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Comparative Clinical Pharmacokinetics and Pharmacodynamics of HIV-1 Integrase Strand Transfer Inhibitors

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Abstract

Dolutegravir (DTG), elvitegravir (EVG) and raltegravir (RAL), are members of latest class of antiretrovirals (ARV) available to treat human immunodeficiency virus (HIV) infection, the integrase strand transfer inhibitors (INSTI). INSTIs are potent inhibitors of the HIV integrase enzyme with $IC_{90/95}$ values in the low nanogram per milliliter range and they retain antiviral activity against strains of HIV with acquired resistance to other classes of ARVs. Each of the INSTIs have unique pharmacokinetic / pharmacodynamic properties, influencing their role in clinical use in specific subsets of patients. RAL and DTG have minimal drug-drug interaction profiles, as their metabolism has minimal cytochrome P450 (CYP) involvement. Conversely, EVG metabolism occurs primarily via CYP3A4 and requires pharmacokinetic boosting to achieve systemic exposures amenable to once daily dosing. EVG and DTG have the added benefit of the availability of fixed dose combination tablets, allowing for convenient and simplified ARV regimens. RAL is the only INSTI to be listed as a preferred agent on the current United States perinatal guidelines. All three of the INSTI agents are recommended regimens for treatment-naïve individuals on the United States Adult and Adolescent HIV treatment guidelines. This review summarizes and compares the pharmacokinetics and pharmacodynamics of the INSTI agents, and describes specific pharmacokinetic considerations for special patient conditions: hepatic impairment, renal dysfunction, pregnancy and co-infections.

1.0 Introduction

There are an estimated 36 million people living with the human immunodeficiency virus (HIV) infection globally. With the advent of antiretroviral therapy (ART), HIV has become a chronic manageable condition. However, in the absence of a sterilizing cure, ART is a life-long commitment. Triple drug combinations consisting of antiretrovirals (ARVs) targeting the virus in two steps in the viral life cycle are the current standard of care for ART [1]. An HIV integrase strand transfer inhibitor (INSTI) co-administered with two nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) are part of five of the six recommended

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Compliance with Ethical Standards

Conflicts of Interest

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regimens for ART-naïve patients in the US Department of Health and Human Services Adult and Adolescent HIV treatment guidelines [1].

The INSTI class is the newest class of drugs available to treat HIV, and targets the HIV integrase enzyme, which incorporates pro-viral HIV-1 DNA into the host cell genome. The first clinically available INSTI, raltegravir (RAL), was approved in 2007, followed by the second-generation INSTIs elvitegravir (EVG) in 2012 and dolutegravir (DTG) in 2013. In addition to their role in therapy for ART-naïve patients, INSTIs retain potency against strains of HIV that are resistant to other classes of ARVs such as protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTI). In this manner, INSTIs offer novel treatment options for patients with both acquired and transmitted resistance to other ARV classes.

This review summarizes the clinical pharmacokinetics (PK) of the three currently FDA approved INSTI agents for the treatment of HIV in adult patients. Because selection of optimal ART for special patient populations may be complicated by changes in ARV PK, drug-drug interactions (DDI), or overlapping adverse events, available evidence for the impact of hepatic impairment, renal dysfunction, pregnancy or co-infections on the PK of INSTIs will be summarized. Finally, the pharmacodynamics (PD) of the INSTI agents will be compared.

2.0 Pharmacokinetics of INSTIs

The PK parameters of the HIV INSTIs in healthy subjects and HIV-infected individuals are summarized in Table 1.

2.1 Dolutegravir

DTG is available as a 50mg film coated tablet, and a fixed dose combination (FDC) tablet containing DTG 50mg, abacavir (ABC) 600mg, and lamivudine (3TC) 300mg. DTG may be given to adults as 50mg once daily for patients without INSTI-associated resistance substitutions, or 50mg twice daily for patients with known or suspected INSTI-associated resistance substitutions.

Studies describe DTG (S/GSK1349572) PK of single and multiple dose strategies with doses ranging from 2mg to 100mg in healthy volunteers. DTG was readily absorbed with a median maximum concentration (C_{max}) achieved between 0.5 and 1.25 hours post dose in healthy volunteers; similar studies in HIV-infected persons found C_{max} occurred within 2.5 hours [2, 3]. Low, moderate and high fat meals increased DTG area under the concentration time curve (AUC) 33%, 41%, and 66%, respectively, although current manufacturer prescribing information indicates DTG may be taken without regard to meals [4, 5]. Consistent with other INSTIs, DTG absorption is impaired by coadministration with divalent or trivalent cations, which may be overcome by dose separation. Once absorbed, DTG extensively binds (>99%) to plasma proteins, both albumin and alpha-1-acid glycoprotein [6, 3]. Bioequivalence of a FDC tablet compared with single tablet DTG 50mg and combination ABC/3TC 600mg/300mg has been demonstrated [7].

DTG exhibits bi-exponential elimination with a terminal half-life ($t_{1/2}$) ranging from 13 to 15 hours in healthy volunteers, while a $t_{1/2}$ of 11 to 12 hours was reported in HIV-infected individuals [3] [2]. DTG exposure, as measured by AUC, was dose proportional from 2mg to 100mg, while C_{max} was slightly less than dose proportional within single dose healthy volunteer studies [3]. Repeated dose studies found AUCτ and plasma concentrations at the end of the dosing interval (C_{trough}) to increase proportionally with doses in the 10mg to 50mg range, while C_{max} increased slightly less than proportionally. Steady state was reached within 5 days of daily dosing in healthy volunteer, multiple dose studies. AUC, C_{max} and C_{trough} accumulation ratios ranged from 1.24 to 1.42, 1.16 to 1.36, and 1.29 to 1.53, respectively, within the doses evaluated [3]. Similar accumulation ratios (1.23 to 1.43) were observed in studies of HIV-infected individuals [2]. After DTG 50mg orally daily, mean steady state DTG C_{trough} are ~25-fold higher than the protein adjusted 90% inhibitory concentration (IC_{90}) in healthy volunteers [3].

In vitro, DTG was found to be a substrate for the efflux transporters P-glycoprotein (P-gp) and human breast cancer resistance protein (BCRP). In human hepatocytes, UDP-glucuronosyltransferase 1A1 (UGT1A1) was the primary enzyme responsible for DTG metabolism while cytochrome P450 (CYP) 3A4 was a minor metabolizing pathway along with minimal contribution from UGT1A3 and UGT1A9. DTG is a substrate for UGT and CYP enzymes, but it does not appear to significantly induce or inhibit these enzymes. DTG also did not inhibit multidrug resistance associated protein 2 (MRP2), organic anion transporting polypeptide (OATP) 1B1/3, organic cation transporter (OCT) 1 or the following CYPs: 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 3A4, or 2B7. Notably, DTG inhibits OCT2 (IC_{50}=1.9 μM), which provides a basis for mild increases in serum creatinine seen in clinical use of DTG in the treatment of HIV infection. Collectively, the in vitro data demonstrate DTG's low potential for clinically meaningful DDIs [8].

The in vivo metabolism and excretion of DTG was studied in a mass balance study of healthy male volunteers. After a 20mg oral dose of DTG, 95.6% of the dose was recovered in feces (64%) and urine (31.6%). Unchanged DTG was the primary circulating entity in blood plasma, while an inactive glucuronide (18.9%) formed via UGT1A1 was the principal metabolite recovered in urine. Minor metabolic pathways were identified via oxidation by CYP3A4 (7.9%) as well as oxidative deflourination and glutathione substitution (1.8%) [9].

Population PK analysis in treatment-naïve HIV-infected persons was performed by combining data from three studies: a proof-of-concept study (ING111521) [2], a Phase 2b study(SPRING-1, ING112276, NCT00951015) [10], and a Phase 3 study (SPRING-2, NCT01227824) [11].

Population parameter estimates, derived from data of a combined 3357 plasma samples from 563 subjects, were: apparent oral clearance (CL/F) 0.901 L/hr; apparent volume of distribution (V_d/F) 17.41 L; absorption rate constant 2.24 hr-1; and absorption lag time 0.263 hr. Weight, smoking status, age and total bilirubin were predictors of CL/F although none of these covariates were found to be clinically significant. Race and ethnicity, hepatitis B virus (HBV) and hepatitis C virus (HCV) co-infection, creatinine clearance (CL_{CR}),

albumin, alanine aminotransferase and aspartate aminotransferase did not impact the PK of DTG within the studied population [12].

DTG benefits from having relatively low PK variability when compared with other INSTI agents. In a phase IIa study investigating DTG PK in HIV-infected individuals, variability was found to be low with coefficients of variation (CV) in the 25-50% range for C_{max}, C_{trough} and AUCτ [3, 2].

2.2 Elvitegravir

EVG (GS9137) is available in two FDC tablets, each given once daily in adults and containing EVG 150mg, the PK enhancer cobicistat (COBI), and emtricitabine (FTC). One product includes tenofovir disoproxil fumarate (TDF), while the other includes tenofovir alafenamide (TAF). Additionally, EVG 85mg is available for use once daily in individuals receiving a ritonavir (RTV) boosted PI-based ART. The manufacturer recommends all formulations be taken with a meal [13-15].

In single dose studies of unboosted EVG at doses of 100mg, 200mg, 400mg and 800mg given orally to healthy individuals mean (%CV) C_{max} concentrations of 108 (55), 160 (19), 264 (30) and 455 (33) ng/mL were reported with each respective dose. T_{max} occurred 1.3-2.5 hours post dose and AUC_{∞} was found to be less than dose proportional [16].

During the clinical development of EVG it was recognized that co-administration of RTV, a potent CYP3A4 inhibitor used for PK boosting of PIs, resulted in substantially higher EVG exposures. EVG AUCτ were ~20 fold higher when given with RTV 100mg compared with EVG alone [17]. COBI (GS-9350), a novel, potent and selective CYP3A4 inhibitor was subsequently studied for its ability to enhance EVG PK. COBI has advantages as an ARV PK enhancer because it inherently lacks any activity against HIV-1 and is better tolerated than RTV. The relative bioavailability of EVG boosted with COBI (EVG/COBI) was compared with EVG boosted with RTV 100 mg (EVG/RTV) in a study of healthy human subjects. Relative to EVG/RTV, the geometric least-squares means ratios [90% CI] for AUCτ, $C_{max,}$ and C_{trough} of EVG were 118 (110 to 126), 108 (100 to 116), and 110 (95.3 to 127), respectively, when EVG 150mg was combined with COBI 150mg[18]. Because EVG efficacy is closely linked with C_{trough} concentrations, a higher dose of 150mg COBI was subsequently investigated. With the higher dose of COBI, the EVG AUCτ were bioequivalent with EVG/RTV exposures, while both C_{max} and C_{trough} were significantly greater than those observed with EVG/RTV. The median (Q1,Q3) $t_{1/2}$ of EVG (with COBI) was 9.15 hr (7.70,12.4) compared with 3 hours when given alone [19, 18]. Collectively, these studies provided evidence for once daily dosing of EVG when given with COBI 150mg. The available EVG FDC products are both formulated with COBI 150mg [14, 15].

The oral bioavailability of EVG is significantly enhanced when it is given with a meal. A food interaction study of EVG, when given as EVG/COBI/FTC/TDF found mean AUC_{∞} and C_{max} increased by 34% and 24%, respectively, when given with food [20]. Follow up studies in healthy Japanese males confirmed these findings, showing decreases in AUC_{∞} of up to 50% when EVG is taken on an empty stomach as compared with either a standard breakfast or protein rich breakfast [21].

When EVG is given orally with food, C_{max} is reached in approximately 4 to 4.5 hours. Although EVG absorption is not changed with alterations in stomach pH, absorption is significantly decreased by co-administration with divalent and trivalent cations such as those found in multivitamins and antacids, which may be overcome by separating the dose times of the two products [22, 23]. EVG absorption does not appear to be significantly altered with changes in intestinal P-gp expression. Ex-vivo experiments demonstrate EVG is highly bound (>99%) to plasma proteins both albumin and alpha-1 acid glycoprotein with a preference for the former.

EVG's metabolism occurs primarily via CYP3A4 in the liver and intestine. Additional metabolism of EVG occurs via UGT1A1 and 1A3 to primary and secondary glucuronidated metabolites. The primary metabolites of EVG have substantially reduced activity against HIV-1 and do not play a major role in EVG efficacy [24]. Mass balance studies in healthy human subjects after a radiolabeled dose of EVG 50mg plus RTV 100mg demonstrated that ~95% of the oral dose was recovered in feces while ~6.7% of the dose was recovered in urine. Untransformed EVG was the primary circulating entity in plasma, accounting for ~93% of the circulating radioactivity.

2.3 Raltegravir

RAL (MK-0518) is available in three formulations: a 400mg film coated tablet, 25mg and 50mg chewable tablets, and 100mg granules for suspension [25]. For adults, the dose of RAL is 400mg twice daily, with or without food RAL PK are distinguished within the INSTI class as having markedly high inter- and intrapatient variability. Coefficients of variation of greater than 200% have been observed from repeated plasma concentrations within individual patients on stable RAL containing ART [26]. RAL is rapidly absorbed with a T_{max} of approximately 3 hours. Once absorbed, RAL is approximately 76 to 83% protein bound, mainly to albumin and not to alpha-1-acid glycoprotein [25, 27]. Secondary plasma concentration versus time peaks often occur with RAL, indicative of either enterohepatic recirculation or possibly delayed oral absorption. Similar to the other INSTIs, RAL PK is altered when given with divalent and trivalent cations, which may be overcome by dose-separation [28]. The absolute bioavailability of RAL has not been established due to the lack of a parenteral formulation, however, HIV-infected individuals have a 25-30% reduced bioavailability relative to healthy subjects [29]. Food appears to increase the amount of variability in the PK of RAL, although the mechanism is not completely clear. Studies of fasted and fed effects on RAL PK revealed significant changes in AUC. Compared with a low fat meal, a 46% decrease in AUC was observed when RAL is given in the fasted state. However, after moderate or high fat meals, AUCs were increased 13 to 212% [30]. Although substantial effects on PK are noted with meals, no significant differences have been noted in efficacy when RAL is given with or without food [25].

In healthy human subjects RAL T_{max} occurred between 1 to 2 hours post dose at steady state. Terminal half-life ($t_{1/2}$) was 7 to 12 hours after multiple doses of 100 mg to 800 mg twice daily. Steady state is reached in approximately two days of twice daily dosing and little accumulation occurs. C_{max} is slightly less than dose proportional with observed geometric means (GM) of 4.97μg/mL and 8.77μg/mL after multiple 400mg and 800mg

doses, respectively. The mean renal clearance of RAL in an adult male at 400mg twice daily at steady state is 3.63 L/hr. AUC_{∞} was found to be similar between adult male and female subjects [31], which is in contrast to combined data from HIV-infected individuals and healthy human subjects, where 65% higher RAL exposures were observed in females than males [29].

In a study of ART-naïve HIV-infected adults given 10 days of RAL twice daily doses of 100mg, 200mg, 400mg, or 600mg, C_{trough} increased with higher doses while C_{max} concentrations increased up to the 400mg dose; the 600mg dose had a slightly lower C_{max} than the 400mg dose (GM 2.0 vs 1.69 μg/mL) [32]. Because of the large PK variability noted in this study, the RAL $t_{1/2}$ could not be estimated. The authors did note the elimination profiles of RAL in this patient population appeared to mimic those seen in healthy volunteer studies where elimination occurred in a bi-exponential fashion with an initial $t_{1/2}$ of approximately 1 hour and a terminal $t_{1/2}$ of 7 to 12 hours [31-33].

A mass balance study performed in healthy human subjects after a single radiolabeled dose of 200 mg RAL indicated 51% of the dose was recovered in the feces while 32% was recovered in urine [34]. Both parent RAL and a glucuronide metabolite of RAL (M2) were present in the urine and represented 9% and 23% of the total RAL dose given. RAL was the only form of the dose recovered in the feces although it is believed RAL recovered from feces includes glucuronidated RAL, which was further hydrolyzed in bile before elimination. The major circulating entity in blood plasma was RAL that represented 70% of the total radioactivity. The remaining radioactivity could be attributed to RAL glucuronide metabolites. Mechanistic studies indicate that UGT1A1 is the major metabolic enzyme responsible for clearance of RAL in humans with minor contributions from UGT1A3 and UGT1A9. Genetic polymorphism in UGT1A1, such as the *28/28, result in lower clearance of RAL and associated higher plasma concentrations (~41% higher), however, this increase is not considered clinically significance [35].

The PK of RAL 800mg once daily were investigated in HIV-infected, treatment-naïve individuals. $AUC\tau$ was similar when RAL was given as 800 mg daily compared with 400mg twice daily [GM ratio (90% CI) 1.17 (0.8-1.72)]. However, C_{max} was ~4 fold higher [3.98 (2.58-6.16)] and C_{trough} was ~6 fold lower [0.15 (0.09-0.26)] with the daily dose. Once daily dosing of RAL was ultimately found to be virologically inferior to twice daily dosing (see section 4.3 for further discussion) [36, 37, 25].

3. Pharmacokinetics in Special Populations

3.1 Hepatic Impairment

Liver disease may influence ARV PK due to changes in liver blood flow or shunting, altered synthesis of plasma proteins, metabolism via CYP enzymes, and to a lesser extent, glucuronidation [38-40] . The FDA has formal guidance for evaluating the effect of hepatic impairment on drug PK [41]. Product labeling for all INSTIs recommends no dosage adjustment for patients with mild to moderate hepatic impairment (Child-Pugh A or B), but none of the labels recommend either the use of, or dosing information for, patients with severe hepatic impairment (Child-Pugh C) [25, 4, 13-15]. Unless indicated, moderate

hepatic impairment was defined as a Child-Pugh Score of 7-9 for all studies described in this section. Table 2 summarizes comparative studies of INSTI PK in patients with hepatic impairment.

3.1.1 Dolutegravir—The Phase II/III efficacy trials for DTG included 71 patients with HIV/HCV and 27 patients with HIV/HBV coinfection without cirrhosis. Population PK in the HCV coinfected patients indicated no clinically relevant effect on DTG PK, but the evaluation was limited for HIV/HBV coinfected patients due to sample size [42, 12]. One study evaluated DTG in HIV-seronegative participants with moderate hepatic impairment compared with healthy participants [43]. After a single dose of DTG 50 mg, no difference was observed in PK parameters for total DTG concentrations. Unbound DTG concentrations were 48-106% higher in the participants with hepatic impairment compared with healthy participants at two time points post-dose. Higher unbound fractions were correlated with a higher Child-Pugh score, lower albumin concentrations, and increased bilirubin concentrations (all $P<0.001$).

3.1.2 Elvitegravir—Population PK evaluations from the Phase II/III efficacy trials in HIV-infected patients with HBV or HCV coinfection identified no impact of coinfection without cirrhosis on EVG PK when combined with COBI (n=24) [44] or RTV (n=56) [13]. The impact of hepatic impairment on steady state exposure of EVG was assessed in HIV-seronegative volunteers receiving EVG/COBI/TDF/FTC [45]. EVG exposure was 35% higher in participants with moderate hepatic impairment. Overall COBI exposure, EVG free fraction, and COBI free fraction was similar between groups.

3.1.3 Raltegravir—The PK of RAL 400mg after a single dose was evaluated in HIV-seronegative volunteers with or without moderate hepatic insufficiency [46]. No clinically significant differences were observed in any of the RAL PK parameters. In another study in HIV-infected patients, no difference in RAL C_{trough} was observed in HIV/HCV co-infected persons without cirrhosis compared with HIV monoinfected persons after 4 weeks of RAL 400mg twice daily [47].

Unique to RAL, published data describe RAL exposure in HIV/HCV coinfected individuals with cirrhosis. HIV/HCV coinfected patients with and without advanced cirrhosis received RAL 400mg twice daily for five days in combination with their existing PI-based ART regimen [48]. The patients with advanced cirrhosis had 72% higher total RAL exposure and a notably higher C_{trough}. The authors reported no adverse events or RAL treatment-discontinuation during the study period.

RAL PK was also evaluated in HIV-infected persons with end stage liver disease (ESLD) and in patients post-liver transplantation [49]. Ten HIV-infected individuals with ESLD (MELD score ≥15) were switched from effective ART (HIV-RNA < 50 copies/mL) to RAL-based ART. After one month on therapy, total RAL exposure was higher in patients with ESLD (median area under the concentration-time curve during a 9 hour time interval (AUC_9): 33.5 mcg*hr/mL) than historical controls with normal hepatic function. In these 10 persons, RAL was well tolerated and all participants remained virologically suppressed on ART. Consistent with RAL PK in other populations, high variability was observed in total

and unbound RAL concentrations (AUC_9 interpatient CV%, 95% and 91%, respectively). The same study reports RAL PK in five HIV-infected persons who underwent liver transplantation and initiated RAL-based ART post-operatively. After one month, the total and unbound RAL exposures were similar to those observed in persons with ESLD.

3.2 Renal Impairment

Because none of the INSTIs are primarily eliminated by renal excretion, a significant impact on INSTI exposure is not expected in persons with renal impairment. Because renal impairment can influence hepatic metabolism and drug transporters, a renal impairment study is required for chronically administered drugs [50]. Table 2 summarizes the comparative studies conducted in severe renal impairment. Unless indicated, severe renal impairment was defined as an CL_{CR}<30 mL/min for all studies discussed in this section.

3.2.1 Dolutegravir—Unexpectedly, total plasma DTG exposure was 40% lower following a single dose of DTG 50mg in HIV-seronegative volunteers with severe renal impairment compared with matched controls [51]. Population PK modeling from the Phase III clinical trial did not find an association between the degree of mild or moderate renal impairment and total DTG exposure, and the reason for lower DTG concentrations during severe renal insufficiency is unclear [42]. Given these results, paired with the PD of DTG (see section 4.1 for further discussion), DTG may be given without dosage adjustment for INSTI-naïve persons with mild, moderate, or severe renal impairment. However, due to this observed decrease in DTG exposure, caution is warranted for those with severe renal impairment and known or suspected INSTI-resistance mutations [4]. DTG has not been evaluated in persons receiving renal replacement therapy, however due to high protein binding (>99%), it is not expected to be removed significantly [4, 51].

3.2.2 Elvitegravir—The EVG/COBI/TDF/FTC coformulated tablet is not recommended for initial therapy in persons with a CL_{CR} ≤70 ml/min due to an imbalance of patients on EVG/COBI/TDF/FTC developing renal adverse events in trials of clinical efficacy (9 vs. 3 persons on comparator regimens) [44]. In addition, EVG/COBI/TDF/FTC should be discontinued in persons whose CL_{CR} falls below 50 ml/min during therapy due to the coformulation with TDF, because TDF requires a dose reduction at CL_{CR} below this threshold. Given these restrictions, there are no PK data available for this formulation in persons with any degree of renal insufficiency [44].

EVG/COBI/TAF/FTC may be used for patients with moderate renal insufficiency (CL_{CR} 30-69 ml/min). The safety and efficacy of EVG/COBI/TAF/FTC was evaluated in 242 patients with stable, moderate renal insufficiency (median CL_{CR} 56 ml/min), and intensive PK was conducted in 30 participants between weeks 4-8 [52]. EVG and COBI exposure (AUC 27.1 and 9.92 mcg*h/mL, respectively) was similar to historical data [44], and was comparable between persons with CL_{CR} above or below 50 ml/min.

Minimal data are available for EVG when co-administered with RTV. Data on file with the company indicate that no clinically relevant differences in EVG PK were observed in participants with severe renal impairment when EVG is boosted with RTV [13] . Removal of

EVG by renal replacement therapy is expected to be low due to high EVG protein binding (98-99%).

3.2.3 Raltegravir—No differences in PK parameters were observed in one evaluation of single dose RAL 400mg in HIV-seronegative participants with severe renal insufficiency [46]. The extent of drug removed by renal replacement therapy is expected to be minimal due to high plasma protein binding, and this is confirmed in case reports to date [53, 54].

3.3 Pregnancy

Similar to non-pregnant adults, ART is recommended for all HIV-infected pregnant women by the U.S. Perinatal HIV treatment guidelines [55]. In addition to the known efficacy, safety, and tolerability of INSTIs in the treatment of non-pregnant adults, INSTIs may play an important role in managing HIV infection during late pregnancy due to the rapid viral decay observed with INSTI therapy. Based on accumulating clinical and PK data, RAL was included as a preferred option for ARV-naïve pregnant women in the 2015 update of the U.S. Perinatal HIV guidelines in 2015 [55].

Physiologic changes during pregnancy are known to impact the PK of some ARVs, resulting in dose adjustment recommendations for select ARVs during pregnancy in order to maintain optimal PK exposure. Specific metabolic pathways that may influence INSTI metabolism include induction of UGT1A1 and CYP3A4 during pregnancy [56, 57]. Therefore, guidelines recommend an assessment of ARV PK during pregnancy prior to routine clinical use [55]. Published data on INSTI PK in pregnant women are summarized in Table 3. In addition to maternal influences on ARV PK, fetal exposure to ARVs during the antepartum period is also important for the prevention of HIV transmission. McCormack and Best recently published a comprehensive review of ARV placental transfer [58]; therefore, only in vivo information published since this recent review is described herein.

3.3.1 Dolutegravir—Perinatal treatment guidelines do not recommend, or make specific dosing recommendations for DTG use in ARV-naïve pregnant women [55]. Since the guideline's last update, the first PK evaluation of DTG in 21 pregnant women was presented [59]. DTG exposure was lower during pregnancy compared with postpartum in the same group of women. Although DTG PK was variable, the authors concluded the postpartum PK was similar to historical data [4], suggesting the postpartum exposure was an appropriate control group. In the same study, the exposure to, and elimination of, DTG was assessed in 10 infants over 5-9 days after delivery. The median concentration 6.9 hours after delivery was 1.96 (IQR 1.42 – 2.48) μg/mL, demonstrating significant maternal:fetal transfer of DTG; the $t_{1/2}$ was 34.5 hours, in contrast to 14 hours reported in historical adult patients [4].

3.3.2 Elvitegravir—No systematic evaluation of EVG PK during pregnancy is available; therefore, it is not recommended by U.S. treatment guidelines [55]. The first case report of EVG use during pregnancy was recently published, administered as EVG/COBI/TDF/FTC once daily [60]. The woman's AUCτ of EVG and COBI were measured at 34 weeks gestational age and 6 weeks postpartum. EVG AUCτ was similar during and after pregnancy (data not provided); however, the patient's AUCτ postpartum was lower than historical data.

The C_{trough} after observed drug intake was 60% lower during pregnancy compared with postpartum, and was below the study defined target concentration 0.13 μg/mL [61]. Exposure to COBI (AUCτ) was 44% lower during pregnancy compared with postpartum, which was similar to historical data. At delivery, the EVG maternal and cord plasma concentrations of EVG were both 0.3 μg/mL; however, COBI was below the lower limit of quantitation (LLQ, 0.03 μg/mL) in both samples.

3.3.3 Raltegravir—Similar to non-pregnant adults, RAL exhibits high PK variability during pregnancy when given either with or without food, as observed in two studies of pregnant and postpartum women. In the first, RAL was given on an empty stomach to 42 women during pregnancy [62]. RAL exposure (AUCτ) was approximately 50% lower during both the 2nd and 3rd trimesters of pregnancy compared with postpartum. The authors selected a target C_{trough} concentration of 0.035 μg/mL based on the 10th percentile value in nonpregnant historical controls [25]; 69%, 80%, and 79% of participants were above this C_{trough} target during the 2nd trimester, 3rd trimester, and postpartum, respectively, with a notably high variability (<0.01 – 0.917 μg/mL).

More recently, RAL was given with a meal (650 kcal; 30 g fat) during the 3rd trimester (median gestational age 33 weeks) and postpartum (median 5 weeks) in 22 women [63]. Overall, RAL AUCτ and C_{trough} were 29% and 36% lower during pregnancy compared with postpartum; significant variability was observed in all PK parameters. Three participants (13.6%) failed to achieve virologic suppression before delivery. Of those, one person's C_{trough} during the 3rd trimester was below the desired threshold established by the authors [0.020 μg/mL, based on the comparison of RAL 800mg once daily to 400mg twice daily [64] (see section 4.3 for further discussion)]. No other patient fell below this threshold during or after pregnancy. Fetal exposure to RAL was evaluated in nine paired cord and maternal blood samples at delivery (median 10 hours post-last RAL dose). The ratio of RAL in cord/maternal blood was 1.21 (IQR 1.02-2.17), similar to prior reports [58].

Given the available data, high interpatient variability, and the virologic efficacy observed in these studies (92% [62] and 86% [63] virologic suppression at delivery), U.S. treatment guidelines currently recommended RAL 400mg twice daily without dose adjustment in ARV-naïve pregnant women [55].

3.4 Co-Infections—PK evidence in both healthy volunteers and individuals co-infected with HIV and tuberculosis (TB) have shown substantial reductions in RAL exposure when given in combination with rifampicin. Two studies have identified approximately 40% lower RAL AUC when combined with rifampicin, presumably from the UGT1A1 induction effect of rifampicin [66, 35]. PD outcomes when combining RAL and rifampicin have also been studied. In individuals co-infected with HIV/TB, the ANRS 12 180 (REFLATE TB) study investigated the use of RAL-based ART in individuals receiving drug-sensitive TB treatment including rifampicin. In an analysis of 153 individuals randomized to either RAL 400mg twice daily, RAL 800mg twice daily or EFV 600mg once daily, all in combination with TDF/3TC, RAL 400mg twice daily performed similarly to either dose-escalated RAL 800mg twice daily or EFV-based regimens: week 24 virologic suppression rates were RAL 400mg, 76%; RAL 800mg, 78%; and EFV, 63% [65]. Studies investigating the use of INSTI

based ART in HIV and hepatitis C virus (HCV) co-infected individuals are lacking. Drug-drug interaction data in healthy volunteers suggest minimal effects of newer HCV direct acting antivirals (DAA) on RAL and DTG PK [1]; however, effects of both disease state and treatment of HCV on INSTI PD remain to be investigated. PK and PD data are deficient for use of INSTI's in individuals co-infected with HIV and malaria. Based on known pathways of metabolism for the INSTI agents, DDIs between RAL and DTG are unlikely with antimalarial agents, while DDIs with EVG/c or EVG/r may be expected.

4. Pharmacodynamics

Table 4 provides a comparison of select PD characteristics for the three INSTIs.

4.1 Dolutegravir

The PD characteristics of DTG have been generated through studies when given as monotherapy, and in combination with NRTIs to treatment-naïve, and treatment-experienced persons with and without documented resistance to RAL and EVG. DTG monotherapy in doses of 2, 10 and 50mg once daily for 10 days was given to 35 INSTI-naïve HIV-infected persons not receiving ARV therapy [67]. Monotherapy was associated with a reduction in plasma HIV-RNA ranging from 1.5 $\log_{10}$ for 2mg, 2.03 for 10mg and 2.46 for 50mg. Seven of 10 recipients of 50mg once daily had plasma HIV-RNA < 50 copies/mL at day 11. Plasma HIV-RNA reductions ($\log_{10}$ change) were best predicted by DTG C_{trough} following a maximum effect (Emax) relationship. The estimated EC_{50} was 36 ng/mL; with a Hill Factor of 1, a concentration of 324 ng/mL was associated with 90% of Emax. The geometric mean C_{trough} observed for the three doses were 2mg, 40 ng/mL; 10mg, 190 ng/mL and 50mg, 830 ng/mL. These data indicate that DTG monotherapy at 50mg once daily produced concentrations well on the plateau portion of the exposure-response relationship. A subsequent dose ranging study evaluated DTG (10mg, 25mg or 50mg once daily) or efavirenz (EFV), in combination with TDF/FTC or ABC/3TC in ARV-naïve persons [10]. At week 48, the proportion of participants who had HIV-RNA < 50 copies/mL were 91%, 88% and 90% for the DTG 10mg, 25mg and 50mg groups, respectively, and 82% for those receiving EFV. The comparability of virologic responses across the three different DTG doses suggests that additive to synergistic anti-HIV responses were achieved when DTG was combined with other ARVs.

DTG 50mg once daily was compared with twice-daily RAL in 822 treatment-naïve adults [11]. Both were given with investigator selected ABC/3TC or TDF/FTC. At the 48-week primary endpoint, 88% of DTG recipients and 85% of RAL recipients had HIV-RNA < 50 copies/mL. At 96 weeks, 81% of DTG compared with 76% of RAL recipients had HIV-RNA < 50 copies/mL. Virologic non-response occurred in 5% of those randomized to DTG and in 10% of those to RAL. In a similar design, once daily DTG (50mg) was compared with once daily DRV/RTV, each given with investigator selected ABC/3TC or TDF/FTC, in 484 ARV-naïve persons [68]. At the week 48 primary endpoint, 90% of DTG recipients and 83% of DRV/RTV recipients had HIV-RNA < 50 copies/mL. DTG was statistically superior (p=0.025) to DRV/RTV. Drug-limiting adverse events were less frequent in the DTG

recipients: 2% of DTG recipients and 4% of DRV/RTV recipients discontinued therapy for adverse events.

The safety and efficacy of DTG (n=354) was compared with RAL (n=361) in INSTI-naïve but ARV-experienced persons with at least two-class resistance [69]. A total of 715 persons were enrolled. At week 48, 71% of DTG recipients vs. 64% of RAL recipients had plasma HIV-RNA < 50 copies/mL (p=0.03). Additionally, significantly fewer DTG recipients had virologic failure with treatment-emergent INSTI resistance (4 vs. 17, p=0.003). In this study, the geometric mean DTG C_{trough} across 335 subjects was 850 ng/mL [42]. Those who had DTG C_{trough} in the lowest quartile (median C_{trough}, 260 ng/mL) had the lowest virologic response rates (HIV-RNA <50 copies/mL at week 24): 76% in lowest quartile vs. 81-87% across the 2nd through 4th quartiles.

Subjects with DTG C_{trough} in the lowest quartile were more likely to have concentrations below the lower limit of quantification (LLQ) likely reflecting poor adherence and/or receiving CYP3A inducers; the median DTG C_{trough} in the lowest quartile is consistent with a 10mg once daily dose.

DTG PK were shown to be less than dose proportional in healthy human volunteers when increasing from 50mg to 100mg daily, for this reason the dose of 50mg twice daily was investigated in an attempt to increase DTG exposures in patients with prior INSTI resistance [70]. 183 treatment-experienced persons with documented resistance to RAL and EVG were enrolled in an evaluation of DTG at 50mg twice daily, first in a functional 7 day monotherapy phase followed by a second phase with optimized ARV background [70]. At week 24, 69% of subjects had plasma HIV-RNA <50 copies/mL. The overall geometric mean DTG C_{trough} was 2330 ng/mL, and was similar between those who achieved HIV-RNA <50 copies/mL and those who did not (2420 ng/mL vs. 2120 ng/mL). A clear relationship was observed between the DTG inhibitory quotient (IQ; the ratio of DTG C_{trough} to baseline susceptibility of the virus to DTG, or IC_{50}) and the percent of subjects at week 24 with HIV-RNA < 50 copies/mL [42]. However, this relationship was strongly driven by differences in IC_{50}, which ranged from 5110 ng/mL in the first quartile to 710 μg/mL in the 4th quartile, compared with DTG C_{trough} that ranged from 1840 to 3860 ng/mL in the 1st to 4th quartiles, respectively [42].

4.2 Elvitegravir

Forty HIV-infected, ARV-naïve and experienced persons not currently on therapy received varying doses of EVG with and without RTV as monotherapy to evaluate PKPD [71]. EVG concentrations were highest when combined with RTV. EVG C_{trough} were strongly associated with anti-HIV effect (log_{10} change in plasma HIV-RNA), where Emax was a 2.32 log_{10} reduction in HIV-RNA, EC_{50} was 14 ng/mL and EC_{90} was 126 ng/mL. Subsequently, 278 HIV-infected persons with HIV-RNA ≥1000 copies/mL and ≥1 PI resistance mutation were randomized to EVG or to a comparator RTV-boosted PI [72]. Three different doses of EVG, all given once daily with 100 mg of RTV were evaluated: 20mg, 50mg and 125mg. The 20 mg EVG arm was stopped at week 8 by a data safety monitoring board because that arm was associated with a higher rate of virologic failure. For the primary endpoint (change in HIV-RNA from baseline to week 24), the two remaining EVG arms (50mg and 125mg)

were non-inferior to the comparator PI arm (−1.44 and −1.66 log_{10} reduction in HIV-RNA vs. −1.19 log_{10} reduction in HIV-RNA). Mean EVG C_{trough} in the three arms were: 20mg, 67 ng/mL; 50mg, 211 ng/mL; and 125mg, 263 ng/mL [44]. C_{trough} with the 20 mg EVG dose was less than the protein binding adjusted IC_{95} of 45 ng/mL, providing a reason for why this dose was subtherapeutic and a rationale to maintain concentrations above this threshold. The EVG 125mg with RTV 100mg arm achieved a statistically greater decrease in HIV-RNA at week 24 compared with the PI arm, which formed the basis for the selection of this dose (and level of systemic exposure) for evaluation in phase III studies.

Two phase III, randomized, double-blind trials compared the efficacy EVG with EFV or ATV/RTV, all given with TDF/FTC [61, 73]. EVG 150mg was given once daily with COBI 150mg. This dose combination (in a FDC with TDF and FTC) was shown to achieve similar concentrations to EVG 125mg with RTV 100mg. Combined these two studies enrolled 1408 treatment-naïve adults. In both studies, for the primary outcome of proportion of subjects with HIV-RNA <50 copies/mL, EVG/COBI was non-inferior to EFV (87.6% vs. 84.1%) and to ATV/RTV (89.5% vs. 86.8%). PD relationships were investigated in an analysis performed by the FDA, where patients were separated into deciles according to EVG C_{trough} and the percentage of subjects with HIV-RNA <50 copies/mL was compared [44]. The median C_{trough} in the lowest decile was 156 ng/mL and the virologic success rate was 87%. Virologic success in deciles with higher trough concentrations (234–916 ng/mL) ranged between 84–97%. This analysis indicates that virologic success was flat across the range of EVG trough concentrations achieved with the 150mg dose. A trend for different rates of virologic success was observed in participants with baseline viral load <100,000 copies/mL (92%) compared with those who had >500,000 copies/mL (79%). Collectively, these phase III trials confirm the efficacy of the 150mg once daily dose of EVG/COBI predicted by the exposure-response relationship.

4.3 Raltegravir

RAL is known to exhibit extremely high intra- and interpatient variability in plasma concentrations. For example, C_{trough} in participants taking 400 mg twice daily ranged from 5.3 to 4067 ng/mL [74, 75]. This variability has clouded the ability to elucidate clear, concentration-effect relationships. A 10-day monotherapy trial in ARV-naïve persons is illustrative. 28 individuals received RAL doses of 100, 200, 400 and 600mg twice daily for 10 days [76]. Median AUC values were 2.3, 5.0, 8.2 and 7.2 μg*h/mL for the 100, 200, 400 and 600mg doses, respectively; median C_{trough} were: 22, 65, 72 and 90 ng/mL, respectively. The ranges for C_{trough} at the 400mg twice-daily dose were 29 to 118 ng/mL, completely encompassing the median C_{trough} range across the dose range of 100 to 600mg twice daily. This interpatient variability in PK concentrations contributes to variability in virologic responses. In a phase II, randomized dose ranging study of 200mg, 400mg and 600mg of RAL twice daily, with an optimized background regimen in treatment-experienced persons, the proportions of participants with HIV-RNA <50 copies/mL at week 24 were 63%, 48%, and 56%, respectively [77]. These data illustrate that high interpatient PK variability, which contributes to the lack of dose proportionality and overlapping concentrations across a range of doses, obscures a quantitative understanding of a concentration-response relationship. The flatness of the response relationship was also observed in the large, pivotal, placebo-

controlled phase III trial of RAL with optimized background therapy in persons in whom ARV therapy had failed with triple class drug resistance [75]. An exposure-response analysis conducted by the FDA found that virologic success (HIV-RNA <400 copies/mL) was similar, 77%, for patients with the lower median C_{trough} of 33 ng/mL and the higher median C_{trough} of 483 ng/mL [74].

The existence of an exposure-response relationship for RAL was clearly shown in a trial of once daily compared with twice-daily RAL dosing. 775 ARV-naïve persons were randomized to receive RAL 800mg once daily or 400mg twice daily, both with TDF/FTC [36]. A significantly lower proportion of participants who received RAL once daily had HIV-RNA <50 copies/mL at week 48 than did those who received 400mg twice-daily (83% vs. 89%). An exposure-response analysis found trough RAL concentrations with once daily dosing correlated with virologic response [64]. Geometric mean RAL C_{trough} was 37 ng/mL for once daily dosing compared with 169 ng/mL for twice-daily dosing. A greater proportion of participants who received once daily had trough concentrations below 14 ng/mL (protein binding adjusted IC_{95}): 42% vs. 14%. Participants who had RAL trough concentrations in the lowest quartile (median C_{trough} 12.5 ng/mL) had a clear fall off in virologic response, with <80% achieving HIV-RNA <50 copies/mL. These data clearly indicate an underlying exposure-response relationship exists for RAL, and provide strong support that trough concentrations should be above the protein binding adjusted IC_{95} to achieve the optimal response. Additionally, they are illustrative that the shape of the concentration curve (C_{max} to C_{min}) can affect PD.

5. Interpretations and Conclusions

The most distinguishing PK characteristic of the INSTIs is the difference in hepatic metabolism: EVG is primarily metabolized by CYP3A4, while DTG and RAL by UGT1A1. EVG must be given with a PK enhancer (booster), usually COBI because of the availability of coformulations. As such, EVG/COBI has a higher likelihood to be a perpetrator of drug-drug interactions. The extensive clinical PK data derived from using RTV as a PK enhancer with PIs, however, largely applies to management strategies for COBI. DTG (in ARV-naïve persons) and EVG/COBI are administered once daily, while RAL requires twice-daily administration. RAL is also distinguished by a substantially higher degree of intra- and interpatient PK variability. There are differences in the PK characteristics for all three INSTIs between healthy volunteers and HIV-infected individuals, and this illustrates the importance of developing clinical PKPD data in the intended population, as discussed elsewhere [78]. Given its longer duration of clinical use, the most evidence supports standard dosing of RAL in patients with hepatic impairment (moderate through advanced cirrhosis), severe renal impairment, and during pregnancy. DTG and EVG may be used at standard doses in patients with moderate hepatic impairment. In patients with severe renal dysfunction, standard dose DTG is recommended for patients without INSTI resistance; however, DTG is not recommended for patients with INSTI resistance due to unexpectedly lower concentrations in patients with severe renal dysfunction. EVG/COBI is not recommended for patients with severe renal dysfunction, but EVG/RTV may be used without dose adjustment. Additional data are required before DTG or EVG are recommended for use in pregnant women.

In vitro $IC_{50, 90, 95}$ values indicate the hierarchy of potency (most potent = lowest IC) is RAL > EVG > DTG. The EC values derived from studies in HIV-infected persons, and only available for EVG and DTG, are consistent with predictions based on in vitro potency that a lower IC value should translate into a lower EC value: the $EC_{50, 90}$ for DTG > EVG. The IQ is the ratio of drug concentration in any biologic fluid (e.g., plasma, CSF) divided by an in vitro inhibitory concentration, thus integrating in vivo PK and in vitro PD (i.e. how much drug you have to how much drug you need) [79]. As discussed by the FDA, the IQ is considered important in ARV drug development because a high IQ indicates sufficient drug can be achieved, which may minimize the emergence of viral resistance, and can inform the selection of doses for phase III and IV studies, as well as for different patient populations [80]. At approved doses, the hierarchy of IQ values is DTG > EVG > RAL, and there are supporting correlates from clinical trials. DTG was shown non-inferior to RAL in ARV-naïve persons and superior to RAL in ARV-experienced but INSTI-naïve [11, 69]. These findings are consistent with DTG having a higher IQ value than RAL (17 vs. 8). For EVG, a dose of 20mg once daily (with RTV) was inferior to doses of 50 and 125mg [72]. The IQ of a 20mg dose would be approximately 1.5 compared with an IQ for the 150mg dose of 10. Once daily dosing of 800mg of RAL was shown to be inferior to 400mg twice daily [36]. The IQ for the once daily regimen (C_{trough} divided by IC_{95}) would be 2.5 compared with a value of 8 for twice daily.

In clinical studies in ARV-naïve persons, at 48-week endpoints, RAL and EVG demonstrated non-inferiority compared with EFV: 86.1% of RAL recipients vs. 81.9% of EFV achieved HIV-RNA < 50 copies/mL; 87.6% of EVG vs. 84.1% of EFV achieved < 50 copies/mL of HIV-RNA [81, 73]. DTG was shown to be statistically superior to EFV in ARV-naïve subjects at 48-weeks: 88% of DTG compared with 81% of EFV recipients had HIV-RNA < 50 copies/mL [82]. DTG was also shown to be statistically superior to DRV/RTV in ARV-naïve subjects at 48-weeks, and in the only head-to-head trial of two INSTIs in ARV-naïve persons, DTG was non-inferior to RAL (88% of DTG compared with 85% of RAL recipients had HIV-RNA at 48 weeks < 50 copies/mL) [83, 68].

Current treatment guidelines in the United States presently recommend INSTI-based regimens as among those preferred for the ARV-naïve individual [1]. There is evidence to support that the use of INSTIs has improved viral suppression rates in the United States. A study of 31,055 persons living with HIV and receiving care at eight clinical sites across the United States examined rates of viral suppression from 1997 to 2015 [84]. The percent of these individuals with undetectable viral load increased from 30% in 1997 to 87% in 2014. In multivariable analyses of participants on ART after 2010, older age, white race, male sex, better adherence, and INSTI use was associated with an undetectable viral load. These findings are concordant with the clinical PKPD profile of these agents: convenient dosing, availability in coformulations with other ARVs, high IQ values conferring high potency and rapid drops in viral load, safe, and well tolerated.

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Key Points

- Integrase strand transfer inhibitors (INSTIs) represent the newest class of antiretrovirals to treat HIV infection.
- The three currently approved INSTIs have unique pharmacokinetic and pharmacodynamic profiles, providing advantages for certain individuals and in special population such as those with renal and hepatic impairment or who are pregnant.
- INSTIs achieve high inhibitory quotients in vivo, rapidly decrease viral load, and are safe and well tolerated.
- There are emerging data to support that the use of INSTIs has improved viral suppression rates in the United States.

Table 1

Pharmacokinetic characteristics of Integrase Strand Transfer Inhibitors in healthy volunteers and HIV-infected persons

	Dolutegravir 50 mg Daily		Elvitegravir 150 mg Daily		Raltegravir 400 mg Twice Daily	
	Healthy	HIV-infected	Healthy[a]	HIV-infected[b]	Healthy[c]	HIV-infected
C_{max} (μg/mL)	6.16 (15)	3.34 (16)	2.66 (27.6)	1.7 + 0.4[e]	Fasted 1.20 (0.8-1.81)[g] Low 0.58 (0.39-0.88)[g] Mod 1.27 (0.84-1.91)[g] High 2.36 (1.57-3.56)[g]	1.502 (135)
C_{min} (μg/mL)	1.64 (25)	0.83 (26)	0.490 (52.9)	0.45 ±0.26[e]	Fasted 0.05 (0.03-0.08)[g] Low 0.42 (0.03-0.07)[g] Mod 0.08 (0.05-0.13)[g] High 0.20 (0.12-0.33)[g]	0.114 (167)
T_{max} (hr)	1.0 (0.5 to 2.0)[f]	2.0 (0.97 to 4.0)[f]	5 (5.0,5.5)[d]	3 to 4	1.0	1.8 (0.5 to 4.0)[f]
$t_{1/2}$ (hr)	13 to 14	11 to 12	11.0 (8.87,13.0)[d]	8.62 (6.1 to 10.9)[f]	Distribution 1.0 Elimination 11.2	9
AUCx iag*hr/mL	76.8 (19)	43.4 (20)	27.0 (29.4)	23.0+7.5[e]	Fasted 4.44 (3.20-6.22)[g] Low 2.39 (1.72-3.33)[g] Mod 5.02 (3.60-7.02)[g] High 9.42 (6.76-13.15)[g]	5.84 (99)
Protein Binding	>99% to both albumin and alpha-1-acid glycoprotein		99.4% albumin >> alpha-1-acid glycoprotein		76% to 83% to Albumin	

Abbreviations: C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; T_{max}, time to reach C_{max}; $t_{1/2}$, elimination half life; AUCx, area under the concentration-time curve over the dosing interval Data are presented as geometric mean (CV) unless otherwise noted.

[a] healthy volunteers receiving EVG 150mg plus 150mg COBI.

[b] HIV-infected data is EVG 150mg plus COBI 150 mg.

[c] Data are presented for fasted, low, moderate and high fat meals.

[d] Data are presented as median (Q1,Q3).

[e] Data are presented as mean (SD)

[f] Data are presented as median (range).

[g] Data are presented as GM (90% CI)

Table 2

Summary of Integrase Strand Transfer Inhibitor pharmacokinetic studies in participants with hepatic impairment or severe renal impairment (estimated creatinine clearance <30 mL/min)

Antiretroviral	Study design	Participants	C_{max} Ratio Impairment vs. Healthy	C_{min} Ratio Impairment vs. Healthy	AUC_{χ} Ratio Impairment vs. Healthy
Moderate hepatic impairment					
Dolutegravir[a] [43]	Parallel-group, single dose, PK evaluation over 72 hours HIV seronegative volunteers	Moderate hepatic impairment:[b] n=8 Matched, healthy volunteers: n=8	1.02 (0.754, 1.37)	na	1.05 (0.745, 1.49)
Elvitegravir[c] [45]	Parallel-group, steady state, PK evaluation over 96 hours HIV seronegative volunteers EVG given as EVG/c/TDF/FTC given daily for 10 days	Moderate hepatic impairment:[b] n=10 Matched, healthy volunteers: n=10	EVG: 1.41 (1.09, 1.83) COBI: 0.861 (0.654, 1.13)	EVG: 1.80 (1.11, 2.91) COBI: 2.08 (1.17, 3.68)	EVG: 1.35 (1.03, 1.77) COBI: 0.997 (0.76, 1.31)
Raltegravir[c] [46]	Parallel-group, single dose, PK evaluation over 96 hours HIV seronegative volunteers	Moderate hepatic impairment:[b] n=8 Matched, healthy volunteers: n=8	0.63 (0.23, 1.70)	1.26 (0.65, 2.43)	0.86 (0.41, 1.77)
Raltegravir[d] [47]	Parallel-group, steady state, C_{trough} evaluation HIV-infected patients with and without HCV co-infection	HIV/HCV co-infection:[e] n=13 HIV-infected: n=16	na	1.16 (0.56, 1.39)	na
Raltegravir[c] [48]	Parallel-group, steady state, PK evaluation over a 12-hour dosing interval HIV-infected patients with HCV co-infection	HIV/HCV co-infection with advanced cirrhosis:[f] n=5 HIV/HCV co-infection without cirrhosis:[g] n=5	1.15 (0.55, 2.43)	6.58 (2.92, 14.85)	1.72 (1.02, 2.92)
Severe renal impairment					
Dolutegravir[a] [51]	Parallel-group, single dose, PK evaluation over 72 hours HIV-seronegative volunteers	CL_{CR}l<30ml/min: n=8 Healthy volunteers: n=8	0.774 (0.532, 1.13)	0.566 (0.352, 0.908)	0.6 (0.37, 0.975)
Raltegravir[c] [46]	Parallel-group, single dose, PK evaluation over 96 hours HIV-seronegative volunteers	CL_{CR}<30ml/min: n=10 Healthy volunteers: n=10	0.68 (0.35, 1.32)	1.28 (0.79, 2,06)	0.85 (0.49, 1.49)

Abbreviations: ART, antiretroviral therapy; AUC∞, area under the concentration time curve; C_{max} maximum concentration observed; C_{min} minimum concentration observed; COBI, cobicistat; CL_{CR}, estimated creatinine clearance; DTG, dolutegravir; EVG, elvitegravir; EVG/c/TDF/FTC, elvitegravir/cobicistat/tenofovir disoproxil fumarate/emtricitabine co-formulated tablet; HCV, hepatitis C virus; HIV, human immunodeficiency virus; na, not available.

[a] Data presented as geometric least squares mean ratio (90% confidence interval).

[b] Moderate hepatic impairment was defined as Child-Pugh score 7-9.

[c] Data presented as geometric mean ratio (90% confidence interval).

[d] Data presented as geometric mean ratio (95% confidence interval).

[e] Patients with mild or moderate hepatic impairment, all without cirrhosis.

[f] Advanced cirrhosis based on biopsy, Metavir score F4.

[g]Non-cirrhosis based on biopsy, Metavir score F0-F1.

Table 3

Summary of Integrase Strand Transfer Inhibitor pharmacokinetic studies during pregnancy.

Antiretroviral	Study design	Participants	AUCt (μg*hr/mL)	Cmin (μg/mL)	Comments
Dolutegravir[a] [59]	Longitudinal, steady state, intensive PK sampling over 24 hours	2nd trimester: n=9	58.4 (47.6 – 64.5)	0.86 (0.78 – 1.05)	No statistically significant differences were observed. Individual AUCx above the 10th percentile of non-pregnant adults (37.5 mcg/mL): • 2nd trimester: 6 of 9 participants • 3rd trimester: 12 of 15 participants • Postpartum: 8 of 9 participants
		3rd trimester: n=15	48.7 (40.3 – 57.6)	1.03 (0.87 – 1.24)	
		Postpartum: n=10	71.1 58.0 – 83.1)	0.70 (0.60 – 0.86)	
Raltegravir[b] [62]	Longitudinal, steady state, intensive PK sampling over 12 hours after an observed dose while fasting	2nd trimester: n=16	6.6 (2.1 – 18.5)	0.047 (<0.01 – 0.162)	AUCx was statistically lower in both the 2nd and 3rd trimester compared to postpartum. C_{min} was statistically lower in the 2nd trimester compared to postpartum. No differences were observed between 2nd and 3rd trimesters.
		3rd trimester: n=41	5.4 (1.4 – 35.4)	0.057 (<0.01 – 0.607)	
		Postpartum: n=38	11.6 (1.6 – 39.9)	0.0474 (<0.01 – 0.917)	
Raltegravir[c] [63]	Longitudinal, steady state, intensive PK sampling over 12 hours after an observed dose with breakfast	3rd trimester: n=21	5.0 (3.56, 7.01)	0.077 (0.043, 0.137)	90% confidence intervals of the geometric mean ratios (3rd trimester:postpartum) of all PK parameters included 1, except AUCτ [0.71 (0.53 - 0.96)]. 11 of 17 patients (65%) with paired visits had lower exposure during the 3rd trimester vs. postpartum.
		Postpartum: n=18	7.11 (4.91, 10.31)	0.120 (0.074, 0.193)	

Abbreviations: AUCx, area under the concentration time curve for the dosing interval; C_{min}, minimum concentration observed; PK, pharmacokinetic.

[a] Data are presented as geometric mean (interquartile range).

[b] Data are presented as median (range).

[c] Data are presented as geometric mean (95% confidence interval).

Table 4

Pharmacodynamic Characteristics of Integrase Strand Transfer Inhibitors

	Dolutegravir	**Elvitegravir**	**Raltegravir**
IC_{50} (ng/mL) IC_{90} (ng/mL) IC_{95} (ng/mL)	16 64 na	7.2 na 44.9	na na 14.7
EC_{50} (ng/mL) EC_{90} (ng/mL)	36 324	14 126	na na
IQ (C_{trough} / $IC_{90\ or\ 95}$)	17	10	8

Abbreviations: C_{trough}, measured concentration at the end of the dosing interval; IC, protein-binding adjusted concentration inhibiting viral replication by 50, 90 or 95% in vitro; EC, concentration producing 50 or 90% effect (reduction of HIV-RNA) in vivo; IQ, inhibitory quotient; na, not available.