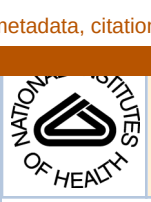

Published in final edited form as:

Clin Pharmacokinet. 2013 November ; 52(11): 981–994. doi:10.1007/s40262-013-0093-2.

Clinical Pharmacokinetic, Pharmacodynamic and Drug-Interaction Profile of the Integrase Inhibitor Dolutegravir

Mackenzie L. Cottrell, PharmD, MS,
UNC Eshelman School of Pharmacy, Division of Pharmacotherapy and Experimental Therapeutics, University of North Carolina at Chapel Hill, North Carolina

Tanja Hadzic, Ph.D., and
UNC Eshelman School of Pharmacy, Division of Pharmacotherapy and Experimental Therapeutics, University of North Carolina at Chapel Hill, North Carolina

Angela D.M. Kashuba, BScPhm, PharmD, DABCP
3318 Kerr Hall, CB# 7569, UNC Eshelman School of Pharmacy, Division of Pharmacotherapy and Experimental Therapeutics, University of North Carolina at Chapel Hill, North Carolina, NC 27599-7569, Tel (919) 966-9998 Fax (919) 962-0644

Angela D.M. Kashuba: akashuba@unc.edu

Abstract

Dolutegravir is a second generation integrase strand transfer inhibitor (INSTI) currently under review by the US FDA for marketing approval. Dolutegravir's *in vitro*, protein adjusted 90% inhibitory concentration (IC_{90}) for wild-type virus is 0.064 μg/ml, and it retains *in vitro* anti-HIV 1 activity across a broad range of viral phenotypes known to confer resistance to the currently marketed INSTIs, raltegravir and elvitegravir. Dolutegravir has a half-life ($t_{½}$) of 13 to 14 hours and maintains concentrations over the *in vitro*, protein adjusted IC_{90} for more than 30 hours following a single dose. Additionally, dolutegravir has comparatively low intersubject variability compared to raltegravir and elvitegravir. A plasma exposure-response relationship has been well described, with antiviral activity strongly correlating to trough concentration (C_{trough}) values. Phase III trials have assessed the antiviral activity of dolutegravir compared with efavirenz and raltegravir in antiretroviral (ARV)-naïve patients and found dolutegravir to achieve more rapid and sustained virologic suppression in both instances. Additionally, studies of dolutegravir activity in patients with known INSTI-resistant mutations have been favorable, indicating that dolutegravir retains activity in a variety of INSTI resistant phenotypes. Much like currently marketed INSTIs, dolutegravir is very well tolerated. Because dolutegravir inhibits the renal transporter, organic cation transporter (OCT) 2, reduced tubular secretion of creatinine leads to non-progressive increases in serum creatinine. These serum creatinine increases have not been associated with decreased glomerular filtration rate or progressive renal impairment. Dolutegravir's major and minor metabolic pathways are UDP glucuronosyltransferase (UGT)1A1 and cytochrome (CYP)3A4, respectively, and it neither induces nor inhibits CYP isozymes. Thus dolutegravir has a modest drug interaction profile. However, antacids significantly decrease dolutegravir plasma exposure and should be separated by 2 hours before, or 6 hours after, a dolutegravir dose. In summary, dolutegravir is the first of the second generation INSTIs, which exhibits a predictable pharmacokinetic profile and a well-defined exposure-response relationship. Dolutegravir retains activity despite the presence of some class resistant mutations and achieves rapid and sustained

Correspondence to: Angela D.M. Kashuba, akashuba@unc.edu.

Conflict of interest: AK spouse is employed by GlaxoSmithKline and has received grant funding from ViiV Healthcare. MC and TH have no conflicts of interest to disclose

virologic suppression in ARV-naïve and -experienced patients. Clinically dolutegravir is poised to become a commonly used component of antiretroviral regimens.

1. Introduction

The well-tolerated integrase strand transfer inhibitors (INSTIs) are the newest class of antiretrovirals (ARVs), demonstrating potent anti-HIV activity through inhibition of the enzyme responsible for incorporating viral DNA into the host genome [1]. Two currently marketed INSTIs include raltegravir (MSD, Whitehouse Station, NJ, USA) and elvitegravir (Gilead Sciences, Foster City, CA, USA). Raltegravir was approved by the US FDA for market in 2007. Stribild (Gilead Sciences, Foster City, CA, USA), a combination tablet containing elvitegravir, was approved in 2012. Despite their comparatively short period of clinical use and a high genetic barrier to resistance, resistant phenotypes have been reported for both [2–5]. Certain mutations, such as Q148H/R, N155H, and Y143R confer cross-resistance between raltegravir and elvitegravir [5], and further necessitate the development of second generation INSTIs.

Dolutegravir, a novel INSTI currently under review by the US FDA for marketing approval, is a chiral, non-racemic compound with a molecular weight of 419 g/mol (Figure 1). Dolutegravir fits loosely into the intasome binding pocket and retains its binding ability despite conformational changes in the pocket structure [6]. The ability to readjust its binding position is believed to enhance the genetic barrier to ARV resistance, subsequently classifying dolutegravir as a second generation INSTI.

Dolutegravir is highly potent, with an *in vitro* half maximal inhibitory concentration (IC_{50}) of 2.7nM and an *in vitro* half maximal effective concentration (EC_{50}) against HIV-1 of 0.51 nM in peripheral blood mononuclear cells [7] (Raltegravir and elvitegravir have an *in vitro* IC_{50} of 3.3nM and 6nM respectively). Dolutegravir dissociates more slowly than raltegravir and elvitegravir from integrase-DNA complexes with mean k_{off} ($s^{-1} \times 10^{-6}$) values of 2.7, 22 and 71, respectively for wild-type complexes, and 37, 1160, and 1130 from complexes expressing a single Q148H mutation [8]. Multiple *in vitro* studies utilizing a large variety of viral phenotypes no longer susceptible to raltegravir demonstrate retained dolutegravir activity [7,9,10]. However, mutations at the 148 position of integrase did impart diminished *in vitro* dolutegravir susceptibility with median *in vitro* IC_{50} fold changes ranging from 3.01 to 27.12 compared to wild-type virus depending on the type and number of secondary mutations [9,10]. These preclinical findings suggest dolutegravir would retain some antiviral activity in individuals previously exposed to raltegravir therapy.

2. Pharmacokinetics

The dolutegravir pharmacokinetic profile under single dose and steady state conditions ranging from 2 to 100 mg per day has been assessed in healthy and HIV infected adults [11,12]. Dolutegravir exhibits rapid absorption, with a median time to maximum concentration (t_{max}) ranging from 0.5 to 2 hours. Dolutegravir also displays extensive protein binding with >99% of the dolutegravir blood plasma concentrations bound to albumin and alpha 1-acid glycoprotein (AAG) [7,13]. The terminal elimination half-life ($t_{½}$) of dolutegravir was 13 to 14 hours in healthy subjects and 11 to 12 hours in HIV infected subjects. Single doses of 5, 10, 25, 50 and 100 mg achieved plasma dolutegravir concentrations greater than the *in vitro*, protein-adjusted IC_{90} of 0.064 μg/ml for more than 30 hours following oral administration. Multiple daily doses ranging from 10 to 50 mg in both uninfected and infected subjects yielded trough plasma concentrations (C_{trough}) 3–25 times greater than this *in vitro* threshold (Table 1) [11,12]. Dolutegravir exhibits lower inter-subject pharmacokinetic variability than other integrase inhibitors. Dolutegravir's

coefficients of variation (CV) are <30% for both AUC and C_{max} in single and multiple dose studies, whereas raltegravir and elvitegravir demonstrate AUC CVs of 212% and 33–72%, respectively [1,14].

Reese *et. al.* extensively characterized the metabolism and transport of dolutegravir using *in vitro* model systems [15]. Dolutegravir is primarily metabolized by UGT1A1, and is only a minor substrate for CYP3A4. Dolutegravir inhibited CYP3A4 but not 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, or 2D6 in pooled human liver microsomes. Furthermore, at clinically relevant concentrations neither inhibition nor induction of the aforementioned CYP enzymes or UGT1A1/2B7 is observed. Dolutegravir is a substrate for the transporters, P-glycoprotein (Pgp) and breast cancer resistance protein (BCRP), but does not demonstrate inhibition or induction of the transporters Pgp, BCRP, organic anion transporter (OAT)P1B1, OATP1B3, multidrug resistance protein (MRP)2 or organic cation transporter (OCT)1 at clinically relevant concentrations. Dolutegravir does potently inhibit the renal transporter OCT2 at concentrations which are below peak concentrations demonstrated in clinical trials (*in vitro* IC_{50}= 1.9 μM, dolutegravir C_{max}=7.97–14.7 μM).

While not believed to be clinically important, dolutegravir absorption is modestly affected by fat content of a meal. Song *et. al.* observed an increase of 133 to 242% in AUC_{∞}, C_{max}, and t_{max} following a single 50 mg dose under fasted conditions compared to a low, moderate, and high fat meal [16]. Favorably, food decreases inter-subject pharmacokinetic variability with a median CV of 27.5% for all pharmacokinetic parameters. Phase 2 and 3 investigations to date have not employed food restrictions for dolutegravir dosing [17–19]. As discussed below, these clinical trials demonstrate good dolutegravir efficacy and tolerability.

Although dolutegravir's pathways of metabolism and transport may indicate that dolutegravir is relatively unaffected by population diversity, there are currently no studies conducted that have specifically assessed the effects of demographic diversity on dolutegravir pharmacokinetic parameters. Further investigations evaluating the effect of sex and race on dolutegravir pharmacokinetics are warranted, as studies to date have primarily enrolled White men between the ages of 19–54 years and BMI of 20.9–29.1mg/m^2 [11], leaving some portions of the HIV infected population underrepresented.

Dolutegravir exposure has been studied in secondary body compartments including the central nervous system, the female genital tract, the male genital tract, and colorectal tissue [20,21]. Letendre *et. al.* investigated the pharmacokinetics of dolutegravir in the cerebrospinal fluid (CSF) of 12 ARV-naïve, HIV infected subjects receiving 50 mg dolutegravir daily with an abacavir/lamivudine backbone regimen [20]. Distribution to the CSF was similar to the unbound dolutegravir fraction in blood plasma at Week 2 (mean CSF dolutegravir= 16.2 ng/ml, mean plasma unbound dolutegravir =16.8 ng/ml) and at Week 16 (mean CSF dolutegravir = 12.6 ng/ml, mean plasma unbound dolutegravir=23 ng/ml). Additionally dolutegravir exposure in the CSF for all subjects at Week 16 ranged from 18 to 90 fold higher than the *in vitro* IC_{50} for wild type virus (0.2ng/ml) [20]. These findings suggest free passage of the small molecule across the blood brain barrier.

After single and multiple dosing, dolutegravir exposure in cervicovaginal fluid (CVF), cervical tissue and vaginal tissue was 5–7% of blood plasma exposure. This is in contrast to raltegravir, that achieves ~200% of blood plasma exposure in CVF [22]. Despite this relatively low penetration, within 4–5 hours after a single dose, the CVF exposure is above the *in vitro*, protein adjusted IC_{90}. Similar to what has been previously identified for maraviroc [23], since concentrations of the major drug-binding proteins (AAG and albumin) are less than 10% of blood plasma concentrations in the CVF [24], it may be that a larger

proportion of this CVF concentration is available as protein-unbound (e.g. pharmacologically active) drug. In semen, dolutegravir concentrations are 6–7% blood plasma concentrations. This is strikingly different from raltegravir, which achieves seminal plasma concentrations that are 425–645% blood plasma concentrations [25,26]. Like CVF, albumin concentrations in seminal plasma are less than 10% of blood plasma concentrations [27]. Therefore, although not directly measured, it is possible that a larger proportion of the dolutegravir seminal plasma concentration is pharmacologically active [21]. Distribution to colorectal tissue was rapid and sustained with 100% of subjects achieving detectable dolutegravir concentrations within one hour of a single dose that remained above the *in vitro*, protein adjusted IC_{90} for the duration of the dosing interval [21]. Overall, dolutegravir exposure was ~18% of plasma concentrations.

2.1 Special populations

Only a small proportion of dolutegravir dose (< 1%) is excreted unchanged in the urine; and therefore, dolutegravir is not expected to require dose adjustments with renal impairment [11]. The results of an open label, single dose clinical trial evaluating dolutegravir's pharmacokinetic profile in 16 subjects with normal or impaired renal function (creatinine clearearence <30ml/min) are currently being evaluated [28]. Initial reports indicate that following a 50 mg single dose dolutegravir AUC_{∞} and C_{max} are reduced by 40% and 23% respectively, which is considered clinically insignificant [29]. One adverse event (dizziness) was reported in the renally impaired group, and 2 (nasal congestion and hemotoma) were reported in the healthy group. Currently no dosage adjustments are recommended for dolutegravir in patients with renal impairment.

Dolutegravir is extensively metabolized in the liver by UGT1A1 [11]. Preliminary study of a single 50 mg dolutegravir dose in a cohort of subjects with moderate hepatic impairment (Child-Pugh score 7–9) revealed that, overall, dolutegravir plasma exposure is unchanged and well tolerated in mild to moderate hepatic impairment [13]. However, it was noted that the unbound fraction of dolutegravir in plasma is higher in hepatically impaired subjects than in healthy volunteers (0.41% vs 0.23%). Further investigation is warranted to assess the tolerability of multiple dolutegravir doses in patients with hepatic impairment.

A large clinical trial evaluating the pharmacokinetic profile and immune response to dolutegravir in infants and adolescents 6 weeks to 18 years of age is currently underway [30]. Preliminary steady state pharmacokinetic data have been reported for 10 adolescent females with a mean age (SD) of 14 years (1.89) [31]. Following a weight based, fixed dose of approximately 1 mg/kg the dolutegravir AUC_{24} (CV) and C_{trough} (CV) were 46mg•hr/ml (43%) and 0.9mg/ml (58%) respectively. These fell within pre-defined target pharmacokinetic exposure ranges for both AUC_{24} (37–67 mg•h/ml) and C_{trough} (0.77–2.26 mg/ml). Furthermore, this exposure was similar to the exposure demonstrated in adult pharmacokinetic studies following a daily 50 mg dose (Table 1). However, higher inter-subject variability was seen in adolescents than adults. Dolutegravir and an optimized backbone regimen were well tolerated with no adverse events leading to discontinuation of study drug.

3. Pharmacodynamics

In 35 ARV-naïve subjects, 10 days of monotherapy was investigated for dolutegravir doses of 2mg, 10mg, and 50mg daily. These doses resulted in a mean ±SD reduction of plasma HIV-1 RNA of −1.51±0.58, −2.03±0.49, and −2.46±0.35 (log_{10} copies/ml), respectively (Figure 2) [12]. Dolutegravir doses of 10 and 50 mg once daily yield C_{trough} values that were ~3 and 13 times higher than the *in vitro*, protein adjusted IC_{90} (0.064 μg/ml). Increased dolutegravir plasma exposure was correlated with reduced plasma HIV-1 RNA. Both log-

linear and sigmoid E_{max} models were evaluated to describe the pharmacokinetic-pharmacodynamic relationship of the compound. Dolutegravir's exposure-response relationship was best described by a sigmoid E_{max} model utilizing the pharmacokinetic parameters, Day 10 AUC_{24}, C_{max} and C_{τ}, with E_{max} fixed at −2.6 and Hill factor fixed to 1[32]. The *in vivo* EC_{50} demonstrated by this E_{max} model was 0.036 μg/ml. The model identified C_{trough} as the pharmacokinetic parameter which best-predicted plasma viral load reduction on Day 11 of monotherapy [12]. Additionally, the inhibitory quotient (IQ), calculated by C_{trough}÷protein adjusted IC_{90}, was also identified as a predictor of virologic response. Based on these data, phase 2 studies investigated daily doses of 10–50mg.

A Phase IIb Study to Select a Once Daily Dose of GSK1349572 Administered with Either Abacavir/Lamivudine or Tenofovir/Emtricitabine in HIV-1 Infected Antiretroviral Therapy Naive Adult Subjects (SPRING-1) [17] assessed daily dolutegravir 10 mg, 25 mg, and 50 mg compared to the active control efavirenz 600 mg in ARV-naïve subjects. All regimens contained a nucleoside reverse transcriptase inhibitor (NRTI) backbone of lamivudine plus abacavir or tenofovir disoproxil fumarate plus emtricitabine. Analysis at 48-weeks demonstrated more rapid and sustained virologic suppression, defined as HIV RNA <50 copies/ml, for all dolutegravir dosing arms compared with the efavirenz control group (Figure 3) [17]. The proportion of subjects achieving virologic suppression in each dolutegravir dosing arm ranged from 90–96% and 88–91% at 16 and 48 weeks respectively. No significant difference in efficacy was observed among the dolutegravir dosing arms.

A Randomized, Double Blind Study of the Safety and Efficacy of GSK1349572 50mg Once Daily to Raltegravir 400mg Twice Daily Both Administered With Fixed-dose Dual Nucleoside Reverse Transcriptase Inhibitor Therapy Over 96 Weeks in HIV-1 Infected Antiretroviral Therapy Naive Adult Subjects (SPRING-2) [19], a phase 3 non-inferiority trial, assessed the efficacy of once daily 50 mg dolutegravir against twice daily 400 mg raltegravir as first line treatment with dual-NRTI backbone therapy in ARV-naïve subjects. Four hundred and eleven subjects were enrolled into each of the two blinded and masked treatment arms and followed for 48 weeks. The primary endpoint of SPRING-2 was the proportion of subjects achieving a viral load of <50 copies/ml at 48 weeks of therapy. The pre-specified non-inferiority criterion was a lower 95% CI bound for the difference in proportion of patients meeting primary endpoints (dolutegravir minus raltegravir) of greater than −10%. Dolutegravir was found to be non-inferior to raltegravir with a difference of 2.5% (95% CI −2.2% to 7.1%) [19]. Consistent with findings from the SPRING-1 trial, dolutegravir demonstrated slightly more rapid and sustained virologic suppression when compared with raltegravir (Figure 3). The more rapid rate of viral attenuation seen with dolutegravir may warrant consideration of this agent in clinical scenarios requiring rapid virologic suppression such as HIV-infected patients presenting with AIDS defining illness or women presenting late in pregnancy. Across most treatment arms, the proportion of virologic non-responders in SPRING-1 and −2 trials was 0–3% higher between efavirenz and raltegravir-treated groups [17,19]. No treatment emergent INSTI resistance was identified among the dolutegravir treatment arms of SPRING-1 and -2.

The phase 3, non-inferiority trial, A Randomized, Double-Blind Study of the Safety and Efficacy of GSK1349572 Plus Abacavir/Lamivudine Fixed-Dose Combination Therapy Administered Once Daily Compared to Atripla Over 96 Weeks in HIV-1 Infected Antiretroviral Therapy Naive Adult Subjects (SINGLE), evaluated the efficacy of dolutegravir 50 mg once daily with an abacavir/lamivudine backbone regimen compared with efavirenz/tenofovir disoproxil fumarate/emtricitabine once daily in 833 subjects [33]. The dolutegravir arm demonstrated statistical superiority to efavirenz/tenofovir disoproxil fumarate/emtricitabine for the primary endpoint, with a difference in proportion of subjects with HIV RNA <50 copies/ml at 48 weeks of +7.4% (95% CI: 2.5% to 12.3%; p=0.003)

favoring the dolutegravir arm (Figure 3). Additionally, the median time to HIV RNA suppression in the dolutegravir group was −56 days compared to the efavirenz group ($p<0.001$). A subgroup analysis of the SPRING-2 and SINGLE studies investigated the efficacy of dolutegravir in subpopulations stratified by baseline viral load, CD4 count, sex, age, and race. Dolutegravir demonstrated equivalent efficacy in all demographic subgroups for both phase 3 trials [34].

To assess whether dolutegravir retained activity in the face of ARV resistance, A Pilot Study to Assess the Antiviral Activity of GSK1349572 Containing Regimen in Antiretroviral Therapy (ART)-Experienced, HIV-1-infected Adult Subjects with Raltegravir Resistance (VIKING) enrolled 51 subjects with documented INSTI resistance and resistance to at least 1 additional agent into 2 treatment cohorts [18]. The VIKING treatment plan consisted of adding dolutegravir to a failing backbone regimen for 10 days before optimizing the backbone regimen. Cohort I received dolutegravir 50 mg once daily and cohort II received 50 mg twice daily. A higher proportion of patients in cohort II met the definition of response at day 11 (HIV RNA ≥ 0.7 $\log_{10}$ copies/ml decrease or <400 copies/ml) and week 24 (HIV RNA <50 copies/ml) than in cohort I (Figure 3). Therefore, in the presence of INSTI resistance, a higher dose of dolutegravir may be warranted.

The single arm, Phase III Study to Demonstrate the Antiviral Activity and Safety of Dolutegravir in HIV-1 Infected Adult Subjects With Treatment Failure on an Integrase Inhibitor Containing Regimen (VIKING-3) [35], was designed to evaluate the efficacy of dolutegravir 50 mg twice daily in subjects with INSTI resistant virus plus resistance to at least 2 other ARV classes. Dolutegravir was added to the failing backbone regimen for 8 days before the regimen was optimized. Interim analysis from VIKING-3 demonstrated that, despite high levels of ARV resistance, 63% of the 72 evaluable subjects had viral loads of <50 copies/ml at 24 weeks [35]. These findings are consistent with preclinical work demonstrating dolutegravir's activity against raltegravir resistant virus. The VIKING studies provide encouraging data supporting the option of using dolutegravir 50 mg twice daily in salvage regimens.

In the first VIKING trial, treatment emergent genotypic resistance was observed in 4/12 and 3/5 subjects experiencing virologic failure in Cohort I and II respectively [18]. All subjects experiencing treatment emergent resistance also exhibited baseline INSTI resistant mutations. In both Cohorts, the presence of Q184H+G140S with additional raltegravir resistant mutations was associated with decreased virologic response to dolutegravir treatment. Similarly, subjects in the VIKING-3 trial with 2 or more primary mutations or a mutation of the Q148 pathway (Q148H/K/R) at baseline were more likely to experience virologic failure [35]. Only 69% of subjects with Q148H/K/R mutation and ≤ 1 secondary mutations and 48% of those with a Q148H/K/R and ≥ 2 secondary mutations met the definition of virologic response (>1 log HIV RNA decline or <50 copies/ml) at day 8.

A Randomized, Double-blind Study of the Safety and Efficacy of GSK1349572 50 mg Once Daily Versus Raltegravir 400 mg Twice Daily, Both Administered With an Investigator-selected Background Regimen Over 48 Weeks in HIV-1 Infected, Integrase Inhibitor-Naïve, Antiretroviral-Experienced Adults (SAILING) is an ongoing, phase 3, non-inferiority investigation of the efficacy of 50 mg dolutegravir once daily in ARV-experienced, INSTI-naive patients compared to 400 mg raltegravir twice daily [36]. A 24-week interim analysis of the SAILING trial demonstrated an adjusted difference in proportion of subjects with viral loads <50 copies/ml of +9.7% (95% CI +3.1%, 15.9%) in favor of the dolutegravir treatment group ($p=0.003$). These preliminary findings further demonstrate that dolutegravir will likely be an effective option in ARV-experienced subjects.

3.1 Adverse Events

Dolutegravir demonstrated a favorable safety profile in phase 2 and 3 trials. Dolutegravir was better tolerated than efavirenz with only 2 (1%) adverse events leading to subject withdrawal in the dolutegravir arm compared with 4 (8%) in the efavirenz arm of SPRING-1 [17]. Of the two adverse events leading to subject withdrawal from a dolutegravir dosing arm, only 1 (grade 2 dyspesia) was deemed related to study drug, while all 4 of the adverse events were related to efavirenz treatment. Similarly 10 subjects (2%) in the SINGLE trial withdrew from the dolutegravir arm secondary to adverse events compared with 42 (10%) from the efavirenz arm [33]. Dolutegravir and raltegravir were similarly tolerated with adverse event related dropout rates of 2% in each arm of the SPRING-2 trial [19].

Table 2 provides a summary of adverse events reported by SPRING-1 and -2, SINGLE and VIKING. The majority of patients in each clinical trial experienced some adverse event during the course of treatment with adverse event rates ranging from 57–89%. Nausea, headache, diarrhea, and sleep disturbances were among the most commonly reported adverse events being reported in 5–23% of subjects. No dose related patterns were identified for any type or frequency of adverse events reported in the dose ranging SPRING-1 trial. The majority of treatment-emergent adverse events were mild or moderate in nature with 5%, 7% and 14% of subjects in dolutegravir treatment arms reporting any serious adverse events in the SPRING-1, -2 and the first VIKING trial respectively [17,18]. Additionally, no serious study drug-related adverse events were reported for the dolutegravir treatment arm of the SPRING-1 or the VIKING trial. Three (<1%) study drug-related serious adverse events were reported for the dolutegravir arm of SPRING-2: arrhythmia, hepatitis, and hypersensitivity [19]. One (<1%), hypersensitivity reaction was reported for the dolutegravir arm of the SINGLE trial [33]. In the efavirenz arm of the SPRING-1 and SINGLE trials, 1 (2%) and 8 (2%) subjects, respectively, reported study drug-related serious adverse events (1 suicide attempt, 4 psychiatric adverse events, 2 hypersensitivity, 1 cerebral vascular accident and 1 renal failure) [17,33]. For the raltegravir arm of the SPRING-2 trial, 5 (1%) study drug-related serious adverse events were reported (aphasia, convulsion, diarrhea, hypersensitivity and increased CPK) [19].

The frequencies of graded laboratory abnormalities reported for the SPRING-1, -2, and SINGLE were similar between all dolutegravir treatment and comparator arms. Laboratory abnormalities reported in 1–5% of subjects included increased cholesterol, lipase, bilirubin, AST/ALT, CPK and prothrombin time as well as decreased phosphorous and neutrophil count [17,19,33]. Early investigation in SPRING-1, -2 and VIKING revealed a modest, non-progressive increase in serum creatinine associated with all dolutegravir dosing groups and cohorts which was apparent after approximately one week of therapy and remained stable through 24 weeks [17–19]. Subsequent iohexol plasma clearance investigations revealed that glomerular filtration rate (GFR) is not affected by dolutegravir [38]. Thus, this observation is likely due to dolutegravir -mediated inhibition of renal OCT2 transporter activity, with reduced tubular secretion of creatinine [15]. Dolutegravir use over 48 weeks of therapy does not appear to impact renal function [17,19] although the long-term effects of dolutegravir on renal function are still unknown.

A supratherapeutic dose of dolutegravir (250 mg once) demonstrated maximal prolongation of the QT interval of 1.99 msec (90% CI −0.55 to 4.53 msec) at 4 hours post dose [39]. Yet, this change was not considered clinically relevant when compared with the QT prolongation of 9.58 msec (90% CI 7.05–12.1) demonstrated by a single 400mg dose of moxifloxacin as a positive control. Much like first generation INSTIs, dolutegravir's side effect profile may make the compound a reasonable alternative in patients who are unable to tolerate the central nervous system or gastrointestinal side effects of efavirenz and protease inhibitors (PIs), respectively.

4. Drug-Drug Interactions

More than 20 drugs (Table 3) have been assessed for potential drug interactions with dolutegravir. These include ARVs likely to be used in combination therapy, such as NRTIs, non-nucleoside reverse transcriptase inhibitors (NNRTIs), and PIs. In addition, studies evaluating the drug interactions between dolutegravir and acid-reducing agents, multivitamins (MVI), oral hormonal contraceptives (OCs), antimycobacterial agents and direct-acting agents for hepatitis C virus (HCV), have been conducted.

4.1 CYP3A probe substrates

As previously discussed in this review, *in vitro* studies have demonstrated low potential for dolutegravir -mediated drug interactions by demonstrating that dolutegravir does not induce or inhibit CYP or UGT isoenzymes at clinically relevant concentrations [15]. To confirm these CYP3A findings *in vivo,* the drug interaction potential of dolutegravir has been examined in a sub study of 10 healthy volunteers receiving dolutegravir 25 mg daily for 10 days and a single dose of 3 mg oral midazolam syrup on day 10. The pharmacokinetic effect of dolutegravir on midazolam was compared to subjects receiving placebo with midazolam (n=2). Plasma midazolam exposure was unchanged by dolutegravir (dolutegravir AUC=15.4 ng•h/ml vs placebo AUC=16.3 ng•h/ml) demonstrating that dolutegravir does not induce or inhibit CYP3A [11]. Thus, dolutegravir mediated drug interactions with CYP3A substrates are unlikely.

4.2 Nucleoside(tide) Reverse Transcriptase Inhibitors

Because NRTIs do not undergo hepatic transformation via the CYP metabolic pathway, drug interactions are not as common with this class compared to NNRTIs and PIs [40]. Thus, drug interaction potential with NRTIs and dolutegravir is low. No clinical studies have quantified the interaction between dolutegravir and commonly used NRTIs such as emtricitabine, abacavir, or lamivudine. However, as discussed previously, phase II/III clinical trials [19,33] have successfully used dolutegravir in combination with these NRTIs without dose adjustments.

Although the mechanistic drivers of tenofovir-mediated drug interactions are not well understood, tenofovir is known to reduce atazanavir exposure possibly through induction of CYP or UGT metabolic pathways. For this reason, an open-label, repeat-dose study was conducted to assess the effects of concomitant dolutegravir and tenofovir disoproxil fumarate [41]. Fifteen healthy volunteers received 5 days of daily 50 mg dolutegravir, followed by a washout period of 6 days. Tenofovir disoproxil fumarate 300 mg daily was then administered for 7 days before daily dolutegravir 50 mg was added for an additional 5 days. The pharmacokinetic parameters of dolutegravir and tenofovir, assessed on the last day of each treatment period, demonstrated no clinically significant drug interaction [41].

4.3 Non-nucleoside reverse transcriptase inhibitors

Efavirenz exhibits a complicated interaction profile. It is primarily a substrate of CYP2B6 and an inducer of UGT1A1 as well as a mixed inducer/inhibitor of CYP3A4 [40, 42]. Since efavirenz has the potential to induce both the major and minor metabolic pathways of dolutegravir, reduced dolutegravir plasma concentrations would be expected if co-administered. The effects of efavirenz on dolutegravir pharmacokinetics have been evaluated in healthy subjects [43,44]. A total of 12 volunteers received 50 mg of dolutegravir once daily for 5 days, then dolutegravir plus 600 mg of efavirenz once daily for 14 days. Co-administration with efavirenz reduced the dolutegravir AUC and C_{max} by 57% and 39% respectively. However, the dolutegravir trough concentrations demonstrated a 75% reduction with a mean C_{trough} of 0.22 μg/ml when co-administered with efavirenz. Although

C_{trough} values remained above the *in vitro*, protein adjusted IC_{90}, they did fall below the *in vivo* EC_{90} (0.324 μg/ml) calculated from the E_{max} model discussed above [32,43,44]. Despite this reduction, the mean C_{trough} was similar to trough concentrations in the 10 mg dolutegravir treatment arm of the SPRING-1 trial (0.3 μg/ml), which demonstrated similar efficacy as the 50mg daily dosing arm [17]. Therefore, no dose adjustments are currently recommended when co-administering dolutegravir and efavirenz in INSTI-naive patients. However, careful clinical consideration should be given to individual patients. For those that may require more forgiveness for missed doses, or who may have increases in HIV RNA documented during careful virologic monitoring, using dolutegravir 50mg twice daily may be considered.

To investigate the drug interaction potential between the CYP3A substrate, rilpivirine, and dolutegravir, an open-label, crossover study was conducted in 16 healthy subjects treated with dolutegravir 50 mg daily for 5 days, then rilpivirine 25 mg daily for 11 days, followed by combination treatment with dolutegravir and rilpivirine for 5 days [45]. Consistent with *in vitro* findings, co-administration did not significantly impact dolutegravir plasma exposure with only slight increases of 10–18% for AUC, C_{max}, and C_{trough}. Similarly, rilpivirine plasma exposure was not significantly altered by the presence of dolutegravir (AUC, C_{max}, and C_{trough} increased by 6–18%).

Due to its ability to induce CYP isozymes and UGT1A1 [46], etravirine, a second generation NNRTI, has the potential to reduce dolutegravir plasma concentrations. Song *et. al.* conducted two open-label, cross-over studies to evaluate the effects of etravirine alone or in combination with ritonavir-boosted PIs on the pharmacokinetics of dolutegravir in healthy subjects. In the first study, 15 subjects received 50 mg dolutegravir daily for 5 days, followed by dolutegravir in combination with 200 mg etravirine twice daily for 14 days. In the second study, 16 subjects received 50 mg dolutegravir daily for 5 days followed by 14 days of dolutegravir in combination with etravirine 200mg plus lopinavir/ritonavir 400/100 mg twice daily (n=8) or darunavir/ritonavir 600/100 mg twice daily (n=9). Pharmacokinetic samples were collected on the last day (day 5 and day 14) of each dosing period [47].

Co-administration of etravirine alone led to a 50–88% reduction in dolutegravir AUC, C_{max} and C_{trough}. Yet, combining etravirine with boosted PIs attenuated this interaction. It was shown that etravirine combined with lopinavir/ritonavir slightly increased dolutegravir AUC, C_{max} and C_{trough} by 7–26%; while etravirine combined with darunavir/ritonavir only reduced dolutegravir AUC, C_{max}, and C_{trough} by 12–37%. Dolutegravir plasma exposure remained >9 fold above the *in vitro*, protein adjusted IC_{90} for the duration of the dosing interval. The authors concluded that, while dolutegravir should not be administered in an etravirine containing regimen alone, this combination might be considered without dose adjustments in a regimen containing lopinavir/ritonavir or darunavir/ritonavir [47].

4.4 Protease Inhibitors

UGT1A1 inhibitors, such as atazanavir have the potential to increase dolutegravir plasma concentrations. Conversely, ritonavir is a well-known inducer of the UGT1A1 pathway and thus has the potential to decrease dolutegravir plasma concentrations. A randomized, open-label, cross-over study was conducted to assess the effect of atazanavir and atazanavir/ritonavir on the pharmacokinetics of dolutegravir [48]. Twenty-four healthy volunteers received dolutegravir 30 mg daily for 5 days, followed by co-administration of dolutegravir and atazanavir 400 mg daily or atazanavir/ritonavir 300/100 mg daily for 14 days. Giving atazanavir alone increased plasma dolutegravir exposures by 50–180%, whereas giving atazanavir/ritonavir increased dolutegravir exposures by only 34–121%. This diminished effect is likely related to ritonavir-mediated UGT1A1 induction with ritonavir attenuating the inhibitory effect of atazanavir on this pathway. The co-administration of both atazanavir

and atazanavir/ritonavir with dolutegravir did produce modest increases in dolutegravir exposure. Yet, no increase in adverse effects was seen, and mean AUC values ($87.4 \mu g ml^{-1} h$) were still lower than the mean AUC values achieved from a well-tolerated single dose of dolutegravir 100 mg in phase I studies ($131\ \mu g ml^{-1} h$) [11]. Thus, despite a modest increase in dolutegravir exposure, it was determined that no dose adjustment for dolutegravir is necessary when co-administered with atazanavir or atazanavir/ritonavir [48].

Darunavir and lopinavir are well known inhibitors of the CYP3A4 pathway, and therefore, may increase dolutegravir plasma concentrations. In a randomized, open-label, crossover study, 30 subjects received 30 mg dolutegravir once daily for 5 days and were then randomized to receive dolutegravir with lopinavir/ritonavir 400/100 mg twice daily or darunavir/ritonavir 600/100 mg twice daily for 14 days. Lopinavir/ritonavir did not significantly affect dolutegravir exposure; whereas darunavir/ritonavir decreased dolutegravir exposure by 11–38% [49]. However, this reduction was not deemed clinically significant as the dolutegravir C_{trough} was still ~7 fold higher than the *in vitro*, protein adjusted IC_{90} despite using a lower dose (30 mg) of dolutegravir than was assessed in phase II/III trials.

Tipranavir exhibits a complicated drug interaction profile, as it is both a substrate and an inducer of CYP3A4, the minor metabolic pathway for dolutegravir [50]. The interaction potential between dolutegravir and tipranavir/ritonavir was investigated in an open-label, single-sequence study. Eighteen healthy volunteers received 50 mg of dolutegravir once daily for 5 days, then 7 days of 500/200 mg of tipranavir/ritonavir twice daily alone, followed by dolutegravir plus tipranavir/ritonavir combined for 5 days [43,44]. Co-administration of tipranavir/ritonavir lowered dolutegravir concentrations pharmacokinetic parameters (AUC, C_{max}, and C_{trough}) by 59%, 46% and 76% respectively. However, dolutegravir concentrations remained well above the *in vitro*, protein adjusted IC_{90} and still achieved C_{trough} values equivalent to the C_{trough} demonstrated by daily 10mg dolutegravir in the phase II dose-ranging trial (0.29 vs 0.3μg/ml). Consequently, it was concluded that dose adjustments are not necessary for dolutegravir combined with tipranavir/ritonavir in INSTI-naive patients [43,44].

The effect of concomitant fosamprenavir/ritonavir on dolutegravir pharmacokinetic profile has also been evaluated. In 12 healthy adult subjects, fosamprenavir/ritonavir was shown to decrease dolutegravir AUC, C_{max} and C_{trough} by 24–50% [51]. Since dolutegravir exposure at the end of the dosing interval remained 4 fold greater than the *in vitro*, protein adjusted IC_{90} this decrease in exposure was deemed clinically insignificant and standard dolutegravir dosing may be used when fosamprenavir/ritonavir is combined with dolutegravir.

4.5 Acid-Reducing Agents

All INSTI activity is dependent on binding to magnesium ions located at the catalytic site of the integrase enzyme to inhibit transfer of the viral DNA strand into the host genome. Therefore, chelation with therapeutic agents containing metal cations can occur. An open-label, randomized, crossover study evaluating the effect of co-administration of dolutegravir with metal cation-containing products, such as antacids and multivitamins (MVIs), was performed [52]. Sixteen subjects received 50 mg dolutegravir alone, together with a single oral dose of a One A Day Maximum MVI (Bayer Corporation, Morristown NY, USA), with a single oral dose of Maalox Advances Maximum Strength Liquid antacid (Novartis, Parsippany NJ, USA), and 2 h before a single dose of antacid. Expectedly, concurrent administration of the MVI resulted in modest (33%) reduction of dolutegravir AUC. Concomitant and staggered antacid administration reduced single-dose dolutegravir exposure by 74% and 26%, respectively. While concomitant administration of MVI and staggered administration of antacids did produce a modest reduction in dolutegravir AUC,

C_{trough} values, in both treatment groups C_{trough} was still 5–6 fold > *in vitro*, protein adjusted IC_{90}. Therefore, it was recommended that dolutegravir should be administered at least 2h before, or 6 hours after, an antacid and may be given concomitantly with a MVI [52].

An interaction between dolutegravir and proton pump inhibitors (PPI) might occur either through a change in absorption-limiting solubility caused by altering gastric pH or through a metabolic interaction *via* CYP isoenzymes. To evaluate the effect of pH-altering agents on dolutegravir exposure, 12 healthy subjects received a single 50 mg dose of dolutegravir under fasted conditions, followed by omeprazole 40 mg once daily for 5 days as part of a randomized, open-label, crossover study. On day 5, subjects also received a single 50 mg dose of dolutegravir 2 h after omeprazole administration [52]. Simultaneous administration of omeprazole resulted in non-significant reduction in dolutegravir exposure, with geometric least squares mean (GLSM) ratios for AUC, C_{max} and C_{24} ranging from 0.92 to 1.00. Since co-administration of omeprazole minimally affected dolutegravir plasma exposure, dolutegravir may provide a clinical alternative to once daily PI containing regimens (specifically atazanavir/ritonavir) in patients requiring acid-controlling pharmacotherapy [52].

4.6 Antimycobacterial agents

Rifamycins are commonly used in the treatment of tuberculosis (TB) and present a challenge in HIV/TB co-infection due to complicated drug interaction profiles. Rifampin is a potent CYP and UGT pathway inducer, and rifabutin, a CYP3A4 substrate, requires bidirectional dose adjustments when used with some CYP3A4 inhibitors. To assess the pharmacokinetic drug interaction potential of rifamycins with dolutegravir, Dooley *et. al.* conducted an open-label, fixed-sequence, crossover study [53]. Eleven healthy subjects in Arm 1 received 50 mg of dolutegravir once daily for 7 days, followed by 50 mg of dolutegravir twice daily for 7 days, and then 50 mg of dolutegravir twice daily co-administered with 600 mg of rifampin once daily for 14 days. Nine healthy subjects in Arm 2 received 50 mg of dolutegravir once daily for 7 days, followed by 50 mg of dolutegravir once daily together with 300 mg of rifabutin once daily for 14 days. Pharmacokinetic comparison in Arm 1 demonstrated that 50 mg dolutegravir twice daily administered with rifampin 600 mg daily resulted in only modestly increased plasma dolutegravir exposure when compared to 50 mg dolutegravir once daily alone (mean AUC = 33% increase, C_{trough} = 22% increase). This indicates that dolutegravir dosing should be increased to 50 mg twice daily when combined with the inducer rifampin. Comparison in Arm 2 showed that co-administration of dolutegravir 50 mg daily and rifabutin 300 mg daily resulted in a modest (30%) decrease in dolutegravir C_{trough} which was still 8 fold greater than the *in vitro*, protein adjusted IC_{90}. Therefore, rifabutin may provide a better clinical option for the treatment of TB in patients on a dolutegravir containing regimen, as no dolutegravir dose adjustments are required [53].

4.7 Oral Contraceptives

Although the potential for a drug interaction between dolutegravir and oral hormonal contraceptives (OCs) is low, a double blind, crossover study was designed to evaluate potential drug interactions. Sixteen healthy females were randomized to receive once daily Ortho-Cyclen, containing norgestimate (NGMN) and ethinyl estradiol (EE), from day 1–21 of their menstrual cycle plus either 50 mg dolutegravir twice daily or placebo twice daily for 10 days. Subjects then switched to the alternate treatment for another 10 days [54]. Expectedly, dolutegravir pharmacokinetic parameters were not altered in the presence of NGMN or EE when dolutegravir to historical controls. Plasma hormonal pharmacokinetic profiles were also unchanged by the presence of dolutegravir as evidenced by GLSM ratios of 1.03 and 0.975 for EE and NGMN, respectively. Additionally, administering dolutegravir

with Ortho-Cyclen had no effect on any pharmacodynamic marker of OC activity (e.g. luteinizing hormone, follicle stimulating hormone, and progesterone levels) [54].

4.8 Hepatitis agents

Boceprevir and telaprevir are HCV PIs prescribed in combination with pegylated interferon and ribavirin for the treatment of HCV. Both boceprevir and telaprevir have demonstrated strong inhibition of CYP3A4/5 metabolic pathways and thus have the potential to increase plasma dolutegravir exposure through inhibition of its minor metabolic pathway. An open-label, two-cohort study in healthy adult subjects was conducted to assess the pharmacokinetics of dolutegravir in the presence of boceprevir and telaprevir [55]. Twenty-eight subjects received dolutegravir 50 mg once daily for 5 days and were then randomized to receive dolutegravir in combination with either boceprevir 800 mg three times daily or telaprevir 750 mg three times daily for 10 days. Co-administration of boceprevir and dolutegravir increased dolutegravir C_{trough} by 8% but had no effect on AUC or C_{max}. Co-administration of telaprevir and dolutegravir resulted in increased dolutegravir plasma exposures relative to dolutegravir alone as evidenced by 25%, 19%, and 37% increases in AUC, C_{max}, and C_{trough}, respectively. Hence, it was concluded that dolutegravir could be co-administered without dose-adjustment in HIV/HCV co-infected patients receiving HCV treatment with boceprevir and telaprevir [55].

4.9 Opioid agonists

Methadone is a racemic opioid receptor commonly used for the management of chronic pain or opioid addiction. Methadone is extensively metabolized by the CYP pathway and interacts with a number of different therapeutic agents. An open-labeled, crossover study evaluated the effects of dolutegravir when co-administered with methadone in 12 opioid dependent subjects receiving individualized doses of daily methadone [54]. Plasma exposure of both R- and S-Methadone was not significantly altered by dolutegravir with GLSM ratios for AUC, C_{max}, and C_{trough} ranging from 0.95 to 1.03. Because study subjects were on stable methadone therapy prior to enrollment, this study was unable to assess the effects of methadone on dolutegravir's pharmacokinetic parameters. Previous *in vitro* study has found that methadone only modestly induces UGT1A1 in hepatic microsomes at concentrations that are higher (10–50 μM) than the mean peak concentrations of methadone treatment demonstrated by Song *et. al.* (1.36 μM) [54,56]. Considering that UGT1A1 is dolutegravir's primary metabolic pathway, a methadone-mediated drug interaction would be unexpected.

5. Conclusions

Dolutegravir is a second-generation INSTI that preferentially blocks the strand transfer step during the viral integration process. Dolutegravir's favorable and predicable pharmacokinetic profile offers several clinical advantages over currently marketed INSTIs. The lack of an effect on drug transporters and CYP enzymes is of value for an HIV infected population requiring poly-pharmacy. Additionally, the drug exposure achieved by once daily dolutegravir dosing negates the need for a concomitant pharmacokinetic enhancing agent (such as ritonavir or cobicistat), which also minimizes drug interaction potential. Dolutegravir also has a favorable safety profile with nausea, headache, and diarrhea being seen in <20% of patients. Dolutegravir has potent antiretroviral activity in both ARV-naïve and experienced patients, including those with first generation INSTI resistance mutations. With its potent activity, tolerability, ease of dosing, and minimal drug interaction profile, dolutegravir is poised to become one of the key components in the treatment of HIV infection.

Acknowledgments

The authors wish to acknowledge the funding sources CFAR P30 AI50410, and U01 AU095031

References

1. Adams JL, Greener BN, Kashuba AD. Pharmacology of HIV integrase inhibitors. Curr Opin HIV AIDS. 2012 Sep; 7(5):390–400. [PubMed: 22789987]
2. Dejesus, E.; Cohen, C.; Elion, R., et al. First report of raltegravir (RAL, MK-0518) use after virologic rebound on elvitegravir (EVT, GS 9137) [abstract no. TUPEB032 plus poster]. 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention; 2007 Jul 22–25; Sydney.
3. Hazuda, DJ.; Miller, MD.; Nguyen, BY., et al. Resistance to the HIV-integrase inhibitor raltegravir: analysis of protocol 005, a phase 2 study in patients with triple-class resistant HIV-1 infection [abstract no. 8]. 16th International HIV Drug Resistance Workshop; 2007 Jun 12–16; Barbados.
4. McColl, DJ.; Fransen, S.; Gupta, S., et al. Resistance and cross-resistance to first generation integrase inhibitors: Insights from a phase 2 study of Elvitegravir (GS-9137). [abstract no. 9]. 16th International HIV Drug Resistance Workshop; 2007 Jun 12–16; Barbados.
5. Garrido C, Villacian J, Zahonero N, et al. Broad phenotypic cross-resistance to elvitegravir in HIV-infected patients failing on raltegravir-containing regimens. Antimicrob Agents Chemother. 2012 Jun; 56(6):2873–2878. [PubMed: 22450969]
6. Hare S, Smith SJ, Metifiot M, et al. Structural and functional analyses of the second-generation integrase strand transfer inhibitor dolutegravir (S/GSK1349572). Mol Pharmacol. 2011 Oct; 80(4): 565–572. [PubMed: 21719464]
7. Kobayashi M, Yoshinaga T, Seki T, et al. In Vitro antiretroviral properties of S/GSK1349572, a next-generation HIV integrase inhibitor. Antimicrob Agents Chemother. 2011 Feb; 55(2):813–821. [PubMed: 21115794]
8. Hightower KE, Wang R, Deanda F, et al. Dolutegravir (S/GSK1349572) exhibits significantly slower dissociation than raltegravir and elvitegravir from wild-type and integrase inhibitor-resistant HIV-1 integrase-DNA complexes. Antimicrob Agents Chemother. 2011 Oct; 55(10):4552–4559. [PubMed: 21807982]
9. Underwood MR, Johns BA, Sato A, et al. The Activity of the Integrase Inhibitor Dolutegravir Against HIV-1 Variants Isolated From Raltegravir-Treated Adults. J Acquir Immune Defic Syndr. 2012 Nov 1; 61(3):297–301. [PubMed: 22878423]
10. Canducci F, Ceresola ER, Boeri E, et al. Cross-resistance profile of the novel integrase inhibitor Dolutegravir (S/GSK1349572) using clonal viral variants selected in patients failing raltegravir. J Infect Dis. 2011 Dec 1; 204(11):1811–1815. [PubMed: 21984737]
11. Min S, Song I, Borland J, et al. Pharmacokinetics and safety of S/GSK1349572, a next-generation HIV integrase inhibitor, in healthy volunteers. Antimicrob Agents Chemother. 2010 Jan; 54(1): 254–258. [PubMed: 19884365]
12. Min S, Sloan L, DeJesus E, et al. Antiviral activity, safety, and pharmacokinetics/pharmacodynamics of dolutegravir as 10-day monotherapy in HIV-1-infected adults. AIDS. 2011 Sep 10; 25(14):1737–1745. [PubMed: 21716073]
13. Song, I.; Borland, J.; Savina, PM., et al. Pharmacokinetics of dolutegravir in subjects with moderate hepatic impairment. [abstract no. N-121 plus poster]. 19th Conference on Retrovirus and Opportunistic Infections; 2012 Mar 5–8; Seattle (WA).
14. DeJesus E, Berger D, Markowitz M, et al. Antiviral activity, pharmacokinetics, and dose response of the HIV-1 integrase inhibitor GS-9137 (JTK-303) in treatment-naive and treatment-experienced patients. J Acquir Immune Defic Syndr. 2006 Sep; 43(1):1–5. [PubMed: 16936557]
15. Reese MJ, Savina PM, Generaux GT, et al. In Vitro Investigations into the Roles of Drug Transporters and Metabolizing Enzymes in the Disposition and Drug Interactions of Dolutegravir, a HIV Integrase Inhibitor. Drug Metab Dispos. 2013 Feb; 41(2):353–361. [PubMed: 23132334]
16. Song I, Borland J, Chen S, et al. Effect of food on the pharmacokinetics of the integrase inhibitor dolutegravir. Antimicrob Agents Chemother. 2012 Mar; 56(3):1627–1629. [PubMed: 22183173]

17. van Lunzen J, Maggiolo F, Arribas JR, et al. Once daily dolutegravir (S/GSK1349572) in combination therapy in antiretroviral-naive adults with HIV: planned interim 48 week results from SPRING-1, a dose-ranging, randomised, phase 2b trial. Lancet Infect Dis. 2012 Feb; 12(2):111–118. [PubMed: 22018760]

18. Eron JJ, Clotet B, Durant J, et al. Safety and Efficacy of Dolutegravir in Treatment-Experienced Subjects With Raltegravir-Resistant HIV Type 1 Infection: 24-Week Results of the VIKING Study. J Infect Dis. 2013 Mar.207:740–8. [PubMed: 23225901]

19. Raffi F, Rachlis A, Stellbrink HJ, et al. Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study. Lancet. 2013 Mar; 381(9868):735–743. [PubMed: 23306000]

20. Letendre, S.; Mills, A.; Tashima, K., et al. Distribution and antiviral activity in cerebrospinal fluid (CSF) of the integrase inhibitor, dolutegravir (DTG): ING116070 week 16 results [abstract no. 178LB plus poster]. 20th Conference on Retroviruses and Opportunistic Infections; 2013 Mar 3–6; Atlanta (GA).

21. Greener, BN.; Adams, JL.; Patterson, KB., et al. Single and multiple dose dolutegravir phrmacokinetics in the genital tract and colorectum of HIV negative men and women [abstract no. 531 plus poster]. 20th Conference on Retroviruses and Opportunistic Infections; 2013 Mar 3–6; Atlanta (GA).

22. Patterson, KB.; Prince, HMA.; Wang, R., et al. Pharmacokinetics (PK) of raltegravir (RAL) in the blood plasma (BP) and genital tract (GT) in HIV+ and HIV- women [abstract no. O-17 plus poster]. 5th Annual HIV Transmission Workshop; 2010 Jul 15–16; Vienna.

23. Dumond JB, Patterson KB, Pecha AL, et al. Maraviroc concentrates in the cervicovaginal fluid and vaginal tissue of HIV-negative women. J Acquir Immune Defic Syndr. 2009 Aug 15; 51(5):546–553. [PubMed: 19546811]

24. Salas Herrera IG, Pearson RM, Turner P. Quantitation of albumin and alpha-1-acid glycoprotein in human cervical mucus. Hum Exp Toxicol. 1991 Mar; 10(2):137–139. [PubMed: 1675106]

25. Antoniou T, Hasan S, Loutfy MR, et al. Pharmacokinetics of maraviroc, raltegravir, darunavir, and etravirine in the semen of HIV-infected men. J Acquir Immune Defic Syndr. 2013 Feb 1; 62(2):e58–60. [PubMed: 23328092]

26. Calcagno A, Bonora S, D'Avolio A, et al. Raltegravir penetration in seminal plasma of healthy volunteers. Antimicrob Agents Chemother. 2010 Jun; 54(6):2744–2745. [PubMed: 20308369]

27. Cao YJ, Hendrix CW. Male genital tract pharmacology: developments in quantitative methods to better understand a complex peripheral compartment. Clin Pharmacol Ther. 2008 Mar; 83(3):401–412. [PubMed: 17786163]

28. US National Institutes of Health. [[Accessed 2013 Feb 26]] ClinicalTrials.gov [online]. Available from URL: http://clinicaltrials.gov/ct2/show/NCT01353716?term=NCT01353716&rank=1

29. Results Summary for 113125. GlaxoSmithKline; A Phase I, Open-Label, Parallel-Group Study to Evaluate the Pharmacokinetics and Safety of Dolutegravir in Subjects with Renal Impairment and Healthy Matched Control Subjects (ING113125). Available from URL: http://www.gsk-clinicalstudyregister.com/result_detail.jsp?protocolId=113125&studyId=F847E25C-9F8F-494E-82AA-DCB140DE7892&compound=dolutegravir&type=Compound&letterrange=A-F [Accessed 2013 May 17]

30. US National Institutes of Health. [Accessed 2013 Feb 27] ClinicalTrials.gov [online]. Available from URL: http://clinicaltrials.gov/ct2/show/NCT01302847?term=NCT01302847&rank=1

31. Hazra, R.; Viani, R.; Acosta, E., et al. Pharmacokinetics, safety and efficacy of dolutegravir (DTG; S/GSK1349572) in HIV-1-positive adolescents: preliminary analysis from IMPAACT P1093 [abstract no. TUAB0203]. 19th International AIDS Conference; 2012 Jul 22–27; Washington DC.

32. Song, I.; Shuguang, C.; Lou, Y., et al. Pharmacokinetic (PK) and pharmacodynamic (PD) relationship of GSK1349572, a next generation integrase inhibitor (INI), in HIV-1 [abstract no. WEPEB250 plus poster]. IAS 2009-5th Conference on HIV Pathogenesis, Treatment and Prevention; 2009 Jul 19–22; Cape Town, South Africa.

33. Walmsley, SL.; Antela, A.; Clumeck, N., et al. Dolutegravir (DTG; S/GSK1349572) + abacavir/lamivudine once daily statistically superior to tenofovir/emtricitabine/efavirenz: 48-week results -

SINGLE (ING114467) [abstract no. H556b and oral presentaation]. 52nd Interscience Conference on Antimicrobial Agents and Chemotherapy; 2012 Sep 9–12; San Francisco (CA).

34. Brinson, C.; Walmsley, SL.; Keikawaus, A., et al. Dolutegravir treatment response and safety by key subgroups in treatment naive HIV infected individuals [abstract no. 554 plus poster]. 20th Conference on Retroviruses and Opportunistic Infections; 2013 Mar 3–6; Atlanta (GA).
35. Nichols G, Mills A, Grossberg R, et al. Antiviral activity of dolutegravir in subjects with failure on an integrase inhibitor-based regimen: week 24 phase 3 results from VIKING-3. J Int AIDS Soc. 2012 Nov 11.15(Suppl 4):18112.
36. Pozniak, A.; Mingrone, H.; Shuldyakov, A., et al. Dolutegravir (DTG) versus raltegravir (RAL) in ART-experienced, integrase-naive subjects: 24-week interim results from SAILING (ING111762) [abstract no. 179LB plus poster]. 20th Conference on Retroviruses and Opportunistic Infections; 2013 Mar 3–6; Atlanta (GA).
37. van Luin M, Kuks PF, Burger DM. Use of therapeutic drug monitoring in HIV disease. Curr Opin HIV AIDS. 2008 May; 3(3):266–271. [PubMed: 19372977]
38. Koteff J, Borland J, Chen S, et al. A phase 1 study to evaluate dolutegravir's effect on renal function via measurement of iohexol and para-aminohippurate clearance in healthy subjects. Br J Clin Pharmacol. 2013 Apr; 75(4):990–996. [PubMed: 22905856]
39. Chen S, Min SS, Peppercorn A, et al. Effect of a single supratherapeutic dose of dolutegravir on cardiac repolarization. Pharmacotherapy. 2012 Apr; 32(4):333–339. [PubMed: 22422361]
40. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services; Available at http://aidsinfo.nih.gov.libproxy.lib.unc.edu/contentfiles/lvguidelines/AdultandAdolescentGL.pdf [Section accessed 03/02/2013]
41. Song I, Min SS, Borland J, et al. Lack of interaction between the HIV integrase inhibitor S/GSK1349572 and tenofovir in healthy subjects. J Acquir Immune Defic Syndr. 2010 Nov; 55(3): 365–367. [PubMed: 20585260]
42. Ward B, Gorski C, Jones D, et al. The cytochrome P450 2B6 (CYP2B6) is the main catalyst of efavirenz primary and secondary metabolism: Implication for HIV/AIDS therapy and utility of efavirenz as a substrate marker of CYP2B6 catalytic activity. The Journal of Pharmacology and Experimental Therapeutics. 2003; 306(1):287–300. [PubMed: 12676886]
43. Song, I.; Borland, J.; Lou, Y., et al. Effects of enzyme inducers, tipranavir and efavirenz, on the pharmacokinetics of the integrase inhibitor, dolutegravir (S/GSK1349572) [abstract no O-02 plus oral presentation]. 12th International Workshop on Clinical Pharmacology of HIV Therapy; 2011 Apr 13–15; Miami (FL).
44. Mascolini, M. No dolutegravir (GSK572, integrase) dose adjustment needed with efavirenz or tipranavir/ritonavir[abstract no. 1111]. 12th International Workshop on Clinical Pharmacology of HIV Therapy; 2011 Apr 13–15; Miami (FL).
45. Ford, SL.; Gould, E.; Chen, S., et al. Lack of pharmacokinetic (PK) interaction between rilpivirine and the integrase inhibitors dolutegravir and S/GSK1265744. 52nd Interscience Conference on Antimicrobial Agents and Chemotherapy; 2012 Sep 9–12; San Francisco (CA).
46. Kakuda TN, Scholler-Gyure M, Hoetelmans RM. Clinical perspective on antiretroviral drug-drug interactions with the non-nucleoside reverse transcriptase inhibitor etravirine. Antivir Ther. 2010; 15(6):817–829. [PubMed: 20834094]
47. Song I, Borland J, Min S, et al. Effects of etravirine alone and with ritonavir-boosted protease inhibitors on the pharmacokinetics of dolutegravir. Antimicrob Agents Chemother. 2011 Jul; 55(7):3517–3521. [PubMed: 21555764]
48. Song I, Borland J, Chen S, et al. Effect of atazanavir and atazanavir/ritonavir on the pharmacokinetics of the next-generation HIV integrase inhibitor, S/GSK1349572. Br J Clin Pharmacol. 2011 Jul; 72(1):103–108. [PubMed: 21342217]
49. Song I, Min SS, Borland J, et al. The effect of lopinavir/ritonavir and darunavir/ritonavir on the HIV integrase inhibitor S/GSK1349572 in healthy participants. J Clin Pharmacol. 2011 Feb; 51(2): 237–242. [PubMed: 20489027]
50. King JR, Acosta EP. Tipranavir: a novel nonpeptidic protease inhibitor of HIV. Clin Pharmacokinet. 2006; 45(7):665–682. [PubMed: 16802849]

51. Song, I.; Borland, J.; Chen, S., et al. Effect of fosamprenavir/ritonavir on the pharmacokinetics of the integrase inhibitor, dolutegravir, in healthy subjects [abstract no. A1-1727]. 51st Annual Interscience Conference on Antimicrobial Agents and Chemotherapy; 2011 Sep 17–20; Chicago (IL).
52. Patel P, Song I, Borland J, et al. Pharmacokinetics of the HIV integrase inhibitor S/GSK1349572 co-administered with acid-reducing agents and multivitamins in healthy volunteers. J Antimicrob Chemother. 2011 Jul; 66(7):1567–1572. [PubMed: 21493648]
53. Dooley KE, Sayre P, Borland J, et al. Safety, Tolerability, and Pharmacokinetics of the HIV Integrase Inhibitor Dolutegravir Given Twice Daily With Rifampin or Once Daily With Rifabutin: Results of a Phase 1 Study Among Healthy Subjects. J Acquir Immune Defic Syndr. 2013 Jan 1; 62(1):21–27. [PubMed: 23075918]
54. Song, I.; Mark, S.; Borland, J., et al. Dolutegravir has no effect on the pharmacokinetics of methadone or oral contraceptives with norgestimate and ethinyl estradiol [abstract no535 plus poster]. 20th Conference on Retroviruses and Opportunistic Infections; 2013 Mar 3–6; Atlanta (GA).
55. Johnson, M.; Borland, J.; Shuguang, C., et al. The effect of boceprevir and telaprevir on dolutegravir pharmacokinetics, in healthy adult subjects [abstract no. 016]. 14th International Workshop on Clinical Pharmacology of HIV Therapy; 2013 Apr 22–24; Amsterdam.
56. Tolson AH, Li H, Eddington ND, et al. Methadone induces the expression of hepatic drug-metabolizing enzymes through the activation of pregnane X receptor and constitutive androstane receptor. Drug Metab Dispos. 2009 Sep; 37(9):1887–1894. [PubMed: 19520773]
57. [Accessed March 16, 2013.] AIDSinfo Drug Database. 2013. Available at: http://aidsinfo.nih.gov/drugs/509/dolutegravir/0/patient/

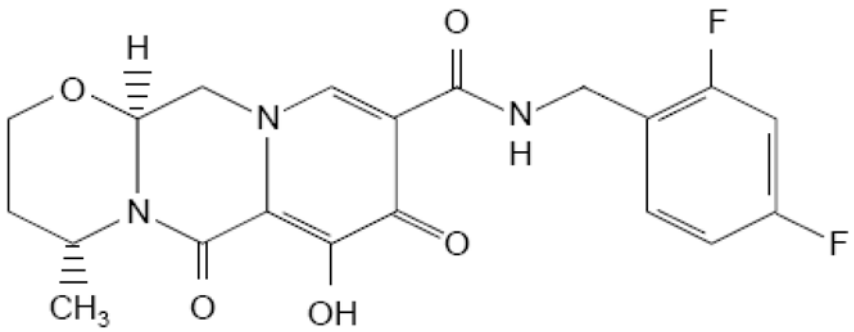

Figure 1. Dolutegravir chemical structure
[57].

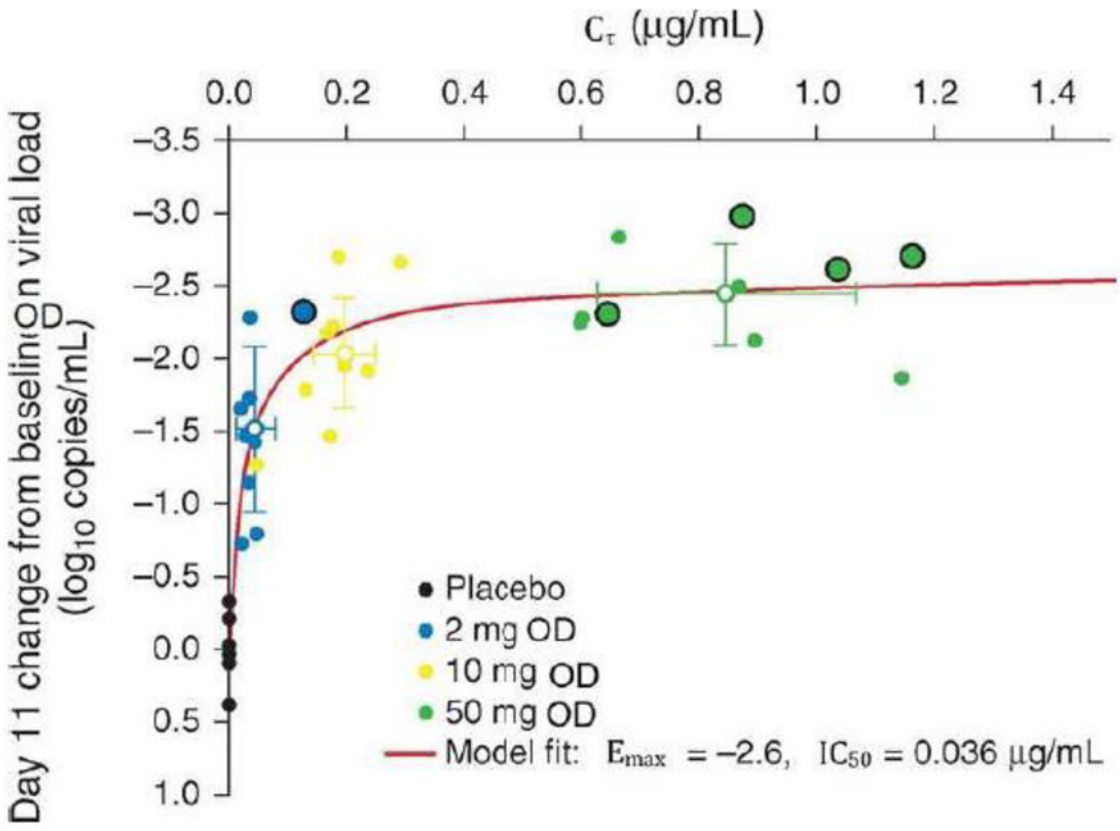

Figure 2.

Mean change from baseline in HIV-1 RNA. BL baseline, C dosage interval, E_{max} maximum effect, FU follow-up, IC_{50} concentration producing 50% inhibition, OD once daily (reproduced with permission from Min S. et al. Antiviral activity, safety, and pharmacokinetics/pharmacodynamics of dolutegravir as 10-day monotherapy in HIV-1-infected adults. AIDS. 27(4): 673.)

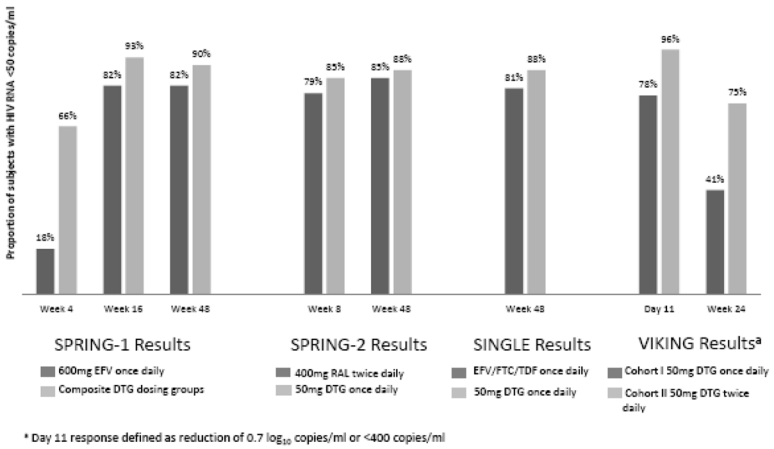

Figure 3. Efficacy results from phase II and III clinical trials

Proportion of subjects with HIV <50 copies/ml in the SPRING-1, -2 [17, 19], SINGLE [33], VIKING [18] and VIKING-3 [35] at various weeks post therapy initiation. DTG dolutegravir, EFV efavirenz, FTC emtricitabine, RAL raltegravir, TDF tenofovir disoproxil fumarate

Table 1

Steady state dolutegravir (DTG) pharmacokinetic parameters reported in healthy and HIV infected subjects.

Treatment Arm (mg DTG once daily)	No. of subjects	C_{max} (μg/ml)	t_{max}(h)	AUC_t (μg•h/ml)	C_{min} (μg/ml)	C_{trough}(μg/ml)
2[a]	9	0.22 (25)	1.00 (0.42–3.00)	2.56 (29)	NA	0.04 (50)
10	8[b]	1.47 (24)	0.50 (0.25–2.00)	16.7(15)	0.27 (25)	0.35 (20)
	7[a]	0.80 (23)	1.48 (0.50–3.00)	10.1 (20)	NA	0.19 (25)
25[b]	10	3.09 (26)	1.00 (0.50–2.00)	38.4 (23)	0.66 (32)	0.84 (33)
50	8[b]	6.16 (15)	1.00 (0.50–2.00)	76.8 (19)	1.48 (25)	1.64 (25)
	10[a]	3.34 (16)	2.00 (0.97–4.00)	43.4 (20)	NA	0.83 (26)

All pharmacokinetic parameters except t_{max} are reported as mean (% coefficient of variation); t_{max}, is reported as median (range).

DTG, Dolutegravir; C_{max}, maximum concentration; t_{max}, time to maximum concentration; AUC_{τ}, area under the concentration time curve during a dosage interval; C_{min}, minimum concentration; C_{trough}, trough plasma concentration

[a] Steady state concentrations obtained from HIV infected adults after 10 doses of monotherapy with DTG tablets [12]

[b] Steady state concentrations obtained from healthy adults after 10 doses of DTG suspension [11]

Table 2

Summary of adverse events reported in phase III clinical trials

Adverse event	SPRING-1 All DTG treatment groups n=155 (%)	SPRING-2 DTG arm N=411 (%)	SINGLE DTG arm N=414 (%)	VIKING[a] Cohort I & II n=51 (%)
Any event	132 (85)	399 (82)	369 (89)	29 (57)
Nausea	19 (12)	59 (14)	59 (14)	NR
Headache	10 (6)	51 (12)	55 (13)	NR
Diarrhea	12 (8)	47 (11)	72 (17)	3 (6)
Nasopharyngitis	NR	46 (11)	62 (15)	NR
Dizziness	5 (3)	23 (6)	37 (9)	NR
Sleep disturbances (insomnia, abnormal dreams etc.)	3 (2)	21 (5)	94 (23)	3 (6)
Fatigue	5 (3)	20 (5)	54 (13)	NR
Upper respiratory tract infection	NR	26 (6)	36 (9)	NR
Pyrexia	NR	20 (5)	NR	NR
Depression	NR	21 (5)	23 (6)	NR
Pharyngitis	NR	14 (3)	NR	NR
Bronchitis	NR	19 (5)	NR	3 (6)
Anxiety	NR	14 (3)	14 (3)	NR
Cough	NR	NR	NR	3 (6)
Rash	2 (1)	NR	14 (3)	NR
Asthenia	4 (3)	NR	NR	NR

DTG, dolutegravir; NR, not reported

[a] Only ≥ Grade 2 adverse events reported

Table 3

Summary of dolutegravir drug interaction data.

Interacting drug class	Interacting drug	Effect on integrase inhibitor or interacting drug concentration	Maintain standard dosing
Antiretrovirals			
NRTIs	TDF	No significant effect observed	Yes
NNRTIs	EFV	DTG AUC, C_{max}, and C_{min} decreased 57, 39, and 75%, respectively	Yes
	RPV	DTG AUC, C_{max}, and C_{trough} increased 10–18%	Yes
	ETR	DTG AUC, C_{max}, and C_{min} decreased 71, 52, and 88%, respectively	Do not co-administer DTG and ETR alone
	ETR/DRV/r	ETR/DRV/r administration results in 25, 11.8, and 37.1% decreases in DTG AUC, C_{max}, and C_{min}, respectively	Administer DTG and ETR only if DRV/r also included in the regimen
	ETR/LPV/r	ETR/LPV/r administration results in 11, 7, and 28% increases in DTG AUC, C_{max}, and C_{min}, respectively	Administer DTG and ETR only if LPV/r also included in the regimen
PIs	DRV/r	DRV/r led to DTG AUC, C_{max}, and C_{min} decreases of 22, 11, and 38%, respectively	Yes
	ATV	DTG AUC, C_{max}, and C_{min} increased 91, 50, and 180%, respectively	Yes
	ATV/r	DTG AUC, C_{max}, and C_{min} increased 62, 34, and 121%, respectively	Yes
	LPV/r	No significant effect observed	Yes
	FPV/r	DTG AUC, C_{max}, and C_{min} decreased 35, 24, and 49%, respectively	Yes
	TPR/r	DTG AUC, C_{max}, and C_{min} decreased 59, 46, and 76%, respectively	Yes
Acid-Reducing Agents			
PPIs	Omeprazole	No significant effect observed	Yes
Antacids	Maalox Advanced Maximum Strength	DTG AUC, C_{max}, and C_{min} decreased 74, 72, and 74%, respectively	Administer antacids 2 h after or 6 h before DTG dosing
Over The Counter Agents			
MVI	One a Day Maximum	MVI co-administration modestly decreased DTG AUC by 33%	Yes
Anti-tuberculosis Agents			
Antimycobacterials	RIF	DTG AUC and C_{min} increased 33 and 22% (DTG 50mg twice daily plus RIF 600 mg once daily versus DTG 50 mg daily)	Increase DTG dosing frequency to 50 mg twice daily
	RBT	DTG AUC and C_{min} decreased 5 and 30%, C_{max} increased 15	Yes
Oral Contraceptives			

Interacting drug class	Interacting drug	Effect on integrase inhibitor or interacting drug concentration	Maintain standard dosing
	Ortho-Cyclen	No significant effect observed	Yes
Anti-Hepatitis C Virus Agents			
NS3A4 PIs	BCV	BCV increased DTG Ctrough 8% but had no effect on AUC or C_{max}	Yes
	TVR	DTG AUC, C_{max}, and C_{trough} increased 25%, 19%, and 37%, respectively	Yes
Opioid Agonist			
	Methadone	Unable to assess the effects of methadone on DTG pharmacokinetic parameters	No dosing recommendation

ATV, Atazanavir; AUC, area under the concentration time curve; BCV, Boceprevir; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; C_{trough}, trough plasma concentration; DRV, Darunavir; DTG, Dolutegravir; EFV, Efavirenz; ETR, Etravirine; EVG, Elvitegravir; FPV, fosamprenavir; LPV, Lopinavir; MVI, Multivitamins; NNRTI, Non-nucleoside reverse transcriptase inhibitor; NRTI, Nucleoside reverse transcriptase inhibitor; PI, Protease Inhibitor; PPI, Proton pump inhibitor; RPV, Rilpivirine; RTV, Ritonavir; RBT, Rifabutin; RIF, Rifampin; TDF, tenofovir disoproxil fumarate; TVR, Telaprevir