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Pharmacokinetic drug interactions of integrase strand transfer inhibitors

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ABSTRACT

The integrase strand transfer inhibitor (INSTI)-containing regimens are currently considered as the first-line treatment of human immunodeficiency virus (HIV) infection. Although possessing a common mechanism of action to inhibit HIV integrase irreversibly to stop HIV replication cycle, the INSTIs, including raltegravir, elvitegravir, dolutegravir, and bictegravir, differ in pharmacokinetic characteristics. While raltegravir undergoes biotransformation by the UDP-glucuronosyltransferases (UGTs), elvitegravir is primarily metabolized by cytochrome P450 (CYP) 3A4 and co-formulated with cobicistat to increase its plasma exposure. The metabolism pathways of dolutegravir and bictegravir are similar, both including CYP3A and UGT1A1, and both agents are substrates to different drug transporters. Because of their differences in metabolism, INSTIs interact with other medications differently through CYP enzymes and transporters as inducers or inhibitors. These drug interactions may become an important consideration in the long-term clinical use because the life expectancy of people with HIV (PWH) approaches to that of the general population. Also, common geriatric challenges such as multimorbidity and polypharmacy have been increasingly recognized in PWH. This review provides a summary of pharmacokinetic interactions with INSTIs and future perspectives in implications of INSTI drug interactions.

1. Introduction

There were an estimated 38 million people living with the human immunodeficiency virus (HIV) at the end of 2019 globally (World Health Organization, 2020). In the United States, there were an estimated 1.04 million adults and adolescents living with HIV and over 50% of people with HIV (PWH) were aged 50 and older in 2018 (Centers for Disease Contr, 2018). With the advent of antiretroviral therapy (ART), the survival and the quality of life in PWH have been dramatically improved (Dionne, 2019). Integrase strand transfer inhibitors (INSTIs) represent one of nine drug categories currently available for the treatment of HIV Type 1 (HIV-1) infection (Department of Health, 2020). In the most recent guidelines from the Department of Health and Human Services (DHHS) and the International Antiviral Society (IAS) - USA Panel, INSTI-based combination ART has been recommended as the first-line initial regimens for treatment-naïve PWH (Panel on Antiretroviral G, 2020; Saag et al., 2020).

INSTIs irreversibly inhibit HIV integrase to prevent the integration of virus DNA into host DNA to block the formation of the provirus and propagation of the virus (Pandey and Grandgenett, 2008; Powderly, 2010). There are four INSTIs currently approved by the Food and Drug Administration (FDA) and available for clinic use including raltegravir (RAL), elvitegravir (EVG), dolutegravir (DTG), and bictegravir (BIC). The superior efficacy of RAL, EVG, and DTG with similar or better safety profiles compared to protease inhibitor (PI) - or non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens were demonstrated in clinical trials and long-term real-world HIV management (Messiaen et al., 2013; Snedecor et al., 2019). The newest approved INSTI in 2018, BIC, is well tolerated and has a relatively equivalent efficacy to DTG against INSTI-resistant mutants of the HIV-1 virus (Tsiang et al., 2016; Sax et al., 2017).

This review summarizes and compares human pharmacokinetics (PK), drug-drug interactions of these INSTIs, and provides future perspectives in clinical implications of INSTI drug interactions.

2. Pharmacokinetics

Despite possessing a common mechanism of action, INSTIs differ in both structural and PK characteristics. This section summarizes major PK features of each INSTI, including absorption, distribution, and

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metabolism which contribute to potential drug-drug interactions. The characteristics of INSTI drug metabolism based on the most recent manufacturers' package inserts and other recent published literature are summarized in Table 1.

2.1. Raltegravir

RAL is currently available in three dosage forms in the United States: (1) film-coated tablets (400 mg and 600 mg); (2) chewable tablets (100 mg and 25 mg); and (3) oral suspension (single-use packet of 100 mg) (Isentress, 2020).

The 400 mg film-coated RAL tablet is rapidly absorbed with a median time to maximum plasma concentration (Tmax) approximately 3 h in the fasted state (Krishna et al., 2018). The 600 mg tablet exhibits similar systemic PK to the 400 mg tablet with a slightly shorter Tmax. The absolute bioavailability of RAL has not been established due to the lack of a parenteral formulation (Podany et al., 2017). However, chewable tablet and oral suspension have higher oral bioavailability compared to the 400 mg film-coated tablet (Isentress, 2020). Although food may increase the plasma concentration of RAL, it can be co-administered with or without food (Isentress, 2020; Podany et al., 2017; Brainard et al., 2011). Following absorption, RAL is approximately 83% bound to human plasma protein, mainly to albumin (Isentress, 2020; Barau et al., 2013). The half-life of RAL is approximately 9 h (Isentress, 2020). The main mechanism of clearance of RAL involves the UDP-glucuronosyltransferases (UGTs), primarily the UGT1A1 isoform, which catalyzed the glucuronidation of a number of endogenous and exogenous substances (Kassahun et al., 2007; Elliot et al., 2017). In addition, the polymorphisms of UGT1A1 may alter the plasma concentration of RAL (Wenning et al., 2009a).

2.2. Elvitegravir

EVG is available in two different fixed-dose combination (FDC) tablets from the same manufacturer (Stribild, 2020; Genvoya, 2020). The FDC tablets are a four-drug combination, including 150 mg EVG, 150 mg of cobicistat (COBI), 200 mg of emtricitabine (FTC), and 300 mg of tenofovir disoproxil fumarate (TDF), or 10 mg of tenofovir alafenamide (TAF). Both of them are listed in the DHHS guideline as the recommended initial HIV regimens if a one-pill, once-daily regimen is desired (Panel on Antiretroviral G, 2020).

The absorption of EVG is significantly increased when it is taken with food, including milk and protein-rich drink (Podany et al., 2017; Stribild, 2020; Genvoya, 2020; Yamada et al., 2018; Yonemura et al., 2018). Therefore, it has been recommended that EVG should be administered with food to maintain the plasma concentration. It takes about 4 h to reach Tmax after taking EVG and it shows extensive protein binding (99%) after absorption (Stribild, 2020; Genvoya, 2020). Unlike RAL, EVG is converted to inactive metabolite primarily via hepatic and intestinal cytochrome P450 (CYP) 3A4 enzymes and secondarily through UGT1A1 and UGT1A3(Elliot et al., 2017). Since the CYP3A4 enzymes would decrease the plasma concentration of EVG extensively, co-administration with a selective CYP3A inhibitor, COBI, may enhance EVG plasma exposure and prolongs its elimination half-life to allow once-daily regimen (Shah et al., 2013; Ramanathan et al., 2011).

Table 1
Characteristics of integrase strand transfer inhibitor drug metabolism.

Medication	Approval	Substrate	Inhibitor	Inducer	Reference
Raltegravir	2007	UGT1A1	–	–	(Isentress, 2020; Podany et al., 2017)
Elvitegravir	2012	CYP3A, UGT1A1/3	–	CYP2C9	(Podany et al., 2017; Stribild, 2020; Genvoya, 2020)
Dolutegravir	2013	CYP3A, UGT1A1/3/9, BCRP, P-gp	OCT2, MATE1	–	(Podany et al., 2017; Tivicay, 2020; Triumeq, 2020; Juluca, 2020; Dovato, 2020)
Bictegravir	2018	CYP3A, UGT1A1	OCT2, MATE1	–	Biktarvy (2019)

Abbrev. BCRP, breast cancer resistance protein; CYP, cytochrome P450; MATE, multidrug/toxin extrusion; OCT, organic cation transporter; P-gp, P-glycoprotein; UGT, UDP-glucuronosyltransferase.

2.3. Dolutegravir

DTG was first approved by the FDA as a 50 mg oral use tablet in 2013 (Tivicay, 2020). As of October 2020, there are multiple products available containing DTG in the United States, including oral tablet (10 mg, 25 mg, and 50 mg), 50 mg tablets for oral suspension, two-drug combination FDC tablets (DTG/lamivudine [3 TC]; DTG/rilpivirine [RPV]), and a three-drug combination tablet (DTG/3TC/abacavir [ABC]) (Tivicay, 2020; Triumeq, 2020; Juluca, 2020; Dovato, 2020). DTG-based regimens could be used as an initial therapy for most people with HIV (Panel on Antiretroviral G, 2020).

Although the meal may increase the area under the concentration-time curve (AUC) of DTG up to 66% and the maximum concentration of drug in plasma (C_{max}) up to 67%, the increases were not expected to alter the clinical safety of the DTG (Podany et al., 2017; Song et al., 2012). Therefore, most DTG tablets may be taken with or without food, excepting the DTG/RPV FDC tablet per recommendations from the manufacturer (Tivicay, 2020; Triumeq, 2020; Juluca, 2020; Dovato, 2020; Song et al., 2012). Moderate- or high-fat meals have been shown to increase the AUC and C_{max} of both DTG and RPV (Mehta et al., 2020). Taking RPV without food may decrease the plasma concentrations which could potentially reduce the efficacy of the DTG/RPV tablet. Tmax of DTG were observed around 2–3 h post-dose and it displays highly bound (≥98.9%) to plasma proteins (Tivicay, 2020). DTG is a substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), UGT1A3, and UGT1A9 (Podany et al., 2017; Tivicay, 2020; Reese et al., 2013). It is extensively metabolized by UGT1A1 with some contribution from CYP3A enzymes and the terminal elimination half-life (t½) of DTG is around 14 h (Reese et al., 2013; Cottrell et al., 2013).

2.4. Bictegravir

BIC was approved in 2018 and it is only available in a three-drug combination (BIC/FTC/TAF) FDC tablet (Biktarvy, 2019). The efficacy and safety of BIC/FTC/TAF compared to other core regimens using on HIV treatment naïve and Treatment-experienced patients or switching from other regimens to BIC/FTC/TAF were confirmed in multiple clinical trials (Sax et al., 2017; Daar et al., 2018; Gallant et al., 2017; Iwuji et al., 2020). Because of the durable virology efficacy, BIC/FTC/TAF is recommended as an initial HIV therapy (Panel on Antiretroviral G, 2020).

The oral availability of BIC is around 70% and it could be taken with or without food even though the high-fat meals may increase the AUC and C_{max} by 24% and 13%, respectively (Biktarvy, 2019; Zeuli et al., 2019). The Tmax of BIC is between 2 and 4 h reflecting the administration of tablets with or without food. Following absorption, BIC is highly bound to human plasma protein (>99%) and the median plasma half-life observed in healthy volunteers were approximately 18 h, which allows taking it once-daily (Zhang et al., 2017). Similar to DTG, the major metabolism pathways of BIC are UGT1A1 with similar contribution from CYP3A enzymes (Biktarvy, 2019).

3. Drug-drug interactions

Drug-drug interactions are commonly seen in other classes of ART such as PI-based regimens due to the inhibition of metabolizing enzymes (Courlet et al., 2020). This section summarizes major drug-drug interactions of each INSTI, and the selection of clinical evidences are listed in Table 2.

3.1. Interactions with other antiretroviral medications

RAL has been evaluated in combination with other HIV medicines. In the presence of efavirenz (EFV) 600 mg, a NNRTI, the PK of RAL 400 mg once daily were weakly affected: the C_{max} geometric mean ratio (GMR) (90% confidence interval [CI]) was 0.64 (0.49, 1.28), and AUC from time 0 extrapolated to infinite time hour ($AUC_{0-\infty}$) was 0.64 (0.52, 0.80) (Iwamoto et al., 2008a). When RAL and etravirine (ETR), another NNRTI, 400/200 mg were used together twice daily, ETR only had a modest effect on the PK of RAL (Anderson et al., 2008). C_{max} was 0.89 (0.68, 1.15), and AUC from 0 to 12 h post-dose (AUC_{0-12}) was 0.90 (0.68, 1.18). Although EFV and ETR are the known CYP inhibitors and inducers, the effects on UGT metabolism are minimal (Gong et al., 2019).

Atazanavir (ATV) is a PI metabolized by CYP enzymes and it is an inhibitor of both CYP3A and UGT1A1 enzymes (Iwamoto et al., 2008b). In the exposure of ATV, it would moderately increase the plasma concentration of RAL 100 mg once daily: C_{max} GMR was 1.53 (1.11, 2.12), and $AUC_{0-\infty}$ 1.72 (1.47, 2.02). A moderate increase of the plasma concentration of RAL 400 mg twice daily was also found with ATV and ritonavir (ATV/r) co-administration [C_{max}, 1.77 (1.39, 2.25); AUC_{0-12}, 1.41 (1.12, 1.78)]. However, the extent of the increase of both combinations was not believed to be clinically important. A similar increase of plasma concentration was found in the combination of RAL and ATV 400/400 mg once daily regimen (Neely et al., 2010). The C_{max} GMR (95% CI) was 1.37 (0.62, 3.02), and AUC from time 0 to end of dosing interval (AUC_{τ}) was 1.72 (0.79, 3.75). Coadministration of RAL and ATV 400/300 mg twice daily increase the AUC_{0-12} [1.536 (1.135, 2.081)] and C_{max} [1.394 (0.990, 1.964)] of RAL as well (Zhu et al., 2010). In summary, this interaction was most likely due to the inductive effect of EFV on UGT1A1, but the interaction was not clinically meaningful and did not require dosage adjustment.

EVG shares similarities to tipranavir (TPV) and darunavir (DRV) in their elimination pathways, metabolized by CYP3A enzymes (Mathias et al., 2008). When EVG used with TPV, it would slightly increase the C_{max} [1.06 (0.89, 1.26)] and AUC_{τ} [0.92 (0.79, 1.08)], respectively. The increase of EVG concentration was observed in the study: C_{max} [1.13 (1.03, 1.24)], and AUC_{τ} [1.10 (0.99, 1.22)]. Gutierrez-Valencia et al. investigated the interaction between the DRV and the EVG/COBI/FTC/TDF single tablet on HIV-infected patients, and the results demonstrated that the concentration reduction effect of DRV on the EVG co-formulated tablet was not significant (p=0.406) (Gutierrez-Valencia et al., 2017). Thus, EVG may be combined with TPV or DRV without dose adjustment.

DTG was also tested with EFV or TPV because of the potential interactions affected by the CYP3A enzymes (Song et al., 2014). In the DTG/EFV arm, the C_{max} [0.608 (0.506, 0.730)] and AUC_{τ} [0.431 (0.346, 0.536)]. In the DTG/TPV arm, the C_{max} [1.06 (0.89, 1.26)] and AUC_{τ} [0.92 (0.79, 1.08)]. The results of the study showed that the decrease in plasma DTG was likely in part due to the induction of CYP3A4 caused by the EFV and TPV. Thus, the dose adjustment may be necessary depends on the DTG dosage.

3.2. Interactions with antacids or mineral supplements

All INSTIs have the triad of heteroatoms responsible for metal chelation to bind to magnesium ions located at the catalytic site of the integrase enzyme to inhibit the activity of HIV-1 integrase (Kaur et al., 2018; Markham, 2018) [Fig. 1]. Thus, the interaction between metal-cation antacids and the INSTIs is predictable.

In a previous study, with the simultaneous antacid administration, the Tmax of RAL 400 mg twice daily occurred 2 h sooner (p=0.002), but had no significant changes in C_{max} and AUC_{0-12} (Kiser et al., 2010). Later on, Krishna et al. reported findings from the once daily RAL 1200 mg regimen co-administered with antacids containing Al^{3+}, Mg^{2+}, or Ca^{2+} ions on HIV-infected patients (Krishna et al., 2016). When the calcium carbonate (Ca^{2+}) was given concomitantly, the GMR for C_{max} and AUC from 0 to 24 h post-dose (AUC_{0-24}) were 0.26 (0.21, 0.32), and 0.28 (0.24, 0.32). Although dose separation of antacids and RAL for 12 h could ease the drug interactions, significant reductions in the trough concentrations (C_{24}) of RAL were observed: 0.43 (0.36, 0.51) taking Ca^{2+} antacids, 0.42 (0.34, 0.52) taking Mg^{2+}/Al^{3+} antacids.

The antacids would reduce the EVG plasma concentration of administered concomitantly: C_{max} [0.531 (0.468, 0.602)] and AUC_{τ} [0.551 (0.504, 0.602)] (Ramanathan et al., 2013). Ramanathan et al. also investigated the drug interactions between EVG and famotidine (H2-receptor antagonist), and omeprazole (proton pump inhibitors), and found no clinically relevant interactions from the study.

HIV-infected patients may take mineral supplements with their HIV medications. Song et al. reported that supplements containing Ca^{2+} and Fe^{2+} would significantly reduce the DTG plasma concentration by 39% [$AUC_{0-\infty}$, 0.61(0.47, 0.80)] and 54% [$AUC_{0-\infty}$, 0.46(0.35, 0.52)] under fasted conditions but no significant effected if taken separately or with a moderate-fat meal (Song et al., 2015). A recent report observed that concomitant use of BIC and high dose of zinc (Zn^{2+}) supplementation may lead to HIV treatment failure (Rock et al., 2020).

In summary, co-administration with products containing divalent or trivalent cations may decrease the plasma concentration of four INSTIs (Panel on Antiretroviral G, 2020). Antacids with Al^{3+}, Mg^{2+} or Ca^{2+} should not be used with RAL 1200 mg; however, there is no limitation for the RAL 400 mg twice daily using with Ca^{2+} antacids. EVG should be given at least 2 h before or 6 h after taking products with polyvalent cations. Dose separation strategy or taking with a meal are recommended with DTG and products containing multivalent cations. For BIC, dose separation should be considered by taking products with Al^{3+} or Mg^{2+}, but antacids with Ca^{2+} could be taken with food. There is no dose adjustment needed when patients are using any INSTIs with H2 receptor antagonists and proton pump inhibitors.

3.3. Interactions with enzyme inhibitors and inducers

The CYP enzymes and UGT enzymes are responsible for drug metabolism (Kiang et al., 2005; Manikandan and Nagini, 2018). All INSTIs are the substrates of UGT1A1 or CYP3A enzymes (Di Perri et al., 2019; Di Perri, 2019). Co-administration of INSTI with drugs that interrupt normal functions of those enzymes may be contraindicated or lead to potential drug-drug interactions.

For example, rifampin, a well-known CYP enzyme inducer, demonstrated a reduction effect on the RAL plasma concentration because it also induced UGT enzymes (Wenning et al., 2009b). When RAL 400 mg twice daily was concurrently used with rifampin 600 mg once daily, the C_{max} and $AUC_{0-\infty}$ of RAL were 0.62 (0.37, 1.04), and 0.60(0.39, 0.91), respectively. This study also showed that doubling the RAL dose did not overcome the rifampin reduction effect on the trough concentrations (C_{12}) of RAL: 0.47 (0.36, 0.61).

In the presence of once daily rifampicin 600 mg, the decrease of DTG 50 mg was observed: C_{max} 0.65 (0.55, 0.75), and AUC_{0-24} 0.44 (0.37, 0.52) (Wang et al., 2019). Doubling the DTG dose could compensate the C_{max}, but not for the AUC_{0-24} [0.74 (0.64, 0.86)]. In a population-based study among 620 HIV patients, the model suggested that the C_{max} and AUC_{0-24} of DTG were 28% and 40 lower after 50 mg/12h with rifampicin compared with a standard dosage of 50 mg/24h without rifampicin (Barcelo et al., 2019). In addition, the AUC_{0-24} after 100 mg/24h was 40% lower than the DTG standard dosage without rifampicin. Similar results were reported when DTG was used with other potent UGT/CYP3A

Table 2
Selection of clinical evidences reporting the drug-drug interactions between integrase strand transfer inhibitors and other medications.

Year		Study design	Patient selection	N	Intervention	GMR of PK parameters	Ref.
Raltegravir							
2008	Study I	Double-blind Placebo-controlled RCT	• Healthy male within 30% of IBW	14	RAL 400 mg + r 100 mg BID versus RAL 400 mg	C_{max} (μM) 0.76 (0.55, 1.04)[a] $AUC_{0-\infty}$ (μM ·h) 0.84 (0.70, 1.01)[a]	Iwamoto et al. (2008a)
	Study II		• 18–45 years of age	14	RAL 400 mg + EFV 600 mg versus RAL 400 mg	C_{max} (μM) 0.64 (0.41, 0.98)[a] $AUC_{0-\infty}$ (μM ·h) 0.64 (0.52, 0.80)[a]	
2008	–	Open-label trial	• Healthy subject within 30% of IBW • 18–45 years of age	20	RAL 400 mg BID + ETR 200 mg BID versus RAL 400 mg BID	C_{max} (μM) 0.89 (0.68, 1.15)[a] AUC_{0-12} (μM ·h) 0.90 (0.68, 1.18)[a]	Anderson et al. (2008)
2008	Study I	Double-blind Placebo-controlled RCT	• Healthy male	12	RAL 100 mg + ATV 400 mg versus RAL 100 mg	C_{max} (μM) 1.53 (1.11, 2.12)[a] $AUC_{0-\infty}$ (μM ·h) 1.72 (1.47, 2.02)[a]	Iwamoto et al. (2008b)
	Study II	Open-label trial	• Healthy subject	10	RAL 400 mg BID + ATV/r 300/100 mg versus RAL 400 mg BID	C_{max} (μM) 1.24 (0.87, 1.77)[a] AUC_{0-12} (μM ·h) 1.41 (1.12, 1.78)[a]	
2009	Study I	Open-label trial	• Healthy subject	10	RAL 400 mg + rifampin 600 mg versus RAL 400 mg	C_{max} (μM) 1.24 (0.87, 1.77)[a] AUC_{0-12} (μM ·h) 1.41 (1.12, 1.78)[a]	Wenning et al. (2009b)
	Study II		• Healthy subject	18	RAL 800 mg + rifampin 600 mg versus RAL 400 mg	C_{max} (μM) 1.24 (0.87, 1.77)[a] AUC_{0-12} (μM ·h) 1.41 (1.12, 1.78)[a]	
2010	–	Open-label cross-over trial	• Healthy subject • ≥18 years of age	19	RAL 400 mg + ATV 400 mg versus RAL 400 mg	C_{max} (ng/ml) 1.37 (0.62, 3.02)[b] AUC_{τ} (ng/ml ·h) 1.72 (0.79, 3.75)[b]	Neely et al. (2010)
2010	–	Open-label trial	• Healthy subject with BMI 18-32 • 18–45 years of age	22	RAL 400 mg BID + ATV 300 mg BID versus RAL 400 mg BID	C_{max} (ng/ml) 1.394 (0.990, 1.964)[a] AUC_{0-12} (ng/ml·h) 1.536 (1.135, 2.081)[a]	Zhu et al. (2010)
2010	–	Crossover RCT	• Healthy subject within 30% of IBW, ≥ 50 kg • 18–60 years of age	12	RAL 400 mg + antacids versus RAL 400 mg	C_{max} (ng/ml) 1.53 (0.9, 2.6)[a] $AUC_{0-\infty}$ (ng/ml ·h) 0.96 (0.62, 1.5)[a]	Kiser et al. (2010)
2016	–	Open-label trial	• HIV-infected patient • ≥18 years of age	20	RAL 1200 mg + Ca^{2+} antacid 1000 mg (co-administered) versus RAL 1200 mg	C_{max} (ng/ml) 0.26 (0.21, 0.32)[a] $AUC_{0-\infty}$ (ng/ml ·h) 0.28 (0.24, 0.32)[a]	Krishna et al. (2016)
					RAL 1200 mg + Mg^{2+}/Al^{3+} antacid 1600/1600 mg (+12 h) versus RAL 1200 mg	C_{max} (ng/ml) 0.86 (0.65, 1.15)[a] AUC_{0-24} (ng/ml ·h) 0.86 (0.73, 1.03)[a]	
					RAL 1200 mg + Ca^{2+} antacid 1000 mg (+12 h) versus RAL 1200 mg	C_{max} (ng/ml) 0.98 (0.81, 1.17)[a] AUC_{0-24} (ng/ml ·h) 0.90 (0.80, 1.03)[a]	
Elvitegravir							
2008	Study I	Open-label trial	• Healthy subject with BMI 19-30 • 18–45 years of age	34	EVG 200 mg + TPV/r 500/200 mg BID versus EVG/r 200/100 mg	C_{max} (ng/ml) 1.06 (0.894, 1.26)[a] AUC_{τ} (ng/ml ·h) 0.924 (0.787, 1.08)[a]	Mathias et al. (2008)
	Study II			33	EVG 125 mg + DRV/r 600/100 mg BID versus EVG//r 125/100 mg	C_{max} (ng/ml) 1.13 (1.03, 1.24)[a] AUC_{τ} (ng/ml ·h) 1.10 (0.991, 1.22)[a]	
2013		Open-label cross-over trial	• Healthy subject with • 18–45 years of age	13	EVG/r 50/100 mg + antacids (co-administered) versus EVG/r 50/100 mg	C_{max} (ng/ml) 0.531 (0.468, 0.602)[a] AUC_{τ} (ng/ml ·h) 0.551 (0.504, 0.602)[a]	Ramanathan et al. (2013)
				22	EVG/COBI 150/150 mg + omeprazole (2 h prior) versus EVG/COBI 150/150 mg	C_{max} (ng/ml) 1.16 (1.04, 1.30)[a] AUC_{τ} (ng/ml ·h) 1.10 (1.02, 1.19)[a]	
					EVG/COBI 150/150 mg + omeprazole (12 h after) versus EVG/COBI 150/150 mg	C_{max} (ng/ml) 1.03 (0.919, 1.15)[a] AUC_{τ} (ng/ml ·h) 1.05 (0.929, 1.18)[a]	
				26	EVG/COBI 150/150 mg + famotidine (12 h after) versus EVG/COBI 150/150 mg	C_{max} (ng/ml) 1.02 (0.894, 1.17)[a]	

(*continued on next page*)

Table 2 (*continued*)

Year		Study design	Patient selection	N	Intervention	GMR of PK parameters	Ref.
					EVG/COBI 150/150 mg + famotidine (co-administered) versus EVG/COBI 150/150 mg	AUC_{τ} (ng/ml ·h) 1.03 (0.949, 1.13)[a] C_{max} (ng/ml) 1.00 (0.917, 1.10)[a] AUC_{τ} (ng/ml ·h) 1.03 (0.981, 1.08)[a]	
2017	–	Clinical trial	• HIV infected patient	88	Group A: EVG 150 mg + DRV 800 mg Group B: EVG 150 mg Group C: DRV/COBI 800/150 mg	No GMR reported in the study Group A EVG concentration was 6.6% lower than group B (p=0.406)	Gutierrez-Valencia et al. (2017)
Dolutegravir							
2014	Study I	Open-label trial	• Healthy subject	12	DTG 50 mg + EFV 600 mg versus DTG 50 mg	C_{max} (μg/ml) 0.608 (0.506, 0.730)[a] AUC_{τ} (μg/ml ·h) 0.431 (0.346, 0.536)[a]	Song et al. (2014)
	Study II			18	DTG 50 mg + TPV/r 500/200 mg versus DTG 50 mg	C_{max} (μg/ml) 0.535 (0.500, 0.572)[a] AUC_{τ} (μg/ml ·h) 0.409 (0.379, 0.443)[a]	
2015	–	Open-label trial	• Healthy subject	21	DTG 50 mg + calcium carbonate 1200 mg (fasted) versus DTG 50 mg (fasted) DTG 50 mg + calcium carbonate 1200 mg (with meal) versus DTG 50 mg (fasted) DTG 50 mg + calcium carbonate 1200 mg (2 h prior) versus DTG 50 mg (fasted) DTG 50 mg + calcium carbonate 1200 mg (with meal) versus DTG 50 mg + calcium carbonate 1200 mg (fasted) DTG 50 mg + ferrous fumarate 324 mg (fasted) versus DTG 50 mg (fasted) DTG 50 mg + ferrous fumarate 324 mg (with meal) versus DTG 50 mg (fasted) DTG 50 mg + ferrous fumarate 324 mg (2 h prior) versus DTG 50 mg (fasted) DTG 50 mg + ferrous fumarate 324 mg (with meal) versus DTG 50 mg + ferrous fumarate 324 mg (fasted)	C_{max} 0.63 (0.50, 0.81)[a] $AUC_{0-\infty}$ 0.61 (0.47, 0.80)[a] C_{max} 1.07 (0.83, 1.38)[a] $AUC_{0-\infty}$ 1.09 (0.84, 1.43)[a] C_{max} 1.00 (0.78, 1.29)[a] $AUC_{0-\infty}$ 0.94 (0.72, 1.23)[a] C_{max} 1.70 (1.32, 2.18)[a] $AUC_{0-\infty}$ 1.78 (1.36, 2.33)[a] C_{max} 0.43 (0.35, 0.52)[a] $AUC_{0-\infty}$ 0.46 (0.38, 0.56)[a] C_{max} 1.03 (0.84, 1.26)[a] $AUC_{0-\infty}$ 0.98 (0.81, 1.20)[a] C_{max} 0.99 (0.81, 1.21)[a] $AUC_{0-\infty}$ 0.95 (0.77, 1.15)[a] C_{max} 2.41 (1.97, 2.94)[a] $AUC_{0-\infty}$ 2.14(1.76, 2.61)[a]	Song et al. (2015)
2016	–	Open-label trial	• Healthy subject	14	DTG 50 mg + carbamazepine 300 mg BID versus DTG 50 mg	C_{max} (μg/ml) 0.666 (0.610, 0.726)[a] AUC_{τ} (μg/ml ·h) 0.512 (0.477, 0.549)[a]	Song et al. (2016a)
2019	–	Open-label trial	• Healthy subject with BMI 18-35 • 18–60 years of age	14	DTG 100 mg + rifampicin 600 mg versus DTG 50 mg + rifampicin 600 mg DTG 50 mg + rifampicin 600 mg versus DTG 50 mg DTG 100 mg + rifampicin 600 mg versus DTG 100 mg DTG 100 mg + rifampicin 600 mg versus DTG 50 mg	C_{max} 1.68 (1.43, 1.97)[a] AUC_{0-24} 1.70 (1.49, 1.95)[a] C_{max} 0.65 (0.55, 0.75)[a] AUC_{0-24} 0.44 (0.37, 0.52)[a] C_{max} 0.64 (0.55, 0.74)[a] AUC_{0-24} 0.42 (0.35, 0.50)[a] C_{max} 1.09 (0.97, 1.21)[a] AUC_{0-24} 0.74 (0.64, 0.86)[a]	Wang et al. (2019)
2019[c]	–	Model simulation study	• HIV infected patient	521	DTG 50 mg BID + rifampicin 600 mg versus DTG 50 mg QD DTG 100 mg QD + rifampicin 600 mg versus DTG 50 mg QD DTG 100 mg BID + rifampicin 600 mg versus DTG 50 mg QD	C_{max} 0.72 AUC_{0-24} 0.60 C_{max} 1.24 AUC_{0-24} 0.60 C_{max} 1.44 AUC_{0-24} 1.20	Barcelo et al. (2019)

ATV, atazanavir; AUC_{0-12}, area under the concentration-time curve from time 0–12 h; $AUC_{0-\infty}$, area under the concentration-time curve from time 0 extrapolated to infinite time hour; BID, twice daily; BMI, body mass index; COBI, cobistat; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; ETR, etravirine; EVG, elvitegravir; GMR, Geometrical Mean Radius; IBW, ideal body weight; PK, pharmacokinetics; r, ritonavir; RAL, raltegravir; RCT, randomized clinical trial; QD, once daily; TPV, tipranavir.

[a] 90% confidence interval (CI).

[b] 95% CI.

[c] No 90%CI reported in the study.

such as carbamazepine (Song et al., 2016a). DTG/carbamazepine versus DTG alone were 0.67 (0.61, 0.73), and 0.51 (0.48, 0.55) for the C_{max}, and AUC_{τ}, respectively.

Since the EVG is primarily metabolized by CYP3A4, it is contra-indicated to used EVG with a drug that also undergo CYP3A4 metabolism extensively (e.g. alfuzosin) which may increase its concentration and lead to severe adverse effects, or used with a strong CYP3A4 enzyme inducer (e.g. rifampin and carbamazepine) which may lower the level of EVG (Panel on Antiretroviral G, 2020). Compared to DTG, BIC is more susceptible to drug-drug interactions via CYP3A4 (e.g. contraindicated with rifampin) (Biktarvy, 2019).

Based on the experiences from previous studies, patients treated with INSTIs and potent enzymes inhibitors/inducers may benefit from therapeutic drug monitoring and individualized dosage. In addition, a Swiss study found that unboosted INSTIs (RAL, DTG, and BIC) had lower chance to cause suboptimal response compared to PI-based regimens (Courlet et al., 2020).

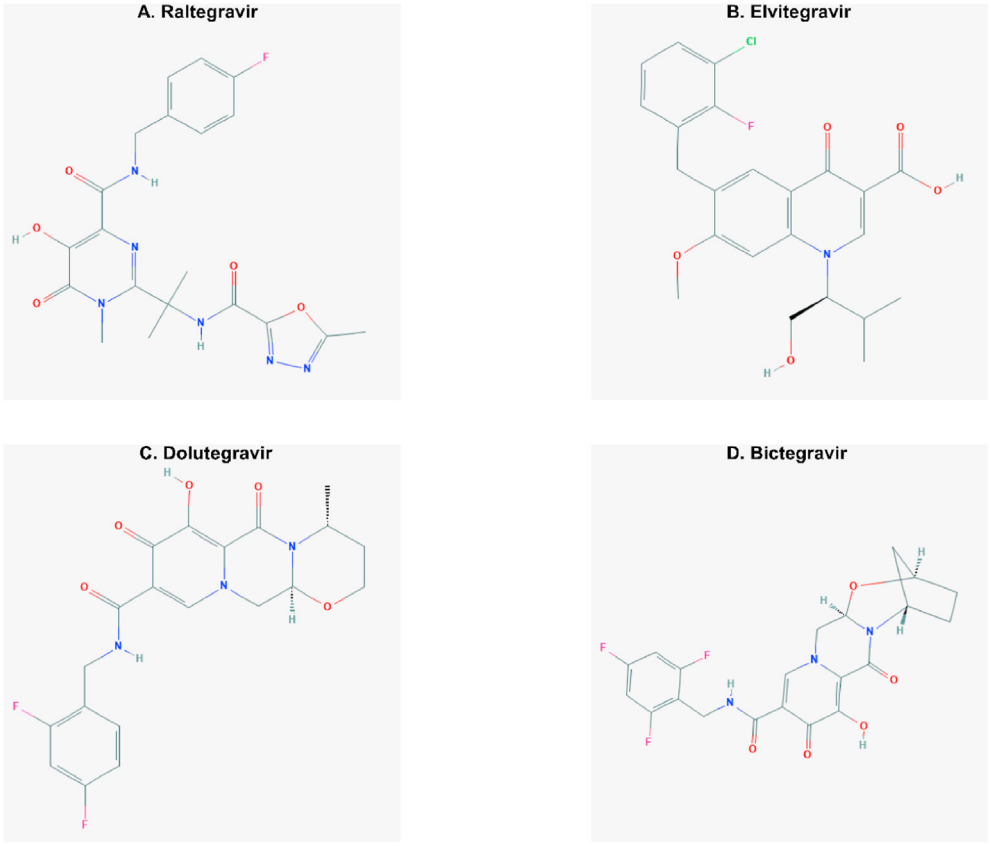

Fig. 1. Chemical structures of integrase strand transfer inhibitor. Adapted from PubChem.

3.4. Interactions with drug transporters

Drug transporters such as P-gp, BCRP, organic cation transporters (OCTs), and multidrug/toxin extrusions (MATEs) are determinants of drug disposition by affecting the pharmacokinetics of drugs (Liu, 2019; Gessner et al., 2019). Screening the new molecular entities as substrates or inhibitors of transporters in the drug development process is now a common practice because serious drug-drug interactions may occur due to the effects of transporters (Gessner et al., 2019). BIC and DTG are inhibitors of OCT2 and MATE1; DTG is also the substrates of P-gp and BCRP (Triumeq, 2020; Biktarvy, 2019; Di Perri, 2019). Therefore, BIC and DTG may increase plasma concentrations of drugs eliminated via OCT2 or MATE1 such as dofetilide and metformin (Triumeq, 2020; Biktarvy, 2019). Due to the narrow therapeutic index of dofetilide, it is contraindicated to used dofetilide with BIC or DTC concurrently. Previous studies showed that both BIC and DTG increased metformin plasma exposure in healthy adults and the dose adjustment of metformin is recommended to maintain optimal blood glucose control (Song et al., 2016b; Custodio et al., 2017). There were no severe adverse effects such as lactic acidosis reported when dolutegravir and metformin were co-prescribed to HIV patients but evaluating concurrent use of metformin and DTG case by case should still be considered (Masich et al., 2017; Naccarato et al., 2017).

4. Aging and polypharmacy

The life expectancy of people living with HIV is approaching that of the general population because of the high efficacy and safety of ARTs (Marcus et al., 2020). The estimated average lifespan in patients who achieved viral suppression and maintained $CD4^+$ cell count $\geq$350 cells/μl is about 80 years (May et al., 2014). In 2018, over half of people living with HIV were aged 50 and older in the United States, and they are at increased risk of poor health outcomes because of the aging related comorbidities (Centers for Disease Contr, 2018; Saag et al., 2020).

With the coexisting comorbidities, the risk of drug-drug interactions increased due to polypharmacy (commonly defined as the concurrent administration of $\geq$5 medications) among elderly patients (Masnoon et al., 2017). Physiological changes related to aging may affect pharmacokinetics putting elderly patients with or without HIV at risk of experiencing drug-drug interactions. In HIV care settings, polypharmacy often refers to non-HIV medications given in addition to standard ARTs (Back and Marzolini, 2020). It is common to see that the total number of medications used in HIV patients is much higher than those patients without HIV and increases the risk of experiencing polypharmacy related drug-drug interactions among those patients. A recent study showed that about 1/3 of elderly had complex ART regimens, and inappropriate medications were found in 14% elderly PLWH (Courlet et al., 2019). Thus, caution is needed when prescribing medications in those populations. As today, there is no large population-based data from clinical trials or PK studies for INSTIs to determine the efficacy and safety in the elderly (Isentress, 2020; Stribild, 2020; Genvoya, 2020; Tivicay, 2020; Triumeq, 2020; Juluca, 2020; Dovato, 2020; Biktarvy, 2019). Dose adjustment for other concomitant non-HIV medicines may be necessary in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function.

5. Conclusion & perspectives

Potent antiretroviral combinations have been established as the gold standard in the DHHS and IAS guidelines (Panel on Antiretroviral G, 2020; Saag et al., 2020). The mechanism of INSTIs blocks HIV integrase to insert viral DNA into the DNA of the host CD4 cell to prevent HIV from replicating demonstrating high potent of efficacy for HIV treatment. Although possessing a common mechanism of action to inhibit HIV

integrase, the INSTIs, can be distinguished on the basis of pharmacokinetic differences, resulting in different dose frequency, combinations and concern of drug-drug interactions.

The clinical significance of INSTI drug interactions needs to be evaluated case by case, as large inter-individual variability exists. In the meantime, the metabolism pathways are slightly different from each INSTIs. For example, RAL only undergoes via the UGT system; EVG has to use with CYP3A booster; DTG and BIC are metabolized by CYP3A and UGT system with a different contribution. With the life expectancy increased in HIV patients, a better understanding of the clinical pharmacology of these agents in the elderly population is crucial to the development of rational therapeutic regimens and dosage adjustment due to limited data.

CRediT authorship contribution statement

Chi-Hua Lu: Conceptualization, data collection and analysis, Writing – original draft, preparation. **Edward M. Bednarczyk:** discussion, Writing – review & editing. **Linda M. Catanzaro:** discussion, Writing – review & editing. **Alyssa Shon:** discussion, Writing – review & editing. **Jia-Chen Xu:** discussion, Writing – review & editing. **Qing Ma:** Conceptualization, Writing – review & editing.

Declaration of competing interest

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