Boosted Elvitegravir (EVG) Interactions (also see drug package inserts)		NYSDOH AI Clinical Guidelines Program | www.hivguidelines.org
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Antacids	EVG chelates with polyvalent cations, which may reduce the efficacy of both agents.	Administer at least 2 hours before or 6 hours after EVG.
Factor Xa inhibitors [Egan, et al. 2014]	• Factor Xa inhibitors are substrates of P-gP and CYP3A. • COBI inhibits P-gP and CYP3A. • May increase concentrations, increasing bleeding risk.	• **Rivaroxaban, edoxaban:** Avoid concomitant use. • **Apixaban:** Reduce apixaban dose to 2.5 mg twice per day, and if patient is already taking 2.5 mg twice per day, avoid concomitant use. • **Dabigatran:** In patients with good renal function, no dose adjustments are necessary. • Do not use this combination in patients with moderate to severe renal dysfunction.
Warfarin	Could potentially decrease (or more rarely) increase metabolism of warfarin.	• Use cautiously with warfarin, and if use is necessary, increase monitoring of INR. • Decrease dose if INR increases. Increase dose slowly if INR decreases.
Cilostazol, ticagrelor, clopidogrel [Egan, et al. 2014; Tseng, et al. 2017]	• **Cilostazol:** Metabolized by CYP3A and boosted EVG will increase concentrations of this drug. • **Ticagrelor:** Results in increased exposure to ticagrelor. • **Clopidogrel:** Results in decreased concentration of clopidogrel's active metabolite.	• **Cilostazol:** Monitor for antiplatelet effect. May be necessary to use an alternative antiplatelet drug or alternative ARV agent. • **Ticagrelor:** Do not use with boosted EVG. • **Clopidogrel:** Do not use with boosted EVG unless an alternative antiplatelet drug (or ARV agent) cannot be used.
Aliskiren	Cobicistat inhibits P-gP, which may decrease aliskiren elimination, increasing risk of adverse events.	Do not coadminister.
Other polyvalent cations (calcium, zinc, iron, etc.)	EVG chelates with polyvalent cations.	Administer at least 2 hours before or 6 hours after EVG.
Atenolol	COBI-boosted EVG may increase atenolol concentrations via inhibition of MATE-1 elimination.	• Start patient at lowest possible dose and monitor for adverse events before slowly increasing dose to effect. • If patient is already taking atenolol but starting a cobicistat-boosted EVG, monitor for atenolol-related adverse events. Reduce dose of atenolol as needed.
Calcium channel blockers (CCBs)	COBI-boosted EVG may increase CCB concentrations by as much as 50%.	Decrease the original dose of CCB by up to 50% when using with boosted EVG and slowly titrate to effect.
Eplerenone [Keating and Plosker 2004; Tseng, et al. 2017]	• Eplerenone is metabolized by CYP3A. • COBI inhibits CYP3A.	• Avoid concomitant use (increased risk of hyperkalemia and hypertension). • If concomitant use is required, use lowest possible effective dose of eplerenone.
Simvastatin, lovastatin [Perry 2014]	• COBI is an inhibitor of CYP3A. • Simvastatin and lovastatin are substrates of CYP3A. • Greatly increases concentrations.	Avoid concomitant use (may increase muscle aches and risk of rhabdomyolysis).

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Pitavastatin [Tseng, et al. 2017]	• Pitavastatin is a substrate of OATP1B1. • COBI inhibits OATP1B1. • Although moderate increases are possible, low doses are considered safe when used with boosted PIs.	• Use the lowest effective dose of pitavastatin and monitor for signs of toxicity, including myopathy. • Dose adjustments are not necessary when using these statins with boosted EVG.
Pravastatin [Tseng, et al. 2017]	• Pravastatin is a substrate of OATP1B1. • COBI inhibits OATP1B1. • Although moderate increases are possible, low doses are considered safe when used with boosted PIs.	• Use the lowest effective dose of pravastatin and monitor for signs of toxicity, including myopathy. • Dose adjustments are not necessary when using these statins with boosted EVG.
Atorvastatin [Tseng, et al. 2017]	• Atorvastatin is a substrate for CYP3A4 and OATP1B1. • Boosted EVG inhibits both CYP3A and OATP1B1. • May moderately increase concentrations.	• Avoid concomitant use of cobicistat and atorvastatin. • If atorvastatin use is necessary, do not exceed 20 mg per day.
Rosuvastatin [Custodio, et al. 2014]	• Rosuvastatin is a substrate of OATP1B1 and OATP1B3. • COBI inhibits OATP. • Rosuvastatin is a substrate of CYP2C9. • EVG is an inducer of CYP2C9. • May moderately increase concentrations.	• When possible, avoid concomitant use of rosuvastatin and COBI-boosted EVG. • If rosuvastatin use is necessary, start with 10 mg per day. Dose should not exceed 20 mg per day.
Fluvastatin	Interaction has not been studied, but potential for moderate increase is possible.	Do not use, but if clinical use is desired, use the lowest effective dose; monitor closely for safety and efficacy before increasing statin dose.
Antidiabetic drugs	• **Metformin:** COBI is known to inhibit MATE1, which plays a role in the elimination of metformin, thus increasing metformin concentrations. • **Glyburide:** Mainly metabolized by CYP3A; concentrations are increased by inhibitors of this enzyme. • **Saxagliptin:** Levels may be increased via inhibition of CYP3A. • **Canagliflozin:** Could lead to reduced canagliflozin exposure because of EVG's induction of UGT enzymes.	• **Metformin:** Monitor for metformin-related adverse events and reduce dose as needed. • **Glyburide or alternative sulfonylureas:** Use lowest effective doses with boosted EVG; monitor for signs of hypoglycemia. • **Saxagliptin:** Limit dose to 2.5 mg once per day. • **Canagliflozin:** Monitor glycemic control. With RTV-boosted EVG and inadequate glycemic control, consider increasing dose to 300 mg per day if patient is tolerating 100 mg and has GFR >60 ml/min/1.73m^2.
Long-acting beta agonists (formoterol, salmeterol, etc.)	• Inhibition of CYP3A increases plasma concentrations of these agents. • Increased risk of salmeterol-associated cardiovascular events.	• Concomitant use is contraindicated unless benefits outweigh risks; consider use of alternative ARV agents. • If coadministration is necessary, monitor frequently for QT prolongation, palpitations, and sinus tachycardia.

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Inhaled and injected corticosteroids	Risk of Cushing's syndrome when coadministered with the following: • **Intranasal or inhaled:** Fluticasone, mometasone, ciclesonide, budesonide, triamcinolone. • **Systemic:** Betamethasone, budesonide, prednisolone, prednisone, dexamethasone. • **Injectable:** Betamethasone, triamcinolone.	• **Intranasal or inhaled fluticasone, mometasone, ciclesonide, budesonide, and triamcinolone:** Do not coadminister unless potential benefits outweigh risk; consider alternative corticosteroid (e.g., beclomethasone). • **Systemic betamethasone, budesonide:** Do not coadminister unless benefits outweigh risk. • **Systemic prednisolone, prednisone:** Do not coadminister unless potential benefits outweigh risk; if use cannot be avoided, use for shortest effective duration. • **Injectable betamethasone, triamcinolone:** Do not coadminister unless benefits outweigh risk. • **Systemic dexamethasone:** Do not coadminister unless potential benefits outweigh risk; consider alternative corticosteroid.
Trazodone	May increase trazodone concentrations.	Monitor antidepressant and/or sedative effects.
Alprazolam, clonazepam, diazepam	These benzodiazepines are substrates of CYP3A and may be increased in the presence of strong inhibitors of this enzyme.	• Consider alternative benzodiazepine (e.g., lorazepam, oxazepam, temazepam). • If used, administer lowest effective dose; monitor closely for adverse events.
Antipsychotics	Several of these agents are substrates of CYP3A, and inhibitors of this enzyme may increase their concentrations.	• **Quetiapine:** Reduce dose to 1/6 if initiating ARVs in patients on stabilized quetiapine. • Use all other antipsychotics at the lowest dose possible in patients taking boosted ARVs, and careful monitoring for adverse events is warranted.
PDE5 inhibitors [Perry 2014]	• COBI is an inhibitor of CYP3A. • PDE5 inhibitors are substrates of CYP3A. • **Flibanserin:** Increased flibanserin concentrations expected.	• Avoid concomitant use or use with lowest effective dose of the PDE5 inhibitor (may increase risk of hypotension, syncope, priapism, and other adverse reactions). • **Sildenafil:** Start with 25 mg every 48 hours; monitor for adverse effects. • **Tadalafil:** Start with 5 mg; do not exceed 10 mg every 72 hours; monitor for adverse effects. • **Vardenafil:** Administer 2.5 mg every 72 hours; monitor for adverse effects. • **Flibanserin:** Coadministration is contraindicated.
Suvorexant [Kishi, et al. 2015]	• Suvorexant is a CYP3A substrate. • COBI is an inhibitor of CYP3A.	Avoid concomitant use or use the lowest effective dose (may increase somnolence, dizziness, and risk of sleep hangover).
Zolpidem, eszopiclone	These drugs are CYP3A substrates and may be increased by strong inhibitors of this enzyme.	• **Zolpidem:** Administer lowest possible dose of zolpidem and monitor for adverse events. • **Eszopiclone:** Start with 1 mg of eszopiclone at bedtime and titrate slowly for maximum effect.
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.

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Eletriptan	Eletriptan is a CYP3A substrate and concentrations may be increased if given with strong inhibitors of this enzyme.	Do not coadminister. Select an alternative triptan medication.
Opioid analgesics	Complex mechanisms of metabolism and formation of both active and inactive metabolites create interactions of unclear significance between these drugs and boosted EVG.	Monitor for signs of opiate toxicity and analgesic effect and dose these analgesics accordingly.
Tramadol	Tramadol exposure is increased with inhibition of CYP3A, but this reduces conversion to the more potent active metabolite seen when tramadol is metabolized by CYP2D6.	When tramadol is given with COBI or RTV, monitoring for tramadol-related side effects and for the analgesic effect may be required as clinically indicated; adjust tramadol dosage if needed.
Hormonal contraceptives	**Drospirenone:** Potential for hyperkalemia.	• **Ethinyl estradiol, norgestimate, metabolites; norethindrone:** Weigh risks/benefits; consider alternative contraceptive method. • **Drospirenone:** Monitor for hyperkalemia; consider alternative contraceptive or alternative ARV agent. • **Etonogestrel:** No data; consider alternative or additional contraceptive or alternative ARV agent.
Immunosuppressants	• **Everolimus, sirolimus:** Metabolism decreased by boosted EVG. • **Cyclosporine, tacrolimus:** Metabolism decreased by boosted EVG.	• **Everolimus, sirolimus:** Do not use with boosted EVG. • **Cyclosporine, tacrolimus:** Dose based upon therapeutic drug monitoring. • Monitor closely for adverse events.

Abbreviations: ARV, antiretroviral; COBI, cobicistat; CYP, cytochrome P450; GFR, glomerular filtration rate; INR, international normalized ratio; MATE, multidrug and toxin extrusion; OATP, organic anion transporting polypeptide; P-gP, P-glycoprotein; PI, protease inhibitor; RTV, ritonavir; UGT, uridine glucuronosyltransferase.
No significant interactions/no dose adjustments necessary: Common oral antibiotics; acid-reducing agents; asthma and allergy medications; tobacco and smoking cessation products; alcohol, disulfiram, and acamprosate; methadone, buprenorphine, naloxone, and naltrexone.

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