Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV

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Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 1 of 15)

This table provides information on known or predicted PK interactions between INSTIs (BIC, DTG, EVG, or RAL) and non-ARV drugs. EVG is always coadministered with COBI. Recommendations for managing a particular drug interaction may differ depending on whether a new ARV drug is being initiated in a patient on a stable concomitant medication or whether a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly.

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Alpha-Adrenergic Antagonists for Benign Prostatic Hyperplasia			
Alfuzosin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ alfuzosin expected	**Contraindicated.**
Doxazosin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ doxazosin possible	Initiate doxazosin at lowest dose and titrate while monitoring for clinical response/toxicity. Dose reduction may be necessary.
Tamsulosin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ tamsulosin expected	**Coadministration is not recommended.** If coadministered, monitor for tamsulosin toxicities.
Terazosin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ terazosin possible	Initiate terazosin at lowest dose and titrate while monitoring for clinical response/toxicity. Dose reduction may be necessary.
Silodosin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ silodosin expected	**Contraindicated.**
Acid Reducers			
Al, Mg, +/- Ca-Containing Antacids Please refer to the Miscellaneous Drugs section of this table for recommendations on use with other polyvalent cation products (e.g., Fe, Ca supplements, multivitamins).	BIC	↔ BIC AUC if antacid is given 2 hours after BIC and under fasting conditions BIC AUC ↓ 79% if given simultaneously with antacid BIC AUC ↓ 52% if antacid is given 2 hours before BIC	With Antacids Containing Al/Mg or Ca: • BIC can be taken under fasting conditions at least 2 hours before antacids containing Al/Mg or Ca. Do not coadminister BIC simultaneously with, or 2 hours after, antacids containing Al/Mg or Ca.
	DTG	DTG AUC ↓ 74% if given simultaneously with antacid DTG AUC ↓ 26% if given 2 hours before antacid	Give DTG at least 2 hours before or at least 6 hours after antacids containing polyvalent cations.
	EVG/c	EVG AUC ↓ 40% to 50% if given simultaneously with antacid EVG AUC ↓ 15% to 20% if given 2 hours before or after antacid; ↔ with 4-hour interval	Separate EVG/c/TDF/FTC and antacid administration by >2 hours.

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 2 of 15)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers, continued			
Al, Mg, +/- Ca-Containing Antacids, continued Please refer to the Miscellaneous Drugs section of this table for recommendations on use with other polyvalent cation products (e.g., Fe, Ca supplements, multivitamins).	RAL	Al/Mg Hydroxide Antacid: • RAL C_{min} ↓ 49% to 63% $CaCO_3$ Antacid: • RAL (400 mg BID) C_{min} ↓ 32% • RAL (1200 mg once daily) C_{min} ↓ 48% to 57%	**Do not coadminister RAL and Al-Mg hydroxide antacids.** Use alternative acid reducing agent. With $CaCO_3$ Antacids: • RAL 1200 mg once daily: **Do not coadminister.** • RAL 400 mg BID: No dose adjustment or separation necessary.
H2-Receptor Antagonists	BIC, DTG, EVG/c	No significant effect	No dose adjustment necessary.
	RAL	RAL AUC ↑ 44% and C_{max} ↑ 60%	No dose adjustment necessary.
PPIs	BIC, DTG, EVG/c	No significant effect	No dose adjustment necessary.
	RAL	RAL AUC ↑ 37% and C_{min} ↑ 24%	No dose adjustment necessary.
Anticoagulants and Antiplatelets			
Apixaban	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ apixaban expected	In Patients Requiring Apixaban 2.5 mg Twice Daily: • **Coadministration is not recommended.** In Patients Requiring Apixaban 5 mg or 10 mg Twice Daily: • Reduce apixaban dose by 50%.
Betrixaban	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ betrixaban expected	Administer initial single dose of betrixaban 80 mg, followed by betrixaban 40 mg once daily.
Dabigatran	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ dabigatran expected Dabigatran AUC ↑ 110% to 127% with COBI 150 mg alone	Dabigatran dosing recommendation depends on indication and renal function. Refer to dabigatran prescribing information for dosing instruction when used with P-gp inhibitors.
Edoxaban	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↔ or ↑ edoxaban expected	For Stroke Prevention in Nonvalvular Atrial Fibrillation: • No dose adjustment necessary. For Deep Venous Thrombosis and Pulmonary Embolism: • Administer edoxaban 30 mg once daily.
Rivaroxaban	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ rivaroxaban expected	**Coadministration is not recommended.**

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 3 of 15)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticoagulants and Antiplatelets, continued			
Ticagrelor	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ ticagrelor expected	**Coadministration is not recommended.**
Vorapaxar	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ vorapaxar expected	**Coadministration is not recommended.**
Warfarin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ or ↓ warfarin possible	Monitor INR and adjust warfarin dose accordingly.
Anticonvulsants			
Carbamazepine	BIC	↓ BIC possible	Consider using an alternative anticonvulsant or ARV.
	DTG	DTG AUC ↓ 49%	Increase DTG dose to 50 mg BID in treatment-naive or treatment-experienced, INSTI-naive patients. Use alternative anticonvulsant for INSTI-experienced patients with known or suspected INSTI resistance.
	EVG/c	Carbamazepine AUC ↑ 43% EVG AUC ↓ 69% and C_{min} ↓ >99% ↓ COBI expected	**Contraindicated.**
	RAL	↓ or ↔ RAL possible	**Coadministration is not recommended.**
Eslicarbazepine	All INSTIs	↓ INSTI possible ↓ COBI possible	Consider using an alternative anticonvulsant or ARV.
Ethosuximide	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ ethosuximide possible	Clinically monitor for ethosuximide toxicities.
Lamotrigine	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	No data	Monitor anticonvulsant level and adjust dose accordingly.
Oxcarbazepine	All INSTIs	↓ INSTI possible ↓ COBI possible	Consider using an alternative anticonvulsant or ARV.
Phenobarbital **Phenytoin**	BIC	↓ BIC possible	**Coadministration is not recommended.**
	DTG	↓ DTG possible	**Coadministration is not recommended.**
	EVG/c	↓ EVG/c expected	**Contraindicated.**
	RAL	↓ or ↔ RAL possible	**Coadministration is not recommended.**
Valproic Acid	All INSTIs	No data	Monitor valproic acid concentration and virologic response.

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 4 of 15)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antidepressants/Anxiolytics/Antipsychotics Also see Sedative/Hypnotics section below.			
Aripiprazole	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ aripiprazole expected	Administer 25% of the usual aripiprazole dose. Titrate based on clinical monitoring for efficacy and toxicity. Refer to aripiprazole label for dosing recommendations in patients who are known to be CYP2D6 poor metabolizers or who have major depressive disorder.
Brexpiprazole	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ brexpiprazole expected	Administer 25% of the usual brexpiprazole dose. Titrate based on clinical monitoring for efficacy/toxicity. Refer to brexpiprazole label for dosing recommendations in patients who are known to be CYP2D6 poor metabolizers or who have major depressive disorder.
Bupropion	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ bupropion possible	Titrate bupropion dose based on clinical response.
Buspirone	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ buspirone possible	Initiate buspirone at a low dose. Dose reduction may be necessary.
Cariprazine	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ cariprazine expected	Starting Cariprazine in a Patient Already on EVG/c: • Administer cariprazine 1.5 mg on Day 1 and Day 3, with no dose given on Day 2. • From Day 4 onward, administer 1.5 mg daily. Can be increased to a maximum dose of 3 mg daily. • If EVG/c is withdrawn, cariprazine dose may need to be increased. Starting EVG/c in a Patient Already on Cariprazine: • For patients receiving cariprazine 3 mg or 6 mg daily, reduce cariprazine dose by half. • For patients taking cariprazine 4.5 mg daily, the dose should be reduced to 1.5 mg or 3 mg daily. • For patients taking cariprazine 1.5 mg daily, change to 1.5 mg every other day. • If EVG/c is withdrawn, cariprazine dose may need to be increased.

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 5 of 15)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antidepressants/Anxiolytics/Antipsychotics, continued Also see Sedative/Hypnotics section below.			
Fluvoxamine	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ or ↓ EVG possible	Consider alternative antidepressant or ARV.
Lurasidone	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ lurasidone expected	**Contraindicated.**
Pimavanserin	BIC, DTG, RAL	↔ expected	Standard doses.
	EVG/c	↑ pimavanserin expected	Reduce pimavanserin dose by 50%. Titrate dose based on efficacy and toxicity.
Pimozide	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ pimozide expected	**Contraindicated.**
Quetiapine	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ quetiapine AUC expected	Initiation of Quetiapine in a Patient Receiving EVG/c: • Start quetiapine at the lowest dose and titrate up as needed. Monitor for quetiapine efficacy and adverse effects. Initiation of EVG/c in a Patient Receiving a Stable Dose of Quetiapine: • Reduce quetiapine dose to 1/6 of the original dose, and closely monitor for quetiapine efficacy and adverse effects.
SSRIs Citalopram, escitalopram, fluoxetine, paroxetine, sertraline	EVG/c	↔ EVG ↔ sertraline	No dose adjustment necessary.
		↑ other SSRI possible	Initiate with lowest dose of SSRI and titrate dose carefully based on antidepressant response.
	BIC, DTG, RAL	↔ BIC, DTG, RAL expected ↔ SSRI expected	No dose adjustment necessary.
TCAs Amitriptyline, desipramine, doxepin, imipramine, nortriptyline	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	Desipramine AUC ↑ 65%	Initiate with lowest dose of TCA and titrate dose carefully.
		↑ TCA expected	Initiate with lowest dose of TCA and titrate dose carefully based on antidepressant response and/or drug levels.
Trazodone	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ trazodone possible	Initiate with lowest dose of trazodone and titrate dose carefully.
Other Antipsychotics (CYP3A4 and/or CYP2D6 substrates)	EVG/c	↑ antipsychotic possible	Initiate antipsychotic at a low dose. Decrease in antipsychotic dose may be necessary.

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antifungals			
Isavuconazole	BIC	↑ BIC possible	No dose adjustment necessary.
	EVG/c	↑ isavuconazole expected ↑ EVG and COBI possible	If coadministered, consider monitoring isavuconazole concentrations and assess virologic response.
Itraconazole	BIC	↑ BIC expected	No dose adjustment necessary.
	DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ itraconazole expected ↑ EVG and COBI possible	Consider monitoring itraconazole level to guide dosage adjustments. High itraconazole doses (>200 mg/day) are not recommended unless dose is guided by itraconazole levels.
Posaconazole	BIC	↑ BIC expected	No dose adjustment necessary.
	DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ EVG and COBI possible ↑ posaconazole possible	If coadministered, monitor posaconazole concentrations.
Voriconazole	BIC	↑ BIC possible	No dose adjustment necessary.
	DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ voriconazole expected ↑ EVG and COBI possible	**Do not coadminister voriconazole and COBI unless benefit outweighs risk.** If coadministered, consider monitoring voriconazole concentrations and adjust dose accordingly.
Antihyperglycemics			
Metformin	BIC	Metformin AUC ↑ 39%	Monitor for metformin adverse effects.
	DTG	DTG 50 mg Once Daily plus Metformin 500 mg BID: • Metformin AUC ↑ 79% and C_{max} ↑ 66% DTG 50 mg BID plus Metformin 500 mg BID: • Metformin AUC ↑ 2.4-fold and C_{max} ↑ 2-fold	Start metformin at lowest dose and titrate based on glycemic control. Monitor for metformin adverse effects. When starting/stopping DTG in patients on metformin, dose adjustment of metformin may be necessary to maintain optimal glycemic control and/or minimize adverse effects of metformin.
	RAL	↔ expected	No dose adjustment necessary.
Saxagliptin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ saxagliptin expected	Limit saxagliptin dose to 2.5 mg once daily.
Dapagliflozin/ Saxagliptin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ saxagliptin expected	**Do not coadminister**, as this coformulated drug contains 5 mg of saxagliptin.
Antimycobacterials			
Clarithromycin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ clarithromycin possible ↑ COBI possible	CrCl 50–60 mL/min: • Reduce clarithromycin dose by 50% CrCl <50 mL/min: • EVG/c **is not recommended.**

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 7 of 15)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antimycobacterials, continued			
Rifabutin	BIC	Rifabutin (300 mg Once Daily): • BIC AUC ↓ 38% and C_{min} ↓ 56%	**Do not coadminister.**
	DTG	Rifabutin (300 mg Once Daily): • DTG AUC ↔ and C_{min} ↓ 30%	No dose adjustment necessary.
	EVG/c	Rifabutin 150 mg Every Other Day with EVG/c Once Daily Compared to Rifabutin 300 mg Once Daily Alone: • ↔ rifabutin AUC • 25-O-desacetyl-rifabutin AUC ↑ 625% • EVG AUC ↓ 21% and C_{min} ↓ 67%	**Do not coadminister.**
	RAL	RAL AUC ↑ 19% and C_{min} ↓ 20%	No dose adjustment necessary.
Rifampin	BIC	BIC AUC ↓ 75%	**Contraindicated.**
	DTG	Rifampin with DTG 50 mg BID Compared to DTG 50 mg BID Alone: • DTG AUC ↓ 54% and C_{min} ↓ 72% Rifampin with DTG 50 mg BID Compared to DTG 50 mg Once Daily Alone: • DTG AUC ↑ 33% and C_{min} ↑ 22%	Dose: • DTG 50 mg BID (instead of 50 mg once daily) for patients without suspected or documented INSTI mutation. Alternative to rifampin should be used in patients with certain suspected or documented INSTI-associated resistance substitutions. Consider using rifabutin.
	EVG/c	Significant ↓ EVG and COBI expected	**Contraindicated.**
	RAL	RAL 400 mg: • RAL AUC ↓ 40% and C_{min} ↓ 61% Rifampin with RAL 800 mg BID Compared to RAL 400 mg BID Alone: • RAL AUC ↑ 27% and C_{min} ↓ 53%	Dose: • RAL 800 mg BID, instead of 400 mg BID **Do not coadminister RAL 1200 mg once daily with rifampin.** Monitor closely for virologic response or consider using rifabutin as an alternative rifamycin.
Rifapentine	BIC, DTG, EVG/c	Significant ↓ BIC, DTG, EVG, and COBI expected	**Do not coadminister.**
	RAL	Rifapentine 900 mg Once Weekly: • RAL AUC ↑ 71% and C_{min} ↓ 12% Rifapentine 600 mg Once Daily: • RAL C_{min} ↓ 41%	For once-weekly rifapentine, use standard RAL 400 mg BID doses. **Do not coadminister with once-daily rifapentine.**

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 8 of 15)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Cardiac Medications			
Antiarrhythmics Amiodarone, bepridil, digoxin, disopyramide, dronedarone, flecainide, systemic lidocaine, mexilitine, propafenone, quinidine	BIC, DTG	↔ expected for the listed antiarrhythmics, except for disopyramide ↑ disopyramide possible	No dose adjustment necessary. Coadminister with caution. Clinical monitoring is recommended.
	RAL	↔ expected for the listed antiarrhythmics	No dose adjustment necessary.
	EVG/c	↑ antiarrhythmics possible Digoxin C_{max} ↑ 41% and no significant change in AUC	Use antiarrhythmics with caution. TDM, if available, is recommended for antiarrhythmics.
Bosentan	BIC, DTG	↓ BIC, DTG possible	Standard doses.
	RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ bosentan possible	In Patients on EVG/c ≥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/c: • Stop bosentan ≥36 hours before EVG/c initiation. At least 10 days after initiation of EVG/c, resume bosentan at 62.5 mg once daily or every other day based on individual tolerability.
Beta-blockers (e.g., metoprolol, timolol)	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ beta-blockers possible	Beta-blocker dose may need to be decreased; adjust dose based on clinical response. Consider using beta-blockers that are not metabolized by CYP450 enzymes (e.g., atenolol, labetalol, nadolol, sotalol).
CCBs	BIC	↑ BIC possible with diltiazem ↔ expected for all other CCBs	No dose adjustment necessary.
	DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ CCBs possible	Coadminister with caution. Titrate CCB dose and monitor for CCB efficacy and toxicities. Refer to Table 21a for diltiazem plus ATV/r recommendations.
Dofetilide	BIC, DTG	↑ dofetilide expected	**Contraindicated.**
	RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ dofetilide possible	**Do not coadminister.**
Eplerenone	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ eplerenone expected	**Contraindicated.**
Ranolazine	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ ranolazine expected	**Contraindicated.**
Ivabradine	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ ivabradine expected	**Contraindicated.**

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 9 of 15)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Corticosteroids			
Beclomethasone Inhaled or intranasal	BIC, DTG, EVG/c, RAL	↔ expected	No dose adjustment necessary.
Budesonide, Ciclesonide, Fluticasone, Mometasone Inhaled or intranasal	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ glucocorticoid possible	Coadministration can result in adrenal insufficiency and Cushing's syndrome. **Do not coadminister unless potential benefits of inhaled or intranasal corticosteroid outweigh the risks of systemic corticosteroid adverse effects.** Consider an alternative corticosteroid (e.g., beclomethasone).
Betamethasone, Budesonide Systemic	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ glucocorticoids possible ↓ EVG possible	Coadministration can result in adrenal insufficiency and Cushing's syndrome. **Do not coadminister unless potential benefits of systemic budesonide outweigh the risks of systemic corticosteroid adverse effects.**
Dexamethasone Systemic	BIC	↓ BIC possible	Consider an alternative corticosteroid for long-term use or an alternative ARV. If coadministration is necessary, monitor virologic response to ART.
	DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↓ EVG and COBI possible	Consider an alternative corticosteroid for long-term use or alternative ART. If coadministration is necessary, monitor virologic response to ART.
Prednisone, Prednisolone Systemic	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ prednisolone possible	Coadministration may be considered if the potential benefits outweigh the risks of systemic corticosteroid adverse effects. If coadministered, monitor for adrenal insufficiency and Cushing's syndrome.
Betamethasone, Methylprednisolone, Prednisolone, Triamcinolone Local injections, including intra-articular, epidural, or intra-orbital	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ glucocorticoids expected	**Do not coadminister.** Coadministration may result in adrenal insufficiency and Cushing's syndrome.
Hepatitis C Direct Acting Antivirals			
Daclatasvir	DTG	↔ daclatasvir	No dose adjustment necessary.
	EVG/c	↑ daclatasvir	Decrease daclastavir dose to 30 mg once daily.
	BIC, RAL	No data	No dose adjustment necessary.
Dasabuvir plus Ombitasvir/ Paritaprevir/RTV	BIC, DTG	No data	No dose adjustment necessary.
	EVG/c	No data	**Do not coadminister.**
	RAL	RAL AUC ↑ 134%	No dose adjustment necessary.

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 10 of 15)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hepatitis C Direct Acting Antivirals, continued			
Elbasvir/Grazoprevir	BIC	↔ BIC expected	No dose adjustment necessary.
	DTG	↔ elbasvir ↔ grazoprevir ↔ DTG	No dose adjustment necessary.
	EVG/c	↑ elbasvir and ↑ grazoprevir expected	**Coadministration is not recommended.**
	RAL	↔ elbasvir ↔ grazoprevir ↔ RAL with elbasvir RAL AUC ↑ 43% with grazoprevir	No dose adjustment necessary.
Glecaprevir/ Pibrentasvir	BIC	↔ BIC expected	No dose adjustment necessary.
	DTG, RAL	No significant effect	No dose adjustment necessary.
	EVG/c	Glecaprevir AUC ↑ 3-fold Pibrentasvir AUC ↑ 57% EVG AUC ↑ 47%	No dose adjustment necessary.
Ledipasvir/ Sofosbuvir	EVG/c/TDF/ FTC	↑ TDF and ↑ ledipasvir expected	**Do not coadminister.**
	EVG/c/TAF/ FTC	↔ EVG/c/TAF/FTC expected	No dose adjustment necessary.
	BIC, DTG, RAL	↔ DTG or RAL	No dose adjustment necessary.
Simeprevir	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ simeprevir expected	**Coadministration is not recommended.**
Sofosbuvir	All INSTIs	↔ expected	No dose adjustment necessary.
Sofosbuvir/ Velpatasvir	All INSTIs	↔ expected	No dose adjustment necessary.
Sofosbuvir/ Velpatasvir/ Voxilaprevir	EVG/c	When Given with Sofosbuvir/Velpatasvir/ Voxilaprevir (400 mg/100 mg/100 mg) plus Voxilaprevir 100 mg: • Sofosbuvir AUC ↑ 22% • ↔ velpatasvir • Voxilaprevir AUC ↑ 2-fold	No dose adjustment necessary.
	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
Herbal Products			
St. John's Wort	BIC, DTG	↓ BIC and DTG possible	**Do not coadminister.**
	EVG/c	↓ EVG and COBI possible	**Contraindicated.**

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 11 of 15)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hormonal Therapies			
Hormonal Contraceptives Oral	BIC, DTG, RAL	↔ ethinyl estradiol, norgestimate, and DTG or RAL	No dose adjustment necessary.
	EVG/c	Norgestimate AUC, C_{max}, and C_{min} ↑ >2-fold Ethinyl estradiol AUC ↓ 25% and 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 using an alternative contraceptive method.
		↑ drospirenone possible	Clinical monitoring is recommended, due to the potential for hyperkalemia.
Hormonal Contraceptives Non-oral	All INSTIs	No data	No drug-drug interaction studies have been conducted with INSTIs and non-oral routes of hormone administration. It is unclear if oral drug-drug interaction data can be extrapolated beyond oral routes of administration.
Menopausal Hormone Replacement Therapy	BIC, DTG, RAL	With Estradiol or Conjugated Estrogen (Equine and Synthetic): • ↔ estrogen expected ↔ drospirenone, medroxyprogesterone, or micronized progesterone expected	No dose adjustment necessary.
	EVG/c	↓ estrogen expected ↑ drospirenone possible ↑ oral medroxyprogesterone possible ↑ oral micronized progesterone possible	Adjust estrogen and progestin dose as needed based on clinical effects.
Gender-Affirming Hormone Therapy	BIC, DTG, RAL	↔ estrogen expected	No dose adjustment necessary.
	BIC, DTG, EVG/c, RAL	↔ finasteride, goserelin, leuprolide acetate, spironolactone expected	
	EVG/c	↓ estradiol expected ↑ dutasteride possible	Adjust dutasteride dosage as needed based on clinical effects and endogenous hormone concentrations.
	EVG/c	↑ testosterone possible	Monitor masculinizing effects of testosterone and for adverse effects and adjust testosterone dose as necessary.
	BIC, DTG, RAL	↔ testosterone expected	No dose adjustment necessary.
HMG-CoA Reductase Inhibitors			
Atorvastatin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	Atorvastatin AUC ↑ 2.6-fold and C_{max} ↑ 2.3-fold	Titrate statin dose carefully and use the lowest dose necessary while monitoring for toxicities. Do not exceed 20 mg atorvastatin daily.
Lovastatin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	Significant ↑ lovastatin expected	**Contraindicated**.
Pitavastatin, Pravastatin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	No data	No dose recommendation.

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 12 of 15)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
HMG-CoA Reductase Inhibitors, continued			
Rosuvastatin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	Rosuvastatin AUC ↑ 38% and C_{max} ↑ 89%	Titrate statin dose carefully and use the lowest dose necessary while monitoring for toxicities.
Simvastatin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	Significant ↑ simvastatin expected	**Contraindicated**.
Immunosuppressants			
Cyclosporine, Everolimus, Sirolimus, Tacrolimus	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ immunosuppressant possible	Initiate with an adjusted immunosuppressant dose to account for potential increased concentration and monitor for toxicities. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with a specialist as necessary.
Narcotics/Treatment for Opioid Dependence			
Buprenorphine Sublingual, buccal, or implant	BIC, DTG	↔ expected	No dose adjustment necessary.
	EVG/c	Buprenorphine AUC ↑ 35% and C_{min} ↑ 66% Norbuprenorphine AUC ↑ 42% and C_{min} ↑ 57%	No dose adjustment necessary. Clinical monitoring is recommended. When transferring buprenorphine from transmucosal administration to implantation, monitor to ensure buprenorphine effect is adequate and not excessive.
	RAL	↔ observed (sublingual) ↔ expected (implant)	No dose adjustment necessary.
Methadone	All INSTIs	No significant effect	No dose adjustment necessary.
PDE5 Inhibitors			
Avanafil	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	No data	**Coadministration is not recommended.**
Sildenafil	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ 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.**

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 13 of 15)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
PDE5 Inhibitors, continued			
Tadalafil	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ tadalafil expected	For Treatment of Erectile Dysfunction: • Start with tadalafil 5-mg dose and do not exceed a single dose of tadalafil 10 mg every 72 hours. Monitor for adverse effects of tadalafil. For Treatment of PAH *In Patients on EVG/c >7 Days:* • Start with tadalafil 20 mg once daily and increase to tadalafil 40 mg once daily based on tolerability. *In Patients on Tadalafil who Require EVG/c:* • Stop tadalafil ≥24 hours before EVG/c initiation. Seven days after EVG/c initiation, restart tadalafil at 20 mg once daily, and increase to tadalafil 40 mg once daily based on tolerability.
Vardenafil	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ vardenafil expected	Start with vardenafil 2.5 mg every 72 hours and monitor for adverse effects of vardenafil.
Sedative/Hypnotics			
Clonazepam, Clorazepate, Diazepam, Estazolam, Flurazepam	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ 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	BIC, RAL	↔ expected	No dose adjustment necessary.
	DTG	With DTG 25 mg: • ↔ Midazolam AUC	No dose adjustment necessary.
	EVG/c	↑ midazolam expected ↑ triazolam expected	**Contraindicated. Do not coadminister triazolam or oral midazolam and EVG/c.** Parenteral midazolam can be used with caution in a closely monitored setting. Consider dose reduction, especially if >1 dose is administered.
Suvorexant	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ suvorexant expected	**Coadministration is not recommended.**
Zolpidem	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ zolpidem expected	Initiate zolpidem at a low dose. Dose reduction may be necessary.

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 14 of 15)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Miscellaneous Drugs			
Calcifediol	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ calcifediol possible	Dose adjustment of calcifediol may be required, and serum 25-hydroxyvitamin D, intact PTH, and serum Ca concentrations should be closely monitored.
Cisapride	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ cisapride expected	**Contraindicated.**
Colchicine	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ colchicine expected	**Do not coadminister in patients with hepatic or renal impairment.** For Treatment of Gout Flares: • Administer colchicine 0.6 mg for 1 dose, followed by colchicine 0.3 mg 1 hour later. Do not repeat dose for at least 3 days. For Prophylaxis of Gout Flares: • If original dose was colchicine 0.6 mg BID, decrease to colchicine 0.3 mg once daily. If regimen was 0.6 mg once daily, decrease 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.
Enzalutamide	DTG	↓ DTG possible	Monitor for ARV efficacy.
	BIC, EVG/c	↓ BIC, EVG/c expected	**Contraindicated.**
	RAL	↔ expected	No dose adjustment necessary.
Ergot Derivatives	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ dihydroergotamine, ergotamine, methylergonovine expected	**Contraindicated.**
Dronabinol	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ dronabinol possible	Monitor for dronabinol-related adverse effects.
Eluxadoline	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ eluxadoline possible	Monitor for eluxadoline-related adverse effects.
Flibanserin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ flibanserin expected	**Contraindicated.**
Mitotane	BIC, EVG/c	↓ BIC and ↓ EVG/c expected	**Contraindicated.**
	DTG	↓ DTG possible	Monitor for ARV efficacy.
	RAL	↔ expected	No dose adjustment necessary.

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 15 of 15)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Miscellaneous Drugs, continued			
Polyvalent Cation Supplements Mg, Al, Fe, Ca, Zn, including multivitamins with minerals **Note:** Please refer to the Acid Reducers section in this table for recommendations on use with Al-, Mg-, and Ca-containing antacids.	BIC	↔ BIC AUC if given simultaneously with Fe or Ca and food BIC AUC ↓ 33% if given simultaneously with $CaCO_3$ under fasting conditions BIC AUC ↓ 63% if given simultaneously with Fe under fasting conditions	With Supplements that Contain Ca or Fe: • BIC and supplements containing Ca or Fe can be taken together with food. **Do not coadminister BIC under fasting conditions simultaneously with, or 2 hours after, supplements containing Ca or Fe.**
	DTG	DTG AUC ↓ 39% if given simultaneously with calcium carbonate under fasting conditions DTG AUC ↓ 54% if given simultaneously with Fe under fasting conditions ↔ DTG when administered with Ca or Fe supplement simultaneously with food	With Supplements That Contain Ca or Fe: • DTG and supplements containing Ca or Fe can be taken together with food; alternately, administer DTG at least 2 hours before or at least 6 hours after supplement. **Do not coadminister DTG under fasting conditions simultaneously with, or 2 hours after, supplements containing Ca or Fe.**
	EVG/c, RAL	↓ INSTI possible	If coadministration is necessary, give INSTI at least 2 hours before or at least 6 hours after supplements containing polyvalent cations, including but not limited to the following products: cation-containing laxatives; Fe, Ca, or Mg supplements; and sucralfate. Monitor for virologic efficacy. Many oral multivitamins also contain varying amounts of polyvalent cations; the extent and significance of chelation is unknown.
Salmeterol	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ salmeterol possible	**Do not coadminister**, due to potential increased risk of salmeterol-associated cardiovascular events.

Key to Symbols:

↑ = increase

↓ = decrease

↔ = no change

Key to Acronyms: Al = aluminum; ART = antiretroviral therapy; ARV = antiretroviral; ATV/r = atazanavir/ritonavir; AUC = area under the curve; BIC = bictegravir; BID = twice daily; Ca = calcium; $CaCO_3$ = calcium carbonate; CCB = calcium channel blocker; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; COBI = cobicistat; CrCl = creatinine clearance; CYP = cytochrome P; DTG = dolutegravir; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; Fe = iron; FTC = emtricitabine; INR= international normalized ratio; INSTI = integrase strand transfer inhibitor; Mg = magnesium; PAH = pulmonary arterial hypertension; PI = protease inhibitor; PK = pharmacokinetic; PTH = parathyroid hormone; RAL = raltegravir; RTV = ritonavir; SSRI = selective serotonin reuptake inhibitors; TAF = tenofovir alafenamide; TCA = tricyclic antidepressants; TDF = tenofovir disoproxil fumarate; TDM = therapeutic drug monitoring; Zn = zinc