Resource: ART Drug-Drug Interactions

August 2024

Table 12: Efavirenz (EFV) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Warfarin	Metabolism of warfarin could potentially increase (or more rarely decrease).	• Use cautiously with warfarin; if use is necessary, increase INR monitoring. • If INR increases, decrease warfarin dose. • If INR decreases, increase warfarin dose slowly.
Bupropion [Robertson, et al. 2008]	EFV induces bupropion metabolism.	Monitor for clinical effect and increase as needed, but do not exceed recommended maximum dose.
Levonorgestrel/norgestimate, levonorgestrel [Scarsi, et al. 2016; Carten, et al. 2012]	EFV may induce CYP3A, the enzyme that is primarily responsible for metabolism of levonorgestrel.	Levonorgestrel or norgestimate effectiveness may be decreased.
Cilostazol	EFV may reduce cilostazol concentrations.	Monitor for antiplatelet effect; may be necessary to use alternative antiplatelet medication or alternative ARV.
Dipyridamole	EFV may induce UGT enzymes, which are responsible for metabolism.	Monitor for antiplatelet effect; use alternative ARV if necessary.
Ticagrelor, clopidogrel	EFV reduces ticagrelor concentrations and conversion of clopidogrel to its active metabolite.	Use with EFV may reduce antiplatelet effect; monitor closely for efficacy and use alternative ARV if necessary.
Statins	• **Simvastatin, lovastatin:** EFV may decrease concentrations. • **Atorvastatin, pravastatin, fluvastatin:** EFV may modestly reduce concentrations.	• **Simvastatin, lovastatin:** Monitor for efficacy. May warrant increases in statin dose. Do not increase dose above maximum recommended statin dose. • **Atorvastatin, pravastatin, fluvastatin:** Monitor for cholesterol-lowering effect of statins. May require increased dose.
Pioglitazone	EFV may increase concentrations through CYP2C8 inhibition. No significant interactions are expected.	Monitor for signs of adverse effects with EFV; decrease dose if necessary.
Saxagliptin, sitagliptin	EFV may decrease concentrations.	Monitor for efficacy; if necessary, increase dose of DPP-4 inhibitor.
Inhaled and injected corticosteroids	Coadministration may reduce corticosteroid concentrations.	**Dexamethasone (systemic):** Consider alternative corticosteroid for long-term use; if benefits of use outweigh risks, monitor for virologic response.
Trazodone	EFV may decrease trazodone concentrations.	Monitor for antidepressant and/or sedative effects.
Benzodiazepines	**Alprazolam, diazepam:** EFV may reduce alprazolam and diazepam concentrations.	• **Alprazolam:** Monitor for benzodiazepine withdrawal with concomitant EFV use. • **Alprazolam, clonazepam, diazepam:** Titrate slowly to achieve clinical effect; monitor for benzodiazepine efficacy.

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Sleep medications	**Zolpidem:** EFV may reduce zolpidem concentrations.	• **Zolpidem, eszopiclone:** Monitor for efficacy; no dose adjustments are recommended. • **Suvorexant:** Monitor for efficacy; do not exceed 20 mg per day.
Antipsychotics	• **Quetiapine:** EFV may reduce quetiapine concentrations. • **Aripiprazole, brexpiprazole:** EFV may decrease aripiprazole and brexpiprazole concentrations. • **Risperidone, olanzapine:** EFV may decrease risperidone and olanzapine efficacy.	**Quetiapine, aripiprazole, brexpiprazole, risperidone, olanzapine:** Titrate slowly to achieve clinical effect; monitor for efficacy and adverse effects.
Carbamazepine, oxcarbazepine, phenobarbital, phenytoin	Coadministration may significantly reduce concentrations of ARVs through induction of CYP450 system.	• Coadministration is not recommended; use alternative anticonvulsant. • If benefit of use outweighs risk, monitor carefully for efficacy and toxicity. • Perform TDM if use cannot be avoided.
Lamotrigine, zonisamide	EFV may reduce lamotrigine or zonisamide efficacy.	Titrate slowly to achieve clinical effect; monitor for efficacy.
Opioid analgesics and tramadol	• **Morphine, hydromorphone:** Metabolism could be reduced by EFV. • **Oxycodone** may be metabolized faster to inactive metabolite by EFV. • **Meperidine:** Coadministration can potentially increase amount of neurotoxic metabolite, thereby increasing seizure risk. • **Tramadol:** EFV may reduce tramadol concentration without affecting pathway that increases development of more potent active metabolites.	• **Morphine, hydromorphone:** Monitor for signs of opiate toxicity when using with EFV. • **Oxycodone:** Dose adjustment of oxycodone may be required when dosing with EFV. • **Meperidine:** If possible, avoid concomitant use; use alternative opiate pain medication or ARV. • **Tramadol:** When given with tramadol, a priori dose adjustments are necessary.
Hormonal contraceptives	EFV decreases concentrations of combined progestins.	• **Ethinyl estradiol; norgestimate and metabolites:** Use alternative or additional contraceptive methods; unintended pregnancies have been reported in individuals using levonorgestrel implants. • **Norethindrone, drospirenone, etonogestrel:** Consider alternative or additional contraceptive method or alternative ARV. • **Ulipristal:** Monitor closely for reduced efficacy.
Erectile and sexual dysfunction agents	• **PDE5 inhibitors:** EFV may reduce effectiveness of PDE5 inhibitors (sildenafil, vardenafil, and tadalafil). • **Flibanserin:** EFV may reduce flibanserin concentrations.	• **PDE5 inhibitors:** Monitor for clinical effect; if dose increase is needed to achieve desired clinical effect, titrate under medical supervision to lowest effective dose. • **Flibanserin:** Do not coadminister.
Methadone [Kharasch, et al. 2012; Gruber and McCance-Katz 2010; Clarke, et al. 2001]	EFV induces methadone metabolism via CYP3A4 and reduces methadone concentrations.	Titrate to achieve clinical effect; monitor for signs and symptoms of opioid withdrawal.

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Buprenorphine (BUP) [Gruber and McCance-Katz 2010; McCance-Katz, et al. 2006]	• EFV induces BUP metabolism via CYP3A4. • When given with BUP (monotherapy), EFV significantly reduces BUP concentrations, but no patients developed opioid withdrawal.	When given with BUP, dose adjustments are unlikely to be required, but monitor for withdrawal symptoms. If withdrawal symptoms occur, increase BUP dose accordingly.
NS3/4A inhibitors (glecaprevir, simeprevir, grazoprevir, etc.) [Garrison, et al. 2018; Soriano, et al. 2017]	EFV induces NS3/4A PI metabolism via CYP3A4.	Concomitant use is not recommended (may result in failure of HCV treatment regimens containing PIs, reducing SVR rates and increasing resistance).
Daclatasvir [Garrison, et al. 2018; Soriano, et al. 2017]	EFV induces daclatasvir metabolism via CYP3A4.	Increase daclatasvir dose to 60 mg per day.
Sofosbuvir/velpatasvir (available as coformulated product) [Greig 2016]	EFV may decrease velpatasvir levels through CYP3A induction.	Coadministration of sofosbuvir/velpatasvir is contraindicated.
Cyclosporine, tacrolimus	EFV may lower concentrations.	• Adjust dose of cyclosporine and tacrolimus based on efficacy and TDM. • Conduct TDM more frequently for 2 weeks when starting or stopping NNRTI therapy.
Rifabutin, rifampin, rifapentine	• **Rifabutin:** EFV induction of CYP3A reduces rifabutin bioavailability, but coadministration does not affect EFV levels. • **Rifampin, rifapentine:** No clinically significant interactions are expected.	• **Rifabutin:** With concomitant EFV, dose rifabutin at 450 mg to 600 mg daily. • **Rifampin:** – Dose EFV at 600 mg daily when administered concomitantly. – Do not use EFV 400 mg daily. • **Rifapentine:** No dose adjustments are necessary.
COVID-19 therapeutics	• **Molnupiravir and monoclonal antibodies** do not affect CYP450, P-gP, or other drug metabolism transporters. • **Nirmatrelvir/RTV:** Inhibition of CYP3A4, P-gP, and other transporters may increase plasma concentrations of other medications.	• **Molnupiravir, monoclonal antibodies:** Drug interactions are unlikely. • **Nirmatrelvir/RTV:** Drug interactions are unlikely; EFV levels may increase.
Mpox treatments	**Tecovirimat** is a weak inducer of CYP3A and a weak inhibitor of CYP2C8 and CYP2C19; use may increase or decrease plasma concentrations of other medications.	**Tecovirimat** may reduce NNRTI levels, though effects are not likely to be clinically relevant. No dose adjustment in either drug is necessary.
Gender-affirming hormones	• **Estradiol:** EFV may reduce estradiol levels via CYP3A induction. • **Finasteride, dutasteride:** EFV may reduce finasteride and dutasteride levels via CYP3A induction. • **Progestins (oral medroxyprogesterone, micronized progesterone):** EFV may reduce progestin levels via CYP3A induction. • **Testosterone:** EFV may reduce testosterone levels via CYP3A induction.	• **Estradiol:** Monitor serum estradiol levels; may require increased estradiol dose. • **Finasteride, dutasteride, progestins (oral medroxyprogesterone, micronized progesterone), testosterone:** No dose adjustments are necessary.

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Lenacapavir (LEN)	CYP3A4 and P-gP induction associated with concomitant HIV treatment potentially deceases LEN levels.	Do not coadminister.
ADHD medications	**Modafinil:** CYP3A4 induction may reduce NNRTI levels.	**Modafinil:** Avoid concurrent use due to potential loss of virologic response.
Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ARV, antiretroviral; CYP, cytochrome P450; DPP-4, dipeptidyl peptidase-4; HCV, hepatitis C virus; INR, international normalized ratio; NNRTI, non-nucleoside reverse transcriptase inhibitor; NS3/4A, nonstructural protein 3/4A; PDE5, phosphodiesterase type 5; P-gP, P-glycoprotein; PI, protease inhibitor; RTV, ritonavir; SVR, sustained viral response; TDM, therapeutic drug monitoring; UGT, uridine diphosphate glucuronosyltransferase; VIGIV, vaccinia immune globulin intravenous. **No significant interactions/no dose adjustments necessary** (see guideline section Drug-Drug Interactions by Common Medication Class)**:** Common oral antibiotics; antihypertensive medications; acid-reducing agents; polyvalent cations; asthma and allergy medications; long-acting beta agonists; nonopioid pain medications; alpha-adrenergic antagonists for benign prostatic hyperplasia; alcohol, disulfiram, and acamprosate.		

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