Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

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Table 15d. Drug Interactions between Integrase Inhibitors and Other Drugs (Last updated February 12, 2013; last reviewed February 12, 2013) (page 1 of 6)

Raltegravir (RAL) is expected to have fewer drug interactions than elvitegravir/cobicistat (EVG/COBI) (see Drug Interactions text). In the following table, where RAL is not listed, no data currently exists and there is either no dosage recommendation or no dosage adjustment is necessary when RAL is used with the concomitant medication.

Concomitant Drug Class/Name	Integrase Inhibitor	Effect on Integrase Inhibitor or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers			
Antacids	EVG/COBI/TDF/FTC	EVG AUC ↓ 15%–20% if given 2 hours before or after antacid; ↔ with 4-hour interval	Separate EVG/COBI/FTC/TDF and antacid administration by more than 2 hours
H2-Receptor Antagonists	EVG/COBI/TDF/FTC	No significant effect	No dosage adjustment necessary.
Proton Pump Inhibitors	EVG/COBI/TDF/FTC	No significant effect	No dosage adjustment necessary.
	RAL	RAL AUC ↑ 212%, C_{max} ↑ 315%, and C_{min} ↑ 46%	No dosage adjustment necessary.
Anticoagulants			
Warfarin	EVG/COBI/TDF/FTC	No data: but warfarin levels may be affected	Monitor INR and adjust warfarin dose accordingly.
Anticonvulsants			
Carbamazepine **Oxcarbazepine** **Phenobarbital** **Phenytoin**	EVG/COBI/TDF/FTC	↑ carbamazepine possible ↓ EVG possible ↓ COBI possible	Consider alternative anticonvulsant.
Ethosuximide	EVG/COBI/TDF/FTC	↑ ethosuximide possible	Clinically monitor for ethosuxamide toxicities.
Antidepressants			
Selective Serotonin Reuptake Inhibitors (SSRIs)	EVG/COBI/TDF/FTC	↑ SSRI possible	Initiate with lowest dose of SSRI and titrate dose carefully based on antidepressant response.
Tricyclic Antidepressants (TCAs) **Amitriptyline** **Desipramine** **Imipramine** **Nortriptyline**	EVG/COBI/TDF/FTC	Desipramine AUC ↑ 65%	Initiate with lowest dose and titrate dose of TCA carefully.
Trazodone	EVG/COBI/TDF/FTC	↑ trazodone possible	Initiate with lowest dose and titrate dose of trazodone carefully.

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Concomitant Drug Class/Name	Integrase Inhibitor	Effect on Integrase Inhibitor or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antifungals			
Itraconazole	EVG/COBI/TDF/FTC	↑ itraconazole expected ↑ EVG and COBI possible	Consider monitoring itraconazole level to guide dosage adjustments. High doses (>200 mg/day) are not recommended unless dose is guided by itraconazole levels.
Posaconazole	EVG/COBI/TDF/FTC	↑EVG and COBI possible ↑ posaconazole possible	Monitor posaconazole concentrations with co-administration.
Voriconazole	EVG/COBI/TDF/FTC	↑ voriconazole expected ↑ EVG and COBI possible	Risk/benefit ratio should be assessed to justify use of voriconazole. If administered, consider monitoring voriconazole level. Adjust dose accordingly.
Antimycobacterials			
Clarithromycin	EVG/COBI/TDF/FTC	↑ clarithromycin possible ↑ COBI possible	CrCl ≥60 mL/min: No dose adjustment necessary CrCl 50–60 mL/min: Reduce clarithromycin dose by 50% CrCl <50 mL/min: EVG/COBI/TDF/FTC is not recommended.
Rifabutin	EVG/COBI/TDF/FTC	Rifabutin (150 mg every other day): No significant change in rifabutin AUC; For 25-O-desacetyl-rifabutin, AUC ↑ 625% compared with rifabutin (300 mg daily) administered alone EVG AUC ↓ 21%, C_{min} ↓ 67%	**Do not co-administer.**
	RAL	RAL AUC ↑ 19%, C_{max} ↑ 39%, and C_{min} ↓ 20%	No dosage adjustment necessary.
Rifampin	EVG/COBI/TDF/FTC	Significant ↓ EVG and COBI expected	**Do not co-administer.**
	RAL	RAL 400 mg: RAL AUC ↓ 40% and C_{min} ↓ 61% Rifampin with RAL 800 mg BID compared with RAL 400 mg BID alone: RAL AUC ↑ 27% and C_{min} ↓ 53%	Dose: RAL 800 mg BID Monitor closely for virologic response or consider using rifabutin as an alternative rifamycin
Rifapentine	EVG/COBI/TDF/FTC	Significant ↓ EVG and COBI expected	**Do not co-administer.**
Benzodiazepines			
Clonazepam **Clorazepate** **Diazepam** **Estazolam** **Flurazepam**	EVG/COBI/TDF/FTC	↑ benzodiazepines possible	Dose reduction of benzodiazepine may be necessary. Initiate with low dose and clinically monitor. Consider alternative benzodiazepines to diazepam, such as lorazepam, oxazepam, or temazepam.
Midazolam **Triazolam**	EVG/COBI/TDF/FTC	↑ midazolam expected ↑ triazolam expected	Do not co-administer triazolam or oral midazolam and EVG/COBI. Parenteral midazolam can be used with caution in a closely monitored setting. Consider dose reduction, especially if >1 dose is administered.

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Concomitant Drug Class/Name	Integrase Inhibitor	Effect on Integrase Inhibitor or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Cardiac Medications			
Anti-Arrhythmics (amiodarone, bepridil, digoxin, disopyramide, dronedarone, flecainide, systemic lidocaine, mexilitine, propafenone, quinidine)	EVG/COBI/TDF/FTC	↑ anti-arrhythmics possible digoxin C_{max} ↑ 41%, AUC no significant change	Use anti-arrhythmics with caution. Therapeutic drug monitoring, if available, is recommended for anti-arrhythmics.
Bosentan	EVG/COBI/TDF/FTC	↑ bosentan possible	In patients on EVG/COBI/FTC/TDF ≥10 days: start bosentan at 62.5 mg once daily or every other day based on individual tolerability. In patients on bosentan who require EVG/COBI/FTC/TDF: stop bosentan ≥36 hours before EVG/COBI/FTC/TDF initiation. After at least 10 days following initiation of EVG/COBI/FTC/TDF, resume bosentan at 62.5 mg once daily or every other day based on individual tolerability.
Beta-blockers	EVG/COBI/TDF/FTC	↑ beta-blockers possible	Adjust beta-blockers according to clinical response. Beta-blocker dose may need to be decreased. Some beta-blockers are metabolized via CYP450 pathway (e.g., metoprolol, timolol). Consider using other beta-blockers (e.g., atenolol, labetalol, nadolol, sotalol) as these agents are not metabolized by CYP450 enzymes.
Dihydropyridine and Non-Dihydropyridine Calcium Channel Blockers	EVG/COBI/TDF/FTC	↑ CCBs possible	Co-administer with caution. Monitor for CCB efficacy and toxicities.
Corticosteroids			
Dexamethasone	EVG/COBI/TDF/FTC	↓ EVG and COBI possible	Co-administer with caution, monitor HIV virologic response
Fluticasone (inhaled/intranasal)	EVG/COBI/TDF/FTC	↑ fluticasone possible	Use alternative inhaled corticosteroid, particularly for long-term use
Hepatitis C NS3/4A—Protease Inhibitors			
Boceprevir	EVG/COBI/TDF/FTC	No data	**Do not co-administer.**
	RAL	No significant effect	No dosage adjustment necessary.
Telaprevir	EVG/COBI/TDF/FTC	No data	**Do not co-administer.**
	RAL	RAL AUC ↑ 31% Telaprevir ↔	No dosage adjustment necessary.

Table 15d. Drug Interactions between Integrase Inhibitors and Other Drugs (Last updated February 12, 2013; last reviewed February 12, 2013) (page 4 of 6)

Concomitant Drug Class/Name	Integrase Inhibitor	Effect on Integrase Inhibitor or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hormonal Contraceptives			
Hormonal contraceptives	RAL	No clinically significant effect	Safe to use in combination
Norgestimate/ethinyl estradiol	EVG/COBI/TDF/FTC	Norgestimate AUC, C_{max}, C_{min} ↑ > 2-fold Ethinyl estradiol AUC ↓ 25%, C_{min} ↓ 44%	The effects of increases in progestin (norgestimate) are not fully known and can include insulin resistance, dyslipidemia, acne, and venous thrombosis. Weigh the risks and benefits of the drug, and consider alternative contraceptive method.
HMG-CoA Reductase Inhibitors			
Atorvastatin	EVG/COBI/TDF/FTC	↑ atorvastatin possible	Titrate statin dose slowly and use the lowest dose possible.
Lovastatin	EVG/COBI/TDF/FTC	Significant ↑ lovastatin expected	**Contraindicated. Do not co-administer.**
Pitavastatin **Pravastatin**	EVG/COBI/TDF/FTC	No data	No dosage recommendation
Rosuvastatin	EVG/COBI/TDF/FTC	Rosuvastatin AUC ↑ 38% and C_{max} ↑ 89%	Titrate statin dose slowly and use the lowest dose possible.
Simvastatin	EVG/COBI/TDF/FTC	Significant ↑ simvastatin expected	**Contraindicated. Do not co-administer.**
Immunosuppressants			
Cyclosporine **Sirolimus** **Tacrolimus**	EVG/COBI/TDF/FTC	↑ immunosuppressant possible	Initiate with an adjusted immunosuppressant dose to account for potential increased concentrations and monitor for toxicities. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with specialist as necessary.
Narcotics/Treatment for Opioid Dependence			
Buprenorphine	EVG/COBI/TDF/FTC	Buprenorphine: AUC ↑ 35%, C_{max} ↑ 12%, C_{min} ↑ 66% Norbuprenorphine: AUC ↑ 42%, C_{max} ↑ 24%, C_{min} ↑ 57%	No dosage adjustment necessary. Clinical monitoring is recommended.
	RAL	No significant effect	No dosage adjustment necessary.
Methadone	EVG/COBI/TDF/FTC	No significant effect	No dosage adjustment necessary.
	RAL	No significant effect	No dosage adjustment necessary.
Neuroleptics			
Perphenazine **Risperidone** **Thioridazine**	EVG/COBI/TDF/FTC	↑ neuroleptic possible	Initiate neuroleptic at a low dose. Decrease in neuroleptic dose may be necessary.

Table 15d. Drug Interactions between Integrase Inhibitors and Other Drugs (Last updated February 12, 2013; last reviewed February 12, 2013) (page 5 of 6)

Concomitant Drug Class/Name	Integrase Inhibitor	Effect on Integrase Inhibitor or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Phosphodiesterase Type 5 (PDE5) Inhibitors			
Avanafil	EVG/COBI/TDF/FTC	No data	**Co-administration is not recommended.**
Sildenafil	EVG/COBI/TDF/FTC	↑ sildenafil expected	For treatment of erectile dysfunction: Start with sildenafil 25 mg every 48 hours and monitor for adverse effects of sildenafil. For treatment of PAH: **Contraindicated**
Tadalafil	EVG/COBI/TDF/FTC	↑ tadalafil expected	For treatment of erectile dysfunction: Start with tadalafil 5-mg dose and do not exceed a single dose of 10 mg every 72 hours. Monitor for adverse effects of tadalafil. For treatment of PAH: *In patients on a EVG/COBI >7 days:* Start with tadalafil 20 mg once daily and increase to 40 mg once daily based on tolerability. *In patients on tadalafil who require EVG/COBI:* Stop tadalafil ≥24 hours before EVG/COBI initiation. Seven days after EVG/COBI initiation restart tadalafil at 20 mg once daily, and increase to 40 mg once daily based on tolerability.
Vardenafil	EVG/COBI/TDF/FTC	↑ vardenafil expected	Start with vardenafil 2.5 mg every 72 hours and monitor for adverse effects of vardenafil.
Sedatives/Hypnotics			
Buspirone	EVG/COBI/TDF/FTC	↑ buspirone possible	Initiate buspirone at a low dose. Dose reduction may be necessary.
Zolpidem	EVG/COBI/TDF/FTC	↑ zolpidem possible	Initiate zolpidem at a low dose. Dose reduction may be necessary.

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Concomitant Drug Class/Name	Integrase Inhibitor	Effect on Integrase Inhibitor or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Miscellaneous Interactions			
Colchicine	EVG/COBI/TDF/FTC	↑ colchicine expected	**Do not co-administer in patients with hepatic or renal impairment.** For treatment of gout flares: Colchicine 0.6 mg x 1 dose, followed by 0.3 mg 1 hour later. Do not repeat dose for at least 3 days. For prophylaxis of gout flares: If original regimen was colchicine 0.6 mg BID, the regimen should be decreased to 0.3 mg once daily. If regimen was 0.6 mg once daily, the regimen should be decreased to 0.3 mg every other day. For treatment of familial Mediterranean fever: Do not exceed colchicine 0.6 mg once daily or 0.3 mg BID.
Salmeterol	EVG/COBI/TDF/FTC	↑ salmeterol possible	**Do not co-administer** because of potential increased risk of salmeterol-associated cardiovascular events.

Key to Abbreviations: AUC = area under the curve, BID = twice daily, CCB = calcium channel blocker, COBI = cobicistat, C_{max} = maximum plasma concentration, C_{min} = minimum plasma concentration, EVG = elvitegravir, PAH = pulmonary arterial hypertension, RAL = raltegravir