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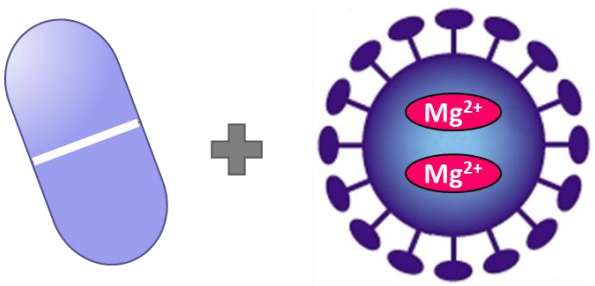
Drug Interactions between Integrase Strand Transfer Inhibitors and Cations

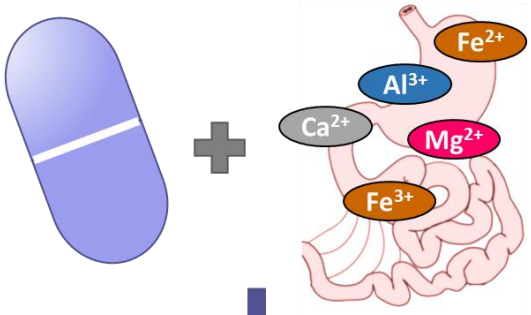
Integrase Strand Transfer Inhibitors (INSTI; **bictegravir**, **dolutegravir**, **elvitegravir**, **raltegravir**) inhibit HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral DNA integration. Mg^{2+} is a critical factor in the integration phase and inactivation of the cation by chelation causes the functional impairment of integrase. However, the flip side of integrase inhibitors binding to polyvalent cations is potentially clinically significant drug interactions with coadministered cation-containing antacids and other supplements.

INSTI binds to Mg^{2+} in active site of integrase



Antiretroviral Effect

INSTI binds to cations in GI tract



Pharmacokinetic Interaction

There are a few important points to note:

- Oral cation administration is the focus for a potential clinically relevant interaction due to high concentrations in the GI tract.
- Polyvalent cations are present at varying amounts in antacids, supplements and multivitamin preparations. If in doubt – check!
- Magnesium and calcium are referred to as divalent cations with a charge of +2 (Mg^{2+}, Ca^{2+}).
- Aluminium is referred to as a trivalent cation with a charge of +3 (Al^{3+}).
- Iron can be either divalent (Fe^{2+}) or trivalent (Fe^{3+}).
- Calcium folinate is the calcium salt of 5-formyl tetrahydrofolic acid, an active metabolite of folinic acid. The risk of chelation with integrase inhibitors is considered low when administering calcium folinate in small doses at frequent intervals.
- There is no risk of chelation with sodium bicarbonate, and the related change in gastric pH does not alter the absorption of integrase inhibitors (exception: raltegravir absorption is increased but to an extent that is not clinically significant).
- The risk of chelation with integrase inhibitors is considered low when supplements are administered as infusions or injections.

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Abbreviations: BIC bictegravir DTG dolutegravir EVG elvitegravir /c cobicistat RPV rilpivirine ABC abacavir FTC emtricitabine 3TC lamivudine TAF tenofovir alafenamide TDF tenofovir-DF

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Integrase Inhibitors and Cations

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Administration Recommendations for Antacids

INSTI	Product	Antacids (containing aluminium/magnesium or calcium)
Bictegravir	**Biktarvy** (BIC/FTC/TAF)	Al/Mg antacids: take Biktarvy at least 2 h before antacids. *OR* take with food 2 h after antacids (GB/European label) *OR* take 6 h after antacids (USA label). Calcium antacids: take together with food (USA label).
Cabotegravir (oral)	**Vocabria** *(oral)*	Al/Mg or Calcium antacids: Take Vocabria at least 4 h before or 2 h after antacids.
Dolutegravir	**Tivicay** (DTG)	Al/Mg antacids: take Tivicay at least 2 h before or 6 h after antacids. Avoid in the presence of integrase class resistance (European label). Calcium antacids: *take Tivicay at least 2 h before or 6 h after antacids.
	Dovato (DTG/3TC)	Al/Mg antacids: take Dovato at least 2 h before or 6 h after antacids. Calcium antacids: *take Dovato at least 2 h before or 6 h after antacids.
	"TLD" (DTG/3TC/TDF)	Al/Mg antacids: take DTG/3TC/TDF at least 2 h before or 6 h after antacids. Calcium antacids: *take DTG/3TC/TDF at least 2 h before or 6 h after antacids.
	Triumeq (DTG/ABC/3TC)	Al/Mg antacids: take Triumeq at least 2 h before or 6 h after antacids. Calcium antacids: *take Triumeq at least 2 h before or 6 h after antacids.
	Juluca (DTG/RPV	Al/Mg or Calcium antacids: Take Juluca at least 4 h before or 6 h after antacids.
Elvitegravir	**Genvoya** (EVG/c/FTC/TAF)	Al/Mg or Calcium antacids: Separate intake from antacids by at least 4 h (GB/European label) or 2 h (USA label).
	Stribild (EVG/c/FTC/TDF)	Al/Mg or Calcium antacids: Separate intake from antacids by at least 4 h (GB/European label) or 2 h (USA label).
Raltegravir	**Isentress**	Al/Mg antacids: Not recommended with twice daily or once daily Isentress. Calcium antacids: No dose adjustment required with twice daily Isentress. Not recommended with once daily Isentress.

Administration Recommendations for Oral Supplements/Multivitamins

INSTI	Product	Supplements or Multivitamins (containing calcium, iron or magnesium)
Bictegravir	**Biktarvy** (BIC/FTC/TAF)	Calcium: take together, without regard to food (GB/European label) *OR* with food (USA label). Iron: take together with food (GB/European and USA labels) *OR* take Biktarvy 2 h before iron supplements (GB/European label). Magnesium or multivitamins: *take together with food.
Cabotegravir (oral)	**Vocabria** *(oral)*	Calcium, iron, magnesium or multivitamins: *take Vocabria at least 4 h before or 2 h after supplements/vitamins.
Dolutegravir	**Tivicay** (DTG)	Calcium, iron or multivitamins: take Tivicay at least 2 h before or 6 h after supplements/vitamins (GB/European and USA labels) *OR* take together with food (USA label). Avoid in the presence of integrase class resistance (GB/European label). Magnesium: *take Tivicay at least 2 h before or 6 h after supplements.
	Dovato (DTG/3TC)	Calcium, iron or multivitamins: take together with food *OR* take Dovato under fasting conditions at least 2 h before or 6 h after supplements/multivitamins (GB/European and USA labels). Magnesium: *take together with food *OR* take Dovato under fasting conditions at least 2 h before or 6h after supplements (GB/European label).
	"TLD" (DTG/3TC/TDF)	Calcium, iron or multivitamins: take together with food *OR* take DTG/3TC/TDF under fasting conditions at least 2 h before or 6 h after supplements/vitamins. Multivitamins: take DTG/3TC/TDF at least 2 h before or 6 h after multivitamins. Magnesium: *take together with food *OR* take DTG/3TC/TDF under fasting conditions at least 2 h before or 6h after supplements.
	Triumeq (DTG/ABC/3TC)	Calcium, iron or multivitamins: take together with food *OR* take Triumeq under fasting conditions at least 2 h before or 6 h after supplements/vitamins (GB/European and USA labels). Magnesium: take together with food *OR* take Triumeq under fasting conditions at least 2 h before or 6 h after supplements/vitamins (GB/European label).
	Juluca (DTG/RPV	Calcium, iron or multivitamins: take together with food *OR* take Juluca at least 4 h before or 6 h after supplements/vitamins (GB/European and USA labels). Magnesium: *take at least 4 h before or 6 h after magnesium.
Elvitegravir	**Genvoya** (EVG/c/FTC/TAF)	Calcium, iron, magnesium or multivitamins: *Separate intake by at least 4 h (GB/European label) or 2 h (USA label).
	Stribild (EVG/c/FTC/TDF)	Calcium, iron, magnesium or multivitamins: *Separate intake by at least 4 h (GB/European label) or 2 h (USA label).
Raltegravir	**Isentress** (RAL)	Calcium, iron, magnesium or multivitamins: *Separate intake by at least 4 h with twice daily Isentress. Not recommended with once daily Isentress (GB/European and USA labels).

Information refers to licensed use of products and is from manufacturers' product labels or from *www.hiv-druginteractions.org

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