Drug-drug interactions of Integrase Strand Transfer Inhibitors among older people living with HIV.
Interazioni farmacologiche degli inibitori delle integrasi tra le persone anziane che vivono con HIV.

Hongmei Wang1,2, Judy O. Ikwuagwu2, Vincent Tran1, Nhat Anh K. Tran1

1 Department of Pharmacy Practice, Texas Southern University College of Pharmacy and Health Sciences, Houston, TX, USA
2 Department of Pharmacy, Houston Methodist Hospital, Houston, TX, USA

Abstract
The advancement of Human Immunodeficiency Virus (HIV) treatment improves the life expectancy of HIV-positive individuals. People living with HIV have more polypharmacy and drug-drug interactions than those without HIV. Integrase strand transfer inhibitors (INSTIs) are the newest class commonly used for HIV treatment. There are five INSTIs currently approved by the Food and Drug Administration, including raltegravir, elvitegravir, dolutegravir, bictegravir, and cabotegravir. INSTIs class contributes to better safety and efficacy profile, making them the preferred or recommended antiretroviral regimens in HIV treatment guidelines worldwide. Despite the shared mechanism of action, INSTIs differ in pharmacokinetics, contributing to different drug-drug interactions. This review summarized the potential drug interactions of INSTIs and the management of the drug interactions in clinical practice.

Introduction
The Human Immunodeficiency Virus (HIV) surveillance reports estimates 1.2 million people living with HIV (PLWH) in the United States. Over half (51%) of them were aged 50 years and older in 2018 (1). The life expectancy of people living with HIV (PLWH) is steadily improving due to revolutionized treatments with highly active antiretroviral therapy (ART). Aging with HIV presents particular challenges, including comorbidities such as cardiovascular diseases, lung diseases, and other chronic diseases (2,3). PLWH may have high risks of immune dysfunctions, unhealthy lifestyle, and coinfections (4,5). Polypharmacy, defined as taking five or more medications a day, is expected in the HIV population on ART therapy using three to four drugs concurrently (6,7). The comorbidities treatment exposes them to a higher risk of potential drug-drug interactions (DDIs), increasing the risk of falls, adverse drug events, cost, morbidity, and even death (8-10).

The incidence of DDIs is highly associated with the specific ART regimens used. Traditional ART regimen consists of two nucleoside reverse transcriptase inhibitors (NRTIs) in combination with an integrase strand transfer inhibitor (INSTI), a nonnucleoside reverse transcriptase inhibitor (NNRTI), or a protease inhibitor (PI) with a booster (e.g., cobicistat or ritonavir) (11,12).

High prevalence of potential DDIs occurred between comedications and the boosters, PIs, or NNRTIs. The drug interactions can affect HIV or comorbidities treatment efficacy and tolerability. Swiss HIV Cohort Studies showed 2% contraindicated interactions and 59% significant drug interactions found in PLWH that required potential dose adjustment and close monitoring (13,14).
With the clinical application of INSTIs and the second generation of NNRTIs, there are much lower drug-drug interactions. Despite drug interactions decreasing in this new INSTIs era, it is still a challenge in PLWH with multimorbidity and polypharmacy (15,16). The impact and consequences of drug interactions could be severe, particularly for the aging population. This review summarized the potential drug interactions of INSTIs and the management of the drug interactions in clinical practices.

Drug interactions involving INSTIs
INSTIs irreversibly inhibit the formation of covalent bonds between integrase and the host DNA to block the production of the provirus and the propagation of the virus. There are five INSTIs currently approved by the Food and Drug Administration (FDA), including raltegravir (RAL), elvitegravir (EVG), dolutegravir (DTG), bictegravir (BIC), and Cabotegravir (CAB). INSTIs class contributes to better safety and efficacy profile, making them the preferred or recommended ART regimens in HIV treatment guidelines worldwide. (17,18). Despite the shared mechanism of action, INSTIs differ in pharmacokinetic characteristics, contributing to different DDIs (Table 1) (19).

The drug interaction can alternate the absorption by changing gastric pH or binding or chelation. All INSTIs are susceptible to chelation interaction with polyvalent cations. Unboosted INSTIs (bictegravir, cabotegravir, dolutegravir, raltegravir) are the substrate of UDP-glucuronosyltransferases (UGT) 1A and/or cytochrome P450 enzyme (CYP) 3A4, which may result in changes in INSTIs concentrations if co-administered with inhibitors or inducers. Elvitegravir, boosted with cobicistat, is a substrate of CYP3A4, resulting in extensive drug interactions due to the booster used; therefore, elvitegravir is not recommended as the first-line therapy. Strategies to mitigate DDIs include alternative comedication, altering drug dosing, monitoring drug levels or side effects, and de-prescribing. Summarized INSTIs drug interactions are shown in Table 2 (20,21).

**BICTEGRAVIR**
Bictegravir was first approved in January 2018 as a novel second-generation INSTI (22,23). Biktarvy® is a combination of bictegravir, emtricitabine, and tenofovir alafenamide; a once-a-day regimen for antiretroviral-naive patients, as well as patients who are virally suppressed (HIV-1 RNA < 50 copies/mL).

Overall, bictegravir is well tolerated and has higher genetic barriers than raltegravir and elvitegravir, but similar to dolutegravir (23,24). The simultaneous administration of bictegravir with polyvalent cations such as aluminum, magnesium, iron, or calcium can significantly reduce the peak plasma concentration (Cmax) and systemic exposure (AUC) of bictegravir (22,25). Hence, bictegravir is recommended under fasting conditions at least 2 hours before or 6 hours after any polyvalent cations containing agents, such as antacids (22).

Co-administered bictegravir with antacids containing calcium on an empty stomach should be avoided. Bictegravir is primarily metabolized by UGT1A1 and CYP3A4 with similar contribution (22). The plasma concentration and systemic exposure of bictegravir can be decreased by the CYP3A4/UGT1A1 strong inducers, e.g. rifampin, rifabutin, rifapentine, primidone, phenobarbital, and St. John’s wort (26).

| Integrase inhibitors | Subtract | Inhibitor | Inducer |
|----------------------|----------|-----------|---------|
| Bictegravir (BTG)    | CYP3A4, UGT1A1 | OCT2, MATE1 |         |
| Cabotegravir (CAB)   | UGT1A1, UGT1A9 (minor); P-gp, BCRP | CYP3A4 (weak) |         |
| Dolutegravir (DTG)   | CYP3A4 (minor); UGT1A1/3/9, P-gp, BCRP | OCT2, MATE1 |         |
| Elvitegravir (EVG)   | CYP3A4, UGT1A1 |             | CYP2C9 (modest) |
| Raltegravir (RTG)    | UGT1A1 |             |         |

Abbreviations: BCRP, breast cancer resistance protein; CYP, cytochrome P450; MATE, multidrug/toxin extrusion; OCT, organic cation transporter; P-gp, P-glycoprotein; UGT, UDP-glucuronosyltransferase.
Table 2. Drug interactions with medications used to treat common comorbidities in aging population.

| Comorbidities | Comedications | INSTI | Effect | Management |
|---------------|---------------|-------|--------|------------|
| GERD & PUD | Al, Mg, +/- Ca-Containing Antacids | BIC | ↓ INSTIs AUC if administered simultaneously with antacid | Administer antacids that contain Al/Mg at least 2 hours after or 6 hours before BIC. Administer BIC and antacids that contain Ca together with food. |
| | CAB PO | DTG | Administer DTG at least 2 hours before or at least 6 hours after antacids that contain polyvalent cations. | |
| | RAL | | Do not co-administer RAL and Al/Mg hydroxide antacids. Use alternative acid-reducing agent. | |
| | | | With CaCO3 Antacids: do not co-administer RAL 1,200 mg; RAL 400 mg BID can co-administer. | |
| Antibacterials | Rifabutin | BIC | ↓ BIC and Cmin | Do not co-administer. |
| | | DTG | ↔ DTG AUC and ↓ Cmin | No dose adjustment needed. |
| | | RAL | ↓ RAL AUC and Cmin | No dose adjustment needed. |
| | Rifampin | BIC/CAB | ↓ BIC and CAB AUC | Contraindicated. |
| | | DTG | ↓ DTG AUC | Use DTG 50 mg twice daily (instead of DTG 50mg once daily) in patients without suspected or documented INSTI-associated resistance mutations. Consider an alternative to rifampin, such as rifabutin, in patients with certain suspected or documented INSTI-associated resistance mutations. |
| | | RAL | ↓ RAL AUC | Use RAL 800 mg twice daily instead of 400mg twice daily. Do not co-administer RAL 1,200 mg once daily with rifampin. Monitor closely for virologic response or consider using rifabutin as an alternative rifamycin. |
| | Rifapentine | BIC | ↓ BIC expected | Do not co-administer. |
| | | CAB | ↓ CAB expected | Contraindicated. |
| | | DTG | ↓ DTG AUC | With once weekly rifapentine, DTG 50 mg daily may be used in patients with viral suppression on daily DTG. Monitor for virologic efficacy. Do not co-administer in INSTI-experienced patients who require twice-daily DTG. Do not co-administer DTG with once daily rifapentine. |
| | | RAL | ↑ RAL AUC | For once weekly rifapentine and RAL 400mg twice daily, no dose adjustment needed. Do not co-administer with once daily rifapentine. |
| | Clarithromycin | BIC | ↑ BIC possible | No dose adjustment needed. |
| | Erythromycin | | | |
| Anticonvulsants | Carbamazepine | BIC | ↓ BIC expected | Do not co-administer. |
| | Phenobarbital | CAB | ↓ CAB expected | Contraindicated. |
| | Phenytion | DTG | ↓ DTG AUC | Increase DTG dose to 50mg twice daily in ART-naive or ART-experienced, INSTI-naive patients. Do not co-administer in INSTI-experienced patients with known or suspected INSTI resistance. |
| | | RAL | ↓ or ↔ RAL possible | Do not co-administer. |
| | Oxcarbazepine | BIC, DTG | ↓ BIC and DTG possible | Do not co-administer. |
| | | CAB (PO and IM) | ↓ CAB expected | Contraindicated. |
| | | RAL | ↓ RAL possible | Consider alternative ARV or anticonvulsant. |
| Antifungals | Itraconazole | BIC, CAB, DTG, RAL | ↓ INSTI possible | No dose adjustment needed |
| | Posaconazole | | | |
| | Voriconazole | | | |
| Corticosteroids | Dexamethasone | BIC | ↓ BIC possible | No dose adjustment needed |
| | Systemic | | | |
| Cardiac | Disopyramide | BIC, CAB, DTG | ↑ disopyramide possible | Monitor for disopyramide-related adverse events. |
| | Bosentan | BIC, DTG | ↑ BIC and DTG possible | No dose adjustment needed. |
| | Diltiazem | BIC | ↑ BIC possible | No dose adjustment needed |
| | Dofetilide | BIC, DTG | ↑ dofetilide expected | Contraindicated. |
| Diabetes | Metformin | BIC | ↑ Metformin AUC and Cmax | Consider alternative corticosteroid for long-term use or alternative ARV if co-administration is necessary; monitor virologic response to ART. |
| Herbal Products | St. John’s Wort | BIC, CAB, DTG | ↓ BIC and DTG possible | Do not co-administer |

Abbreviations: ↑, increase; ↓, decrease; ↔, no change; ARV, antiretroviral; AUC, area under concentration; BIC, bictegravir; CAB, cabategravir; DTG, dolutegravir; GERO, Gastroesophageal reflux disease; INSTIs: integrase strand transfer inhibitors; PO, per os orally; PUD, peptic ulcer disease; RAL, raltegravir; CAB, means PO and IM if not indicated PO.
The concomitant use should be avoided. In addition, concomitant use with strong CYP3A4 inducers (e.g., carbamazepine, oxcarbazepine, and phenytoin) is contraindicated because of their inductive effect on bictegravir metabolism, potentially leading to virologic failure (26).

In contrast, co-administration of bictegravir with CYP3A4 inhibitors, including protease inhibitors (PI) such as atazanavir, ritonavir, or anti-hepatitis C viral agents, may cause increased plasma concentration and systemic exposure of bictegravir (27), which warrants the need for close monitoring.

Apart from its metabolism via UGT1A1 and CYP3A4, bictegravir is an inhibitor of organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter 1 (MATE1). Bictegravir can increase the plasma concentration of OCT2 and MATE1 substrates, like dofetilide, resulting in a heightened risk of QT prolongation. Due to the high risk of this lethal cardiovascular event, bictegravir and dofetilide are contraindicated for concomitant use (26). Bictegravir may increase blood concentration and effects of metformin, another substrate of OCT2 and MATE1. Co-administration may require metformin dosage adjustment despite a lack of clinically relevant interactions between bictegravir and metformin (28).

CABOTEGRAVIR

One of the recent FDA-approved INSTI agents in 2021, cabotegravir, is available in two different formulations (29). It comes as a long-acting injectable suspension consisting of cabotegravir/rilpivirine (Cabenuva®) and an oral tablet cabotegravir (Vocabria®) which is approved only to be used with rilpivirine (Edurant®), an NNRTI. Cabotegravir (Vocabria®) is given as one 30 mg tablet with one 25 mg tablet of rilpivirine (Edurant®) once a day. Cabotegravir has low potential to cause DDIs; however, it can be victims of DDIs (30).

Intramuscular administration allows the bypass of the gastrointestinal tract to eliminate the gut-based DDIs and bypass first-pass metabolism, leading to different DDI profiles compared to oral administration (30). Cabotegravir is mainly metabolized by UGT1A1 with some contribution by UGT1A9.29 The liver metabolizing enzyme pathway affects intramuscular and oral administration. Previous data suggested the bypass of the gastrointestinal tract does not mitigate the magnitude of drug interaction with liver enzyme inducers, but possibly less with inhibitors (30-32).

Cabotegravir oral administration is susceptible to chelation-type drug interaction with polyvalent cations such as aluminum, magnesium, iron, and calcium (29). Interaction with the polyvalent cations causes oral cabotegravir levels to decrease, thus decreasing the effectiveness. Therefore avoid concomitant use; however, if the use of antacid is required, it is recommended to administer at least 2 hours before or 4 hours after taking oral cabotegravir (20).

Due to cabotegravir extensive metabolism by UGT1A1 and UGT1A9, the UGT enzyme inducer can decrease the effectiveness and plasma levels of both intramuscular and oral cabotegravir (29). Some agents are contraindicated for use because of their effect on cabotegravir (Vocabria®) metabolism, including anticonvulsants (e.g., carbamazepine, oxcarbazepine, phenobarbital, phenytoin) and antimycobacterial (e.g., rifampin, and rifapentine) (21).

In brief, when administering antacids with polyvalent cations, antacids should be taken at least 2 hours prior or 4 hours after administration of oral cabotegravir. Anticonvulsants such as carbamazepine, oxcarbazepine, phenobarbital, phenytoin, and antimycobacterial such as rifampin and rifapentine are contraindicated for concomitant use with intramuscular and oral cabotegravir.

DOLUTEGRAVIR

Dolutegravir, a second-generation INSTI, was approved by FDA in 2013 (33). As an individual tablet, it is supplied as Tivicay® tablet and pediatric formulation Tivicay PD® tablet for oral suspension. Dolutegravir is usually used as initial therapy for HIV treatment in combination with backbones. Dolutegravir combined with rilpivirine can be used for virologically suppressed (HIV-1 RNA <50 copies/mL) patients (33). Dolutegravir has a higher barrier to virus resistance than first-generation INSTI, making it a potential drug in salvage regimens (34).

Dolutegravir is primarily metabolized by UGT1A1 with a minor contribution from CYP3A (33).
Dolutegravir is a substrate of several enzymes and has many interactions with different enzymes and transports. Dolutegravir is a substrate of UGT1A3, UGT1A9, BCRP, and P-GP in vitro; and interacts with transporters such as OCT2, MATE1, OAT1, and OAT3 in vivo and in vitro (34). Dolutegravir can inhibit the renal organic cation transporters, OCT2, and MATE1, similarly to bictegravir, which may lead to increased plasma concentrations of certain drugs eliminated by OCT2 and MATE1 such as dofetilide, dalfampridine, and metformin (33). Due to this interaction, dofetilide is contraindicated in concomitant use with dolutegravir. The use of dalfampridine and metformin with dolutegravir should be evaluated, and dose adjustment may be considered (35,36). Dolutegravir can increase plasma creatinine by inhibiting tubular secretion via OCT2 and MATE1 with no effect on GFR.37 Dolutegravir is a substrate of the listed enzymes. Its plasma concentration may be decreased by agents that can induce the enzymes such as protease inhibitors, rifampin, carbamazepine, oxcarbazepine, phenytoin, and phenobarbital, and St. John’s wort (33). Dolutegravir requires dose adjustment if co-administered with efavirenz, carbamazepine, rifampin, and protease inhibitors, such as fosamprenavir/ritonavir and tipranavir/ritonavir. It is contraindicated to co-administer dolutegravir with nevirapine, oxcarbazepine, phenytoin, phenobarbital, and St. John’s wort (20). Similarly, across INSTI agents, dolutegravir interacts with medications or supplements containing polyvalent cations such as magnesium, aluminum, calcium, and iron via chelation bindings (33). Administration of such agents should be taken 2 hours before or 6 hours after taking dolutegravir, except for calcium and/or iron supplements. Dolutegravir can be taken with calcium and iron if with food (20,38). In short, dolutegravir dose adjustments are required for etravirine, efavirenz, carbamazepine, rifampin, fosamprenavir/ritonavir, tipranavir/ritonavir. Dose time reschedule is needed if co-administered agents contain polyvalent cations. Co-administer dolutegravir with nevirapine, oxcarbazepine, phenytoin, phenobarbital, and St. John’s wort is contraindicated. Dolutegravir can cause creatinine elevation without effect on GFR.

ELVITEGRAVIR
Elvitegravir, always boosted with cobicistat, was the second INSTI that received FDA approval (39,40). It is available as two different fix-dose single-tablet antiretroviral regimens with cobicistat, emtricitabine, and tenofovir disoproxil fumarate (Stribild®) or tenofovir alafenamide (Genvoya®). Like raltegravir, elvitegravir is the first-generation INSTI with a lower barrier to viral resistance (41). Elvitegravir is primarily metabolized via CYP3A4 with a minor component via UGT 1A1 and 1A3. Elvitegravir is contraindicated with the drugs that extensively undergo CYP3A4 metabolism, which may cause severe side effects (42). Elvitegravir required cobicistat booster to enhance the plasma exposure since CYP3A4 enzymes would decrease its blood level extensively. However, cobicistat is a potent inhibitor of CYP3A4, which causes extensive drug interactions. Cobicistat boosted elvitegravir has many clinically significant drug-drug interactions; therefore, it is not in the current recommendations for starting antiretroviral in treatment-naive patients (42).

RALTEGRAVIR
Raltegravir was the first INSTI approved by the FDA in 2007 (45). Raltegravir is well tolerated and absorbed rapidly under fasting conditions dosed at 400 mg twice daily; however, based on more recent pharmacokinetic data, 1200 mg can be used as a once-daily regimen (45). While raltegravir can be taken with or without food, a high-fat meal has shown to slow the absorption rate as evidence of increasing AUC and Cmax by approximately twofold for 400 mg formulation in some healthy volunteers (46). The absolute bioavailability has not been established. No significant efficacy difference has been noted when raltegravir is given with or without food (45). Raltegravir is primarily metabolized by UGT1A1 and is not metabolized by CYP450 enzymes, which accounts for its fewer drug-drug interactions compared to other INSTIs.47 Drugs that can induce or inhibit UGT1A1 enzymes can affect raltegravir
pharmacokinetics, therefore, must be used with caution when co-administered with raltegravir. The common UGT1A1 polymorphisms may alter raltegravir plasma concentration, but there is no evidence showing meaningful clinical extent (48,49). Raltegravir is a di-ketoacid integrase inhibitor. Its divalent cation binder selectively binds to the catalytic core domain of the integrase inhibiting the strand transfer reaction (45,50).

Through this mechanism of action, polyvalent cations in the gastrointestinal tract can alter the absorption of raltegravir (51). Co-administration of raltegravir and polyvalent cations containing drugs, such as aluminum, magnesium, and calcium antacids, should be avoided. In patients who require calcium, iron, magnesium, or multivitamins, raltegravir should be given at least 2 hours before or 6 hours after the administration of these supplements (20,38,52).

Concomitant use of raltegravir and fosamprenavir (prodrug of amprenavir) can simultaneously decrease the plasma concentrations of both amprenavir and raltegravir, in which amprenavir acts as a potential inducer of UGT1A1 (53). Therefore, concomitant use of raltegravir and fosamprenavir is not recommended due to risk of virological failure.

In summary, raltegravir is contraindicated for concomitant use with fosamprenavir or polyvalent cation containing agents such as aluminum, magnesium, and calcium antacids.

Overall, raltegravir has the fewest drug interaction in the INSTI class.

**Conclusion**

Modern INSTIs like bictegravir, cabotegravir, dolutegravir, and raltegravir have a low potential for DDIs, but the few drug interactions may have significant clinical consequences. INSTIs have slightly different drug metabolism pathways within the class, so clinicians should be familiar with the possible drug-drug interactions. The clinically significant drug interactions with INSTIs should be evaluated, particularly in the aging population. HIV and aging increase the risk of comorbidities leading to polypharmacy, making it challenging to manage their pharmacotherapy. Clinicians should remain vigilant to possible drug interactions and adjust therapies as needed.

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**Conflict of Interest Disclosures**

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