

**Table 22b. Drug Interactions Among Antiretrovirals and Other Drugs: NNRTIs (Updated January 29, 2008)**

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<b>Drug Interactions Requiring Dose Modifications or Cautious Use</b>				
<b>Drugs Affected</b>	<b>Delavirdine (DLV)</b>	<b>Efavirenz (EFV)</b>	<b>Etravirine (ETR)</b>	<b>Nevirapine (NVP)</b>
<b>ANTIFUNGALS</b>				
<b>Fluconazole</b>	No clinically significant changes in DLV or fluconazole concentrations.	No clinically significant changes in EFV or fluconazole concentrations.	↑ ETR, ↔ fluconazole Dose: standard	Levels: NVP: Cmax, AUC, and Cmin ↑ 100%. Fluconazole: No change. Risk of hepatotoxicity may ↑ with this combination. If coadministered, monitor NVP toxicity.
<b>Itraconazole</b>			↑ ETR, ↓ itraconazole Dose adjustments for itraconazole may be necessary depending on other coadministered drugs, monitor itraconazole level.	
<b>Ketoconazole</b>	DLV: Cmin ↑ 50%. Ketoconazole: No data. Dose: Standard.	No data.	↑ ETR, ↓ ketoconazole Dose adjustments for ketoconazole may be necessary depending on other coadministered drugs.	Levels: Keto ↓ 63%. NVP ↑ 15%–30%. Dose: Not recommended.
<b>Posaconazole</b>			↑ ETR, ↔ posaconazole Dose: standard	
<b>Voriconazole</b>	Metabolism of voriconazole may be inhibited by DLV. Voriconazole may inhibit NNRTI metabolism. Frequently monitor for NNRTI toxicity and antifungal outcome.	Levels: EFV ↑ 44%. Voriconazole ↓ 77%. This combination is not recommended.	↑ ETR, ↑ voriconazole Dose adjustments for voriconazole may be necessary depending on other coadministered drugs, consider monitoring voriconazole level	Metabolism of voriconazole may be induced by NVP. Voriconazole may inhibit NNRTI metabolism. Carefully monitor for NNRTI toxicity and antifungal outcome.
<b>ANTI-MYCOBACTERIALS</b>				
<b>Clarithromycin</b>	Levels: Clarithromycin ↑ 100%. DLV ↑ 44%. Adjust dosage for renal failure.	Levels: Clarithromycin ↓ 39%. Monitor for efficacy or use alternative agent.	↑ ETR AUC 42%, ↓ clarithromycin AUC 39%, Cmin 53%, ↑ 14-OH-clarithromycin AUC 21% Alternatives to clarithromycin, such as azithromycin, should be considered for the treatment of MAC	Levels: NVP ↑ 26%. Clarithromycin ↓ 30%. Monitor for efficacy or use alternative agent.
<b>Rifabutin</b>	Levels: DLV ↓ 80%. Rifabutin ↑ 100%. Not recommended.	Levels: EFV unchanged. Rif ↓ 35%. Dose: ↑ rifabutin dose to 450–600mg QD or 600mg 3x/week.* EFV: Standard.	↓ ETR AUC 37% and Cmin 35%, ↓ rifabutin AUC 17% Cmin 24%, ↓ 25-O-desacetyl-rifabutin AUC 17% Cmin 22% Rifabutin dose of 300 mg daily if ETR is NOT coadministered with a RTV boosted PI If ETR is coadministered with DRV/RTV or SQV/RTV, and rifabutin is needed, consider alternative antiretroviral agent to ETR	Levels: NVP ↓ 16%. No dose adjustment.*
<b>Rifampin/ Rifapentine</b>	Levels: DLV ↓ 96%. Contraindicated.	Levels: EFV ↓ 25%. Dose: Maintain EFV dose at 600mg QD in patients weighing <60 kg or consider ↑ EFV to 800mg QD.	Potential for significant ↓ ETR Do not coadminister ETR with rifampin or rifapentine	Levels: NVP ↓ 20%–58%. Virologic consequences are uncertain; the potential for additive hepatotoxicity exists. If used, coadministration should be done with careful monitoring of virologic responses and toxicities.
<b>HORMONAL CONTRACEPTIVES</b>				
	Levels of ethinyl estradiol may increase. Clinical significance is unknown.	Levels: Ethinyl estradiol ↑ 37%. No data on other component. Use alternative or additional methods.	↑ ethinylestradiol AUC 22%, ↔ Norethindrone Dose: standard	Levels: Ethinyl estradiol ↓ approx 20%. Use alternative or additional methods.

\* These recommendations apply to regimens that do not include PIs, which can substantially increase rifabutin levels.

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<b>LIPID-LOWERING AGENTS</b>				
<b>Atorvastatin</b>	Potential for inhibition of atorvastatin metabolism. Use lowest possible dose and monitor for toxicity.	Levels: Atorvastatin AUC ↓ 43%; EFV unchanged. Dose: Adjust atorvastatin dose according to lipid responses, not to exceed the maximum recommended dose.	↔ ETR, ↓ atorvastatin AUC 37%, ↑ 2-OH-atorvastatin AUC 27% Cmax 76% Dose: standard; adjust atorvastatin dose based on response	No data.
<b>Fluvastatin</b>			↔ ETR, ↑ fluvastatin Dose adjustments for these HMG-CoA reductase inhibitors may be necessary	
<b>Pravastatin Rosuvastatin</b>	No data.	No data.	↔ ETR, ↔ pravastatin, ↔ rosuvastatin Dose: standard	No data.
<b>Simvastatin Lovastatin</b>	Levels: Potential for large increase in statin levels. Avoid concomitant use.	Levels: Simvastatin AUC ↓ by 58%; EFV unchanged. Dose: Adjust simvastatin dose according to lipid responses, not to exceed the maximum recommended dose.	↔ ETR, ↓ lovastatin, ↓ simvastatin Dose adjustments for these HMG-CoA reductase inhibitors may be necessary. If used with ritonavir-boosted PI, simvastatin and lovastatin should be avoided.	No data.
<b>ANTICONVULSANTS</b>				
<b>Carbamazepine Phenobarbital Phenytoin</b>	Levels: DLV Cmin ↓ 90% when coadministered with phenytoin, phenobarbital, or carbamazepine. Contraindicated.	Use with caution. CBZ and EFV AUCs ↓ 27% and 36%, respectively, when combined. One case report showed low EFV concs with phenytoin. Monitor anticonvulsant and EFV levels. If possible, use alternative anticonvulsant.	Potential for ↓ ETR & Anticonvulsant concentrations Do not coadminister ETR with carbamazepine, phenobarbital or phenytoin. Consider alternative anticonvulsants.	
<b>Methadone</b>	Levels: DLV unchanged; no data on methadone levels but potential for increased levels. Monitor for methadone toxicity; may require a dose reduction.	Levels: Methadone ↓ 60%. Opiate withdrawal common; increased methadone dose often necessary. Titrate methadone dose to effect.	↔ ETR, ↔ methadone Dose: standard; however, monitor for methadone withdrawal symptoms and adjust methadone as needed	Levels: NVP unchanged. Methadone ↓ significantly. Opiate withdrawal common when this combination is used; increased methadone dose often necessary. Titrate methadone dose to effect.
<b>Miscellaneous</b>	May increase levels of dapsone, warfarin, and quinidine. <b>Sildenafil:</b> Potential for increased concentrations and adverse effects. Use cautiously. Start with reduced dose of 25mg every 48 hours and monitor for adverse effects. <b>Vardenafil:</b> No data, but vardenafil AUC may be substantially increased. Start with a 2.5mg dose and do not exceed a single 2.5mg dose in 24 hours. <b>Tadalafil:</b> No data, but concomitant administration will likely result in substantial increase in tadalafil AUC and half-life (normal = 17.5 h). Start with a 5mg dose and do not exceed a single dose of 10mg every 72 hours. Coadministration of fluoxetine increases DLV Cmin 50%.	Monitor warfarin when used concomitantly.	↓ antiarrhythmics Dose: use with caution with antiarrhythmics concentration monitoring if available ↑ warfarin, Monitor INR ↑ diazepam - a decrease in diazepam may be needed dexamethasone (systemic) ↓ ETR Use with caution or alternative corticosteroid particularly for long term use ↓ cyclosporine, sirolimus, tacrolimus – monitor immunosuppressant levels ↓ sildenafil AUC 57% Dose: standard, may need to alter sildenafil dose based on clinical effect	No data.