Efavirenz (EFV) Interactions (also see drug package inserts)		NYSDOH AI Clinical Guidelines Program | www.hivguidelines.org
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Warfarin	Could potentially increase (or more rarely decrease) metabolism of warfarin.	• Use cautiously with warfarin, and if use is necessary, increase monitoring of INR. • Increase dose slowly if INR decreases. Decrease dose if INR increases.
Bupropion [Robertson, et al. 2008]	EFV may induce CYP2B6, the enzyme that is primarily responsible for metabolism of bupropion.	Monitor clinical effect and increase as needed, but do not exceed recommended maximum dose.
Levonorgestrel/norgestimate, levonorgestrel [Carten, et al. 2012; Scarsi, et al. 2016]	EFV may induce CYP3A, the enzyme that is primarily responsible for metabolism of levonorgestrel.	Effectiveness of levonorgestrel or norgestimate may be decreased.
Cilostazol	May reduce concentrations of cilostazol.	Monitor for antiplatelet effect; may be necessary to use an alternative antiplatelet drug or alternative ARV agent.
Dipyridamole	EFV may induce UGT enzymes, which are responsible for metabolism.	Monitor for antiplatelet effect; use another ARV agent if necessary.
Ticagrelor, clopidogrel	EFV reduce ticagrelor concentrations and the conversion of clopidogrel to its active metabolite.	Use with EFV may reduce the antiplatelet effect; monitor closely and use an alternative ARV agent if necessary.
Statins	• **Simvastatin, lovastatin:** Could potentially decrease concentrations. • Atorvastatin, pravastatin, fluvastatin: May modestly reduce concentrations. • Pitavastatin, rosuvastatin: No interactions expected.	• **Simvastatin, lovastatin:** Monitor for efficacy. May warrant increases in statin dose. Do not increase dose above maximum recommended statin dose. • **Atorvastatin, pravastatin, fluvastatin:** Monitor cholesterol-lowering effect of statins. May require increased dose. • **Pitavastatin, rosuvastatin:** No dose adjustments necessary.
Pioglitazone	EFV may increase concentrations by inhibition of CYP2C8. No significant interactions expected.	Monitor for signs of adverse events with EFV; decrease dose if necessary.
Saxagliptin, sitagliptin	EFV may decrease concentration.	Monitor for efficacy; if necessary, increase dose of the DPP-4 inhibitor.
Inhaled and injected corticosteroids	Coadministration may reduce concentrations of corticosteroids.	**Systemic dexamethasone:** Consider alternative corticosteroid for long-term use; if benefits of use outweigh risks, monitor virologic response.
Trazodone	May decrease trazodone concentrations.	Monitor antidepressant and/or sedative effects.
Bupropion	EFV induces bupropion metabolism.	Monitor clinical effect and increase as needed, but do not exceed recommended maximum dose.
Benzodiazepines	**Alprazolam, diazepam:** Potential for reduced alprazolam and diazepam concentrations.	• **Alprazolam:** Monitor for benzodiazepine withdrawal if EFV is added. • **Alprazolam, clonazepam, diazepam:** Monitor for benzodiazepine efficacy; titrate slowly as needed for effect.

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Class or Drug	**Mechanism of Action**	**Clinical Comments**
Sleep medications	**Zolpidem:** Potential for reduced concentrations of zolpidem.	• **Zolpidem, eszopiclone:** Monitor for efficacy; no dose adjustments recommended. • **Suvorexant:** Monitor for efficacy; do not exceed 20 mg per day.
Antipsychotics	• **Quetiapine:** Concentrations of quetiapine may be reduced. • **Aripiprazole, brexpiprazole:** Concentrations of aripiprazole and brexpiprazole may be decreased. • **Risperidone, olanzapine:** May decrease efficacy of risperidone and olanzapine.	• **Quetiapine:** Monitor for efficacy; titrate slowly as needed; monitor for adverse effects. • **Aripiprazole, brexpiprazole:** Monitor for efficacy; titrate dose slowly as needed; monitor for adverse effects. • **Risperidone, olanzapine:** Monitor for efficacy; titrate slowly as needed; monitor for adverse effects.
Carbamazepine, oxcarbazepine, phenobarbital, phenytoin	Coadministration may significantly reduce concentrations of ARV agents 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 therapeutic drug monitoring if use cannot be avoided.
Lamotrigine, zonisamide	EFV may reduce efficacy of lamotrigine or zonisamide.	Monitor efficacy; titrate dose slowly as needed.
Opioid analgesics and tramadol	• **Morphine, hydromorphone:** Metabolism could potentially be reduced by EFV. • **Oxycodone:** May be metabolized faster to an inactive metabolite by EFV. • **Meperidine:** Coadministration can potentially increase amount of neurotoxic metabolite and thereby increase risk of seizures. • **Tramadol:** May reduce concentration of tramadol 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 agent. • **Tramadol:** When given with tramadol, a priori dose adjustments are necessary.
Hormonal contraceptives	Decreased concentrations of combined progestins.	• **Ethinyl estradiol; norgestimate, metabolites:** Use alternative or additional contraceptive methods; unintended pregnancies have been reported in individuals using levonorgestrel implant. • **Norethindrone, drospirenone, etonogestrel:** Consider alternative or additional contraceptive method or alternative ARV agent. • **Ulipristal:** Efficacy may be reduced; monitor closely.
Erectile and sexual dysfunction agents	• **PDE5 inhibitor:** Potential for reduced effectiveness of PDE5 inhibitors (sildenafil, vardenafil, and tadalafil). • **Flibanserin:** Potential for reduced concentrations of flibanserin.	• **PDE5 inhibitors:** Monitor 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 [Clarke, et al. 2001; Gruber and McCance-Katz 2010; Kharasch, et al. 2012]	EFV induces methadone metabolism via CYP3A4. Reduces methadone concentrations.	Monitor for signs and symptoms of opioid withdrawal and titrate methadone dose to effect.

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Class or Drug	**Mechanism of Action**	**Clinical Comments**
Buprenorphine (BUP) [McCance-Katz, et al. 2006; Gruber and McCance-Katz 2010]	• EFV induces BUP metabolism via CYP3A4. • When given with BUP (monotherapy), 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.) [Soriano, et al. 2017; Garrison, et al. 2018]	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 [Soriano, et al. 2017; Garrison, et al. 2018]	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 levels of velpatasvir through induction of CYP3A.	Coadministration of sofosbuvir/velpatasvir is contraindicated.
Cyclosporine, tacrolimus	Concentrations may be lower when used with EFV.	• Dose adjust cyclosporine and tacrolimus based on efficacy and therapeutic drug monitoring (TDM). • Conduct TDM more frequently for 2 weeks when starting or stopping NNRTI therapy.

Abbreviations: ARV, antiretroviral; BUP, buprenorphine; CYP, cytochrome P450; HCV, hepatitis C virus; INR, international normalized ratio; NNRTI, non-nucleoside reverse transcriptase inhibitor; NS3/4A, nonstructural protein 3/4A; PDE5, phosphodiesterase type 5; PI, protease inhibitor; SVR, sustained viral response; UGT, uridine diphosphate glucuronosyltransferase.
No significant interactions/no dose adjustments necessary: Common oral antibiotics; drugs used as antihypertensive medicines; acid-reducing agents; polyvalent cations; asthma and allergy medications; long-acting beta agonists; non-opioid pain medications; alcohol, disulfiram, and acamprosate.

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