ART Drug-Drug Interactions: Etravirine (ETR) Interactions

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Table 13: Etravirine (ETR) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Aliskiren	ETR is a minor inhibitor of P-gP and may minimally increase aliskiren concentrations, but this has not been studied.	When using with ETR, monitor for aliskiren-related adverse effects; switch to alternative antihypertensive medicine or ARV if necessary.
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.
Antiplatelet drugs [Kakuda, et al. 2011; Rathbun and Liedtke 2010]	• **Cilostazol:** ETR may reduce cilostazol concentrations. • **Dipyridamole:** ETR may induce UGT enzymes, which are responsible for metabolism. • **Ticagrelor, clopidogrel:** ETR reduces ticagrelor concentrations and conversion of clopidogrel to its active metabolite. • **Vorapaxar:** When coadministered with ETR, vorapaxar levels expected to be reduced.	• **Cilostazol:** Monitor for antiplatelet effect; may be necessary to use alternative antiplatelet drug or alternative ARV. • **Dipyridamole:** Monitor for antiplatelet effect; use another ARV if necessary. • **Ticagrelor, clopidogrel:** Use with ETR may reduce antiplatelet effect; monitor closely for efficacy and use alternative ARV if possible. • **Prasugrel:** When coadministered with ETR, no dose adjustments are necessary. • **Vorapaxar:** No data available.
Statins	• **Simvastatin, lovastatin:** ETR may decrease concentrations. • **Atorvastatin, pravastatin, fluvastatin:** ETR 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 if necessary.
Saxagliptin, sitagliptin	ETR 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	ETR may decrease trazodone concentrations.	Monitor for antidepressant and/or sedative effects.
Bupropion	No significant interactions are expected.	Monitor for clinical effect and increase as needed, but do not exceed recommended maximum dose.

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Alprazolam	ETR may reduce alprazolam concentrations.	Monitor for benzodiazepine withdrawal.
Diazepam	ETR may reduce diazepam concentrations.	No dose adjustments are necessary.
Sleep medications	**Zolpidem:** ETR 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	• **Aripiprazole, brexpiprazole:** ETR may decrease aripiprazole and brexpiprazole concentrations. • **Risperidone:** ETR may decrease risperidone efficacy.	**Aripiprazole, brexpiprazole, risperidone:** 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	ETR may reduce lamotrigine or zonisamide efficacy.	Titrate slowly to achieve clinical effect; monitor for efficacy.
Hormonal contraceptives	Information is based on what is known with EFV drug interactions.	• **Etonogestrel:** No data available; consider alternative or additional contraceptive methods or alternative ARV. • **Ulipristal:** Monitor closely for reduced efficacy.
Erectile and sexual dysfunction agents	• **PDE5 inhibitors:** ETR may reduce effectiveness of PDE5 inhibitors (sildenafil, vardenafil, and tadalafil). • **Flibanserin:** ETR 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.
Buprenorphine	No significant interactions are expected.	Titrate opioid or antagonist as required to achieve clinical effect; monitor for signs of withdrawal or opioid toxicity.
Methadone	ETR may slightly increase methadone concentrations.	• Titrate opioid or antagonist as required to achieve clinical effect; monitor for signs of withdrawal or opioid toxicity. • Monitor for signs of methadone toxicity; reduce dose if necessary.
Cyclosporine, tacrolimus	ETR may lower concentrations.	• Adjust cyclosporine and tacrolimus dose based on efficacy and TDM. • Conduct TDM more frequently for 2 weeks when starting or stopping NNRTI therapy.
HCV PIs ("-previr" drugs) [Mak, et al. 2018; Kaur, et al. 2015; Yeh 2015]	ETR may decrease HCV PI levels through CYP3A induction.	Do not coadminister.

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Sofosbuvir/velpatasvir (available as coformulated product) [Greig 2016]	ETR may decrease velpatasvir levels through CYP3A induction and (weak) P-gP inhibition.	Do not coadminister.
Daclatasvir [Garrison, et al. 2018]	ETR induces CYP3A, lowering daclatasvir levels.	Increase dose of daclatasvir to 90 mg per day.
Atazanavir (ATV) [Marzolini, et al. 2016; Orrell, et al. 2015]	• ETR is a substrate and inducer of CYP3A4. • COBI and ATV are substrates and inhibitors of CYP3A4.	• Administration with RTV-boosted ATV results in decreased ATV exposure, but decrease is not considered relevant; no dose adjustments are necessary. • Due to potential for decreased ARV efficacy, avoid use of ETR with COBI. When these medications are given together, COBI concentrations are decreased. • When possible, avoid concomitant use of ETR and unboosted ATV. ETR with unboosted ATV results in significant decreases in ATV exposure.
Dolutegravir (DTG) [Green, et al. 2017]	• ETR induces UGT1A1 and CYP3A enzymes. • DTG is a substrate of UGT1A1 and CYP3A enzymes.	ETR reduces DTG concentrations. Do not use concomitantly unless boosted PI is also part of treatment regimen.
Rifabutin, rifampin, rifapentine	• **Rifabutin:** When used concomitantly, increased rifabutin levels are expected and decreased ETR levels may occur. • **Rifampin, rifapentine**: CYP3A induction reduces ETR bioavailability.	• **Rifabutin:** – If ETR and rifabutin are used concomitantly, dose rifabutin at 300 mg daily, with no changes to ETR dose. Continue rifabutin 300 mg daily dosing until at least 2 weeks after rifabutin is stopped. – Concomitant use of boosted PI with ETR and rifabutin is contraindicated. • **Rifampin, rifapentine:** Concomitant use is contraindicated.
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. • **Brincidofovir, cidofovir, VIGIV:** Drug interactions are unlikely.
Gender-affirming hormones	• **Estradiol:** ETR could induce CYP3A and could decrease estradiol levels. • **Finasteride, testosterone:** Levels may decrease when taken concomitantly with ETR.	• **Estradiol:** No dose adjustments are recommended; when taken concomitantly with ETR, monitor for signs of estrogen deficiency or excess. • **Finasteride, testosterone:** No dose adjustments are recommended.

Abbreviations: ARV, antiretroviral; COBI, cobicistat; CYP, cytochrome P450; DPP-4, dipeptidyl peptidase-4; EFV, efavirenz; HCV, hepatitis C virus; INR, international normalized ratio; NNRTI, non-nucleoside reverse transcriptase inhibitor; P-gP, P-glycoprotein; PDE5, phosphodiesterase type 5; PI, protease inhibitor; RTV, ritonavir; TDM, therapeutic drug monitoring; UGT, uridine diphosphate glucuronosyltransferase; VIGIV, vaccinia immune globulin intravenous.

No significant interactions/no dose adjustments necessary: Common oral antibiotics (Table 19); acid-reducing agents (Table 25); polyvalent cations (Table 26); asthma and allergy medications (Table 27); long-acting beta agonists (Table 28); nonopioid pain medications (Table 35); opioid analgesics and tramadol (Table 36); alpha-adrenergic antagonists for benign prostatic hyperplasia (Table 39); alcohol, disulfiram, and acamprosate (Table 41); COVID-19 therapeutics (Table 45).

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