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Comparative Clinical Pharmacokinetics and Pharmacodynamics of HIV-1 Integrase Strand Transfer Inhibitors: An Updated Review

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Abstract

Bictegravir (BIC), cabotegravir (CAB), 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. CAB, approved for use in Canada but not yet by the United States (US) Food and Drug Administration (FDA), is formulated in both oral and intramuscular formulations; the latter of which has shown efficacy as a long-acting, extended release formulation. CAB, 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. BIC metabolism has similar contributions from both CYP3A4 and UGT1A1. BIC, DTG and RAL are recommended components of initial regimens for most people with HIV in 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 persons with hepatic impairment, renal dysfunction, pregnancy and co-infections.

1.0 Introduction

There are an estimated 36 million people living with 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. Two and three drug combinations consisting of antiretrovirals (ARVs) targeting the virus in two different steps in the viral life cycle are the current standard of care [1]. An HIV integrase strand transfer inhibitor (INSTI) co-administered with either one or

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Conflicts of Interest

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two nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) are currently part of all recommended initial regimens for most ART-naïve patients in the US Department of Health and Human Services Adult and Adolescent HIV treatment guidelines [1]. Additionally, the World Health Organization currently list two INSTI's, raltegravir (RAL) and dolutegravir (DTG) as first line ART regimens [2].

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, RAL, was US Food and Drug Administration (FDA) approved in 2007, followed by elvitegravir (EVG) in 2012, DTG in 2013 and bictegravir (BIC) in 2018. Cabotegravir (CAB), currently formulated in both oral and intramuscular products, has completed phase 3 clinical trial evaluation, is approved in Canada and is undergoing US FDA review. 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 and compares the clinical pharmacokinetics (PK) and pharmacodynamics (PD) of the four FDA-approved INSTI agents, along with CAB, for the treatment of HIV in adult patients. The summary includes PK considerations for hepatic impairment, renal dysfunction, pregnancy and co-infections. We previously reviewed the clinical PK and PD of RAL, EVG and DTG in this journal in 2017 [3] . In this paper we present the PK and PD of the newest INSTIs, BIC and CAB, include new information for RAL, EVG and DTG, and retain essential information on RAL, EVG and DTG from the 2017 review.

2.0 Pharmacokinetics of INSTIs

The PK parameters of the HIV INSTIs in healthy subjects and people living with HIV (PLWH) are summarized in Table 1.

2.1 Bictegravir

BIC is solely available in a fixed dose combination (FDC) tablet containing 50mg BIC, 200mg emtricitabine (FTC) and 25mg of tenofovir alafenamide (TAF). The once-daily BIC FDC is indicated for ART treatment-naïve adults as well as a replacement regimen for PLWH who are currently virologically suppressed for a minimum of three months on alternative ART [4].

BIC may be given without regard to food. After an oral dose of the FDC, BIC is readily absorbed with oral bioavailability >70% [4, 5]. High fat meals have been shown to increase AUC and Cmax of BIC by ~24% and 13% respectively[4] . Consistent with other INSTIs, BIC absorption may be altered by coadministration with cation containing antacids and administration of BIC should occur at least two hours prior to cation administration. BIC primarily circulates as parent drug, with BIC accounting for 68% of plasma radioactivity in a mass balance study [5].

Metabolism is the major route of clearance for BIC with similar contributions from CYP3A4 and UGT1A1 [5]. Mass balance studies indicate <1% of the dose is collected in urine as unchanged drug, while 35% is collected as glucuronide metabolite and ~60% can be found in feces as oxidative metabolites. With respect to drug transporters, BIC is an inhibitor of OCT2 and MATE1; at clinically relevant concentrations BIC does not inhibit OAT1B1, OAT1B3, OCT1, BSEP, and renal transporters OAT1 and OAT3. Potent induction of both CYP3A4 and UGT1A1 leads to clinically significant reduced BIC exposures, as evidenced when BIC is coadministered with rifampin leading to a 75% reduction in BIC AUC [5].

In healthy volunteer studies terminal elimination half-lives ($t_{1/2}$) were found to be 16 to 18 hours, consistent with the half-life in PLWH of 17 hours [6] .The PK of BIC in PLWH was evaluated in a 10-day monotherapy phase IIb study of BIC. Doses of 5, 25, 50 and 100mg were evaluated and BIC exposure was approximately dose proportional from 5–50mg [6]. At steady state on day 10, the 50mg dose of BIC produced troughs values (C_{tau} 2053ng/mL) that were >10 fold above the 95% inhibitory concentration (IC_{95}) of BIC. Clearance of BIC on day 10 was 0.62 L/hr [6].

2.2 Cabotegravir

CAB has been studied in two large phase 3 clinical trials as switch therapy in both treatment-naïve and treatment-experienced individuals. In each, CAB was given as a once monthly intramuscular injection paired with intramuscular long-acting rilpivirine (RPV) [7, 8] . For each of the studies, an oral CAB 30mg tablet was used as lead in therapy, together with oral RPV, prior to switching to the LA-CAB regimens. A 30mg dose was ultimately selected for clinical development and a 10-day PK study in PLWH observed a slightly lower C_{max} than healthy volunteers [6.37ug/mL (23%CV)], with a mean t_{max} and C_{min} of 2.5 hours and 2.85ug/mL (35%CV) respectively[9] . At steady state the concentrations observed at the end of the dosing interval are more than 20-fold greater than the protein adjusted IC_{90} of 0.166ug/mL for CAB. High fat meals minimally increase exposures to oral CAB, as a non-clinically-significant increase of 14% was observed in both AUC and C_{max} [10] .

A mass balance study of oral CAB showed that after absorption approximately 59% of the dose was recovered in feces, largely as CAB, and ~27% was recovered in urine, largely as glucuronidated M1 metabolite [11] . The mass balance study showed that only CAB was detected in plasma, while no untransformed CAB was detected in urine. Human liver microsome studies have shown that UGT1A1 and UGT1A9 are the two primary enzymes responsible for CAB metabolism [11] . Unlike DTG, which shares close structural similarity to CAB, CAB does not appear to be a substrate for CYP enzymes. This difference in metabolism has also been confirmed in DDI studies of DTG and CAB, together with etravirine, a known inducer of both UGT and CYP enzymes. CAB exposures are largely unaffected by etravirine coadministration, where-as DTG exposures are reduced by ~71% [12, 13] .

The PK of CAB when given IM have been described by Spreen et al. After a single IM dose of 400mg in healthy subjects, a median t_{max} of 69 days (range 2–213) was observed. The geometric mean (CV) C_{max} was 0.7ug/mL (55.2) while the concentration observed at 4-weeks post injection was 0.4ug/mL (54.6) [14] . CL/F was 0.1 L/hr (29.8) with a $t_{1/2}$

reflective of absorption and elimination, of 38.3 days (57.3) [14] . Splitting the 400mg dose into 2 × 200mg IM injections resulted in an increased C_{max} of 1.4ug/mL (53.4), a more than two-fold increase in AUC from 0 to 4 weeks (644 vs 290 ug*hr/mL) and an increased week 4 concentration of 1.1ug/mL (49.3) [14] Notably, total CAB exposures extrapolated to time infinity were similar between the 400mg × 1 and 200mg × 2 doses, suggesting that overall amount of CAB absorption is similar between the two dosing strategies and rate of absorption is faster with the split dose of 200mg × 2. A subsequent study by Spreen looked at the PK of LA-CAB when given as repeat doses together with a long-acting nanosuspension of RPV in healthy adults. All subjects received an 800mg loading dose of IM LA-CAB, followed by three monthly doses of either 200mg or 400mg IM. CAB plasma PK parameters for the 400mg IM dose are summarized in table 1. [15]

2.3 Dolutegravir

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

DTG (S/GSK1349572) PK after single and multiple doses ranging from 2mg to 100mg in healthy volunteers have been determined. Low, moderate and high fat meals increased DTG AUC 33%, 41%, and 66%, respectively, although current manufacturer prescribing information indicates DTG may be taken without regard to meals [16, 17]. Consistent with other INSTIs, DTG absorption is impaired by coadministration with divalent or trivalent cations, which may be overcome by dose separation. Bioequivalence of a FDC tablet compared with single tablet DTG 50mg and combination ABC/3TC 600mg/300mg has been demonstrated [18].

DTG exhibits bi-exponential elimination with a $t_{1/2}$ ranging from 13 to 15 hours in healthy volunteers, while a $t_{1/2}$ of 11 to 12 hours was reported in PLWH [19] [20]. 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 [19]. 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 [19]. Similar accumulation ratios (1.23 to 1.43) were observed in studies of PLWH [20]. After DTG 50mg orally daily, mean steady state DTG C_{trough} are ~25-fold higher than the protein adjusted IC_{90} in healthy volunteers [19].

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, UGT1A1 was primarily responsible for DTG metabolism while CYP3A4 was a minor metabolizing pathway along with minimal contribution from UGT1A3 and UGT1A9. DTG does not appear to significantly induce or inhibit UGT1A1 or CYP3A4 . 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 with clinical use of DTG for treatment of HIV infection. Collectively, the in vitro data demonstrate DTG's low potential for clinically meaningful DDIs [21].

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%) [22].

Population PK analysis in treatment-naïve PLWH was performed by combining data from three studies: a proof-of-concept study (ING111521) [20], a Phase 2b study (SPRING-1, ING112276, NCT00951015) [23], and a Phase 3 study (SPRING-2, NCT01227824) [24]. 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 were not 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 [25].

DTG benefits from having relatively low PK variability when compared with EVG and RAL. In a phase IIa study investigating DTG PK in PLWH, coefficients of variation (CV) were in the 25–50% range for C_{max}, C_{trough} and AUCτ [19, 20].

2.4 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 10mg tenofovir alafenamide (TAF). The manufacturer recommends all formulations be taken with a meal [26–28].

In single dose studies of unboosted EVG at doses of 100mg, 200mg, 400mg and 800mg given orally to healthy individuals, AUC_{∞} was less than dose proportional [29]. Co-administration of EVG with ritonavir (RTV), a potent CYP3A4 inhibitor used for PK boosting of PIs, resulted in substantially higher EVG exposures; EVG AUCτ was ~20 fold higher with RTV 100mg compared with EVG alone [30]. The relative bioavailability of EVG boosted with COBI (EVG/COBI) was compared with EVG boosted with RTV 100 mg (EVG/RTV) in 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[31]. 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 [32, 31]. Collectively, these studies provided

evidence for once-daily dosing of EVG when given with COBI 150mg. COBI has advantages as an ARV PK enhancer because it inherently lacks any activity against HIV-1 and is better tolerated than RTV. The available EVG FDC products are both formulated with COBI 150mg [27, 28].

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 [33]. 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 [34].

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. This may be overcome by separating the dose times of the two products [35, 36]. EVG absorption does not appear to be significantly altered with changes in intestinal P-gp expression.

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 [37]. 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.

2.5 Raltegravir

RAL (MK-0518) is available in three formulations: film coated tablets (both 400mg and 600mg), chewable tablets (25mg and 100mg), and 100mg granules for suspension [38]. For adults, the dose of RAL is either 400mg twice-daily, or 1200mg (two 600mg tablets) once-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 >200% have been observed from repeated plasma concentrations within individual patients on stable RAL-containing ART [39]. Secondary plasma concentration versus time peaks often occur with RAL, indicative of either enterohepatic recirculation or possibly delayed oral absorption. Similar to other INSTIs, RAL PK is altered when given with divalent and trivalent cations, which may be overcome by dose-separation [40]. The absolute bioavailability of RAL has not been established due to the lack of a parenteral formulation, however, PLWH have a 25–30% reduced bioavailability relative to healthy subjects [41]. Food appears to increase the PK variability 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. After moderate or high fat meals, AUCs were increased 13 to 212% [42]. 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 [38].

In healthy human subjects RAL 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 similar between adult male and female subjects [43], in contrast to combined data from PLWH and healthy human subjects, where 65% higher RAL exposures were observed in females than males [41].

In ART-naïve adults with HIV 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) [44]. 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 [43–45].

A mass balance study performed in healthy human subjects after a single radiolabeled dose of 200mg RAL indicated 51% of the dose was recovered in the feces while 32% was recovered in urine [46]. 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 drug 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 polymorphisms 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 significant [47].

The PK of RAL 800mg once-daily were investigated in treatment-naïve PLWH. AUC_{τ} was similar when RAL was given as 800mg 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 800mg daily. [48, 49, 38]. A study of RAL 1200mg daily was ultimately shown to be non-inferior to RAL 400mg twice-daily [50]. PK parameters achieved with RAL 1200mg once-daily in adults were: $AUC_{0–24}$ 24.58 ug*hr/mL (41.5%CV), C_{max} 6.98 ug/mL (45.8%CV), C_{24} 0.048 ug/mL (97.5%CV) [38] .

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 [51–53]. In addition, HBV and HCV infections are common comorbidities in patients living with HIV. For persons coinfected with chronic HBV, both BIC and EVG are co-formulated with NRTIs that are also effective for chronic HBV therapy (FTC, TAF, or TDF), and DTG or RAL may be co-administered with any NRTI combination effective against HBV. There are limited data regarding the use of injectable CAB and RPV in patients with hepatitis coinfection [54] and the combination will not provide adequate treatment of persons co-infected with chronic HBV without the addition of oral NRTIs effective for the treatment of HBV. Drug-drug interactions are possible with INSTIs, particularly EVG boosted with COBI, or their co-formulated NRTIs when combining ART with direct acting antiviral agents for the treatment of HCV. The US Adult and Adolescent HIV Treatment Guidelines provides detailed information on drug-drug interactions in sections dedicated to HIV plus HBV or HCV coinfection[1].

Table 2 summarizes comparative studies of INSTI PK in persons with hepatic impairment. Moderate hepatic impairment was defined as a Child-Pugh Score of 7–9 for all studies described in this section, unless indicated. Modestly lower total exposure is observed for some INSTIs in participants with hepatic dysfunction compared to those without hepatic dysfunction. It is possible this change relates to a higher volume of distribution in those with hepatic disfunction resulting in lower Cmax, or a greater unbound fraction resulting in more rapid metabolism/clearance. No dosage adjustment is required for persons with mild to moderate hepatic impairment (Child-Pugh A or B) for any FDA approved INSTI, but none of the labels recommend either the use of, or dosing information for, persons with severe hepatic impairment (Child-Pugh C) [4] [38, 16, 26–28] [54]. RAL remains the only INSTI with published PK data in HIV/HCV coinfected individuals with cirrhosis, end stage liver disease (ESLD), and post-liver transplantation.

3.1.1 Bictegravir—One study evaluated single dose BIC PK in participants with moderate hepatic impairment versus matched healthy controls. The total plasma BIC AUC_{∞} was 41% lower in participants with hepatic impairment compared with the AUC_{∞} of those with normal hepatic function, however, the unbound AUC_{∞} was only 23% lower[55].

3.1.2 Cabotegravir—The PK of oral CAB 30mg, given as a single dose, was evaluated in participants with moderate hepatic impairment and matched healthy controls [56]. While total plasma CAB PK parameters were modestly lower in participants with hepatic impairment, the unbound fraction was higher in participants with moderate hepatic impairment than in healthy volunteers [GLS mean ratio (90%CI): 2.14 (1.57, 2.90) and 1.90 (1.14, 3.18) at 2 hours and 24 hours post dose, respectively], resulting in a trend toward higher unbound CAB concentrations [GLS mean ratio (90%CI): 1.55 (0.82, 2.94) at 24 hours post-dose]. This higher unbound fraction was associated with lower serum albumin concentrations and was not considered clinically significant by the authors. Based on these data, Shaik et al. propose that a similar change in exposure will be observed with the injectable, long-acting CAB formulation [56].

3.1.3 Dolutegravir—DTG was evaluated in HIV-seronegative participants with moderate hepatic impairment compared with healthy participants [57]. 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 those with hepatic impairment compared with healthy participants. Population PK from 71 HIV/HCV coinfected patients without cirrhosis in Phase II/III efficacy trials indicated no clinically relevant effect on DTG PK; HIV/HBV coinfected participants could be not be adequately evaluated due to a small sample size (n=27) [58, 25].

3.1.4 Elvitegravir—In HIV-negative volunteers with moderate hepatic impairment, EVG exposure was 35% higher compared with matched healthy volunteers, while COBI exposure and both EVG and COBI free fraction was similar between groups [59]. Population PK evaluations from the Phase II/III efficacy trials in PLWH and HBV or HCV coinfection without cirrhosis found no difference in EVG PK when combined with COBI (n=24) [60].

3.1.5 Raltegravir—No clinically significant differences were observed in the PK of RAL 400mg after a single dose in volunteers with or without moderate hepatic insufficiency [61]. In patients living with HIV, no difference in RAL C_{trough} was observed in participants coinfected with HIV/HCV without cirrhosis compared to participants with HIV mono-infection after 4 weeks of RAL 400mg twice-daily [62].

Participants with HIV/HCV coinfection with and without advanced cirrhosis received RAL 400mg twice daily for five days in combination with their existing PI-based ART regimen [63]. Those with advanced cirrhosis had 72% higher total RAL exposure, though no adverse events or RAL treatment-discontinuation were reported during the study period. In patients with ESLD (MELD score ≥15), virologically-suppressed participants were switched from their current ART to RAL-based ART [64]. After one month, RAL exposure was higher in patients with ESLD (median AUC over 9 hours: 33.5 mcg*hr/mL) than historical data in persons with normal hepatic function, but high variability in both free and total RAL PK was noted (AUC_9 interpatient CV%, 95% and 91%, respectively. In these 10 participants, RAL was well tolerated and all remained virologically suppressed on ART. Finally, the authors reported RAL PK in five patients with HIV who initiated RAL-based ART after liver transplantation. After one month, the total and unbound RAL exposures were similar to those observed in persons with ESLD.

3.2 Renal Impairment

The impact of severe renal impairment on INSTI PK parameters were explored in HIV-seronegative volunteers and are summarized in Table 2. Severe renal impairment was defined as a creatinine clearance (CL_{CR})<30 mL/min without any form of renal replacement therapy for all studies discussed in this section, unless indicated. Because the INSTIs are not primarily eliminated by renal excretion, a significant impact on PK exposure is not expected in persons with renal impairment [38, 16, 26–28, 4, 54].. No dose adjustment is necessary for persons with mild through severe renal insufficiency for any INSTI. Similarly, due to the high plasma protein binding, INSTIs are not expected to be eliminated by hemodialysis. However, when INSTIs are given as a FDC, their use may be limited by the coformulated NRTI component in persons with renal insufficiency.

3.2.1 Bictegravir—The single dose PK of BIC 75mg was compared in participants with severe renal impairment, defined as a CL_{CR}15 to 29 mL/min, and participants with a CL_{CR} ≥90 mL/min. Though the total BIC AUC_{∞} was 27% lower in participants with renal impairment, the unbound BIC AUC_{∞} was unchanged [GLSM (90% CI): 0.99 (0.80, 1.24)], due to a higher fraction unbound in participants with renal insufficiency [55]. However, because BIC is only available as a co-formulated tablet with TAF/FTC, it is not recommended for use in participants with an estimated CL_{CR} <30 mL/min [4].

3.2.2 Cabotegravir—No change in plasma CAB exposure was observed after a single, 30mg oral dose in participants with severe renal impairment compared to matched participants [65]. However, the unbound CAB fraction was higher in participants with severe renal impairment [GLS mean ratio (90%CI) 1.51 (1.19, 1.92) at 24 hours post dose], resulting in a 67% higher unbound CAB concentration at 24 hours post dose in participants with renal dysfunction [GLS mean ratio (90%CI) 1.67 (1.33–2.09)]. Based on these results, oral CAB may be used without dose adjustment for participants with severe renal dysfunction. Parasrampuria et al. proposed that these results may be extended to those with mild to moderate renal insufficiency and that hemodialysis is not expected to influence CAB PK due to its high protein binding [65]. The product labeling for CAB recommend no dose adjustment for the injectable CAB formulation for persons with moderate renal dysfunction (> 30ml/min) but suggest that those with severe renal dysfunction or on dialysis should be monitored due to insufficient clinical experience in this population [54].

3.2.3 Dolutegravir—Plasma DTG exposure was 40% lower in volunteers with severe renal impairment compared with matched controls after a single dose of DTG 50mg [66]. Population PK modeling from clinical trials 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 [58]. 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, for patients with severe renal impairment and known or suspected INSTI-resistance mutations, caution is warranted due to this observed decrease in DTG exposure [16].

3.2.4 Elvitegravir—The PK of EVG coadministered with COBI in volunteers with severe renal impairment were compared to participants with normal renal function [67]. The EVG AUC was 24% lower in those with severe renal impairment, but German at al. noted that EVG exposure in participants with normal renal function was higher than previously observed. Further, the free fraction of EVG was modestly higher in participants with renal impairment [Mean (SD): 1.16% vs 1.42% (0.17%]).

Because EVG is only available coformulated with COBI plus TDF/FTC or TAF/FTC, additional consideration of renal function is required. The EVG/COBI/TDF/FTC coformulated tablet is not recommended for initial therapy in persons with a CL_{CR} ≤70 ml/min and should be discontinued in persons whose CL_{CR} falls below 50 ml/min during therapy due to renal adverse events observed clinical trials and because TDF requires dose reduction at CL_{CR} below 50 ml/min [60]. However, EVG/COBI/TAF/FTC may be used for

patients with moderate renal insufficiency (CL_{CR} 30–69 ml/min) [28]. 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 [68]. EVG exposure (AUC 27.1, respectively) was similar to historical data [60], and was comparable between persons with CL_{CR} above or below 50 ml/min.

The safety and efficacy of EVG/COBI/TAF/FTC was also explored in 55 virologically-suppressed participants with end-stage renal disease (CL_{CR}<15ml/min) on chronic dialysis who were switched to EVG/COBI/TAF/FTC from a suppressive ART regimen[69]. The PK of EVG was explored in a sub-study of 12 participants two or four weeks after ART switch. Lower EVG exposure was observed compared to data from Phase 2 trial participants with normal renal function (AUC mean (% coefficient of variation) 14,300 (55%) and 22,800 (35%) ng*h/ml, respectively). The authors conclude the exposures were within safe and effective ranges of other phase 3 trials, and data through 96 weeks suggest the regimen remained effective and did not result in excess treatment-related adverse effects [70, 69].

3.2.5 Raltegravir—No differences in PK parameters were observed in one evaluation of single dose RAL 400mg in volunteers with severe renal insufficiency [61].

3.3 Pregnancy

Physiologic changes during pregnancy are known to impact the PK of some ARVs, resulting in recommendations to dose adjust or avoid 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 [71, 72]. PK data of INSTIs during pregnancy and the mechanisms underlying potential changes in INSTI exposure during pregnancy, were recently reviewed by van der Galien et al. [73] 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 prevention of HIV transmission. McCormack and Best published a comprehensive review of ARV placental transfer in 2014 [74]; therefore, only in vivo information on placental transfer published since this review is described herein.

Given the available PK, safety and effectiveness data observed to date, U.S. treatment guidelines currently recommended RAL 400mg twice daily or DTG 50mg once daily as preferred regimens in ARV-naïve pregnant women [75]. Because RAL given as 1200mg once daily results in lower C_{trough} concentrations compared with 400mg twice daily, decreased RAL exposure during pregnancy may be more clinically significant for this dosing regimen. Therefore, the guidelines do not recommend once-daily RAL, citing insufficient clinical and pharmacokinetic data during pregnancy. Elvitegravir is not recommended during pregnancy due to suboptimal exposure during pregnancy, and cases of associated virologic failure during pregnancy. Bictegravir and cabotegravir do not yet have sufficient evidence to support their use during pregnancy.

3.3.1 Bictegravir—There are no data available on the PK of BIC during pregnancy, and there are limited clinical data on the use of BIC/FTC/TAF in pregnant women [75]. Two

studies are currently recruiting participants to evaluate the PK, efficacy, and safety of BIC/FTC/TAF in pregnant women with HIV (NCT03960645 and IMPAACT study 2026).

3.3.2 Cabotegravir—The PK of CAB has not been evaluated during pregnancy. A study conducted by the IMPAACT network is expected to evaluate CAB during pregnancy for the prevention of HIV (NCT03164564). The PK tail of CAB in individuals who became pregnant during Phase 3 clinical trials of the long-acting, injectable formulation has recently been reported [76]. At the time of pregnancy detection, participants were switched from injectable therapy to standard of care, oral ART. CAB PK after injectable treatment discontinuation was available from three participants. CAB remained measurable above effective concentrations (>0.5 μg/mL) throughout pregnancy in two participants, while faster elimination was observed in the third participant (undetectable concentrations by week 28 after the last injection). This difference was hypothesized to be related to a smaller BMI in the third participant. In the two participants with detectable concentrations, CAB remained measurable through weeks 40 to 52 weeks after the last injection, reflecting the timepoint of the last reported measurement in each participant. The authors conclude this elimination pattern is similar to non-pregnant adults receiving long-acting CAB. These data emphasize the importance of determining the safety of CAB during pregnancy, due to the expected, prolonged PK tail after discontinuation.

3.3.3 Dolutegravir—Clinical controversy exists regarding DTG use of at the time of conception and in early pregnancy due to the risk of neural tube toxicities. The product labeling does not recommend use during conception or the first trimester, but the 2020 update to the US DHHS Perinatal HIV Treatment Guidelines describe DTG-based ART as a preferred regimen during pregnancy [75], irrespective of trimester. Three studies described DTG PK of during pregnancy and all compared PK within the same individuals during pregnancy and postpartum.

The US-based IMPAACT P1026 study examined the PK of DTG 50mg once-daily as part of ART in women during the second and third trimester, and 6–12 weeks postpartum. Although DTG exposure was 25–51% lower during pregnancy, the median AUCτ was similar to nonpregnant adults and the postpartum exposures were higher than historic controls. The European PANNA cohort evaluated similar participants during the third trimester of pregnancy and 4–6 weeks postpartum and observed 7–26% lower exposure during pregnancy [77]. Finally, a study conducted in Uganda and South Africa evaluated DTG PK in women initiating DTG-based ART during pregnancy and reported 15–20% lower DTG exposure during pregnancy compared with concentrations 2 weeks postpartum [78]. Though all three studies observed concentrations below the desired C_{trough} concentration based on Phase IIb dose-finding studies (324 ng/mL) or the 10^{th} percentile AUCτ in non-pregnant patients (16.1 mcg*h/mL), each concluded the differences in DTG PK between pregnancy and postpartum were not clinically significant based on rates of virologic suppression during pregnancy.

To investigate placental transfer of DTG during pregnancy, each study assessed the cord blood/maternal plasma concentration ratio and found similar results, ranging from 1.21 to 1.38 [77, 79, 78]. In breastfeeding infants, breast milk of mothers receiving ART, is a source

of drug exposure. Waitt et al. reported data on the breast milk to plasma ratio [geometric mean (90% CI)] of DTG: 0.3 (0.02–0.04), and detected a DTG C_{max} [geometric mean (range)] in breast milk of 84.6 (43.8–171) ng/mL. In breastfeeding infants, this DTG dosing via breast milk resulted in a DTG C_{max} of 66.7 (21–654) ng/mL [78].

3.3.4 Elvitegravir—Two studies described EVG PK of during pregnancy, providing intraindividual comparisons during pregnancy and postpartum. The IMPAACT P1026 study evaluated EVG/COBI PK as part of a fixed-dose combination with TDF/FTC or TAF/FTC and found EVG exposure was 24–44% lower during pregnancy compared with postpartum [80]. Similarly, the COBI AUCτ was 44–59% lower in the third trimester. The PANNA study demonstrated similar results, with 33% lower EVG exposure and 56% lower COBI exposure during the third trimester [81]. Both studies report a median cord blood/maternal plasma concentration ratio of approximately 0.9 for EVG [81, 80], while COBI appears to have a low placental transfer with a median ratio of 0.09 [80].

Results of both studies suggest that decreased PK enhancement by COBI and/or increased clearance of EVG result in suboptimal EVG exposure, and may increase the risk of virologic failure during pregnancy [73]. This is supported by the finding that only 74% of participants maintained virologic suppression at delivery [75]. Based on these data, the DHHS Perinatal Guidelines do not recommend EVG/COBI for women initiating ART during pregnancy, and further, recommend clinicians consider switching EVG/COBI to a more effective ART option in those who become pregnant while receiving EVG/COBI.

3.3.5 Raltegravir—Two PK studies of RAL found lower exposure during pregnancy, which did not influence the effectiveness of RAL-based ART based on clinical evidence of virologic suppression at the time of delivery [75]. When RAL 400mg twice-daily was given on an empty stomach, the AUCτ was approximately 50% lower during both the 2nd and 3rd trimesters of pregnancy compared with postpartum [82]. Separately, RAL 400mg twice-daily was given with a meal (650 kcal; 30 g fat) and the AUCτ and C_{trough} were 29% and 36% lower during pregnancy compared with postpartum [83]. Both studies demonstrated high variability in RAL concentrations. Fetal exposure to RAL was evaluated in nine paired cord and maternal blood samples at delivery (median 10 hours post-last RAL dose); the cord/maternal blood ratio was 1.21 (IQR 1.02–2.17), similar to prior reports [74].

4. Pharmacodynamics

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

4.1 Bictegravir

The PD knowledge of BIC arises from short-term evaluations of antiviral activity when given as monotherapy and phase 3 studies of BIC plus FTC/TAF compared with DTG in ARV-naïve and PLWH suppressed on DTG- or PI-based regimens who switched to BIC plus FTC/TAF. A 10-day monotherapy study evaluated BIC doses of 5, 25, 50 and 100mg once-daily in 20 INSTI-naïve individuals with HIV [6]. Mean $\log_{10}$ change (copies/mL) in HIV-RNA from baseline to day 11 was −1.45, −2.06, −2.08 and −2.43 for 5, 25, 50 and 100mg doses, respectively. The progressive decrease in HIV-RNA as BIC dose increased indicates a

dose and concentration response relationship. This relationship is also seen in slopes of the viral decay curve, with steeper declines in HIV-RNA seen with increasing doses. These data are indicitive of Emax type of PD relationships between concentrations and HIV-RNA response; unfortunately, formal PD modeling was not performed. This study provided the basis for a randomized phase 2 study of BIC compared with DTG both with FTC and TAF in ARV-naïve adults [84, 85] . The BIC dose evaluated was 75mg once-daily; DTG, FTC and TAF doses were the usual, FDA-approved. 98 individuals were enrolled. At the week 24 primary endpoint, 96.9% (63 of 65) and 93.9% (31 of 33) of BIC and DTG recipients, respectively, had plasma HIV-RNA <50 copies/mL. No participant in either group discontinued therapy for lack of anti-HIV efficacy and no serious treatment-related adverse events occurred. At completion of the blinded portion of this study (week 48), all participants were offered the option of taking a FDC tablet of BIC (50mg), FTC (200mg) and TAF (25mg) developed for phase 3 studies. PK evaluations showed BIC plasma concentrations at 50mg in the FDC were equivalent to those at 75mg used in the phase 2 study [86]. 92 of 98 participants completed the blinded study and all switched to the FDC tablet. At week 72, 91 of 92 who progressed to this open evaluation had HIV-RNA <50 copies/mL. Collectively, this phase 2 study provided a PD basis for evaluation of BIC in phase 3 studies and the PK basis for the 50mg dose when given in a FDC tablet.

BIC and DTG were directly compared (both plus FTC and TAF) in a phase 3 multicenter, placebo-controlled, randomized study in 657 ARV-naïve adults with HIV [50]. At the week 48 primary endpoint, plasma HIV-RNA was <50 copies/mL in 286/320 (89%) of BIC and 302/325 (93%) of DTG recipients, demonstrating non-inferiority of BIC. Both regimens were well-tolerated: 5 (2%) of BIC and 1 (<1%) of DTG recipients discontinued therapy for adverse drug reactions; study-related adverse drug events were less common (p=0.022) with BIC (18%) than with DTG (26%). A second phase 3, multicenter, randomized, active-controlled study compared BIC/FTC/TAF with DTG/3TC/ABC in 631 ARV-naïve adults [6]. At the week 48 primary endpoint, participants with HIV-RNA <50 copies/mL were 290/314 (92/4%) for BIC/FTC/TAF versus 293/315 (93%) for DTG/3TC/ABC, demonstrating non-inferiority of the BIC regimen. Both regimens were well-tolerated; neuropsychiatric and sleep disorder events were similar. However, nausea was significantly less common with BIC/FTC/TAF versus DTG/3TC/ABC, 5% vs 17% (p<0.0001); this difference appears most likely the result of a tolerance difference between TAF and ABC. The FDA investigated exposure-response relationships for BIC in these phase 3 trials, using AUC values by quartile and proportion of subjects with HIV-RNA <50 copies/mL at week 48 [87]. This analysis, with all participants receiving BIC 50 mg once-daily, found a consistent response at all quartiles. At the lowest quartile, AUC values were ≥49,174–85,291 ng*h/mL and the percent of subjects with undetectable HIV-RNA was 93%; at the highest quartile, AUC values were ≥117,682–205,983 ng*h/mL and the proportion undetectable was 94%. Relationships among BIC concentrations and headache and diarrhea (both occurred in >10% of participants receiving BIC) were investigated and no exposure-response relationships were identified.

4.2 Cabotegravir

Ten-day monotherapy studies with oral CAB at doses of 5mg and 30mg once-daily, each to 10 PLWH revealed evidence for a dose and concentration-effect relationship [9]. Plasma HIV-RNA changes from baseline to day 11 were −2.17 $\log_{10}$ and −2.34 $\log_{10}$, respectively, for the 5 and 30mg doses. PD analyses found the HIV-RNA change from baseline was associated with CAB trough concentration in an Emax relationship: Emax was 2.56 $\log_{10}$ and EC_{50} was 82ng/mL. 29% of those in the 5mg and 75% in the 30mg group had HIV-RNA <50 copies/mL at the end of monotherapy. CAB dose selection was further informed in a phase 2 study in ARV-naïve persons with HIV randomly assigned to CAB doses of 10mg, 30mg or 60mg, or EFV, plus dual NRTIs (either FTC/TAF or ABC/3TC) [88]. This study had a 24-week induction phase followed by a 72-week maintenance phase for those with HIV-RNA <50 copies/mL at week 24. The maintenance regimen was CAB, at the dose the subject was randomly assigned to plus RPV 25mg once-daily, or continued EFV with dual NRTIs. 243 individuals received treatment, 181 assigned to CAB and 62 to EFV. At completion of the 72-week maintenance phase, using the FDA snapshot algorithm, proportions with HIV-RNA <50 copies/mL were: CAB 10mg, 68%; CAB 30mg, 75%; CAB 60mg 84%; and EFV, 63%. Participants discontinued for lack efficacy were: CAB 10mg, 3% CAB 30mg, 2%; CAB 60mg 2%; and EFV, 2%. Rates of discontinuation for adverse events or death were: CAB 10mg, 2%; CAB 30mg, 2%; CAB 60mg 7%; and EFV, 13%. The rates of insomnia and nausea, respectively, with CAB were: CAB 10mg, 8% and 23%; CAB 30mg, 12% and 20%%; and CAB 60mg, 18% and 26%. CAB trough concentrations (geometric mean) at week 36 were: CAB 10mg, 1340ng/mL; CAB 30mg, 3930ng/mL; CAB 60mg 8220ng/mL. Collectively, the phase 2 data indicate relationships between dose/concentration and HIV-RNA response and suggest relationships with insomnia and nausea. An oral CAB dose of 30mg once-daily was selected for further clinical evaluation, which evolved to oral lead-in for intramuscular (IM) administration of long-acting CAB (LA-CAB).

LA-CAB has been evaluated in single and multiple dose studies in adults without HIV. The PK goal was to maintain end of dosing interval CAB concentrations greater than 4-fold the protein-binding adjusted IC_{90} of 166 ng/mL, or 664 ng/mL. These studies found a LA-CAB dosing strategy of an 800mg IM loading dose followed by three every 4-week IM doses of 400 mg produced geometric mean trough concentrations of 3270 ng/mL (CV, 27%) [15]. A subsequent phase 2 study evaluated LA-CAB [plus LA-rilpivirine (LA-RPV)] given as either 400mg IM every 4-weeks or 600mg IM every 8-weeks after 20-weeks of lead in treatment with oral CAB plus RPV[89] . At 48 weeks of therapy, CAB trough concentration: every 4-week IM, 2580 ng/mL; every 8-week IM, 1460 ng/mL; and were 4470 ng/mL for continued ors (geometric mean) wereal CAB, 30mg once-daily. No participant receiving every 4-week IM had virologic non-response but five (4%) receiving every 8-week IM did. Measures of interpatient PK variability were not given, but graphical inspection showed some receiving 600mg IM every 8-weeks had CAB concentrations less than those with 10mg orally once-daily. As discussed above, virologic response was better with CAB 30 mg once-daily than 10 mg once-daily. A LA-CAB monthly dose of 400mg IM, following a 600 mg IM loading dose, was selected for phase 3 trials.

The ATLAS trial enrolled 616 persons with HIV on oral ART and HIV-RNA <50 copies/mL for 6 months. Participants were randomized to monthly injections of LA-CAB+RPV (600mg load of IM LA-CAB followed by 400mg IM once-monthly; 900mg IM load of LA-RPV then 600mg IM once-monthly) or to continued oral ART. At week 48, the proportion of participants with HIV-RNA <50 copies/mL were LA, 93% and oral ART, 95%. Serious adverse events were rare at 4% and 5%, respectively for LA and oral ART. The FLAIR study enrolled ARV-naïve individuals; 566 were randomized to monthly LA-CAB+RPV or oral ART with DTG/ABC/3TC. At week 48 the proportions with HIV-RNA <50 copies/mL were 93.6% for LA and 93.3% for oral. Serious adverse events were rare at 6% and 4%, respectively for LA and oral [7, 8]. The LA CAB dosing regimen was designed to achieve trough concentrations >4-fold the protein-binding adjusted IC_{90}. The average week 48 CAB concentration from the ATLAS and FLAIR studies was approximately 3000 ng/mL, 17-fold above the protein-binding adjusted IC_{90}. This ratio for CAB, and a 7-fold protein-binding adjusted IC_{90} ratio for RPV, provide a PD basis for the 93% with HIV-RNA <50 copies/mL response rate at week 48 in the two trials.

LA-CAB and RPV accumulate to steady-state slowly, even following an oral lead-in and IM loading dose; CAB reaches steady-state at approximately 44 weeks while RPV is at 80% of steady-state by week 48. For both drugs, between weeks 8–12 after the start of IM dosing, average plasma concentrations are 2-fold lower, approximately 1400 ng/mL for CAB and 40 ng/mL for RPV, than at week 48. Furthermore, even in the setting of no missed injections (i.e., perfect adherence) interpatient PK variability with injectable CAB and RPV is higher than oral. In ATLAS and FLAIR combined, six participants receiving LA-CAB+RPV had virologic failure; none missed any injections. All six had CAB and RPB plasma concentrations lower than the mean of those receiving LA-CAB+RPV, and some were less than the 5^{th} percentile, approximately 380 ng/mL for CAB and 17 ng/mL for RPV, values only 2-fold above the protein-binding adjusted IC_{90} (versus the intended >4-fold above). In the ATLAS trial, it is notable that virologic failure was detected between weeks 8–20 in the three participants.

4.3 Dolutegravir

The PD characteristics of DTG were generated through monotherapy studies and in combination with NRTIs to treatment-naïve, and treatment-experienced persons with and without documented resistance to RAL and EVG. Plasma HIV-RNA reductions (log_{10} change) with DTG monotherapy (2, 10 and 50mg once daily for 10 days) were best predicted by DTG C_{trough} following a maximum effect (Emax) relationship [90]. 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. A 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 [23]. At week 48, the proportion of participants with HIV-RNA <50 copies/mL were 91%, 88% and 90% for the DTG 10mg, 25mg and 50mg groups, respectively, and 82% for 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 was compared with twice-daily RAL, both given with ABC/3TC or TDF/FTC, in 822 treatment-naïve adults [24]. At 96 weeks, 81% of DTG versus 76% of RAL recipients had HIV-RNA <50 copies/mL. Virologic non-response occurred in 5% of DTG and in 10% of RAL recipients. DTG was compared with once-daily DRV/RTV, each given with ABC/3TC or TDF/FTC, in 484 ARV-naïve persons [91]. DTG was superior (p=0.025) to DRV/RTV: at week 48, 90% of DTG and 83% of DRV/RTV recipients had HIV-RNA <50 copies/mL. Drug-limiting adverse events were less frequent in DTG recipients: 2% of DTG 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 [92]. At week 48, 71% of DTG vs. 64% of RAL recipients had plasma HIV-RNA <50 copies/mL (p=0.03). Fewer DTG recipients had virologic failure with treatment-emergent INSTI resistance (4 vs. 17, p=0.003). The geometric mean DTG C_{trough} across 335 subjects was 850 ng/mL [58]. Those with DTG C_{trough} in the lowest quartile (median C_{trough}, 260 ng/mL) had the lowest virologic response rates (HIVRNA <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 was consistent with a 10mg once-daily dose. 183 persons with documented resistance to RAL and EVG were enrolled in an evaluation of DTG at 50mg twice-daily [93]. 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 did or didn't achieve HIV-RNA <50 copies/mL (2420 ng/mL vs. 2120 ng/mL). A 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 percent of subjects with HIV-RNA <50 copies/mL at week 24 [58]. 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 [58].

DTG has recently been evaluated in two dual-therapy regimens, combined with RPV or with lamivudine (3TC). The combination of DTG+RPV was evaluated in a phase 3, open-label, multicenter study in persons with HIV-RNA <50 copies/mL for 6 months. Participants were randomized to switch to DTG+RPV or remain on their current ARV regimen (CAR) [94] . At the week 48 primary endpoint, 94.7% of DTG+RPV recipients and 94.9% of those who remained on CAR had HIV-RNA <50 copies/mL. More subjects on DTG+RPV reported adverse drug events leading to study withdrawal than those who stayed on CAR, 3% vs. <1%, respectively. Overall drug-related adverse events were more frequent with DTG+RPV at 19% compared with 2% for those on CAR; headache and diarrhea were most common. The DTG+3TC dual therapy regimen was evaluated in two identical randomized, double-blind trials (GEMINI-1 and GEMINI-2) [95] . In these studies, ARV-naïve persons were randomized to DTG+3TC or DTG+TDF+FTC. At the week 48 primary endpoint, the rates of participants with HIV-RNA <50 copies/mL were: GEMINI-1, DTG+3TC, 90%; DTG +TDF+FTC, 93%; GEMINI-2, DTG+3TC, 93%; DTG+TDF+FTC, 94%. The DTG+3TC regimen met the definition of non-inferiority to DTG+TDF+FTC. More drug-related adverse

drug events occurred in the triple therapy arm compared with dual therapy, 24% vs. 18%; there was no difference in serious drug-related adverse events with rates <1% in both arms. The efficacy of both DTG-based dual therapy regimens, in particular the head-to-head DTG +3TC vs DTG+TDF+FTC study in ARV-naïve persons, can be taken as illustrations of the high IQ (high virologic potency and barrier to resistance) of DTG.

4.4 Elvitegravir

EVG C_{trough}, in 40 ARV-naïve and experienced persons not currently on therapy, 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 [96]. 278 PLWH and HIV-RNA ≥1000 copies/mL and ≥1 PI resistance mutation were randomized to EVG or to a comparator RTV-boosted PI [97]. EVG doses of 20mg, 50mg and 125mg, all given with RTV, were evaluated. The 20mg EVG arm was stopped at week 8 because of a higher rate of virologic failure. At week 24, the two remaining EVG arms 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 arms were: 20mg, 67 ng/mL; 50mg, 211 ng/mL; and 125mg, 263 ng/mL [60]. C_{trough} with the 20 mg EVG dose approximated the protein-binding adjusted IC_{95} of 45 ng/mL, providing a basis 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, and this dose (and level of systemic exposure) was selected for evaluation in phase III studies.

Two phase III, randomized, double-blind trials compared EVG with EFV or ATV/RTV, all given with TDF/FTC [98, 99]. EVG 150mg was given once-daily with COBI 150mg. Combined these two studies enrolled 1408 treatment-naïve adults. In both studies, for the primary endpoint of 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 [60]. 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 >500,000 copies/mL (79%). Collectively, these phase III trials confirmed efficacy of the 150mg once-daily EVG/COBI dose predicted by the exposure-response relationship.

4.5 Raltegravir

RAL is known to exhibit high intra- and interpatient variability in plasma concentrations (CV >200%), which has clouded the ability to elucidate clear, concentration-effect relationships and contributes to variability in virologic responses [39]. The existence, however, of an exposure-response relationship for RAL was clearly shown in a trial of RAL 800mg once-daily compared with 400mg twice-daily in 775 ARV-naïve persons [48]. 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%). Exposure-response analyses found RAL trough concentrations with once-daily dosing correlated with virologic response [100].

Geometric mean RAL C_{trough} was 37 ng/mL for once-daily 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. A new once-daily formulation of RAL, given as 2 × 600mg tablets once-daily, has been approved that has faster absorption, greater bioavailability and lower intersubject variability. This once-daily RAL dose and formulation was evaluated vs. the original formulation at the usual dose of 400mg twice-daily, both given with TDF+FTC in 797 ARV-naïve persons [50]. At 96 weeks, the proportions of participants with HIV-RNA <40 copies/mL were 81.5% for 1200 once-daily and 80.1% for 400mg twice-daily. The 1200mg once-daily dose/formulation performed equally well in all subgroups (e.g., participants with >100,000 HIV-RNA).

5. Interpretations and Conclusions

The most distinguishing PK characteristic of INSTIs is the difference in hepatic metabolism: EVG is primarily metabolized by CYP3A4; CAB, DTG and RAL by UGT1A1; while BIC has a similar contribution of CYP3A4 and UGT1A1. EVG must be given with a PK enhancer, 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. From a formulation standpoint, CAB is the only INSTI developed as a once every 4-week IM injection. With oral formulations, BIC, DTG (in INSTI-naïve persons) and EVG/COBI are administered once-daily, while RAL can be given either once or twice-daily depending on the dose (400mg BID vs 1200mg QD). RAL is distinguished by a substantially higher degree of intra- and interpatient PK variability. There are differences in PK characteristics for all INSTIs between healthy volunteers and PLWH, and this illustrates the importance of developing clinical PKPD data in the intended population, as discussed elsewhere [101]. Given its longer duration of clinical use, most evidence supports standard dosing of RAL in persons with hepatic impairment (moderate through advanced cirrhosis), severe renal impairment, and during pregnancy. BIC, DTG and EVG may be used at standard doses in persons with moderate hepatic impairment. In persons with severe renal dysfunction, standard dose DTG is recommended for those without INSTI resistance; however, DTG is not recommended for persons with INSTI resistance due to unexpectedly lower concentrations in those with severe renal dysfunction. BIC is not recommended for individuals with severe renal impairment. EVG/COBI is not recommended for persons with severe renal dysfunction.

In vitro $IC_{50, 90, 95}$ values indicate the hierarchy of potency (most potent = lowest IC) is RAL > EVG > DTG > CAB ≈ BIC. The EC values derived from studies in PLWH, and only available for CAB, DTG and EVG, are consistent with predictions based on in vitro potency that a lower IC value should translate into a lower EC value. 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) [102]. 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 3 and 4 studies, as well as for different patient populations [103]. At recommended oral doses, the hierarchy of IQ values is CAB > DTG > BIC > EVG > RAL, and there are supporting correlates from clinical trials. Consistent with DTG having a higher IQ value than RAL, DTG was shown non-inferior to RAL in ARV-naïve persons and superior to RAL in ARV-experienced but INSTI-naïve [24, 92]. For EVG, a dose of 20mg once daily (with RTV) was inferior to doses of 50 and 125mg [97]. The IQ of a 20mg dose is approximately 1.5 compared with an IQ for the 150mg dose of 10. Once-daily dosing of RAL 800mg was inferior to 400mg twice-daily [48]. The IQ for the once-daily regimen (C_{trough} divided by IC_{95}) would be 2.5 compared with 8 for twice-daily. Finally, there is growing evidence that the resistance barrier of BIC and DTG are higher than that of RAL and EVG.

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 [104, 99]. DTG was 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 [105]. DTG was also statistically superior to DRV/RTV in ARV-naïve subjects at 48-weeks, and in a 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) [106, 91]. BIC and DTG have been directly compared in ARV-naïve persons [84, 85]. At the week 48 primary endpoint, plasma HIV-RNA was <50 copies/mL in 89% of BIC and 93% of DTG recipients, demonstrating non-inferiority of BIC.

Clinical use of INSTIs in the US today is largely dominated by DTG and BIC. Both are first-line agents and the availability of FDC tablets lends to their ease of use. Both agents have favorable PK profiles congruent with once-daily dosing and potent virologic response at clinically indicated doses. The major discriminating factor between the two resides in the co-administered NRTI combination. While DTG is available as a single agent, BIC is only available in a FDC tablet with TAF/FTC. The DTG only tablet allows for ease of BID dosing when needed along with added flexibility when choosing a NRTI backbone. In the international setting, DTG uptake has largely outpaced other INSTI agents in treatment of adults with HIV, where it is widely available as a generic FDC tablet together with TDF and FTC (TLD) and is a component of many international guidelines. Finally, the availability of a long-acting, extended release product has been realized with CAB/RPV given once-monthly to potentially every two-months. However, data from phase 3 studies with long-

acting injectable CAB, in the setting of perfect adherence, suggest an increased risk of virologic failure associated with low CAB concentrations. These findings point to the need for optimization of the dosing regimen generally, and particularly as this strategy moves outside of clinical trials and to scenarios of less than perfect adherence, as well as investigations of individual characteristics, such as gender and high body-mass-index that may be associated with an increased risk for virologic failure.

Current treatment guidelines in the United States recommend INSTI-based regimens as the sole preferred first-line regimens for most PLWH [107]. There is evidence to support the use of INSTIs has improved viral suppression rates. A study of 31,055 PLWH and receiving care at eight clinical sites across the United States examined viral suppression rates from 1997 to 2015 [108]. The percent of 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 at birth, better adherence, and INSTI use was associated with an undetectable viral load [109]. 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 2 to treat HIV infection.
- The five 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 accumulating 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

	BIC		CAB Oral		CAB IM	DTG		EVG		RAL		
	Healthy	**HIV-infected**	**Healthy[h]**	**HIV-infected[i]**	**Healthy[g]**	**Healthy**	**HIV-infected**	**Healthy**	**HIV-infected**	**Healthy[b]**	**HIV-infected**	**HIV-infected**
Dose	50mg	50mg	25mg	30mg	400mg	50mg	50mg	150mg[a]	150mg[a]	400mg BID	400mg BID	1200mg QD
C_{max} µg/mL)	~8.0[1]	6.15 (22.9)	9.47 (19)	6.37 (23)	4.4 (31)	6.16 (15)	3.34 (16)	2.66 (27.6)	1.7 ± 0.4[d]	Fasted 1.20 (0.81.81)[f] Low 0.58 (0.39–0.88)[f] Mod 1.27 (0.84–1.91)[f] High 2.36 (1.57–3.56)[f]	1.502 (135)	6.98 (45.8)
C_{max} (µ g/mL)	2.24 (28)	2.61 (35.2)	5.22 (22)	2.85 (35)	3.27 (27)	1.64 (25)	0.83 (26)	0.490 (52.9)	0.45 ±0.26[d]	Fasted 0.05 (0.03–0.08)[f] Low 0.42 (0.03–0.07)[f] Mod 0.08 (0.05–0.13)[f] High 0.20 (0.12–0.33)[f]	0.114 (167)	0.048 (97.5)
T_{max} (hr)	2.0 – 4.0	2.0 – 4.0	1.25 (0.5–4.0)	2.5 (1.04.0)	6.0 (1–13.1)[j]	1.0 (0.5 to 2.0)[f]	2.0 (0.97 to 4.0)[e]	5 (5.0,5.5)[d]	3 to 4	1.0	1.8 (0.5 to 4.0)[e]	1.5–2.0
$t_{1/2}$ (hr)	16.7 (15.8,17.1)[c]	17.3 (14.8, 20.7)[c]	38.8 (10)		38.3 (57.3)	13 to 14	11 to 12	11.0 (8.87,13.0)[c]	8.62 (6.1 to 10.9)[e]	Distribution 1.0 Elimination 11.2	9	9
AUCτ µ g*hr/mL	89.7 (23)	102 (26.9)	160 (20)	104 (28)	2473 (26)[k]	76.8 (19)	43.4 (20)	27.0 (29.4)	23.0±7.5[d]	Fasted 4.44 (3.20–6.22)[f] Low 2.39 (1.72–3.33)[f] Mod 5.02 (3.60–7.02)[f] High 9.42 (6.76–13.15)[f]	5.84 (99)	24.58 (41.5)
Protein Binding	>99% to albumin		>99% to albumin			>99% to both albumin and alpha-1-acid glycoprotein		99.4% albumin >> alpha-1-acid glycoprotein		76% to 83% to Albumin		

Abbreviations: BIC, bictegravir; CAB, cabotegravir; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; DTG, dolutegravir; EVG, elvitegravir; RAL, raltegravir; T_{max}, time to reach C_{max}; $t_{1/2}$, elimination half life; AUCτ, area under the concentration-time curve over the dosing interval

Data are presented as geometric mean (CV) unless otherwise noted.

[a] data is with 150mg COBI.

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

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

[d] Data are presented as mean (SD)

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

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

[g] C_{min} derived 4 weeks post single IM injection

[j] T_{max} data for CAB-LA are in days

[k] AUC data for CAB-LA are 0–4 weeks.

[l] Data are unpublished, extrapolated from Zhang et al CROI 2017, Abstract #40

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_{∞} Ratio Impairment vs. Healthy
Moderate hepatic impairment					
Bictegravir[a] [55]	Parallel-group, single dose, PK evaluation over 144 hours HIV seronegative volunteers	Moderate hepatic impairment:[b] n=10 Matched, healthy volunteers: n=10	0.64 (0.50, 0.81)	na	0.59 (0.41, 0.84)
Cabotegravir[a] [56]	Parallel-group, single dose, PK evaluation over 168 hours HIV seronegative volunteers	Moderate hepatic impairment:[b] n=8 Matched, healthy volunteers: n=8	0.69 (0.51, 0.93)	0.73 (0.53, 1.02)	0.73 (0.50, 1.06)
Dolutegravir[a] [57]	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 (0.75, 1.37)	na	1.05 (0.75, 1.49)
Elvitegravir[c] [59]	Parallel-group, multiple dose, 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] [61]	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] [62]	Parallel-group, steady state, C_{trough} evaluation HIV-positive participants with or without HCV co-infection	HIV/HCV co-infection:[e] n=13 HIV monoinfection: n=16	na	1.16 (0.56, 1.39)	na
Raltegravir[c] [63]	Parallel-group, steady state, PK evaluation over a 12-hour dosing interval HIV-positive participants 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					
Bictegravir[a] [55]	Parallel-group, single dose, PK evaluation over 144 hours HIV-seronegative volunteers	CL_{CR} 15–29ml/min: n=10 Matched, healthy volunteers: n=8	0.80 (0.60, 1.08)	na	0.73 (0.49, 1.08)
Cabotegravir[a] [65]	Parallel-group, single dose, PK evaluation over 168 hours HIV-seronegative volunteers	CL_{CR} <30ml/min: n=8 Matched, healthy volunteers: n=8	1.01 (0.87, 1.17)	1.02 (0.87–1.20)	0.97 (0.84, 1.14)
Dolutegravir[a] [66]	Parallel-group, single dose, PK evaluation over 72 hours HIV-seronegative volunteers	CL_{Cr}I <30ml/min: n=8 Matched, healthy volunteers: n=8	0.774 (0.532, 1.13)	0.566 (0.352, 0.908)	0.6 (0.37, 0.975)
Elvitegravir[c] [67]	Parallel-group, multiple dose, PK evaluation over 24 hours HIV-seronegative volunteers	CL_{Cr} <30ml/min: n=12 Matched, healthy volunteers: n=12	0.67 (0.55, 0.83)	0.76 (0.63, 0.91)	0.69 (0.52, 0.92)

Antiretroviral	Study design	Participants	C_{max} Ratio Impairment vs. Healthy	C_{min} Ratio Impairment vs. Healthy	AUC_{∞} Ratio Impairment vs. Healthy
	EVG given as EVG/c given daily for 7 days				
Raltegravir[c] [61]	Parallel-group, single dose, PK evaluation over 96 hours HIV-seronegative volunteers	CL_{Cr} <30ml/min: n=10 Matched, 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	AUCτ (μg*hr/mL)	C_{min} (μg/mL)	Comments
Dolutegravir[a]	Longitudinal, steady state, intensive PK sampling over 24 hours	2nd trimester: n=15	47.6 (33.4 – 63.7)	0.69 (0.56 – 1.28)	AUCτ C_{max}, and C_{min} were statistically lower in both the 2nd and 3rd trimester compared to postpartum. Individual AUCτ above the 10th percentile of non-pregnant adults (37.5 mcg*h/mL): • 2nd trimester: 9 of 15 participants • 3rd trimester: 20 of 28 participants • Postpartum: 23 of 23 participants
		3rd trimester: n=28	49.2 (36.4 – 62.0)	0.81 (0.55 – 1.31)	
		Postpartum: n=22	65.0 (47.8 – 88.4)	0.97 (0.70 – 2.06)	
Dolutegravir[b] [77]	Longitudinal, steady state, intensive PK sampling over 24 hours	3rd trimester: n=15	40.8 (35)	0.66 (90)	No statistical differences were observed across PK parameters evaluated.
		Postpartum: n=10	47.0 (42)	0.92 (84)	Individuals who met the study defined C_{24} (≥0.32 mg/L) • 3rd trimester: 13 of 15 participants Postpartum: 10 of 10 participants
Dolutegravir[c] [78]	Longitudinal, steady state, intensive PK sampling over 24 hours	3rd Trimester: n=28	35.3 (19.2 – 67.9)	0.64 (0.19 – 3.09)	No statistical differences were observed across PK parameters evaluated. Individuals who met the study defined C24 (≥0.32 mg/L) • 3rd trimester: 19 of 28 participants • Postpartum: 21 of 27 participants
		Postpartum: n=17	40.1 (22.8 – 59.6)	0.78 (0.35 – 1.21)	
Elvitegravir[a] [80]	Longitudinal, steady state, intensive PK sampling over 24 hours	2na Trimester: n=17	15.3 (11.9 – 19.0)	0.017 (0.011 – 0.022)	Individuals meeting target AUCτ (16.1 mcg*h/mL): • 2nd trimester: 8 of 17 participants • 3rd trimester: 10 of 26 participants • Postpartum: 18 of 25 participants
		3rd Trimester: n=26	14.0 (9.1 – 18.8)	0.018 (0.005 – 0.061)	
		Postpartum: n=25	21.0 (13.5 – 32.8)	0.19 (0.048 – 0.38)	
Raltegravir[d] [82]	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)	AUCτ 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[e] [83]	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 (3nd 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: AUCτ, area under the concentration time curve for the dosing interval; C_{24}, Concentration 24 hours post-dose; C_{min}, minimum concentration observed; PK, pharmacokinetic.

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

[b] Data are presented as geometric mean (CV%).

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

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

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

Table 4.

Pharmacodynamic Characteristics of Integrase Strand Transfer Inhibitors

	Bictegravir	Cabotegravir	Dolutegravir	Elvitegravir	Raltegravir
IC_{50} (ng/mL)	108	41.4	16	7.2	na
IC_{90} (ng/mL)	na	166	64	na	na
IC_{95} (ng/mL)	162	na	na	44.9	14.7
EC_{50} (ng/mL)	na	82	36	14	na
EC_{90} (ng/mL)	na	na	324	126	na
IQ($C_{throught}$ / $IC_{90\ or\ 95}$	13.4	23.7[a]	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.

[a] IQ is calculated using trough concentrations with 30 mg orally.