



Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

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Table 19b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 1 of 7)

This table provides information relating to PK interactions between NNRTIs and non-ARV drugs. For interactions between ARV agents and for dosing recommendations, refer to Tables 19c, 20a and 20b.

Note: DLV is **not** included in this table. Please refer to the DLV FDA package insert for information regarding drug interactions.

Concomitant Drug Class/Name	NNRTI ^a	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers			
Antacids	RPV	↓ RPV expected when given simultaneously	Give antacids at least 2 hours before or at least 4 hours after RPV.
H2-Receptor Antagonists	RPV	↓ RPV	Give H2-receptor antagonists at least 12 hours before or at least 4 hours after RPV.
PPIs	RPV	<u>With omeprazole 20 mg daily:</u> • RPV AUC ↓ 40%, C _{min} ↓ 33%	Contraindicated. Do not coadminister.
Anticoagulants/Antiplatelets			
Warfarin	EFV, NVP	↑ or ↓ warfarin possible	Monitor INR and adjust warfarin dose accordingly.
	ETR	↑ warfarin possible	Monitor INR and adjust warfarin dose accordingly.
Clopidogrel	ETR	↓ activation of clopidogrel possible	ETR may prevent metabolism of clopidogrel (inactive) to its active metabolite. Avoid coadministration, if possible.
Anticonvulsants			
Carbamazepine Phenobarbital Phenytoin	EFV	<u>Carbamazepine plus EFV:</u> • Carbamazepine AUC ↓ 27% • EFV AUC ↓ 36% <u>Phenytoin plus EFV:</u> • ↓ EFV • ↓ phenytoin possible	Monitor anticonvulsant and EFV levels or, if possible, use alternative anticonvulsant to those listed.
	ETR	↓ anticonvulsant and ETR possible	Do not coadminister. Consider alternative anticonvulsant.
	NVP	↓ anticonvulsant and NVP possible	Monitor anticonvulsant and NVP levels and virologic responses or consider alternative anticonvulsant.
	RPV	↓ RPV possible	Contraindicated. Do not coadminister. Consider alternative anticonvulsant.
Oxcarbazepine	RPV	↓ RPV possible	Contraindicated. Do not coadminister. Consider alternative anticonvulsant.
Antidepressants			
Bupropion	EFV	Bupropion AUC ↓ 55%	Titrate bupropion dose based on clinical response.
Paroxetine	EFV, ETR	No significant effect	No dosage adjustment necessary.
Sertraline	EFV	Sertraline AUC ↓ 39%	Titrate sertraline dose based on clinical response.

Table 19b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 2 of 7)

Concomitant Drug Class/Name	NNRTI ^a	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antifungals			
Fluconazole	EFV	No significant effect	No dosage adjustment necessary.
	ETR	ETR AUC ↑ 86%	No dosage adjustment necessary. Use with caution.
	NVP	NVP AUC ↑ 110%	Increased risk of hepatotoxicity possible with this combination. Monitor NVP toxicity or use alternative ARV agent.
	RPV	↑ RPV possible	No dosage adjustment necessary. Clinically monitor for breakthrough fungal infection.
Isavuconazole	EFV, ETR, NVP	↓ isavuconazole possible	Dose adjustments for isavuconazole may be necessary. Consider monitoring isavuconazole level and antifungal response.
	RPV	↓ isavuconazole possible (likely to a lesser extent than with other NNRTIs) ↑ RPV possible	No dosage adjustment necessary. Clinically monitor for breakthrough fungal infection.
Itraconazole	EFV	Itraconazole and OH-itraconazole AUC, C _{max} , and C _{min} ↓ 35% to 44%	Failure to achieve therapeutic itraconazole concentrations has been reported. Avoid this combination if possible. If coadministered, closely monitor itraconazole concentration and adjust dose accordingly.
	ETR	↓ itraconazole possible ↑ ETR possible	Dose adjustments for itraconazole may be necessary. Monitor itraconazole level and antifungal response.
	NVP	↓ itraconazole possible ↑ NVP possible	Avoid combination if possible. If coadministered, monitor itraconazole concentration and adjust dose accordingly.
	RPV	↓ itraconazole possible ↑ RPV possible	No dosage adjustment necessary. Clinically monitor for breakthrough fungal infection.
Posaconazole	EFV	Posaconazole AUC ↓ 50% ↔ EFV	Avoid concomitant use unless the benefit outweighs the risk. If coadministered, monitor posaconazole concentration and adjust dose accordingly.
	ETR	↑ ETR possible	No dosage adjustment necessary.
	RPV	↓ posaconazole possible ↑ RPV possible	No dosage adjustment necessary. Clinically monitor for breakthrough fungal infection.
Voriconazole	EFV	Voriconazole AUC ↓ 77% EFV AUC ↑ 44%	Contraindicated at standard doses. <u>Dose adjustment:</u> • Voriconazole 400 mg BID, EFV 300 mg daily
	ETR	Voriconazole AUC ↑ 14% ETR AUC ↑ 36%	No dosage adjustment necessary; use with caution. Consider monitoring voriconazole level.
	NVP	↓ voriconazole possible ↑ NVP possible	Monitor for toxicity and antifungal response and/or voriconazole level.
	RPV	↓ voriconazole possible ↑ RPV possible	No dosage adjustment necessary. Clinically monitor for breakthrough fungal infection.

Table 19b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 3 of 7)

Concomitant Drug Class/Name	NNRTI ^a	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antimalarials			
Artemether/ Lumefantrine	EFV	Artemether AUC ↓ 79% DHA AUC ↓ 75% Lumefantrine AUC ↓ 56%	Consider alternative ARV or antimalarial drug. If used in combination, monitor closely for antimalarial efficacy and malaria recurrence.
	ETR	Artemether AUC ↓ 38% DHA AUC ↓ 15% Lumefantrine AUC ↓ 13% ETR AUC ↑ 10%	Clinical significance of the reduced antimalarial drug concentrations unknown. If used in combination with ETR, monitor closely for antimalarial efficacy.
	NVP	Artemether AUC ↓ 67% to 72% <u>DHA:</u> • Study results are conflicting. AUC ↓ 37% in one study, no difference in another. <u>Lumefantrine:</u> • Study results are conflicting. Lumefantrine AUC ↓ 25% to 58% in 2 studies but ↑ 56% in another.	Clinical significance unknown. If used, monitor closely for antimalarial efficacy and lumefantrine toxicity.
Atovaquone/ Proguanil	EFV	Atovaquone AUC ↓ 75% Proguanil AUC ↓ 43%	No dosage recommendation. Consider alternative drug for malaria prophylaxis, if possible.
Antimycobacterials			
Bedaquiline	EFV	↓ bedaquiline possible	Not recommended.
	NVP	↔ bedaquiline AUC	No dosage adjustment necessary.
Clarithromycin	EFV	Clarithromycin AUC ↓ 39%	Monitor for effectiveness or consider alternative agent, such as azithromycin, for MAC prophylaxis and treatment.
	ETR	Clarithromycin AUC ↓ 39% ETR AUC ↑ 42%	Consider alternative agent, such as azithromycin, for MAC prophylaxis and treatment.
	NVP	Clarithromycin AUC ↓ 31%	Monitor for effectiveness or use alternative agent, such as azithromycin, for MAC prophylaxis and treatment.
	RPV	↔ clarithromycin expected ↑ RPV possible	Consider alternative macrolide, such as azithromycin, for MAC prophylaxis and treatment.
Rifabutin	EFV	Rifabutin ↓ 38%	<u>Dose:</u> • Rifabutin 450–600 mg/day; or • Rifabutin 600 mg 3 times/week if EFV is not coadministered with a PI.
	ETR	Rifabutin and metabolite AUC ↓ 17% ETR AUC ↓ 37%	If ETR is used with an RTV-boosted PI, rifabutin should not be coadministered. <u>Dose:</u> • Rifabutin 300 mg once daily if ETR is not coadministered with a PI/r.
	NVP	Rifabutin AUC ↑ 17% and metabolite AUC ↑ 24% NVP C _{min} ↓ 16%	No dosage adjustment necessary. Use with caution.
	RPV	Rifabutin plus RPV 50 mg once daily compared to RPV 25 mg once daily alone: ↔ RPV AUC, C _{min}	Increase RPV dose to 50 mg once daily.

Table 19b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 4 of 7)

Concomitant Drug Class/Name	NNRTI ^a	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antimycobacterials, continued			
Rifampin	EFV	EFV AUC ↓ 26%	Maintain EFV dose at 600 mg once daily and monitor for virologic response. Consider therapeutic drug monitoring.
	ETR	Significant ↓ ETR possible	Do not coadminister.
	NVP	NVP ↓ 20% to 58%	Do not coadminister.
	RPV	RPV AUC ↓ 80%	Contraindicated. Do not coadminister.
Rifapentine	EFV	↔ EFV concentrations	No dosage adjustment necessary.
	ETR, NVP, RPV	↓ NNRTI possible	Do not coadminister.
Antipneumocystis and Antitoxoplasmosis Drugs			
Atovaquone	EFV	Atovaquone AUC ↓ 44% to 47%	Consider alternative agent for PCP or toxoplasmosis treatment or use alternative ARV drug. If used in combination, monitor therapeutic efficacy of atovaquone.
Benzodiazepines			
Alprazolam	EFV, ETR, NVP, RPV	No data	Monitor for therapeutic effectiveness of alprazolam.
Diazepam	ETR	↑ diazepam possible	Decreased dose of diazepam may be necessary.
Lorazepam	EFV	Lorazepam C _{max} ↑ 16%, AUC ↔	No dosage adjustment necessary.
Midazolam	EFV	Significant ↑ midazolam expected	Do not coadminister with oral midazolam. Parenteral midazolam can be used with caution as a single dose and can be given in a monitored situation for procedural sedation.
Triazolam	EFV	Significant ↑ triazolam expected	Do not coadminister.
Cardiac Medications			
Dihydropyridine CCBs	EFV, NVP	↓ CCBs possible	Titrate CCB dose based on clinical response.
Diltiazem Verapamil	EFV	Diltiazem AUC ↓ 69% ↓ verapamil possible	Titrate diltiazem or verapamil dose based on clinical response.
	NVP	↓ diltiazem or verapamil possible	
Corticosteroids			
Dexamethasone	EFV, ETR, NVP	↓ EFV, ETR, NVP possible	Consider alternative corticosteroid for long-term use. If dexamethasone is used with NNRTI, monitor virologic response.
	RPV	Significant ↓ RPV possible	Contraindicated with more than a single dose of dexamethasone.
Hepatitis C Direct-Acting Antiviral Agents			
Daclatasvir	EFV, ETR, NVP	Daclatasvir C _{min} ↓ 17%, following daclatasvir 120 mg once daily + EFV 600 mg daily	Daclatasvir 90 mg once daily.
	RPV	No data	No dosage adjustment necessary.

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Concomitant Drug Class/Name	NNRTI ^a	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments	
Hepatitis C Direct-Acting Antiviral Agents, continued				
Dasabuvir plus Paritaprevir/Ombitasivir/RTV	EFV	No data	Contraindicated. Do not coadminister.	
	ETR, NVP	↓ DAAs possible	Do not coadminister.	
	RPV	RPV AUC ↑ 150% to 225%	Do not coadminister because of potential for QT interval prolongation with higher concentrations of RPV.	
Elbasvir/Grazoprevir	EFV	Elbasvir AUC ↓ 54% Grazoprevir AUC ↓ 83% EFV ↔ by grazoprevir EFV ↔ AUC by elbasvir	Contraindicated.	
	ETR, NVP	↓ elbasvir, grazoprevir expected	Do not coadminister.	
	RPV	Elbasvir, grazoprevir and RPV ↔	No dosage adjustment necessary.	
Ledipasvir/Sofosbuvir	EFV	Ledipasvir AUC, C _{min} , C _{max} – all ↓ 34% Sofosbuvir: no significant effect	No dosage adjustment necessary.	
	ETR, NVP, RPV	No significant effect expected		
Simeprevir	EFV	Simeprevir AUC ↓ 71%, C _{min} ↓ 91% ↔ EFV	Coadministration is not recommended.	
	ETR, NVP	↓ simeprevir expected	Coadministration is not recommended.	
	RPV	↔ simeprevir and RPV	No dosage adjustment necessary.	
Herbal Products				
St. John's Wort	EFV, ETR, NVP, RPV	↓ NNRTI	Do not coadminister.	
Hormonal Contraceptives				
Hormonal Contraceptives	EFV	Ethinyl estradiol ↔ Levonorgestrel (oral) AUC ↓ 64% Norelgestromin AUC ↓ 64% Etonogestrel (implant) AUC ↓ 63% Levonorgestrel (implant) AUC ↓ 48%	Use alternative or additional contraceptive methods. Norelgestromin and levonorgestrel are active metabolites of norgestimate. Unintended pregnancies were observed in women who used EFV and levonorgestrel implant concomitantly.	
		ETR	Ethinyl estradiol AUC ↑ 22% Norethindrone: no significant effect	No dosage adjustment necessary.
		NVP	Ethinyl estradiol AUC ↓ 29%, C _{min} ↓ 58% Norethindrone AUC ↓ 18% Etonogestrel (metabolite of oral desogestrel) ↓ 22%	Consider alternative or additional contraceptive methods.
			DMPA: no significant change Levonorgestrel implant: AUC ↑ 30%	No dosage adjustment necessary. No dosage adjustment necessary.
	RPV	Ethinyl estradiol: no significant change Norethindrone: no significant change	No dosage adjustment necessary.	

Table 19b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 6 of 7)

Concomitant Drug Class/Name	NNRTI ^a	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Levonorgestrel For emergency contraception	EFV	Levonorgestrel AUC ↓ 58%	Effectiveness of emergency postcoital contraception may be diminished.
HMG-CoA Reductase Inhibitors			
Atorvastatin	EFV, ETR	Atorvastatin AUC ↓ 32% to 43%	Adjust atorvastatin according to lipid responses, not to exceed the maximum recommended dose.
	RPV	Atorvastatin AUC ↔ Atorvastatin metabolites ↑	No dosage adjustment necessary.
Fluvastatin	ETR	↑ fluvastatin possible	Dose adjustments for fluvastatin may be necessary.
Lovastatin Simvastatin	EFV	Simvastatin AUC ↓ 68%	Adjust simvastatin dose according to lipid responses, not to exceed the maximum recommended dose. If EFV is used with a PI/r, simvastatin and lovastatin should be avoided.
	ETR, NVP	↓ lovastatin possible ↓ simvastatin possible	Adjust lovastatin or simvastatin dose according to lipid responses, not to exceed the maximum recommended dose. If ETR or NVP is used with a PI/r, simvastatin and lovastatin should be avoided.
Pitavastatin	EFV	Pitavastatin AUC ↓ 11%, C _{max} ↑ 20%	No dosage adjustment necessary.
	ETR, NVP, RPV	No data	No significant effect expected. No dosage adjustment necessary.
Pravastatin Rosuvastatin	EFV	Pravastatin AUC ↓ 44% Rosuvastatin: no data	Adjust statin dose according to lipid responses, not to exceed the maximum recommended dose.
	ETR	No significant effect expected	No dosage adjustment necessary.
Immunosuppressants			
Cyclosporine Sirolimus Tacrolimus	EFV, ETR, NVP	↓ immunosuppressant possible	Increase in immunosuppressant dose may be necessary. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with specialist as necessary.
Narcotics/Treatments for Opioid Dependence			
Buprenorphine sublingual/buccal	EFV	Buprenorphine AUC ↓ 50% Norbuprenorphine ^b AUC ↓ 71%	No dosage adjustment recommended; monitor for withdrawal symptoms.
	ETR	Buprenorphine AUC ↓ 25%	No dosage adjustment necessary.
	NVP	No significant effect	No dosage adjustment necessary.
Buprenorphine implant	EFV, ETR, NVP	No data	Clinical monitoring is recommended if NNRTI is initiated after insertion of buprenorphine implant.
Methadone	EFV	Methadone AUC ↓ 52%	Opioid withdrawal common; increased methadone dose often necessary.
	ETR	No significant effect	No dosage adjustment necessary.
	NVP	Methadone AUC ↓ 37% to 51% NVP: no significant effect	Opioid withdrawal common; increased methadone dose often necessary.
	RPV	R-methadone ^c AUC ↓ 16%	No dosage adjustment necessary, but monitor for withdrawal symptoms.

Table 19b. Drug Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 7 of 7)

Concomitant Drug Class/Name	NNRTI ^a	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
PDE5 Inhibitors			
Avanafil	EFV, ETR, NVP, RPV	No data	Coadministration is not recommended.
Sildenafil	ETR	Sildenafil AUC ↓ 57%	May need to increase sildenafil dose based on clinical effect.
	RPV	↔ sildenafil	No dosage adjustment necessary.
Tadalafil	ETR	↓ tadalafil possible	May need to increase tadalafil dose based on clinical effect.
Vardenafil	ETR	↓ vardenafil possible	May need to increase vardenafil dose based on clinical effect.

^a Approved dose for RPV is 25 mg once daily. Most PK interaction studies were performed using 75 to 150 mg per dose.

^b Norbuprenorphine is an active metabolite of buprenorphine.

^c R-methadone is the active form of methadone.

Key to Symbols: ↑ = increase, ↓ = decrease, ↔ = no change

Key to Acronyms: ARV = antiretroviral; AUC = area under the curve; BID = twice daily; CCB = calcium channel blockers; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; DAAs = direct-acting antivirals; DHA = dihydroartemisinin; DLV = delavirdine; DMPA = depot medroxyprogesterone acetate; EFV = efavirenz; ETR = etravirine; FDA = Food and Drug Administration; HMG-CoA = hydroxy-methylglutaryl-coenzyme A; INR = international normalized ratio; MAC = *Mycobacterium avium* complex; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; OH-itraconazole = active metabolite of itraconazole; **PCP = *Pneumocystis jiroveci* pneumonia**; PDE5 = phosphodiesterase type 5; PI = protease inhibitor; PK = pharmacokinetic; PPI = proton pump inhibitor; RPV = rilpivirine; RTV = ritonavir