓ 35% at day 14 post-switch. AUC of EVG glucuronidated metabolite were ↑ 46% and ↑ 32% on days 35 and 42, respectively. Mean EVG Ctrough was ~3-fold and ~5-fold > than protein-adjusted IC95 of 45 ng/mL on days 35 and 42, respectively, and 7-8 fold ↑ at 5 weeks post switch.⁵⁰</p>	<p>compared to either drug administered alone. These 2 antiretrovirals can be used together without dose adjustment.⁵¹</p>		
Enfuvirtide			Use of enfuvirtide had no effect on etravirine AUC12h from population PK data from substudy in Duet trials. ⁵²		
Etravirine	<p>Potential for increased etravirine concentrations. Combining two NNRTIs has not been shown to be beneficial. Etravirine should not be coadministered with other NNRTIs.⁴</p>	<p>Steady-state efavirenz 600 mg QD plus single-dose etravirine 900 mg resulted in 41% ↓ AUC and 18% ↓ Cmax of etravirine.⁴⁶ Etravirine should not be coadministered with other NNRTIs.⁴</p> <p>In a healthy volunteer study, etravirine was administered 400 mg QD or 200 mg BID for 14 days at baseline and then again after 14 days of efavirenz treatment to assess</p>		<p>Steady-state nevirapine 200 mg BID plus single-dose etravirine 900 mg resulted in 55% ↓ AUC and 36% ↓ Cmax of etravirine.⁴⁶ Etravirine should not be coadministered with other NNRTIs.⁴</p>	<p>Rilpivirine should not be co-administered with other NNRTIs.⁷</p>

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Fosamprenavir	Combination is contraindicated due to potential loss of virologic response and possible resistance to delavirdine. ⁵³	In healthy volunteer study, FPV 700/rtv 100 mg BID plus EFV did not change APV levels vs. FPV/rtv alone. However, with FPV 1395/rtv 200 mg QD , addition of EFV led to 13% ↓ AUC, 36% ↓ Cmin of APV. Negative interaction corrected when rtv dose ↑ to 300 mg QD. ⁵⁴ Therefore, when coadministering FPV/r and EFV: no change in FPV dose if BID regimen used; if QD, use FPV 1400 mg/rtv 300 mg QD.	In an open-label interaction trial of HIV-infected subjects on stable FPV 700/rtv 100 mg BID, addition of etravirine 800 mg BID for 14 days (phase II formulation) led to 69% ↑ AUC, 62% ↑ Cmax and 77% ↑ Cmin of amprenavir compared to FPV/rtv alone. Etravirine parameters were similar to historical controls. ⁵⁵ Etravirine should not be co-administered with fosamprenavir/ritonavir. ⁴	In HIV+ subjects, FPV 1400 mg BID + NVP 200 mg BID for 14 days led to 33% ↓ AUC, 39% ↓ Cmin of APV, and 29% ↑ AUC and 34% ↑ Cmin of NVP. ⁵⁶ When FPV 700/rtv 100 mg BID administered with NVP for 14 days, APV AUC ↓ 11%, Cmin ↓ 19%, NVP AUC ↑ 14%, Cmin ↑ 21% vs. controls. ⁵⁶ Recommend FPV 700/rtv 100 mg BID with NVP 200 mg BID.	Potential for ↑ concentrations of rilpivirine. Rilpivirine is not expected to affect the plasma concentrations of co-administered PIs. ⁷

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Indinavir	<p>IDV 600 mg q8h + DLV: ↑ IDV AUC, Cmin vs. IDV 800 mg q8h alone.^{57, 58}</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, Cmax, but Cmin IDV ↓ 35-40% (vs. IDV 800 mg q8h)</p> <p>b) 1200/600 mg BID: similar Cmin, ↑ AUC (50-70%), ↑ Cmax (20-50%)</p> <p>Thus, 1200/600 mg BID may be preferable (NB: risk nephrolithiasis?); may take +/- food.⁵⁹</p>	<p>IDV alone:</p> <p>30-35% ↓ indinavir levels; no change in efavirenz levels. Increase IDV dosage to 1000 mg q8h.⁶⁰</p> <p>Indinavir/rtv BID</p> <p>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.⁶¹</p> <p>Indinavir/rtv QD:</p> <p>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.⁶²</p>	<p>Steady-state study of etravirine 1600 mg BID plus indinavir 800 mg TID (n=10) resulted in 51% ↑ AUC and Cmax of etravirine, likely due to CYP3A inhibition; indinavir AUC ↓ 46%, Cmax ↓ 28%.⁴⁶</p> <p>Etravirine should not be co-administered with PIs without low-dose ritonavir.⁴</p>	<p>28% ↓ IDV AUC, <10% ↓ NVP AUC (non-significant). Suggest ↑ IDV dose to 1000 mg q8h when using with NVP 200 mg BID.⁶³</p> <p>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.⁶⁴</p>	<p>Potential for ↑ concentrations of rilpivirine. Rilpivirine is not expected to affect the plasma concentrations of co-administered PIs.⁷</p>
Lopinavir/ritonavir	<p>In a healthy volunteer study (n=26), DLV 600 mg BID plus lopinavir 400/100 mg BID resulted in higher lopinavir levels (Cmin ↑ 53%, AUC ↑ 24%, Cmax 13%); however, DLV exposure was ↓ 25-30%. Further studies are ongoing to establish optimal doses of both agents.⁶⁵</p>	<p>With LPV/r capsules:</p> <ul style="list-style-type: none"> EFV 600 mg + LPV/r 400/100 mg BID resulted in 25% ↓ AUC and 44% ↓ Cmin of lopinavir. Using lopinavir 533 mg/ritonavir 133 mg BID plus EFV resulted in similar lopinavir concentrations to those achieved in the absence of EFV.⁶⁶ <p>With LPV/r tablets:</p> <ul style="list-style-type: none"> Can use 400/100 mg 	<p>In healthy volunteers, coadministration of etravirine 200 mg BID and lopinavir/ritonavir tablets 400/100 mg BID for 8 days resulted in 45% ↓ Cmin, 30% ↓ Cmax and 35% ↓ AUC of ETV, and 20% ↓ Cmin, 11% ↓ Cmax and 13% ↓ AUC of LPV compared to each drug administered alone.⁷⁰ Because the ↓ in mean ETV exposures in the presence of LPV/r is similar to the ↓ observed in the presence of darunavir/ ritonavir, ETV and LPV/r may</p>	<p>With LPV/r capsules:</p> <ul style="list-style-type: none"> Nevirapine ↓ lopinavir AUC and Cmin. Using lopinavir 533 mg/ritonavir 133 mg BID plus nevirapine will result in similar lopinavir concentrations to those achieved in the absence of nevirapine.⁷² <p>With LPV/r tablets:</p> <ul style="list-style-type: none"> Can use 400/100 mg BID with NVP in ARV-naïve subjects ↑ to 600/150 	<p>In healthy volunteers, rilpivirine 150 mg QD plus LPV/r 400/100 mg BID soft gel capsules resulted in 52% ↑ AUC, 29% ↑ Cmax, 74% ↑ Cmin of rilpivirine; LPV kinetics not affected.⁷³</p> <p>No dose adjustment is required with coadministration.⁷</p>

	Delavirdine (Rescriptor®)	Efavirenz (Sustiva®)	Etravirine (Intelligence®)	Nevirapine (Viramune®)	Rilpivirine (Edurant®)
		<p>BID with EFV in ARV-naïve subjects</p> <ul style="list-style-type: none"> • ↑ to 600/150 mg (3 tablets) BID in treatment-experienced subjects; this significantly ↑ LPV concentrations ~35% and RTV concentrations ~56-92% versus LPV/r tablets 400/100 mg BID without EFV⁶⁷ • in 19 healthy volunteers, LPV/r 500/125 mg BID plus EFV 600 mg led to similar LPV levels as seen with LPV/r 400/100 mg BID alone (6% ↑ AUC, 10% ↓ C_{min})⁶⁸ • QD lopinavir/rtv in the presence of NNRTIs may not provide adequate lopinavir C_{trough}⁶⁹ 	<p>be co-administered without dose adjustment.⁴</p> <p>Etravirine 800 mg BID did not affect kinetics of LPV 400/RTV 100/SQV 800-1000 mg BID in 15 HIV-infected male subjects.⁷¹</p>	<p>mg (3 tablets) BID when co-administering in treatment-experienced subjects</p>	
Maraviroc		<p>When maraviroc 100 mg BID was given with efavirenz 600 mg QD, maraviroc AUC ↓ 50%, C_{max} ↓ 60%. Doubling maraviroc dose to 200 mg BID corrected maraviroc exposures. When administering maraviroc with EFV (in the absence of PIs), doubling maraviroc dose is recommended.⁷⁴</p> <p>An in vitro-in vivo extrapolation model was developed to describe the kinetics of maraviroc in HIV-infected patients switching from</p>	<p>Total maraviroc concentrations over a 12-hour period are reduced by 53% (AUC₁₂) and peak levels of maraviroc (C_{max}) by 60% in the presence of etravirine.</p> <p>Therefore, if a patient isn't also taking a potent CYP3A4 inhibitor such as RTV-boosted protease inhibitor, maraviroc dose should be increased to 600mg twice daily. No dose adjustment of etravirine is required.</p> <p>In 64 HIV-positive</p>	<p>In a cohort of HIV+ subjects (n=8) stabilized on nevirapine, 3TC and tenofovir, kinetics of single dose maraviroc 300 mg were unchanged vs. control data in HIV+ subjects receiving maraviroc alone for 10 days.⁷⁸</p>	

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		<p>efavirenz-containing therapy. The model predicted that MVC exposures similar to those with MVC 300 mg BID alone could be achieved via two scenarios following a switch from EFV:</p> <ul style="list-style-type: none"> • MVC 600 mg BID x 1 week followed by standard 300 mg BID dosing • MVC 450 mg BID x 2 weeks followed by standard BID dosing⁷⁵ 	<p>patients taking maraviroc 300 or 600 mg BID plus etravirine 200 mg BID without PIs, 67% Ctrough were <75 ng/mL (75% with maraviroc 300 mg BID and 63% with maraviroc 600 mg BID). Mean maraviroc Ctrough was 53 and 60 ng/mL in the 300 and 600 mg BID groups, respectively. Etravirine Ctrough was 723 ng/mL, approximately 180-fold higher than the protein-adjusted EC50 for wild type virus⁷⁶</p> <p>In a cohort of patients receiving maraviroc and raltegravir with or without etravirine, significantly lower maraviroc Ctrough were observed when combined with etravirine vs. without etravirine (57 vs 173.5 ng/mL respectively, p=0.01). Patients treated with maraviroc had significantly greater CD4 increases versus those not on maraviroc.⁷⁷</p> <p>See additional entry for darunavir/ritonavir + etravirine plus maraviroc.</p>		
Nelfinavir	<p>Interaction data in HIV subjects taking DLV 600 mg TID + standard NFV: approx. 2-fold ↑ NFV AUC, and DLV Cmin similar to that with DLV 400 mg TID alone.⁷⁹ Recommendations on dosage</p>	<p>Healthy volunteer study: efavirenz 600 mg + nelfinavir 750 mg q8h x 7 days: 20% ↑ NFV levels, 37% ↓ M8 levels; no change in efavirenz levels.⁸⁰</p> <p>However, subsequent kinetic</p>	<p>Potential for increased nelfinavir concentrations. Etravirine should not be co-administered with PIs without low-dose ritonavir.⁴</p>	<p>No statistically significant changes in NFV levels after the addition of NVP (AUC +8%, Cmax +14%, and Cmin +2%). Compared to historical controls, NVP levels appear to be unchanged.⁸² Similar results were</p>	<p>Potential for ↑ concentrations of rilpivirine. Rilpivirine is not expected to affect the plasma concentrations of co-administered PIs.⁷</p>

	Delavirdine (Rescriptor®)	Efavirenz (Sustiva®)	Etravirine (Intelence®)	Nevirapine (Viramune®)	Rilpivirine (Edurant®)
	adjustments not available. Use together with caution and monitor for drug toxicities, incl. Neutropenia. Regimens currently being studied: NFV 750 mg TID + DLV 600 mg TID, and NFV 1250 mg BID + DLV 600 mg BID.	study in HIV+ subjects of efavirenz 600 mg qhs and nelfinavir 1250 mg BID showed ↓ 65% nelfinavir C _{min} (p=0.04), ↓ 38% AUC and ↓ 21% C _{max} at 32 weeks. ⁸¹ Therefore, monitor for antiretroviral efficacy when using this combination. Nelfinavir dosage adjustment may be necessary, consider therapeutic drug monitoring where available.		demonstrated in a separate study, and NFV C _{min} remained above minimum effective concentration during nevirapine coadministration. ⁸³ Thus, dosage adjustments not required.	
Nevirapine		Combination of nevirapine 400 mg daily plus efavirenz 600 mg daily in HIV-infected individuals resulted in reduced efavirenz concentrations (22% ↓ AUC, 36% ↓ C _{min}); nevirapine levels were not changed. Thus, may need to administer higher doses of efavirenz (e.g., 800 mg daily) in conjunction with nevirapine. ⁴⁸	Steady-state nevirapine 200 mg BID plus single-dose etravirine 900 mg resulted in 55% ↓ AUC and 36% ↓ C _{max} of etravirine. ⁴⁶ Etravirine should not be coadministered with other NNRTIs. ⁴		In HIV infected patients on steady state nevirapine, administration of a single dose of rilpivirine 50 mg did not significantly alter rilpivirine exposures compared to rilpivirine alone (historical controls). Rilpivirine should not be co-administered with other NNRTIs. ⁷
Raltegravir		In a placebo-controlled, 2 period study in 12 subjects who received 400 mg MK-0518 alone or with 600 mg EFV for 14 days, MK-0518 kinetic parameters were modestly reduced in the presence of EFV: C _{12 hr} GMR [90% CI] = 0.79 [0.49, 1.28], AUC _{0-∞} = 0.64 [0.52, 0.80] and C _{max} = 0.64 [0.41, 0.98]. There were no substantial differences in T _{max} or t _{1/2} . This interaction is likely	In healthy subjects, raltegravir 400 mg BID and etravirine 200 mg BID for 4 days resulted in modest decreases in raltegravir concentrations (AUC ↓ 10%, 11% ↓ C _{max} , 34% ↓ C _{12h}) compared to raltegravir alone, while etravirine levels were not altered. These changes are not considered to be clinically meaningful; etravirine may be coadministered with raltegravir without	Drugs may be coadministered. No Raltegravir dose modification is required. ⁸⁷ The kinetics of raltegravir 400/nevirapine 200 mg BID (n=21) and raltegravir/nevirapine 800/400 mg QD (n=10) were assessed in a cohort of HIV+ subjects. Patients in the QD group showed significantly lower RAL [28 ng/mL (17-79) vs 152 ng/mL (56-285), p = 0.002] but	In healthy volunteers, coadministration of rilpivirine 25 mg QD and raltegravir 400 mg BID for 11 days did not significantly alter the pharmacokinetics of either drug compared to each drug administered alone. The combination may be administered without dose adjustment. ⁸⁹

	Delavirdine (Rescriptor®)	Efavirenz (Sustiva®)	Etravirine (Intelence®)	Nevirapine (Viramune®)	Rilpivirine (Edurant®)
		not clinically meaningful. ⁸⁴	dose adjustment. ⁸⁵ In 29 HIV-positive subjects receiving regimens including raltegravir, raltegravir/darunavir 600 mg/ritonavir 100 mg BID, or raltegravir/darunavir /ritonavir/ etravirine BID, no differences in raltegravir Ctrough were noted between the groups. ⁸⁶	similar NVP concentrations [5969 ng/mL (3957-7228) versus 5250 ng/mL (3890-8020), $p = 0.88$], as compared to the BID group. One raltegravir Ctrough was below the IC95 (15 ng/mL) in the QD arm, while exposures in the BID arm were consistent with previous data. ⁸⁸	
Rilpivirine	Rilpivirine should not be co-administered with other NNRTIs. ⁷	In HIV infected patients on steady state efavirenz, administration of a single dose of rilpivirine 75 mg resulted in 70% ↓ AUC and 30% ↓ Cmax of rilpivirine compared to rilpivirine alone (historical controls). Rilpivirine should not be co-administered with other NNRTIs. ⁷ In healthy volunteers, subjects received rilpivirine 25 mg QD for 14 days (period A) followed by a 14-21 day washout, then efavirenz 600 mg QD for 14 days (period B), followed immediately by rilpivirine 25 mg QD for 28 days (period C). At days 1, 14 and 21 of period C, rilpivirine AUC and Cmax were lower than in period A: day 1 - AUC ↓ 46%, Cmax ↓ 36%, day 14 - AUC ↓ 18%, Cmax ↓ 19%, Cmin ↓ 28%, day 21 - AUC ↓ 16%, Cmax ↓ 13%, Cmin ↓ 28%. By day 28 of period C, rilpivirine AUC and Cmin	Rilpivirine should not be co-administered with other NNRTIs. ⁷	In HIV infected patients on steady state nevirapine, administration of a single dose of rilpivirine 50 mg did not significantly alter rilpivirine exposures compared to rilpivirine alone (historical controls). Rilpivirine should not be co-administered with other NNRTIs. ⁷	

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		were similar to period A, while C _{min} ↓ 25%. Plasma EFV was undetectable by 7 days after period B. ⁴⁹			
Ritonavir	70% ↑ RTV concentrations; kinetics of delavirdine and its metabolite unchanged with concomitant administration of full dose therapy. ^{90, 91} Similar effect (80% ↑ ritonavir AUC) seen in healthy volunteers given delavirdine 600 mg BID plus ritonavir 100 mg BID. No effect on delavirdine kinetic parameters ⁹²	Healthy volunteer study of EFV 600 mg/day + RTV 500 mg BID: 21% ↑ EFV AUC, 17% ↑ RTV AUC. Combination associated with higher frequency of adverse effects (e.g., dizziness, nausea, paresthesia) and ↑ LFTs. Recommended to monitor LFTs when using combination; if RTV intolerance occurs, may consider RTV dosage reduction. ⁹³	Single dose etravirine 400 mg plus steady-state ritonavir 600 mg BID (n=11) resulted in 46% ↓ AUC and 32% ↓ C _{max} of etravirine, likely due to induction of glucuronidation. ⁴⁶ Ritonavir concentrations not measured. Etravirine should not be co-administered with ritonavir 600 mg BID. ⁴ In healthy volunteers, there was no evidence of a pharmacokinetic interaction between single-dose etravirine 200 mg and single-dose ritonavir 100 mg administered either simultaneously after breakfast, or when ritonavir was given 4 hours before or after etravirine. Simultaneous administration of ritonavir 400 mg plus etravirine 200 mg also had no effect on etravirine exposure relative to ritonavir 100 mg. ⁹⁴	11% ↓ RTV AUC, no effect on NVP levels. Interaction considered clinically insignificant; no dosage adjustment suggested. ⁹⁵ Preliminary data suggest that dosing nevirapine 400 mg once daily may have a more pronounced effect on decreasing indinavir concentrations compared to nevirapine dosed 200 mg twice daily (median 31% decrease). These findings require further substantiation; may consider monitoring indinavir levels/response if switching nevirapine dosage regimen. ⁶⁴	
Saquinavir	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. ⁹⁶	Multiple dose healthy volunteer study of efavirenz 600 mg/day + SQV-sgc 1200 mg q8h: 12% ↓ efavirenz AUC (not clin. significant), and 62% ↓ SQV AUC. ⁹⁸ Can avoid this negative interaction by adding ritonavir	Etravirine AUC ↓ 33% when co-administered with Saquinavir 1000 /ritonavir 100 mg BID . No dose adjustments required. ⁴ Etravirine 900 mg BID at steady state plus single-dose	Coadministration of saquinavir 600 mg TID plus nevirapine 200 mg BID (after 200 mg daily lead-in for 14 days) resulted in a 27% ↓ saquinavir AUC; clinical significance unknown. ¹³⁴ This decrease is not	Potential for ↑ concentrations of rilpivirine. Rilpivirine is not expected to affect the plasma concentrations of co-administered PIs. ⁷

	Delavirdine (Rescriptor®)	Efavirenz (Sustiva®)	Etravirine (Intence®)	Nevirapine (Viramune®)	Rilpivirine (Edurant®)
	<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. SQV alone; SQV Cmin was higher in the TID vs. BID arm, both were greater than Cmin SQV alone.⁹⁷</p>	<p>to combination at the following doses:</p> <ul style="list-style-type: none"> • saquinavir-sgc 400 mg BID • ritonavir 400 mg BID • efavirenz 600 mg qhs⁹⁹ 	<p>saquinavir 1200 mg (n=12) resulted in 52% ↓ AUC and 46% ↓ Cmax of saquinavir, likely due to CYP3A induction.⁴⁶ Etravirine concentrations not measured. Etravirine should not be administered with unboosted PIs.⁴</p> <p>Etravirine 800 mg BID did not affect kinetics of LPV 400/RTV 100/SQV 800-1000 mg BID in 15 HIV-infected male subjects.⁷¹</p>	<p>thought to be clinically significant and no dose adjustments of saquinavir or nevirapine are recommended. The safety and efficacy of the combination of nevirapine and saquinavir/ritonavir have not been established.¹⁰⁰</p>	
Tenofovir		<p>In healthy volunteers, tenofovir 300 mg daily plus efavirenz 600 mg daily did not result in significant changes to the kinetics of either drug. Efavirenz and tenofovir may be coadministered without dosage adjustment.¹⁰¹</p>	<p>Coadministration of tenofovir 300 mg QD plus etravirine 200 mg BID in healthy volunteers led to 19% ↓ Cmax and AUC and 18% ↓ Cmin of etravirine, while tenofovir Cmax and AUC ↑ 15%. Combination may be coadministered without dosage adjustment.¹⁰²</p> <p>Tenofovir was associated with 26% ↓ etravirine AUC_{12h} from population PK data from substudy in DUET trials.⁵²</p>	<p>Trough nevirapine levels (23-25 hours post-dose) were obtained in subjects taking NVP 400 mg QD with or without concomitant tenofovir. The mean NVP concentration was 3420 (range 3170-3670) ng/mL in those taking NVP and tenofovir (n=171) and 3260 (range 2980-3540) ng/mL in those taking NVP without tenofovir (n=87).¹⁰³ No dosage adjustments necessary.</p>	<p>In healthy volunteers, coadministration of rilpivirine 150 mg QD and tenofovir 300 mg QD for 8 days resulted in 24% ↑ AUC, 21% ↑ Cmax and 24% ↑ Cmin of tenofovir, while kinetics of rilpivirine were not affected.¹⁰⁴ No dosage adjustments necessary.</p>
Tipranavir		<p>Healthy volunteer open-label, randomized, parallel group study (n=68) of either TPV/r 500 mg/100 mg or TPV/r 750 mg/200 mg plus EFV 600 mg daily. PK sampling done after single dose and at steady state. At steady state, ↑ in TPV AUC, Cmax and C_{12h} observed</p>	<p>In healthy volunteers, tipranavir 500 mg/rtv 200 mg BID plus TMC125 800 mg BID (old formulation) led to 71% ↓ Cmax, 76% ↓ AUC and 82% ↓ Cmin of TMC125, while TPV AUC ↑ 18%. Do not co-administer tipranavir/ritonavir and etravirine.⁴</p>	<p>Healthy volunteer study of 1250 mg TPV BID plus 200 mg BID NVP +/- 200 mg RTV BID:¹⁰⁷</p> <ul style="list-style-type: none"> • no sig. impact on TPV levels • NVP AUC ↓37% by TPV (stat. sig).; levels improved with addition of RTV • RTV clearance was sig. ↑ in 	<p>Potential for ↑ or ↓ concentrations of rilpivirine. Rilpivirine is not expected to affect the plasma concentrations of co-administered PIs.⁷</p>

	Delavirdine (Rescriptor®)	Efavirenz (Sustiva®)	Etravirine (Intence®)	Nevirapine (Viramune®)	Rilpivirine (Edurant®)
		with EFV. ¹⁰⁵ In a separate healthy subject study (n=16), EFV 600 mg QD plus TPV/r 500/200mg BID for 14 days did not result in clinically important changes on the steady state PK of TPV or RTV, and EFV AUC levels were comparable to historical controls. ¹⁰⁶ May consider using TPV/RTV plus EFV without further dosage adjustment.		presence of TPV and NVP, but still higher than historical controls May consider using TPV/RTV plus NVP without further dosage adjustment.	
Zidovudine (GT 60-75% > CYP3A, minor)	No kinetic interaction noted. May prevent emergence of AZT resistance. ¹⁰⁸	No interaction noted with combination. ¹⁰⁹		No interaction noted. ¹¹⁰	

INTERACTIONS WITH OTHER AGENTS:

Acetaminophen					In HIV negative subjects, coadministration of rilpivirine 150 mg QD for 11 days and single dose acetaminophen 500 mg did not significantly affect acetaminophen exposure. No dose modification of rilpivirine is needed. ⁸
Antacids (see separate entries for H2-blockers and proton-pump inhibitors)	50% ↓ DLV AUC; administer DLV 1 hour before antacids.	No effect on EFV concentrations when administered with 30 mL Mylanta DS (AlOH, MgOH, simethicone). ¹⁰⁹		Absorption of NVP not affected by antacids. ¹¹⁰	Use combination with caution. Antacids should be administered at least 2 hours before or at least 4 hours after rilpivirine. ⁷
Antihistamines, non-sedating (i.e., astemizole, terfenadine) (CYP3A4)	Potential cardiotoxicity; combination contraindicated. ¹⁰⁸	Possible ↑ antihistamine AUC and cardiotoxicity. Avoid combination. ¹⁰⁹			Avoid combination.
Atovaquone/proguanil (Malarone®)		In 20 HIV-positive patients on EFV, single dose atovaquone 250/			

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Atovaquone: GT Proguanil: CYP2C19 to active metabolite, cycloguanil, 40- 60% Clr		proguanil 100 mg resulted in atovaquone AUC ↓ 75% and proguanil AUC ↓ 69% (only in those who had no CYP2C19*2 or -*3 alleles) compared to healthy volunteers. ¹¹¹			
Benzodiazepine • alprazolam, midazolam, triazolam, zolpidem (CYP3A4) • diazepam (2C19>3A4)	Potential for ↑ sedation. Avoid combination if possible or adjust BZ dose. ¹⁰⁸	Risk of prolonged sedation. Avoid combination , or use agents which are glucuronidated (e.g., lorazepam, oxazepam, temazepam). ¹⁰⁹			
Cisapride (CYP3A4)	Potential cardiotoxicity; combination contraindicated. ¹⁰⁸	Possible ↑ cisapride AUC and cardiotoxicity. Avoid combination. ¹⁰⁹			
Clarithromycin (parent: CYP3A4; inhibits CYP3A4, 1A2?) (CLA-14 OH: renal, CYP3A4)	Clarithromycin AUC doubled. ¹⁰⁸ Inhibition of CLA- OH metabolite (i.e., ↓ Gram-neg. activity, such as H. flu) observed (data on file, Pharmacia & Upjohn). Adjust clarithromycin dose in renal impairment. ¹⁰⁸	39% ↓ clarithromycin AUC, 34% ↑ CLA-OH AUC; clinical significance unknown. 11% ↑ efavirenz AUC observed, not clinically important. However, ↑ incidence of rash observed; may wish to consider alternatives to clarithromycin. No significant interaction with azithromycin. ¹¹²	In healthy subjects, clarithromycin 500 mg BID plus etravirine 200 mg BID led to 46% ↑ Cmax, 42% ↑ AUC and 46% ↑ Cmin of etravirine, with a corresponding 39% ↓ clarithromycin AUC and 21% ↑ in CLA-OH AUC. For treatment of MAC infection, may wish to consider using azithromycin instead, since CLA- OH metabolite is 4- 7 times less active than parent against MAC. ¹¹³ No dose adjustment for clarithromycin or etravirine needed in patients with normal renal function; consider clarithromycin dose adjustment for patients with impaired renal function.	Interaction study of NVP 200 mg BID + clarithromycin 500 mg BID: significant reduction in CLA concentrations: 29.5% ↓AUC, 20.8% ↓ Cmax, 46% ↓ Cmin; also 27% ↑ AUC of CLA- OH metabolite. Since ↑ metabolite ≅ same magnitude as ↓ in parent drug, dosage adjustment of CLA likely not necessary with NVP. ¹¹⁴	Coadministration of macrolides including clarithromycin, erythromycin and troleandomycin with rilpivirine should be done with caution, as rilpivirine concentrations may be increased. Azithromycin does not inhibit CYP3A4 and is the preferred macrolide option. ⁷
Clopidogrel (metabolized to its active metabolite, in part by			Avoid concomitant use of drugs that inhibit CYP2C19, including etravirine, as coadministration		

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CYP2C19)			may result in ↓ concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition. ^{4, 115}		
Crofelemer	Clinically significant interaction not expected.	Population PK of ART and crofelemer were assessed in HIV+ subjects receiving placebo or crofelemer 125, 250, or 500 mg BID in a phase 3 trial. At all doses, crofelemer had no statistically significant effect on the kinetics of ritonavir (p=1.0), tenofovir (p=0.09), FTC (p=1.00), 3TC (p=0.33), lopinavir/ritonavir (p=1.00), or efavirenz (p=1.00). ¹¹⁶	Clinically significant interaction not expected.	Clinically significant interaction not expected.	Clinically significant interaction not expected.
Digoxin			<p>Open label randomized crossover trial in male volunteers (n=16) to evaluate effect of ETR 200mg BID on single dose digoxin 0.5mg. Co-administration led to 19% ↑ Cmax, 18% ↑ AUC of digoxin, no change in urinary excretion. ETR mean Cmax and AUC12 comparable to historical controls. Authors recommend to monitor digoxin levels.¹¹⁷</p> <p>Manufacturer recommends that for patients initiating etravirine and digoxin therapy, the lowest dose of digoxin should be initially prescribed. For patients on a stable digoxin regimen who are initiating etravirine,</p>		<p>Open label randomized crossover trial in healthy volunteers (n=22) to evaluate the effect of rilpivirine 25 mg daily on single dose digoxin 0.5mg. Plasma and urine digoxin pharmacokinetics were unaffected by coadministration of steady-state rilpivirine, and rilpivirine kinetics were comparable to historical controls. At the recommended dose of 25 mg daily, rilpivirine does not exert a clinically relevant effect on digoxin pharmacokinetics.¹¹⁸</p>

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			no dose adjustment of either ETV or digoxin is required. Serum digoxin concentrations should be monitored. ⁴		
Diltiazem		In a pharmacokinetic study of healthy subjects, efavirenz 600 mg plus diltiazem 240 mg for 14 days led to a significant decrease in AUC of diltiazem and its two major metabolites (69% ↓ and 36-74% ↓, respectively), while efavirenz AUC ↑ 11% (not clinically relevant). If co-administration is required, adjustments in diltiazem dose may be required based on response. ¹¹⁹			
Ergot alkaloids (CYP3A>others)	Use DLV with caution in combination with ergot derivatives; potential for ↑ drug concentrations and toxicity. ¹⁰⁸	Use combination with caution and monitor for potential toxicity.	Avoid combination until data available.		
Fluconazole (~80% C _{renal} , 11% metabolized via CYP3A4; inhibits 3A4 (weak), 2C9, 2C19)	No interaction noted. ¹⁰⁸	No interaction noted with combination. ¹²⁰	In healthy volunteers, coadministration of etravirine 200 mg BID plus fluconazole 200 mg daily for 9 days resulted in 109% ↑ C _{min} , 75% ↑ C _{max} and 86% ↑ AUC of etravirine, while fluconazole parameters were unchanged compared to either drug administered alone. The combination was well tolerated. ¹²¹	In a study of 24 HIV+ subjects, combination of nevirapine 200 mg BID and fluconazole 200 mg daily resulted in ~100% ↑ AUC of nevirapine compared with historical data; 25% of subjects also developed elevated liver transaminases >5 times upper limit of normal. Nevirapine did not affect the pharmacokinetics of fluconazole. ¹²² In a retrospective study of 122 HIV-infected patients receiving nevirapine, those	Potential for increased concentrations of rilpivirine and decreased azole concentrations with concomitant administration. No rilpivirine dose adjustment is required. Monitor for breakthrough fungal infections. ⁷

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				also taking fluconazole 200 or 400 mg daily (n=41) had NVP Cmin 76% higher compared to those not taking fluconazole. One patient on fluconazole developed clinical hepatitis. ¹²³ Use combination with caution.	
Ginko biloba	Potential for ↓ delavirdine concentrations due to CYP3A induction by ginko biloba. ¹²⁴ Case report of viral breakthrough and resistance to efavirenz after introduction of ginko biloba. ¹²⁵ Avoid concomitant use.	Case report of HIV-positive male on efavirenz/tenofovir/emtricitabine who developed viral breakthrough and resistance with K103N and M184V mutations after two years of therapy with excellent adherence and viral suppression. Efavirenz concentrations were 1.48 mg/L while the patient was suppressed, and 0.48 mg/L after viral breakthrough. The only change in the patient's routine was the addition of ginko biloba, a known CYP3A inducer. ¹²⁵ Avoid concomitant use.	Potential for ↓ etravirine concentrations due to CYP3A induction by ginko biloba. ¹²⁴ Case report of viral breakthrough and resistance to efavirenz after introduction of ginko biloba. ¹²⁵ Avoid concomitant use.	Potential for ↓ nevirapine concentrations due to CYP3A induction by ginko biloba. ¹²⁴ Case report of viral breakthrough and resistance to efavirenz after introduction of ginko biloba. ¹²⁵ Avoid concomitant use.	Potential for ↓ rilpivirine concentrations due to CYP3A induction by ginko biloba. ¹²⁴ Case report of viral breakthrough and resistance to efavirenz after introduction of ginko biloba. ¹²⁵ Avoid concomitant use.
H2-antagonists (including cimetidine, famotidine, nizatidine, ranitidine, etc.) <i>*equivalent doses:</i> <u>H2RAs (treatment):</u> Famotidine 20 mg BID or 40 mg qhs Nizatidine 150 mg BID or 300 mg qhs Ranitidine 150 mg BID or 300 mg qhs	Take H2-blocker at night if possible and ingest DLV with acidic beverage. ¹⁰⁸ Similar measures may need to be followed with concomitant proton-pump inhibitor therapy. ¹²⁶	No effect on EFV concentrations when administered with 40 mg famotidine. ¹⁰⁹	In healthy subjects, single-dose etravirine 100 mg was administered in the presence of steady-state ranitidine 150 mg BID; etravirine AUC and Cmax were 86% and 94% compared to etravirine alone. Etravirine may be coadministered with H2-antagonists without dose adjustments. ¹²⁷	Steady-state NVP trough concentrations ↑ 21% with concurrent cimetidine; clinical significance unknown. ¹¹⁰	In healthy subjects, single dose rilpivirine 150 mg was administered alone, two hours after, four hours before, or twelve hours after famotidine 40 mg. When rilpivirine was administered 2 hours after famotidine, rilpivirine Cmax and AUC were reduced by 85% and 76%, respectively. Rilpivirine concentrations were not affected when rilpivirine was

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<p><i>H2RAs</i> <i>(maintenance qhs dosing):</i> Famotidine 20 mg Nizatidine 150 mg Ranitidine 150 mg</p>					<p>administered either 4 hours before or 12 hours after famotidine; famotidine pharmacokinetics were unchanged by rilpivirine. Therefore, rilpivirine should be separated at least 4 hours before or 12 hours following famotidine.¹²⁸</p>
<p>Hmg-CoA Reductase inhibitors</p> <ul style="list-style-type: none"> atorvastatin (CYP3A) fluvastatin (2C9>>3A) pravastatin (40-50% C_{lr}, > 3A4) simvastatin (CYP3A) 	<p>Potential for ↑ concentrations of atorvastatin and simvastatin, possibly fluvastatin due to enzyme inhibition by delavirdine. Consider using pravastatin if treatment with an Hmg-CoA reductase inhibitor is desired, or use a fibric acid derivative for hypertriglyceridemia.</p>	<p>Potential for ↓ concentrations of Hmg-CoA reductase inhibitor, due to enzyme induction by efavirenz.</p> <p>In a prospective kinetic study, efavirenz 600 mg/day significantly ↓ simvastatin AUC by 58% (active metabolite AUC ↓ 60%) and atorvastatin AUC ↓ 43% (active metabolite AUC ↓ 48%); EFV concentrations not affected. Patients on combination should be closely monitored for anti-lipid activity; statin dose may need to be titrated.¹²⁹</p> <p>In healthy volunteers, coadministration of pitavastatin 2 mg daily with efavirenz 600 mg daily did not result in significant interactions. Pitavastatin AUC ↓ 11% and C_{max} ↑ 20% in the presence of efavirenz, while efavirenz AUC and C_{max} ↓ 10%.¹³⁰</p>	<p>In healthy volunteers, atorvastatin 40 mg QD plus etravirine 800 mg BID (old formulation) led to 37% ↓ AUC of atorvastatin and 27% ↑ AUC atorvastatin active metabolite. Etravirine exposures were not affected. Combination may be coadministered.</p>	<p>Potential for ↓ concentrations of Hmg-CoA reductase inhibitor, due to enzyme induction by nevirapine.</p>	<p>In healthy volunteers, atorvastatin 40 mg QD plus rilpivirine 150 mg QD did not lead to significant alterations in plasma exposures of either rilpivirine or atorvastatin. A modest increase in exposure to atorvastatin hydroxylated metabolites (via mild induction of CYP3A activity by rilpivirine) resulted in an increase in the total lipid-lowering activity of atorvastatin during rilpivirine coadministration; this was considered clinically relevant. Combination may be coadministered without dose adjustment.¹³¹</p>
Itraconazole		In a pharmacokinetic study of healthy	Itraconazole is a potent inhibitor as well as substrate of	In a healthy volunteer, cross-over study of	Potential for increased concentrations of

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		<p>subjects, efavirenz 600 mg plus itraconazole 200 mg BID for 14 days led to a 39% ↓ AUC of itraconazole and 37% ↓ AUC of its hydroxyl-metabolite; EFV exposures were not affected. There are no data using higher doses of itraconazole; therefore, no dose recommendation can be made. Use of alternate treatment may be necessary for optimal antifungal therapy.¹¹⁹</p> <p>Case report of HIV-positive male with disseminated histoplasmosis who had undetectable itraconazole concentrations and persistently elevated urinary <i>Histoplasma</i> antigen levels while on efavirenz and itraconazole 200 mg BID. Therapeutic itraconazole levels and a decrease in urinary <i>Histoplasma</i> antigen levels were observed after efavirenz was replaced with atazanavir/ritonavir.¹³²</p> <p>In a retrospective cohort analysis, itraconazole levels were assessed in 10 HIV-positive patients with disseminated histoplasmosis; 4 patients were on PI therapy, 4 on NNRTIs, and 2 on both PIs and NNRTI therapy. All NNRTI patients had undetectable itraconazole concentrations,</p>	<p>CYP3A4. Concomitant systemic use of itraconazole and etravirine may ↑ plasma concentrations of etravirine. Simultaneously, plasma concentrations of itraconazole may be decreased by etravirine. Dose adjustments for itraconazole may be necessary depending on other co-administered drugs.^{4, 134}</p>	<p>itraconazole 200 mg QD, nevirapine 200 mg QD or the combination (each for 7 days), itraconazole Cmax ↓ 38% and AUC ↓ 61% in the presence of nevirapine. NVP parameters were not changed.¹³⁵</p> <p>Avoid combination if possible. If coadministered, monitor itraconazole concentration and adjust dose accordingly.¹³⁴</p>	<p>rilpivirine and decreased azole concentrations with concomitant administration. No rilpivirine dose adjustment is required. Monitor for breakthrough fungal infections.^{7, 134}</p>

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		<p>vs. 1/4 PI patients. Two patients who switched from NNRTI to PI therapy subsequently had therapeutic itraconazole levels.¹³³</p> <p>Avoid this combination if possible. If coadministered, closely monitor itraconazole concentration and adjust dose accordingly.¹³⁴ Use of alternate antifungal treatment may be necessary or replacement of efavirenz with a non-inducing class of antiretrovirals such as protease inhibitors, integrase or CCR5 inhibitors if possible.</p>			
Ketoconazole (CYP3A4; inhibits 3A, 2C9)	No delavirdine dosage adjustment recommended with inhibitors of CYP3A4 or CYP2D6. ¹⁰⁸	In a pharmacokinetic study of 12 HIV-infected patients, the kinetics of single-dose ketoconazole 400 mg was measured alone and after 14 days of efavirenz/3TC/d4T. In the presence of steady-state efavirenz, ketoconazole Cmax ↓ 44% and AUC ↓ 72%. ¹³⁶	Ketoconazole is a potent inhibitor as well as substrate of CYP3A4. Concomitant systemic use of ketoconazole and etravirine may ↑ plasma concentrations of etravirine. Simultaneously, plasma concentrations of ketoconazole may be decreased by etravirine. Dose adjustments for ketoconazole may be necessary depending on other co-administered drugs. ⁴	Ketoconazole levels sig. reduced (63% ↓ AUC, 40% ↓ Cmax,) 15-20% ↑ NVP concentrations. Consider alternative antifungal. ¹³⁷	In healthy subjects, steady-state coadministration of rilpivirine 150 mg QD plus ketoconazole 400 mg QD, rilpivirine AUC ↑ 49%, Cmax ↑ 30% and Cmin ↑ 76%, while ketoconazole AUC ↓ 24%, Cmax ↓ 15% and Cmin ↓ 66% compared to each agent alone. ¹³⁸ No rilpivirine dose adjustment is required. Monitor for breakthrough fungal infections. ⁷
Methadone (CYP3A4>>GT; weak inhibitor of CYP2D6)	In study of HIV-negative volunteers on stable methadone (n=16) and 15 controls, addition of delavirdine 600 mg BID for 5 days did not alter the kinetics of delavirdine or its	Significant decreases in methadone concentrations may occur, with risk of withdrawal occurring within 4-10 days after starting efavirenz. ^{140, 141}	In 16 subjects stabilized on methadone maintenance therapy, addition of TMC125 100 mg BID for 14 days led to 11% ↓ Cmax, AUC and Cmin of S-Methadone and	Significant decreases in methadone concentrations may occur, with risk of withdrawal occurring within 4-10 days after starting nevirapine. ^{142 141}	In the presence of rilpivirine, active R-isomer exposures decreased (mean Cmin ↓ 22%, Cmax ↓ 14%, AUC ↓ 16%); exposures of inactive S-methadone also decreased to a

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	metabolite. Effects of delavirdine on methadone not studied. ¹³⁹	Monitor for withdrawal with concomitant therapy; methadone dosage ↑ may be necessary.	6% ↑ AUC of R-methadone. Combination may be coadministered. ⁴	Monitor for withdrawal with concomitant therapy; methadone dosage ↑ may be necessary.	similar extent. The AUC ratio for S-/R-methadone did not change. No methadone withdrawal symptoms were observed. No dose adjustment of methadone is recommended. Patients should be monitored for symptoms of clinical withdrawal in case methadone dosage needs to be adjusted. ⁷
Mycophenolate mofetil (MMF)				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, NVP clearance ↑ 27% in the presence of chronic MMF administration. Clinical significance unclear. ¹⁴³	
Oral Contraceptives (GT, sulphatase (primary)> CYP3A (~30%); inhibits 1A2, 3A) *See separate entry for depo-medroxy-progesterone acetate (Depo-Provera®) below <i>Please also see separate chart on "Interactions between antiretrovirals and hormonal contraceptives".</i>	A clinically significant interaction is unlikely, since delavirdine does not have any effect on oral contraceptive metabolism (conjugation).	No pharmacokinetic interaction observed in healthy volunteer PK study. ¹⁴⁴ In a separate healthy volunteer study of women taking Ortho Cyclen® alone or with EFV 600 mg daily for 14 days, ethinyl estradiol Cmax and AUC were unchanged in the presence of EFV. However, concentrations of norelgestromin and levonorgestrel (active metabolites of norelgestromin) were significantly reduced (64% and 83% ↓ AUC, respectively). Therefore, alternate methods of contraception are recommended. ¹⁴⁵	In a study of 30 HIV negative volunteers, ↑ 22% AUC24H ethinyl estradiol when given with etravirine BID X 15 days. No loss in contraceptive efficacy of OC is expected when etravirine is coadministered. ¹⁴⁷	20% ↓ AUC of ethinyl estradiol and norethindrone when coadministered with nevirapine. ¹⁴⁸ The steady-state kinetics of a combined OC (norgestrel 300 mg and ethinyl estradiol 30 ug) once daily were studied in 3 groups of women: HIV-positive on nevirapine plus 3TC/d4T (group 1), HIV-positive not on antiretrovirals (group 2), and HIV-negative (group 3). Median levonorgestrel AUC and Cmin and ethinyl estradiol AUC were highest in group 1, and women in group 1 demonstrated ovulation	When rilpivirine 25 mg daily was coadministered with norethindrone 1 mg/ethinylestradiol 0.035 mg in 18 HIV-negative women, no statistically significant changes in norethindrone PK and ethinylestradiol AUC and Cmin were observed. Ethinylestradiol Cmax ↑ 17% in the presence of rilpivirine, but this is not expected to be clinically significant. Rilpivirine 25 mg daily can be co-administered with norethindrone/ethinylestradiol-based contraceptives without dose modifications. ¹⁵²

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		In 21 HIV-negative women, the effect of EFV 600 mg QD for 14 days on the kinetics of single dose levonorgestrel 0.75 mg (dose for emergency contraception) was studied. In the presence of EFV, levonorgestrel AUC ↓ 56%, and Cmax and Cmin were also significantly reduced. While the minimum effective concentration of levonorgestrel is unknown, higher doses may be needed to prevent pregnancy in women taking EFV. Alternate methods of contraception, including barrier methods, are recommended. ¹⁴⁶		suppression. ¹⁴⁹ Some studies suggest preservation of COC efficacy with nevirapine coadministration. ¹⁴⁹⁻¹⁵¹ Alternate/additional methods of contraception may still be considered.	
Depo-medroxy-progesterone acetate, DMPA (Depo-Provera®) <i>Please also see separate chart on “Interactions between antiretrovirals and hormonal contraceptives”.</i>		In a prospective, open-label study of 15 HIV-infected women on stable EFV therapy, EFV 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. ¹⁵³ In an open-label, nonrandomized, clinical trial, 30 HIV-infected women (15 on AZT, 3TC and EFV, 15 not on ARVs) received a single injection of DMPA 150 mg IM. AUC, Cmin, t1/2 of DMPA were similar between		In a prospective, open-label study of 14 HIV-infected women on stable NVP therapy, NVP AUC was higher in the presence of DMPA, although this increase was not felt to be clinically relevant. Efficacy of DMPA did not appear to be altered, with no evidence of ovulation occurring based on progesterone levels through week 12. ¹⁵³	

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		the 2 groups, suggesting that EFV-based therapy is not likely to interfere with the contraceptive effectiveness of DMPA. ¹⁵⁴			
Posaconazole (UGT1A4; inhibits CYP3A4) <i>Please also see separate chart on "Interactions between antiretrovirals and oral azole antifungal agents".</i>		In healthy subjects randomized to receive EFV 400 mg QD alone or with posaconazole 400 mg BID for 10 days, posaconazole Cmax ↓ 45% and AUC ↓ 50% in the presence of efavirenz. Avoid co-administration unless benefit to patient outweighs the risk. ¹⁵⁵	Possible ↑ etravirine concentrations due to CYP3A4 inhibition by posaconazole. No anticipated effect on posaconazole concentrations. ⁴	Potential for ↓ posaconazole levels; avoid co-administration until further data are available.	Potential for increased concentrations of rilpivirine and decreased azole concentrations with concomitant administration. No rilpivirine dose adjustment is required. Monitor for breakthrough fungal infections. ⁷
Proton-pump inhibitors (PPIs), including esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, etc. <i>*equivalent doses: PPIs (daily standard dose): Esomeprazole 20 mg Lansoprazole 30 mg Omeprazole 20 mg Pantoprazole 40 mg Rabeprazole 20 mg</i>	Take H2-blocker at night if possible and ingest DLV with acidic beverage. ¹⁰⁸ Similar measures may need to be followed with concomitant proton-pump inhibitor therapy. ¹²⁶		In healthy subjects, single-dose etravirine 100 mg was administered in the presence of steady-state omeprazole 40 mg QD; etravirine AUC and Cmax were 141% and 117% compared to etravirine alone. Etravirine may be coadministered with proton-pump inhibitors without dose adjustments. ¹²⁷		In healthy subjects, coadministration of omeprazole 20 mg QD and rilpivirine 150 mg QD led to 40% ↓ in Cmax and AUC and 37% ↓ Cmin of rilpivirine, while omeprazole AUC ↓ 14%. Therefore, rilpivirine should not be coadministered with proton pump inhibitors. ⁷
Rifabutin (CYP3A > deacetylase; moderate inducer of CYP3A)	50-60% ↓ delavirdine concentrations ¹⁵⁶ (not adequately compensated with 600 mg TID dose); also >200% ↑ RFB AUC. ¹⁵⁷ Therefore, avoid concomitant use.	Rifabutin AUC ↓ 38%. Case report of treatment failure with combination; rifabutin levels remained below target despite ↑ rifabutin dose to 1350 mg daily. ¹⁵⁸ Increase rifabutin to 450-600 mg/day or 600 mg three times	In healthy subjects, rifabutin 300 mg QD plus etravirine 800 mg BID (old formulation) led to 37% ↓ Cmax and AUC and 35% ↓ Cmin of etravirine, while rifabutin AUC ↓ 17% and Cmin ↓ 24%. ¹¹³ Etravirine can be	16% ↓ nevirapine concentrations, no significant changes in rifabutin concentrations. Combination may be safely co-administered without dosage adjustment. ¹⁶² May give rifabutin 300 mg daily or 3 times per week. ¹⁶¹	When rilpivirine 25 mg daily was coadministered with rifabutin 300 mg daily, rilpivirine Cmax ↓ 31%, AUC ↓ 42% and Cmin ↓ 48%. When rilpivirine 50 mg daily was coadministered with rifabutin 300 mg daily, rilpivirine

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		per week with concomitant efavirenz. ¹⁵⁹⁻¹⁶¹	coadministered with 300 mg of rifabutin once daily in the absence of an additional potent cytochrome P450 inducer. ¹¹³		Cmax ↑ 43%, AUC ↑ 16% and Cmin ↓ 7% compared to rilpivirine 25 mg administered alone. Use rilpivirine 50 mg once daily with rifabutin. ⁷
Rifampin (<i>Deacetylase</i> > hydrolysis, <i>GT?</i> , <i>CYP?</i> ; potent inducer of CYP3A and GT)	Virtually undetectable DLV concentrations; combination contraindicated. ¹⁶³	26% ↓ AUC, 20% ↓ Cmax of efavirenz; clinical significance unknown. ¹⁶⁴ Two retrospective analyses of TDM databases indicated no difference in EFV levels when given at either 600 or 800 mg daily with rifampin. ^{165, 166} A randomized trial in Thai subjects (median weight 50 kg) receiving EFV 600 or 800 mg plus RIF, median plasma EFV levels were 3.02 mg/L (range 0.07-12.21) in the 600 mg group and 3.39 mg/L (range 1.03-21.31) in the 800 mg group (P = 0.632). Plasma EFV levels were < 1 mg/L in 3/38 (7.9%) patients in the 600 mg group and in none of the 800 mg group (P = 0.274). ~40 and 45% of patients had EFV levels > 4 mg/L, respectively. ¹⁶⁷ Similar virologic & immunologic outcomes were noted at 48 weeks. ¹⁶⁸ NB: these results may not be applicable to other populations with higher body weight. HIV/TB coinfectd patients from Cote d'Ivoire receiving RIF were	Avoid combination as significant decreases in etravirine exposure may occur. ⁴	No change in RIF AUC or Cmax; 58% ↓ NVP average levels, 68% ↓ Cmin. Authors suggest ↑ NVP dose by 50% (i.e., to 300 mg BID) with concomitant RIF therapy. ¹⁷³ However, caution re: ↑ risk hepatotoxicity. In a separate study of 10 subjects with HIV/TB coinfection, NVP exposure was reduced in the presence of rifampin (31% ↓ AUC, 36% ↓ Cmax, 21% ↓ Cmin); however, NVP Cmin remained above IC50 wild type. ¹⁷⁴ Avoid combination if possible. ¹³⁴ In a case series (n=32) of HIV-infected patients with TB, coadministration of rifampin 600 mg/d and nevirapine 400 mg/d for a median of 9 months resulted in 100% clinical and microbiological cure of TB; mean NVP Cmin was 4.5 +/- 1.9 ug/mL. ¹⁷⁵ In a prospective study in 140 treatment-naïve HIV-positive Thai subjects (70 with active TB and on rifampin 450-600 mg/day), those	In healthy subjects, coadministration of rilpivirine 150 mg QD and rifampin 600 mg QD resulted in 80% ↓ AUC, 69% ↓ Cmax and 89% ↓ Cmin of rilpivirine compared to rilpivirine dosed alone. Exposures of rifabutin and its active metabolite were not significantly changed in the presence of rilpivirine. Avoid concomitant use since rilpivirine efficacy may be compromised. ^{172, 180}

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		<p>randomized to receive EFV 600 or 800 mg QD (n=65 per group). Plasma EFV levels were higher at months 3 and 6 in the 800 mg group (>4 mg/mL) compared to the 600 mg group (~2 mg/mL), with a higher incidence of adverse events (17% vs. 7%, respectively). At 24 weeks, 59% in the 800 mg group had VL<300 copies/mL vs. 70% in the 600 mg group, p=0.38.¹⁶⁹</p> <p>Individuals from the CIPRA-South Africa cohort taking EFV-based therapy with concomitant TB received either 600 or 800 mg EFV during TB treatment with RIF; after TB therapy, all individuals took 600 mg EFV. EFV levels were measured after 4 weeks of concomitant EFV and RIF therapy, and ≥4 weeks after completion of TB therapy.</p> <p>EFV concentrations in the 800 mg group were higher with RIF than without (2.9 vs. 2.1 mg/L, respectively, p=0.0003). In the 600 mg EFV group, there was no significant difference in EFV concentrations with RIF or without (2.4 vs. 2.2 mg/L, respectively). There was no increase in EFV-linked adverse effects in either group. The proportion of virologically</p>		<p>taking rifampin + NVP had significantly ↓ (17.7% lower, p=0.048) median NVP plasma levels vs. those taking NVP without RIF. However, in this cohort, there was no different in viral or immunologic response at 24 weeks between the two treatment arms.¹⁷⁶</p> <p>In a prospective randomised open-label trial comparing NVP 400mg (without lead-in dosing) vs. EFV 600mg -based ART initiated 4 weeks after starting TB therapy with rifampin, NVP pk was measured in 20 patients during RIF co-administration and 4 weeks after completion of RIF therapy. NVP Ctrough at 2 weeks was 5.83 mg/L (target >3 mg/L), and 89.5% patients achieved VL<400 at week 12. Upon completion of RIF therapy, NVP Cmin ↑ 14% and AUC ↑ 20%.¹⁷⁷</p> <p>In a prospective evaluation of 20 HIV-patients on stable nevirapine who started rifampin-based TB treatment, nevirapine AUC ↓ 22% by day 14. Six patients had subtherapeutic levels at day 14, with the reduction beginning as early as day 3.¹⁷⁸</p> <p>In an open-label,</p>	

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		<p>suppressed individuals at 48 weeks was similar in both groups. Dose escalation of EFV 600 mg to 800 mg is not required during concomitant TB therapy in South Africa.¹⁷⁰</p> <p>In a systematic review of 12 efavirenz-rifampin drug interaction studies, efavirenz C_{min} was reduced 19-54% in the presence of short-course (<8 days) rifampin. In longer-term studies (4-24 weeks of combined efavirenz-rifampin), increases in efavirenz C_{min} of 6-26% were observed with concomitant therapy. In two longitudinal studies, differences in efavirenz C_{min} were only noted during the first 1-4 weeks of co-administration. There were no significant changes in efavirenz concentrations after 4-24 weeks of combined treatment.¹⁷¹</p> <p>The efavirenz product monograph recommends increasing EFV dose to 800 mg daily with rifampin in patients weighing >50 kg. However, current guidelines suggest that standard EFV dose may be used with close monitoring of EFV drug levels and virologic response.¹³⁴ Use of efavirenz 600mg</p>		<p>multi-centre study, HIV+ patients with TB were given a standard short course 4-drug anti-TB regimen for 2 months and then randomized to receive once daily efavirenz (600 mg) or once daily nevirapine (400 mg with lead-in dosing) plus ddl/3TC with continued isoniazid/rifampin for an additional 4 months. At 24 weeks, 50/59 patients in the efavirenz group and 37/57 patients in the nevirapine group had virological suppression (p=0.024). There were no deaths, 1 SAE, and 5 treatment failures in the EFV arm, compared with 5 deaths, 2 SAEs, and 10 treatment failures in the NVP arm. The authors concluded that the NVP-based regimen was inferior and was associated with more frequent virologic failure and death compared to the efavirenz arm, presumably due to the magnitude of the induction effect of rifampicin on nevirapine.¹⁷⁹</p>	

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		with 2 NRTIs, along with rifampin-based tuberculosis treatment is the preferred strategy for co-treatment of HIV and tuberculosis. ¹⁷²			
Rifapentine	Significant reduction in NNRTI concentrations expected with coadministration. Avoid combination. ¹³⁴				
Sildenafil/ Viagra® (CYP3A4>>2C9 ; weak inhibitor of CYP1A2, 2C9, 2C19, 2D6, 2E1, 3A4 - unlikely to cause significant interactions)	Elevated concentrations of sildenafil expected with combination. Do not exceed sildenafil dose of 25 mg every 48 hours. ¹⁰⁸	No information on combination. Since efavirenz may act as either an inducer or inhibitor of CYP3A4, consider starting with an initial sildenafil dose of 25 mg q24-48 hours and titrating up based on patient response and tolerability. ¹⁸¹	In healthy volunteers, single-dose sildenafil 50 mg in the presence of steady-state etravirine led to 57% ↓ in exposures of sildenafil and its active metabolite. Combination may be co-administered, adjust sildenafil dose according to response. ¹⁸²	No information on combination. Expected that 3A4 inducers will ↓ sildenafil levels. Titrate sildenafil dose based on patient response and tolerability.	In healthy volunteers taking rilpivirine 75 mg once daily for 12 days, the kinetics of single dose sildenafil 50 mg were similar as compared to sildenafil alone. In the presence of steady-state rilpivirine, sildenafil AUC ↓ 3% and Cmax ↓ 7% and N-desmethyl sildenafil AUC ↓ 8% and Cmax ↓ 10%. Rilpivirine exposures were not affected by sildenafil. Combination may be coadministered without dose modifications. ¹⁸³
Sulfamethoxazole (SMX) (primarily N-acetylase> GT > CYP2C9 (minor))	No interaction noted. ¹⁰⁸			May be ↑ risk rash with combination. ¹¹⁰	
Trimethoprim (10-20% metabolized, via CYP?)	No interaction noted. ¹⁰⁸				
Voriconazole (CYP2C19, 2C9, 3A; inhibits CYP3A4, 2C9, 2C19)	Although not studied <i>in vivo</i> , <i>in vitro</i> studies show that the metabolism of voriconazole may be inhibited by delavirdine. Voriconazole may also inhibit the metabolism of an NNRTI. Use combination with caution and monitor closely for toxicity. (Vfend prescribing info)	Standard voriconazole dose contraindicated with efavirenz because of 77% ↓ voriconazole AUC and 44% ↑ in efavirenz concentrations. (Vfend prescribing info). If Sustiva is coadministered with voriconazole, the voriconazole	In healthy volunteers, coadministration of etravirine 200 mg BID plus voriconazole 200 mg BID for 9 days resulted in 52% ↑ Cmin, 26% ↑ Cmax and 36% ↑ AUC of etravirine, and 23% ↑ Cmin and 14% ↑ AUC of voriconazole (although no ↑ was	Although not studied, the metabolism of voriconazole may be induced by nevirapine. Voriconazole may also inhibit the metabolism of an NNRTI. Use combination with caution and monitor closely for efficacy and toxicity. (Vfend prescribing info).	Potential for increased concentrations of rilpivirine and decreased azole concentrations with concomitant administration. No rilpivirine dose adjustment is required. Monitor for breakthrough fungal infections. ⁷

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	info).	<p>maintenance dose should be increased to 400 mg every 12 hours and the efavirenz dose should be decreased to 300 mg once daily using the capsule formulation.</p> <p>Case report of HIV positive subject with cirrhosis on stable EFV regimen (600mg/day) who required addition of IV voriconazole at 3 times normal dose to amphotericin/ flucytosine for disseminated cryptococcosis. Patient experienced remission of cryptococcal symptoms, viral load < 50 copies/ml. After 35 days, patient was switched to maintenance voriconazole 300mg po BID + EFV 600mg daily. TDM was performed q3weeks. EFV was ↓ to 400 mg/day and then to 300 mg/day. Voriconazole was ↓ to 200 mg BID when EFV was ↓ to 300 mg/day. Authors comment that EFV 300mg daily + voriconazole maintenance dose which is 2X that recommended for cirrhotic patients (Child Pugh A) appeared effective and safe during long term follow up.¹⁸⁴</p>	<p>observed in carriers of CYP2C19*2 allele) compared to either drug administered alone. The combination was well tolerated.¹²¹ Dose adjustments are not required. Monitor closely for toxicity.</p>		
Warfarin, Acenocoumarol /nicoumalone (racemic mixture; R: CYP1A2, 3A,	May potentially inhibit anticoagulant metabolism; monitor for ↑ INR and adjust anticoagulant dose accordingly when	<p>May potentially induce or inhibit anticoagulant metabolism.</p> <p>One patient</p>	Anticoagulant concentrations may be increased when co-administered with etravirine. The international	May potentially induce anticoagulant metabolism; case reports where warfarin dosage	May potentially induce anticoagulant metabolism. Monitor for ↓ INR and adjust

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<p>2C19; S: 2C9 primarily)</p> <p>NB: The S-enantiomer of <u>warfarin</u> exhibits 2 to 5 times more anticoagulant activity than the R-enantiomer in humans, but generally has a more rapid clearance.</p> <p>The R(+) and S(-) enantiomers of <u>acenocoumarol</u> have comparable anticoagulant effects, but the S-enantiomer has a very short half-life; thus only the R-enantiomer provides a pharmacologic effect in vivo.</p>	starting and discontinuing therapy.	<p>required a 4-fold reduction in warfarin dose while on concomitant efavirenz and warfarin,¹⁸⁵ while another patient required a 50% increase in acenocoumarol dosage after initiating efavirenz therapy.¹⁸⁶</p> <p>Monitor for changes in INR and adjust anticoagulant dose accordingly when starting and discontinuing therapy.</p>	<p>normalized ratio (INR) should be monitored when an anticoagulant is combined with etravirine.⁴</p> <p>In a 50 year old HIV-positive patient stabilized on warfarin and emtricitabine monotherapy, initiation of the TRIO regimen (etravirine, darunavir/ritonavir and raltegravir) required a 45% increase in mean warfarin dose.¹⁸⁷</p>	<p>had to be doubled or exceeded maximum recommended daily dose to maintain therapeutic INR.¹⁸⁸ Monitor for ↓ INR and adjust anticoagulant dose accordingly when starting and discontinuing therapy.</p>	<p>anticoagulant dose accordingly when starting and discontinuing therapy.</p>
Enzyme Inducers (e.g., phenytoin, phenobarbital, carbamazepine, oxcarbazepine)	Significant ↓ delavirdine concentrations. Concomitant use of DLV and CYP3A inducers not recommended. ¹⁰⁸	Possible ↓ efavirenz concentrations. Dosage adjustments may be required.	Possible ↓ etravirine concentrations. Avoid combination. ⁴	Potential for ↓ NVP concentrations with concomitant use of agents which induce CYP3A4.	Avoid concomitant administration with potent CYP3A4 inducers, as rilpivirine concentrations may be reduced.
Enzyme Inhibitors (e.g., fluconazole, macrolides, nefazodone)	No delavirdine dosage adjustment recommended with inhibitors of CYP3A4 or CYP2D6. ¹⁰⁸			Potential for ↑ NVP concentrations.	Coadministration of CYP3A4 inhibitors with rilpivirine should be done with caution, as rilpivirine concentrations may be increased. Alternative agents without CYP3A4 inhibitory effects should be used whenever possible. If there is no alternative, additional safety monitoring is strongly recommended, including ECGs at baseline and 3-7

	Delavirdine (Rescriptor®)	Efavirenz (Sustiva®)	Etravirine (Intelence®)	Nevirapine (Viramune®)	Rilpivirine (Edurant®)
					days following initiation of the enzyme inhibitor.
Other classes: analgesics, antiarrhythmics, antidepressants, calcium channel blockers, neuroleptics, psychotropics.	Use delavirdine with caution in combination with calcium channel blockers, ergot derivatives (potential for ↑ drug conc. and toxicity). ¹⁰⁸	Efavirenz should not be administered concurrently with astemizole, bepridil, cisapride, midazolam, pimozide, triazolam, or ergot derivatives because competition for CYP3A4 by efavirenz could result in inhibition of metabolism of these drugs and create the potential for serious and/or life-threatening adverse events (eg, cardiac arrhythmias, prolonged sedation, or respiratory depression).	Concentrations of antiarrhythmics may be decreased in presence of etravirine. Coadminister with caution and measure drug concentrations if possible. ⁴	Potential for ↓ in concentrations of agents which are substrates of CYP3A4.	

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

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