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Pharmacology of HIV Integrase Inhibitors

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Abstract

Purpose of Review—The purpose of this paper is to review recent and relevant pharmacology data for three HIV integrase inhibitors: raltegravir (marketed), dolutegravir and elvitegravir (both in Phase III drug development).

Recent Findings—Data from January 2011 to April 2012 were evaluated. These data better characterized integrase inhibitor pharmacokinetics, assessed dosing regimens and investigated previously undescribed drug-drug interactions. Due to formulation challenges, raltegravir inter- and intra-patient pharmacokinetic variability is high. Twice daily 400mg dosing has been shown to be clinically superior to 800mg once daily dosing. A pediatric formulation of raltegravir with less variable pharmacokinetics and greater bioavailability was FDA approved in December 2011. Cobicistat-boosted elvitegravir, and the second generation integrase inhibitor dolutegravir, have lower pharmacokinetic variability and are dosed once daily. Dolutegravir drug interactions are similar to raltegravir, while boosted elvitegravir participates in additional CYP3A mediated interactions.

Summary—Raltegravir's potent antiretroviral activity has resulted in widespread use in both treatment naïve and experienced patients. Dolutegravir and cobicistat-boosted elvitegravir have some pharmacokinetic advantages. Pharmacokinetic data in special populations (pregnancy, pediatrics) to optimize dosing are still required.

Keywords

HIV Integrase Inhibitors; Raltegravir; Dolutegravir; Elvitegravir

Introduction

Integrase inhibitors are an important addition to antiretroviral therapy. With a unique mechanism of action, potent anti-HIV activity, and a mild side effect profile, raltegravir (the first integrase inhibitor) has become a vital part of therapy for both antiretroviral naïve and experienced patients. Dolutegravir and cobicistat-boosted elvitegravir have improved pharmacokinetic profiles, resulting in less variability within and between patients, and longer half-lives for once daily dosing.

Raltegravir

Raltegravir is dosed at 400mg twice daily. In 35 HIV positive, treatment naïve subjects given 100, 200, 400, or 600mg of raltegravir or placebo twice daily for 10 days, raltegravir was found to be potent and safe throughout the range of doses [1]. The C_{12h} (or "trough" concentration) geometric mean plasma concentrations at all doses exceeded 33nM, the mean in vitro IC_{95} for wild-type virus [1]. Raltegravir is metabolized by glucuronidation primarily by uridine glucuronosyl transferase (UGT) 1A1 [2]. Metabolism by this low affinity, high capacity pathway results in limited drug interactions. Table 1 summarizes the pharmacologic properties of the integrase inhibitors included in this review.

Pharmacokinetic Variability

Raltegravir has a high level of intra- and inter-patient pharmacokinetic variability. In a study of 15 HIV-infected patients [15], raltegravir area under the concentration time curve from 0–12hours ($AUC_{0–12h}$) ranged from 1495 to 49051 ng*h/ml. From two visits, intra-patient variability for C_{12h} (or "trough" concentration) and $AUC_{0–12h}$ ranged from 1 to 113%, and 1 to 77%, respectively. Despite this variability, raltegravir's large therapeutic window and mild side effect profile make this variability less clinically relevant.

Pharmacokinetics of Once Daily Dosing

Given raltegravir's wide therapeutic window, and the potential for improved adherence with once daily dosing regimens, a study was conducted to determine once daily efficacy and toxicity. The QDMRK study, was a phase 3 non-inferiority study comparing raltegravir 800mg once daily to raltegravir 400mg twice daily in combination with tenofovir and emtricitabine in 775 HIV patients with HIV RNA ≥ 5000 copies/ml [16]. After 48 weeks, once daily dosing of 800mg was found to be inferior to twice daily dosing: 83% of the patients who were dosed once daily and 89% of patients dosed twice daily achieved a virologic response. Time to virologic response was significantly longer in the once daily versus twice daily arm (log-rank test p=0.008). Of those patients with HIV RNA >100,000 copies/ml or CD4 counts <200 cells/mm^3 prior to initiating therapy, virologic response rates were 10% lower with once daily dosing. The authors concluded that despite high response rates in both groups, once daily raltegravir cannot be recommended. Because this study was a double-blind, placebo-controlled study, potential adherence advantages of once-daily dosing over twice-daily dosing could not be assessed and the authors concluded that these data are insufficient to recommend whether a once-daily regimen could be used in specific patients struggling with adherence to a twice-daily regimen.

Intensive pharmacokinetic analysis of a subset of 42 patients form the QDMRK study found the AUC to be similar between once and twice daily dosing groups (least-squares mean (CV %) of 30.87 (70) versus 13.14 (99) with a geometric mean ratio (90% CI) of 1.17 (0.80–1.72)). However, the concentrations at the end of the dosing interval were substantially lower in the once daily dosing group (least-squares mean (CV %) of 40(111) versus 257(167) with a geometric mean ratio (90% CI) of 0.15(0.09–0.26)[16].

Pharmacokinetics of Pediatric Dosing

In December 2011, the FDA approved two new dosages of chewable tablets (100mg and 25mg) for pediatric populations. The approval was supported by a preliminary data analysis of the currently-ongoing IMPAACT P1066 trial in which either the 400mg film-coated tablets were given to HIV positive children 6 to 18 years of age or the chewable tablets were given to children 2 to less than 12 years of age. Doses were given to target adult AUCs and C_{12h}. Pharmacokinetic data from 10 children aged 6 to 11 years receiving the chewable tablets were analyzed to determine a pediatric dosing recommendation [17]. At 6mg/kg, the

raltegravir $AUC_{0–12h}$ was 22.6 μM*h (12.8–40.6 μM*h), with geometric mean C_{12h} of 128 nM (62–397 nM). These exposures are similar to those measured in adults (median C_{12h} 149 (60–245 nM) [18]. When compared to the adult dosage form, the pharmacokinetic variability (expressed as CV%) was significantly less for the chewable tablets: variability in AUC was 34% (compared to 120%) and variability in C_{12h} was 84% (compared to 221%). The chewable tablets also have an overall increased bioavailability compared to the film-coated tablets with a 1.8-fold increase in AUC and a 3.2-fold higher C_{max} [19].

Drug-Drug Interactions

Raltegravir does not have the substantial drug-drug interaction potential of many other antiretrovirals because it is metabolized by glucuronidation: a low affinity high capacity pathway. The primary enzyme is UGT1A1, and interactions can occur when concomitant medications induce or inhibit the activity of this enzyme. For example, raltegravir ‘s AUC decreased by 40% when used concomitantly with the potent UGT1A1 inducer rifampin [20]. Conversely, the UGT1A1 inhibitor atazanavir increased raltegravir’s AUC by 72% [21].

Raltegravir interactions with protease inhibitors have been explored. The pharmacokinetics of raltegravir twice daily combined with darunavir/ritonavir once daily was investigated in 24 HIV positive patients both in plasma and at the intracellular site of action [22]. This study found no remarkable interactions between either in plasma or intracellularly, with AUC geometric mean ratios (90% CI) of 1.24 (1.13 to 1.45) for plasma darunavir, and 0.90 (0.73 to 1.44) for plasma raltegravir. A recent pharmacokinetic substudy of the EASIER-ANRS 138 Trial measured tipranavir and darunavir concentrations in 20 HIV positive subjects at steady state before and after switching from efuvirtide to raltegravir [23]. The geometric mean ratios (90% CI) for tipranavir C_{12h}, C_{max}, and AUC were 0.49 (0.42 to 0.56), 0.76 (0.63 to 0.92), and 0.67 (0.55 to 0.82). The geometric mean ratios (90% CI) for darunavir C_{12h}, C_{max}, and AUC were 0.82 (0.61 to 1.10), 0.68 (0.59 to 0.79), and 0.64 (0.53 to 0.77). The reason for these decreased tipranavir and darunavir concentrations is not apparent. The authors suggest that these decreased concentrations may have been due to previously increased PI concentrations while on enfuvirtide therapy, or by unknown drug transporter effects. However, there were no virologic failures observed up to 48 weeks while on raltegravir. The effect of tipranavir on raltegravir concentrations was not measured in this study, although a previous investigation revealed a 55% decrease in raltegravir C_{12h} when combined with tipranavir/ritonavir without significant changes to AUC [24].

Lersivirine, an NNRTI currently in development, is glucuronidated by UGT2B7 and metabolized by CYP3A4. A recent pharmacokinetic study in which lersivirine was given in combination with raltegravir to 18 healthy volunteers found a 15–29%% decrease in raltegravir AUC and C_{max} and a 25% mean increase in the C_{12h}. No significant changes in lersivirine’s pharmacokinetic parameters were seen. The authors concluded that lersivirine and raltegravir could likely be co-administered without need for dose adjustments [25]. Additionally, the NNRTI rilprivirine was studied and also found to have little effect on the concentrations of raltegravir when used in combination [26].

Hepatitis C co-infection occurs in about 25% of HIV infected patients in the United States [27]. With a lower drug interaction potential than other antiretrovirals, raltegravir is a good option for co-infected patients requiring treatment of both HIV and Hepatitis C. A recent study evaluated the pharmacokinetics of raltegravir and ribavirin when dose separately and together [28]. No statistically significant changes in the pharmacokinetic parameters of raltegravir were observed when given with ribavirin, but a decrease in ribavirin C_{max} (GMR (95% CI) = 0.79 (0.62 to 1.00)) and an increase in Tmax (GMR (95% CI) = 1.39 (1.08 to 1.78)) were observed. With no additional safety concerns, the authors concluded that the changes to ribavirin C_{max} and T_{max} are not likely to have a clinically significant impact.

Additionally, raltegravir has been studied in combination with the Hepatitis C protease inhibitors boceprevir and telaprevir. No clinically significant interaction was found with either drug. Geometric mean ratios (90% CI) for raltegravir AUC and C_{max} were 1.01 (0.85 to 1.20) and 1.09 (0.89 to 1.33), respectively when given with boceprevir [29]. When given with telaprevir, least squares mean ratios (90% CI) for raltegravir AUC, C_{max}, and C_{min} were increased 1.31 (1.03 to 1.67), 1.26 (0.97 to 1.62), and 1.78 (1.26 to 2.53), respectively [30].

Tuberculosis is a common opportunistic infection in HIV positive patients. Rifampin is known to potently induce UGT1A1 and therefore a 100% increase in raltegravir dose is required when the two are used together [20, 31]. In vitro studies have previously determined that rifabutin is a less potent inducer of UGT1A1, and the DHHS guidelines do not recommend a raltegravir dose adjustment when used concomitantly [18, 31]. A pharmacokinetic study was recently conducted to correlate these in vitro data with clinical effects [32]. In 19 healthy participants, raltegravir was given at 400mg twice daily for four days alone, then with rifabutin 300mg daily for 14 days. The geometric mean ratio of the AUC of raltegravir plus rifabutin versus raltegravir alone (90% confidence interval) was 1.19 (0.86 to 1.63), the C_{12h} ratio was 0.80 (0.68 to 0.94), and the C_{max} ratio was 1.39 (0.87 to 2.21). Based on these data, the authors concluded that rifabutin alterations of raltegravir exposure are not clinically relevant. A summary of previously evaluated drug-drug interactions between integrase inhibitors and commonly coadministered agents is provided in Table 2.

Elvitegravir

Elvitegravir (GS-9137, JTK-303) is a first generation integrase strand transfer inhibitor currently in phase 3 clinical testing by Gilead Sciences, inc [Foster City, CA]. As elvitegravir undergoes extensive primary metabolism by hepatic and intestinal cytochrome P450 (CYP) 3A and secondary metabolism by UGT1A1/3, its pharmacokinetics has been evaluated with the CYP3A inhibitors ritonavir and cobicistat (an investigational compound). These pharmacokinetic "boosting" agents were considered to render elvitegravir's pharmacokinetic profile more favorable to once daily dosing [4].

Pharmacokinetics and Boosting

Elvitegravir has an elimination half-life of approximately 3 hours when dosed alone and 9 hours when dosed with ritonavir 100 mg [5]. DeJesus et al have suggested that the antiviral activity of elvitegravir can be described by a simple E_{max} model fitted to C_{24h} (or "trough" concentrations) rather than C_{max} or $AUC_{0–24h}$. Elvitegravir dose selection has therefore been based on maintaining C_{24h} approximately 10-fold above the protein adjusted IC_{95} of 45 ng/mL [5].

An early 10 day monotherapy study in both treatment-experienced and treatment-naive subjects demonstrated a potent reduction in HIV-1 RNA with a mean $\log_{10}$ change from baseline of −1.91 ± 0.60 with elvitegravir 800 mg twice daily dosing or −1.99 ± 0.38 with elvitegravir 50 mg once daily boosted by ritonavir 100 mg [5]. Although similar in short-term antiviral response, the exposure achieved with elvitegravir 50 mg boosted with 100 mg of ritonavir ($AUC_{0–24h}$ = 8840 ng*h/mL, 26 %CV; C_{24h} = 135.0 ng/mL, 37 %CV) could not be achieved with twice daily 800 mg dosing of elvitegravir alone ($AUC_{0–24h}$ = 3570 ng*h/mL, 37 %CV; C_{24h} = 48.0 ng/mL, 33 %CV) [5]. Maximal boosting of elvitegravir is observed with 100 mg of ritonavir: no further reduction in apparent oral clearance occurs with 200 mg of ritonavir [6,56].

Cobicistat [Gilead Sciences, Foster City, CA], a potent inhibitor of CYP3A that lacks antiviral activity and has demonstrated a favorable safety profile, is under development as a pharmacokinetic boosting agent for elvitegravir and protease inhibitors. A once daily fixed dose Quad regimen containing elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir 300 mg is currently in Phase 3 trials [25]. The Quad formulation has recently demonstrated 48 week non-inferiority in treatment naïve HIV-infected patients to atazanavir/ritonavir plus emtricitabine/tenofovir (90% vs. 87%, respectively) and to efavirenz/emtricitabine/tenofovir (88% vs. 84%, respectively) in maintenance of viral RNA ≤ 50 copies/mL [57,58].

Once daily elvitegravir has been compared directly to twice daily raltegravir in an ongoing phase 3, randomized, double-blind, double-dummy trial of 702 treatment-experienced HIV-1 infected patients receiving a ritonavir boosted background regimen [59]. Elvitegravir was found to be non-inferior to raltegravir (p=0.001) with 59% and 58% achieving the primary endpoint of maintenance of <50 HIV-1 RNA copies/mL through 48 weeks.

Drug-Drug Interactions

It has previously been shown that ritonavir-boosted elvitegravir does not participate in clinically important drug interactions with the NNRTI etravirine, or the PIs darunavir/ritonavir, tipranavir/ritonavir, and fosamprenavir/ritonavir [37,38,39]. However, UGT1A1-mediated inhibition interactions between elvitegravir/ritonavir and lopinavir/ritonavir or atazanavir/ritonavir suggest that the elvitegravir dose should be reduced from 150 mg to 85 mg [40,42]. Consistent with this recommendation, elvitegravir 85 mg/cobicistat 150 mg coadministered with atazanavir results in comparable elvitegravir exposure with an 83% increase in C_{24h} compared to elvitegravir 150mg/cobicistat 150 mg [41]. Cobicistat boosted elvitegravir should be administered with food for a 34% and 87% increase in $AUC_{0\text{-}inf}$ with low and high calorie meals, respectively [8]. Although no clinically important interaction was observed with omeprazole or famtotidine, elvitegravir should be separated from aluminum and magnesium containing antacids by two hours [45,46]. Administration of ritonavir-boosted elvitegravir results in a 2 to 4 fold increase in maraviroc C_{max}, $AUC_{0–24}$, and C_{24h}, and requires a 50% decrease in maraviroc dose to 150 mg [43]. Elvitegravir/ritonavir can be coadministered with rifabutin 150 mg every other day, resulting in comparable rifabutin exposure with a 5 to 20 fold increase in rifabutin metabolite [44]. As elvitegravir C_{24h} decreased 67.1% when elvitegravir/cobicistat was coadministered with rifabutin 150 mg every other day, this combination should be avoided [41]. Since elvitegravir must be administered with a boosting agent, additional interactions with CYP3A substrates are likely to occur due to potent CYP3A inhibition by cobicistat or ritonavir.

Dolutegravir

Dolutegravir (S/GSK1349572) is a second generation HIV integrase inhibitor in development by Shionogi and ViiV Healthcare. Dolutegravir is currently in phase 3 testing in treatment-naive and treatment-experienced subjects as a once daily and a once or twice daily 50 mg dose, respectively [60–63]. It is primarily metabolized via UGT1A1 with a minor contribution by CYP3A, and is a substrate for P-glycoprotein. Dolutegravir did not alter oral midazolam exposure, suggesting that it is not an inducer or inhibitor of CYP3A [11].

Pharmacokinetics

Dolutegravir has a terminal half-life of approximately 12 to 15 hours [11,12]. It does not require boosting and its favorable pharmacokinetic profile is characterized by relatively low variability (C_{24h}, 25–26 %CV) [11,12]. Dolutegravir $AUC_{0–24h}$ and C_{max} are slightly less

than dose proportional over the range of 2 to 50 mg following single and multiple doses [12]. Because of the decrease in C_{max} and AUC seen with increasing dose, a twice daily 50 mg regimen is being evaluated in the phase 3 ARV-experienced clinical trial rather than a single daily 100 mg dose [12].

A monotherapy study in integrase inhibitor-naive HIV-1 infected adults demonstrated a 2.48 mean $\log_{10}$ reduction in HIV-1 RNA following 10 days of dolutegravir 50 mg daily [12]. This reduction was sustained 4 days after discontinuation of dolutegravir, likely due to plasma concentrations maintained above the protein adjusted IC_{90}. Similar to elvitegravir, the exposure-response relationship is best described by incorporation of C_{24h} into the E_{max} model. Overall, variability in exposure was minimal: 50 mg dosing to steady-state conditions achieved a geometric mean C_{max} of 3.34 μg/mL (16 %CV), an $AUC_{0–24h}$ of 43.4 μg*h/mL (20 %CV), a $t_{1/2}$ of 12.0 h (22 %CV) and a C_{24h} of 0.83 μg/mL (26 %CV) [12]. A pediatric granule formulation of dolutegravir is currently in development. Preliminary data suggests that granules mixed in purified water have increased exposure compared to the tablet formulation with a geometric least squares mean ratio (90% CI) for $AUC_{0\text{-}inf}$ of 1.57 (1.45 to 1.69) [64].

Drug-Drug Interactions

The effect of food on dolutegravir pharmacokinetics has been evaluated in a single-dose crossover study [13]. The median T_{max} increased from 2 h to 3 h, 4 h, and 5 h for low-fat, moderate-fat, and high-fat meals, respectively, suggesting that fat content of meals impacts the absorption of dolutegravir. While $AUC_{0\text{-}inf}$ increased 33% to 66% when taken with food, inter-individual variability was comparable to other studies [12, 13]. These changes in exposure are not expected to impact safety or efficacy and dolutegravir can be dosed without regard to food.

Dolutegravir $AUC_{0\text{-}inf}$ is reduced by greater than 3-fold when coadministered with antacids. Therefore antacid administration should be delayed by at least 2 hours after dolutegravir dosing. Although $AUC_{0–24h}$ was reduced from a geometric mean of 34.6 μg*h/mL (31 %CV) to 23.0 μg*h/mL (29 %CV) with multivitamins containing divalent cations and to 30.0 μg*h/mL (22 %CV) with omeprazole, no dolutegravir dosage adjustment is necessary [55].

Dolutegravir does not interact with the NRTI tenofovir, or the PI lopinavir/ritonavir [47,50]. Darunavir/ritonavir reduces dolutegravir C_{24h} from 0.77 μg/mL (29 %CV) to 0.45 μg/mL (37 %CV), and $AUC_{0–24h}$ from 36.9 μg*h/mL (19 %CV) to 27.3 μg*h/mL (23 %CV). However, this interaction is considered modest and clinically unimportant [50]. Atazanavir and atazanavir/ritonavir administration results in increased dolutegravir $AUC_{0–24h}$ (91% and 62%), C_{max} (50% and 34%) and C_{24h} (180% and 121%). This interaction is unlikely to impact safety and no dosage adjustment is suggested [51].

The interaction between dolutegravir and etravirine has also been characterized both alone and with boosted protease inhibitors. Etravirine reduced dolutegravir $AUC_{0–24h}$ greater than 3-fold and C_{24h} greater than 10-fold. Introduction of boosted darunavir or lopinavir to the regimen restored exposure comparable to dolutegravir alone. Etravirine should only be administered with dolutegravir if darunavir/ritonavir or lopinavir/ritonavir is included in therapy [49]. Efavirenz and tipranavir/ritonavir decreased dolutegravir AUC_{24} by 57% and 59%, C_{max} by 39% and 46%, and C_{24h} by 75% and 76% [48]. Despite these significant reductions in exposure, the authors conclude that dolutegravir C_{24h} remains far above the IC_{90} so no dosage adjustment is necessary.

Studies investigating dolutegravir interactions with the anti-mycobacterial agents, rifampin and rifabutin, have also been completed. Rifampin 600 mg once daily administered with dolutegravir 50 mg twice daily resulted in minor increases in dolutegravir AUC_{24h} (33%) and C_{24h} (22%) compared to dolutegravir 50 mg once daily dosing [53]. This dose adjustment is not necessary with rifabutin 300 mg once daily since coadministration results in only a modest 30% decrease in dolutegravir C_{24h} [54].

Integrase Inhibitor in Clinical Development

S/GSK1265744, an integrase inhibitor initially evaluated in a once daily oral formulation, is currently being developed into a novel, long acting parenteral product. Phase 1 studies are ongoing to determine the optimal dose and frequency of administration and to gather information regarding safety and efficacy. S/GSK1265744 is being investigated for monthly to quarterly administration. This dosing strategy could lead to improved adherence and viral control in select patients, and may be amenable to prophylaxis against HIV infection [65].

Conclusions

The integrase inhibitors are potent antiretrovirals with considerably lower drug interaction potential than non-nucleoside reverse transcriptase inhibitors or protease inhibitors. For these reasons, as well as a mild side effect profile, raltegravir has become an agent widely used in both antiretroviral naïve regimens, as well as a novel agent for use in treatment experienced patients. The emerging HIV integrase inhibitors elvitegravir and dolutegravir have many of the same advantages and potential uses as raltegravir with more favorable pharmacokinetics and dosing. Pharmacologic data are still needed in special populations (eg pregnancy) and to elucidate additional drug interactions.

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Key Points

- Post-marketing raltegravir studies have determined once daily raltegravir to be inferior to standard twice daily dosing.
- A pediatric formulation of raltegravir has been FDA approved with less pharmacokinetic variability than the film-coated tablets.
- The investigational agent elvitegravir displays a favorable pharmacokinetic profile allowing for once daily dosing when boosted by either cobicistat or ritonavir, however, it is more likely to participate in CYP3A mediated interactions in addition to the UGT1A1 interactions seen with the other integrase inhibitors.
- Once daily dosing of dolutegravir results in low inter-individual variability, prolonged exposure, and predictable antiviral effects that are associated with C_{24h}.

Table 1

Pharmacologic Parameters of Integrase Inhibitors

Drug	Formulations	Dosing	Metabolism	Elimination Half-life	Protein Binding	Protein-adjusted Inhibitory Concentration	PK Parameters (CV%)	Food effects	Dosing in renal/ hepatic impairment
Raltegravir[1,2,3]	400mg tablet 100mg chewtabs 25mg chewtabs	Adults: 400mg bid Children: 6mg/kg bid	UGT1A1	~9 hours	83%	IC_{95}=16 ng/mL	Geometric Mean AUC_{0-12h}= 6900ng*h/mL C_{12h}=68.5ng/mL (212)	Dosed without regard to meals Film-coated tab: AUC increased two-fold with high fat meal Chew tabs: AUC decreased slightly with fat	No dose adjustments warranted in renal or hepatic impairment
Elvitegravir[4, 5,6,7,8,9,10]	150mg tablet “Quad” tablet (combination with tenofovir 300mg, emtricitabine 200mg, cobicistat 150mg)	Adults: 150mg daily with 150mg cobicistat daily or 100mg ritonavir daily	CYP3A4 (major) UGT1A1/3 (minor)	~3 hours alone ~9 hours boosted with 100mg ritonavir or 150mg cobicistat	>99%	IC_{95}=45 ng/mL	With ritonavir: AUC_{0-24h} = 22500ng*h/ml (23.4) C_{24h}= 410ng/ml (40.5) C_{max}= 2500ng/ml (32.1) With cobicistat: AUC_{0-24h} = 27000ng*h/mL (29.4) C_{24h} = 490ng/mL (52.9) C_{max}=2660ng/mL (27.6)	Administer with food. AUC increased 34% with low fat meal and 87% with high fat meal	Severe renal impairment data not yet available, No dose adjustment for mild to moderate hepatic impairment
Dolutegravir[11, 12, 13, 14]	50mg tablet “572-Tri” tablet (combination with abacavir 600mg and lamivudine 300mg)	Adults: 50mg daily	UGT1A1 (major) CYP3A (minor)	~12–15 hours	>99%	IC_{90}=64 ng/mL	AUC_{0-24h} = 43400ng*h/ml (20) C_{24h}=830ng/ml (26) C_{max}=3340ng/ml (16)	Dosed without regard to meals despite increases in t_{max}, AUC, and C_{max} with food	No dose adjustment for severe renal impairment, No dose adjustment for mild-moderate hepatic impairment

Table 2

Integrase Inhibitor Drug Interaction Data

Integrase Inhibitor	Interacting Drug Class	Interactin g Drug	Effect on Integrase Inhibitor or Interacting Drug Concentration	Dosing Recommendation
Raltegravir[18]	Other Antiretrovirals *	NRTIs	Tenofovir: RAL AUC increased 49%, Cmax 64%[33]	Maintain standard dosing
		NNRTIs	Efavirenz: RAL AUC decreased 36% Etravirine: ETR Cmin increased 17%, RAL Cmin decreased 34% Rilpivirine: No significant effect[26] Lesivirine: RAL AUC and Cmax decreased 19–25%[25]	Maintain standard dosing for all
		PIs	Atazanavir: RAL AUC increased 72% Atazanavir/r: RAL AUC increased 41% Darunavir/r: RAL AUC decreased 29% and Cmin increased 38% Lopinavir/r: RAL concentrations may be decreased Tipranavir/r (500mg/200mg bid): RAL AUC decreased 24%	Maintain standard dosing for all
		CCR5	Maraviroc RAL AUC decreased 37%, MVC AUC decreased 21%	Maintain standard dosing
	Tuberculosis Agents	Rifampin	RAL AUC decreased 40% and Cmin decreased 61%	Increase raltegravir dose to 800mg bid
		Rifabutin	RAL AUC increased 19%, Cmax increased 39%, and Cmin decreased 20%[32]	Maintain standard dosing
	Hepatitis C Protease Inhibitors	Boceprevir	No significant effect	Maintain standard dosing
		Telaprevir	RAL AUC increased 31%, Cmax 26%, and Cmin 78%[30]	Maintain standard dosing
	Acid Reducing Agents	PPIs/H2 RA	Omeprazole: RAL AUC increased 212%, Cmax increased 315%, and Cmin increased 46%	Maintain standard dosing
		Antacids	RAL Cmin decreased by 67%, AUC and Cmax unchanged[34]	Maintain standard dosing
Elvitegravir	Other Antiretrovirals *	NRTIs	No significant effect observed when EVG/r was coadministered with Abacavir, Emtracitabine, Tenofovir, Didanosine, Zidovudine, or Stavudine.[35,36]	Maintain standard dosing
		NNRTIs	Etravirine (with EVG/r): Inconsequential changes in EVG and ETR expsoure.[37]	Etravirine: Maintain standard dosing
		PIs	Inconsequential effects observed with Darunavir/r, Tipranavir/r, and Fosamprenavir/r [38,39] Atazanavir/r: EVG AUC, Cmax, and Cmin increased by 100%, 85%, and 188%. ATV AUC, Cmax, and Cmin decreased 20.8%, 15.7%, and 34.5%. EVG 85 mg AUC and Cmin increased 7% and 38% and Cmax decreased 9.1% compared to EVG 150 mg alone. ATV AUC, Cmax, and Cmin decreased 11.4%, 4%, and 17.4% with 85 mg EVG.[40] Atazanavir with EVG 85 mg/cobi: EVG AUC and Cmin increased 17% and 83%, Cmax decreased 15.8%. ATV AUC, Cmax, and Cmin decreased 9.5%, 23.9%, and 19.5%.[41] Lopinavir/r: EVG AUC, Cmax, and Cmin increased by 75%, 52%, and 138%. Inconsequential decrease in LPV exposure.[42]	Darunavir/r, Tipranavir/r and Fosamprenavir/r: Maintain standard dosing Atazanavir/r and Lopinavir/r: Reduce elvitegravir dose to 85 mg qd
		CCR5	Maraviroc: MVC 150 mg bid AUC, Cmax, and Cmin increased by 186%, 115%, and 323% with EVG/r. Inconsequential increase in MVC exposure.[43]	Reduce MVC dose to 150 mg bid with EVG/r

Curr Opin HIV AIDS. Author manuscript; available in PMC 2013 September 01.

Integrase Inhibitor	Interacting Drug Class	Interactin g Drug	Effect on Integrase Inhibitor or Interacting Drug Concentration	Dosing Recommendation
	Tuberculosis Agents	Rifampin	Data not available. Potential for CYP3A mediated interaction.	No dosing recommendation
		Rifabutin	Rifabutin 150 mg qod with EVG/r resulted in inconsequential changes in EVG exposure and a rifabutin Cmax increase of 21%, with 9.5-, 5.4-, and 19.4-fold increases in rifabutin metabolite AUC, Cmax, and Cmin compared to rifabutin 300 mg qd.[44] Rifabutin 150 mg qod with EVG/cobi resulted in rifabutin exposures similar to rifabutin 300 mg qd. EVG AUC, Cmax, and Cmin decreased 20.6%, 8.9%, and 67.1%.[41]	Reduce rifabutin dose to 150 mg qod with EVG/r Rifabutin dosing not recommended with EVG/cobi
	Hepatitis C Protease Inhibitors	Boceprevir	Data not available	No dosing recommendation
		Telaprevir	Data not available	No dosing recommendation
	Acid Reducing Agents	PPIs/H2 RA	Omeprazole: No significant effect observed with EVG/r or EVG/cobi.[45,46] Famotidine: No significant effect observed with EVG/cobi for simultaneous or 12 hour staggered dosing.[46]	Maintain standard doing
		Antacids	EVG AUC, Cmax, and Cmin decreased 45%, 47%, and 41%.[45]	Separate elvitegravir/r dose from antacids by 2 hours
Dolutegravir	Other Antiretrovirals *	NRTIs	Tenofovir: No significant effect observed.[47 <]	Maintain standard dosing
		NNRTIs	Efavirenz: DTG AUC, Cmax, and Cmin decreased 57%, 39%, and 75%.[48] Etravirine: DTG AUC, Cmax, and Cmin decreased 70.6%, 51.6%, and 87.9%. ETR/DRV/r administration results in 25%, 11.8%, and 37.1% decreases in DTG AUC, Cmax, and Cmin. ETR/LPV/r administration results in 11%, 7%, and 28% increases in EVG AUC, Cmax, and Cmin.[49]	Maintain standard dosing with efavirenz Do not coadminister dolutegravir and etravirine unless darunavir/ritonavir or lopinavir/ritonavir are also included in the regimen
		PIs	Darunavir/r: DTG AUC, Cmax, and Cmin decreased 22%, 11%, and 38%.[50] Atazanavir: DTG AUC, Cmax, and Cmin increased 91%, 50% and 180%.[51] Atazanavir/r: DTG AUC, Cmax, and Cmin increased 62%, 34%, and 121%.[51] Lopinavir/r: No significant effect observed.[50] Fosamprenavir: DTG AUC, Cmax, and Cmin decreased 35%, 24%, and 49%.[52] Tipranavir: DTG AUC, Cmax, and Cmin decreased 59%, 46%, and 76%.[48]	Maintain standard dosing for all
	Tuberculosis Agents	Rifampin	DTG AUC and Cmin increased 33% and 22% with DTG 50mg bid + rifampin 600 mg qd compared to DTG 50mg daily.[53]	Increase dolutegravir dosing frequency to 50mg bid
		Rifabutin	DTG AUC and Cmin decreased 5% and 30%, Cmax increased 15%.[54]	Maintain standard dosing
	Hepatitis C Protease Inhibitors	Boceprevir	Study Ongoing	No dosing recommendation
		Telaprevir	Study Ongoing	No dosing recommendation
	Acid Reducing Agents	PPIs/H2 RA	Omeprazole: no significant effect observed.[55]	Maintain standard dosing
		Antacids	DTG AUC, Cmax, and Cmin decreased 73.6%, 72.4%, and 74.4%.[55]	Administer antacids 2 hours after or 6 hours before dolutegravir dosing

* Only those antiretrovirals with data in combination with INSTI are included in the table