Resource: ART Drug-Drug Interactions

April 2023

Table 8: Boosted Elvitegravir (EVG) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Antacids	EVG chelates with polyvalent cations, which may reduce absorption of both agents.	**Aluminum-, magnesium-, and/or calcium-containing antacids:** When taken with EVG, separate doses by at least 2 hours.
Alpha-adrenergic antagonists for benign prostatic hyperplasia	COBI-boosted EVG inhibits CYP3A4 and other transporters and is likely to increase levels of select drugs in this class.	• **Alfuzosin, silodosin:** Concomitant use is contraindicated. • **Doxazosin, terazosin:** May be used; increased levels are possible. • **Tamsulosin:** Avoid unless benefits outweigh risk. If used together, monitor for tamsulosin-associated adverse effects, such as hypotension.
Factor Xa inhibitors [Egan, et al. 2014]	• Factor Xa inhibitors are substrates of P-gP and CYP3A. • COBI inhibits P-gP and CYP3A. • Concentrations may increase, increasing bleeding risk.	• **Rivaroxaban:** Do not coadminister. • **Apixaban:** Reduce apixaban dose to 2.5 mg twice per day; 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. – In patients with moderate to severe renal dysfunction, do not use this combination. – Consider switching to another ARV regimen without booster to avoid interaction. • **Edoxaban:** – For stroke prevention in patients with nonvalvular atrial fibrillation: No dose adjustments are necessary. – For patients with DVT and PE: Administer edoxaban 30 mg once daily.
Warfarin	Metabolism of warfarin could potentially decrease (or more rarely) increase.	Use cautiously with warfarin. If use is necessary, increase INR monitoring. • If INR increases, decrease warfarin dose. • If INR decreases, increase warfarin dose slowly.
Cilostazol, ticagrelor, clopidogrel	• **Cilostazol** may be metabolized by CYP3A; COBI-boosted EVG can increase concentrations of this drug.	• **Cilostazol:** Monitor for antiplatelet effect. May be necessary to use alternative antiplatelet or alternative ARV.

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[Tseng, et al. 2017; Egan, et al. 2014]	• **Ticagrelor:** Strong CYP3A4 inhibitors may increase ticagrelor exposure. • **Clopidogrel:** Boosted EVG significantly decreases production of clopidogrel's active metabolite. • **Prasugrel:** Boosted EVG decreases prasugrel's active metabolite; however, adequate antiplatelet activity is maintained. • **Vorapaxar:** Increased vorapaxar levels are expected.	• **Ticagrelor:** To avoid increased bleeding risk, do not use ticagrelor with strong CYP3A inhibitors, particularly COBI and RTV. • **Clopidogrel, vorapaxar:** Do not coadminister. • **Prasugrel:** No dose adjustments are necessary.
Aliskiren	P-gP inhibitors, including boosted EVG, decrease aliskiren elimination, increasing adverse effects of medication.	Do not coadminister.
Other polyvalent cations (calcium, zinc, iron, etc.)	EVG chelates with polyvalent cations, which may reduce absorption of both agents.	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 at lowest possible dose and titrate slowly to achieve clinical effect while monitoring for adverse effects. • If patient is already using atenolol but starting COBI-boosted EVG, monitor for atenolol-related adverse effects. Reduce atenolol dose as needed.
Calcium channel blockers (CCBs)	COBI-boosted EVG may increase CCB concentrations by as much as 50%.	When using with boosted EVG, decrease original CCB dose by as much as 50% and titrate slowly to achieve clinical effect.
Eplerenone [Tseng, et al. 2017; Keating and Plosker 2004]	• 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 eplerenone dose.
Simvastatin, lovastatin [Perry 2014]	• COBI inhibits CYP3A. • Simvastatin and lovastatin are CYP3A substrates. Boosted EVG greatly increases concentrations.	Concomitant use is contraindicated; may increase muscle aches and risk of rhabdomyolysis; choose alternative statin.
Pitavastatin, pravastatin [Tseng, et al. 2017]	• Pitavastatin and pravastatin are OATP1B1 substrates. • COBI inhibits OATP1B1. • Although moderate increases are possible, low doses are considered safe when used with boosted EVG.	Use lowest effective doses of pitavastatin and pravastatin; monitor for signs of toxicity, including myopathy.
Atorvastatin [Tseng, et al. 2017]	• Atorvastatin is a substrate of CYP3A4 and OATP1B1. • Boosted EVG inhibits both CYP3A and OATP1B1. • Boosted EVG may moderately increase concentrations.	• Avoid concomitant use of COBI 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, OATP1B3, and CYP2C9. • COBI inhibits OATP. • EVG induces CYP2C9. • Boosted EVG may moderately increase concentrations.	Use lowest effective dose of rosuvastatin and titrate carefully to achieve clinical effect; monitor for adverse effects.

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Fluvastatin	Interaction has not been studied, but potential for moderate increase is possible.	Do not coadminister. If use is required, use lowest effective dose; monitor closely for safety and efficacy before increasing statin dose.
Antidiabetic drugs	• **Metformin:** COBI is known to inhibit MATE1, which is involved in metformin elimination, thus increasing metformin concentrations. • **Glyburide** is mainly metabolized by CYP3A; concentrations are increased by inhibitors of this enzyme. • **Saxagliptin** levels may be increased via CYP3A inhibition. • **Canagliflozin** exposure could be reduced through EVG induction of UGT enzymes.	• **Metformin:** Monitor for metformin-related adverse effects; 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 for glycemic control. – If glycemic control is inadequate in patient taking EVG/RTV, consider increasing canagliflozin dose to 300 mg per day if patient is tolerating 100 mg and has GFR >60 mL/min/1.73 m^2.
Long-acting beta agonists (formoterol, salmeterol, etc.)	CYP3A inhibition increases plasma concentrations of these agents.	• Concomitant use is contraindicated unless benefits outweigh risks; consider alternative ARV. • If coadministration is necessary, monitor frequently for QT prolongation, palpitations, and sinus tachycardia. • **Salmeterol:** Monitor for increased risk of cardiovascular-related adverse events.
Inhaled and injected corticosteroids	Risk of Cushing's syndrome occurs when boosted EVG is coadministered with the following corticosteroids: • Intranasal or inhaled: Fluticasone, mometasone, ciclesonide, budesonide, triamcinolone • Systemic: Betamethasone, budesonide, prednisolone, prednisone, dexamethasone • Injectable: Betamethasone, triamcinolone	• **Fluticasone, mometasone, ciclesonide, budesonide, triamcinolone (intranasal or inhaled):** Do not coadminister unless potential benefits outweigh risk; consider alternative corticosteroid (e.g., beclomethasone). • **Betamethasone, budesonide (systemic):** Do not coadminister unless potential benefits outweigh risk. • **Betamethasone, triamcinolone (injectable):** Do not coadminister unless benefits outweigh risk. • **Prednisolone, prednisone (systemic):** Do not coadminister unless potential benefits outweigh risk; if use cannot be avoided, use for shortest effective duration. • **Dexamethasone (systemic):** Do not coadminister unless potential benefits outweigh risk; consider alternative corticosteroid. Beclomethasone and flunisolide are likely safe alternatives.
Trazodone	Boosted EVG may increase trazodone concentrations.	Monitor for antidepressant and/or sedative effects.
Alprazolam, clonazepam, diazepam	Boosting with cobicistat may increase benzodiazepine concentrations via CYP3A4 inhibition.	Consider alternative benzodiazepine (e.g., lorazepam, oxazepam, temazepam); if used, administer lowest effective dose; monitor closely for adverse effects.

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Midazolam, triazolam	Levels likely to be increased by COBI-boosted EVG.	• **Midazolam:** – Oral: Concomitant use is contraindicated. – Parenteral: Administer in closely monitored setting. Consider dose reduction, especially if >1 dose is administered. • **Triazolam:** Concomitant use is contraindicated.
Antipsychotics	Several antipsychotic agents are CYP3A substrates, and inhibitors of this enzyme may increase their concentrations.	• **Quetiapine:** Reduce dose to 1/6 if initiating ART in patient on stabilized quetiapine. • **All other antipsychotics:** Use at lowest dose possible in patients taking boosted ARVs; monitor carefully for adverse effects.
PDE5 inhibitors [Perry 2014]	• PDE5 inhibitors are CYP3A substrates. Increased PDE5 inhibitor concentrations are expected. • COBI inhibits CYP3A.	• **PDE5 inhibitors:** Avoid concomitant use or use with lowest effective dose of PDE5 inhibitor (may increase risk of hypotension, syncope, priapism, and other adverse effects). • **Avanafil:** No data available; do not coadminister. • **Sildenafil:** Start with 25 mg every 48 hours; monitor for adverse effects. • **Tadalafil:** Start with 5 mg and do not exceed 10 mg every 72 hours; monitor for adverse effects. • **Vardenafil:** Administer 2.5 mg every 72 hours; monitor for adverse effects.
Suvorexant [Kishi, et al. 2015]	• Suvorexant is a CYP3A substrate. • COBI inhibits CYP3A.	Avoid concomitant use or use 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; monitor for adverse effects. • **Eszopiclone:** Start with 1 mg of eszopiclone at bedtime and titrate slowly to achieve clinical effect.
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.
Eletriptan	Eletriptan is a CYP3A substrate and concentrations may be increased if given with strong inhibitors of this enzyme.	Do not coadminister; use 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.

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Tramadol	Tramadol exposure is increased with CYP3A inhibition, 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 adverse effects and analgesic effect may be required as clinically indicated; adjust tramadol dosage if needed.
Hormonal contraceptives	**Drospirenone:** Concomitant use may cause hyperkalemia.	• **Ethinyl estradiol, norgestimate and metabolites; norethindrone:** Weigh risks and benefits; consider alternative contraceptive methods. • **Drospirenone:** Monitor for hyperkalemia; consider alternative contraceptive methods or alternative ARV. • **Etonogestrel:** No data available; consider alternative or additional contraceptive methods or alternative ARV.
Immunosuppressants	**Everolimus, sirolimus, cyclosporine, tacrolimus:** Metabolism decreased by boosted EVG.	• **Everolimus, sirolimus:** Do not use with boosted EVG. • **Cyclosporine, tacrolimus:** Dose based on TDM; monitor closely for adverse effects.
Rifabutin, rifampin, rifapentine	• **Rifabutin:** CYP3A induction is expected to decrease EVG levels. • **Rifampin, rifapentine:** CYP3A induction reduces EVG bioavailability.	• **Rifabutin:** Concomitant use is not recommended. When concomitant use cannot be avoided, dose rifabutin at 150 mg 3 times per week, and monitor for response to EVG-containing regimen. • **Rifampin, rifapentine:** Concurrent use with boosted EVG is not recommended.
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:** Patients on RTV- or COBI-containing regimens should continue treatment as indicated. Monitor for increased EVG-related adverse effects.
Mpox treatments	• **Brincidofovir** is a substrate for OATP1B1, OATP1B3. • **Tecovirimat** is a weak inducer of CYP3A and weak inhibitor of CYP2C8 and CYP2C19.	• **Brincidofovir:** Coadministration with EVG/COBI will likely increase brincidofovir levels. Consider avoiding concurrent EVG/COBI if possible. If unable to change EVG/COBI, monitor for brincidofovir-related adverse effects, e.g., LFT elevations, hyperbilirubinemia, diarrhea, or other GI adverse effects. Postpone EVG/COBI dosing for at least 3 hours *after* brincidofovir administration. • **Tecovirimat** may reduce EVG/COBI levels, though effects are not likely to be clinically relevant. No dose adjustment in either drug is necessary.
Abbreviations: ART, antiretroviral therapy; ARV, antiretroviral; COBI, cobicistat; CYP, cytochrome P450; DVT, deep vein thrombosis; GFR, glomerular filtration rate; GI, gastrointestinal; INR, international normalized ratio; LFT, liver function test; MATE, multidrug and toxin extrusion; OATP, organic anion transporting polypeptide; PDE5, phosphodiesterase type 5; PE, pulmonary embolism; P-gP, P-glycoprotein; PI, protease inhibitor; RTV, ritonavir; TDM, therapeutic drug monitoring; UGT, uridine diphosphate glucuronosyltransferase.		

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No significant interactions/no dose adjustments necessary: Common oral antibiotics (Table 19); acid-reducing agents (Table 25); asthma and allergy medications (Table 27); tobacco and smoking cessation products (Table 40); alcohol, disulfiram, and acamprosate (Table 41); methadone, buprenorphine, naloxone, and naltrexone (Table 42); gender-affirming hormones (Table 47).		

References

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