Physiologically-based pharmacokinetic modelling of long-acting injectable cabotegravir and rilpivirine in pregnancy

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Abstract

Aim Long-acting cabotegravir and rilpivirine have been approved to manage HIV in adults, but data regarding safe use in pregnancy are limited. Physiologically-based pharmacokinetic modelling (PBPK) can predict drug disposition in complex populations. Approved dosing regimens were simulated in pregnancy to explore if Ctrough was maintained above target concentrations (664 ng/ml and 50 ng/ml respectively). Methods An adult PBPK model was developed and validated using clinical data of cabotegravir and rilpivirine in non-pregnant adults. This was modified by incorporating pregnancy-induced metabolic and physiological changes. The pregnancy PBPK model was validated with data on oral rilpivirine and raltegravir (UGT1A1 probe substrate) in pregnancy. Acceptance criteria for both adult and pregnancy models was absolute average-fold error (AAFE) < 2 between clinical and simulated values. The pregnancy PBPK model was used to simulate 12 weeks' disposition of monthly and bimonthly dosing of long-acting cabotegravir and rilpivirine, initiated at different trimesters. Results Models were successfully qualified with all AAFE values below 2. Predicted Ctrough at week 12 for both monthly and bimonthly long-acting cabotegravir was above 664 ng/ml throughout pregnancy. Similarly, predicted Ctrough at week 12 for monthly long-acting rilpivirine was above 50 ng/ml throughout pregnancy. However, for bimonthly rilpivirine administration, predicted Ctrough at week 12 were <50 ng/ml in 1, 0.5, and 2.3% of the pregnant population when initiated in first, second, and third trimester respectively. Conclusion Model predictions suggest monthly and bimonthly long-acting cabotegravir is likely to maintain antiviral efficacy throughout pregnancy. However, bimonthly long-acting rilpivirine requires careful clinical evaluation in pregnancy.

Introduction

As of 2021, the Joint United Nations Programme on HIV/AIDS (UNAIDS) reported that 38.4 million people were living with HIV across the world and about half of these were women and girls [1]. Many countries around the world have adopted the test-and-treat strategy for managing HIV treatment as recommended by WHO [2, 3]. This implementation has contributed to improvement of viral suppression and has been associated with a reduced risk of HIV transmission, better quality of life, and increased life expectancy in people living with HIV [4-7]. Despite this overwhelming evidence, UNAIDS estimates that only 81% of pregnant women accessed antiretroviral drugs in 2021 to prevent transmission of HIV to their children [1].

Pregnant women often experience nausea and vomiting and/or difficulty swallowing which could contribute to the challenges associated using oral antiretroviral drugs in this population [8, 9]. Frequent oral administration of drugs can also pose different pharmacological and psychosocial challenges when managing a chronic condition like HIV [10, 11]. Reduction in drug adherence is often observed over time with increased risk of therapeutic failure and development of drug resistance [10, 12]. In contrast, long-acting formulations

have advantages including, significantly reducing pill burden, consequently improving drug adherence and by-passing various barriers associated with oral administration [11, 13]. These characteristics make them a potential suitable treatment option for pregnant women experiencing the difficulties regarding oral administration. Recently, long-acting injectable (LAI) cabotegravir (CAB) and LAI rilpivirine (RPV) were approved by the FDA and EMA [11]. Both LAI CAB and LAI RPV are co-packaged in separate vials with approved doses of 600 mg & 400 mg CAB and 900 mg & 600 mg RPV, prepared for intra-muscular injections.

Pregnancy is associated with anatomical, physiological, and metabolic changes that influence pharmacokinetics (PK) [14]. Though intramuscular (IM) administration of antiretrovirals might overcome some effects of pregnancy on oral drug absorption, it remains vulnerable to pregnancy effects on drug distribution, metabolism, and elimination [14, 15]. For instance, CAB and RPV are mainly metabolised by uridine diphosphate-glucuronosyltransferase (UGT) 1A1 and cytochrome P450 (CYP) 3A4 respectively, with minor contributions from UGT1A9 for CAB [13, 16] and studies have suggested that the activities of both enzymes are upregulated in pregnancy [17, 18]. Limited clinical PK data on LAI CAB and LAI RPV during pregnancy at the time of approval by regulatory agencies implies there is inadequate information to guide the dosing of the IM formulations of the drugs in pregnant women [16]. With LAI CAB and LAI RPV, pregnant women might benefit from the less frequent drug administration and as an alternative regimen unaffected by nausea and vomiting. However, the approved dosing regimen of these drugs in adults could be at risk of reduced drug concentrations in pregnancy which might fall below the effective plasma concentration thresholds associated with adequate viral suppression. The commonly adopted target C_{trough} for CAB is 4 times the protein-adjusted-IC_{90} (4*$PAIC_{90}$ = 0.664 μg/ml). For RPV, different C_{trough} targets exist which include the protein binding-adjusted EC_{90} for RPV ($PAEC_{90}$ = 12 ng/ml) and 50 ng/ml (an approximation of its 4*$PAEC_{90}$ = 48 ng/ml) [19, 20]. Another higher target C_{trough} of 70 ng/ml was recently recommended for clinical practice to reduce the risk of the development of viral resistance to RPV [19]. Inadequate viral suppression increases the risk of perinatal HIV transmission and potential development of viral drug resistance. Currently, there is insufficient clinical data on the PK of LAI CAB and LAI RPV in pregnancy. Moreover, a small amount of data suggests that plasma concentrations of oral RPV are reduced in pregnancy [20, 21]. The common exclusion of pregnant women from many clinical trials leads to limited clinical data available to guide drug dosing in the pregnant population [22]. However, computational tools are increasingly employed to predict the impact of pregnancy on PK [18, 23, 24].

Physiologically-based pharmacokinetic (PBPK) models are mechanistic tools capable of representing the mechanisms involved in drug disposition within biological systems. PBPK models employ mathematical equations to integrate biological system information of a population along with drug-specific parameters towards characterising the disposition of the drug within the system [25]. Usually, anatomical, physiological, and demographical data of a population are used to define the biological system parameters. Similarly, the drug-specific parameters are comprised of physicochemical properties of the drug (e.g. acid dissociation constant and lipophicility) and in vitro data on the drug (e.g. fraction of unbound drug in plasma and intrinsic enzymatic clearance of the drug) [25, 26]. In this study, we developed and qualified a pregnancy PBPK model to evaluate if the dosing regimens of LAI CAB and LAI RPV approved or us in adults could maintain the respective C_{trough} targets for CAB and RPV during pregnancy.

2 Methods

2.1 PBPK model description

A full-body adult PBPK model was developed in SimBiology® a product of MATLAB® software, version R2019a (MathWorks, Natick, USA; 2019). Initially, a virtual cohort with 100 healthy individuals was simulated for the validation of the nonpregnant adult PBPK model. The ratio of male:female in this virtual cohort was 50:50 to represent the mixed gender in the clinical studies within the nonpregnant population. For the validation of the pregnancy PBPK model (developed from the adult PBPK model; see section 2.7), another virtual cohort with 100 healthy individuals (100% female) was simulated with the pregnancy PBPK model

to represent a pregnant population. For each model prediction, 4 different virtual cohorts were simulated, each with 100 healthy individuals.

The distribution of other demographic characteristics (e.g. age, weight and body mass index) of the virtual cohort was modelled to replicate the individuals, where reported, in the clinical studies used for the model qualification. Organ weights were determined using anthropometric equations previously reported by Bosgra et al 2012 [27]. Organ volumes were calculated from the organ weights and the respective organ densities reported in literature [28]. Regional blood flow to organs and tissue were calculated as fractions of the cardiac output [29].

2.2 Oral absorption and LAI administration

Oral drug absorption was modelled using the compartmental absorption and transit model that has been previously described in literature [30]. Rate constant of oral drug absorption (Ka) was determined using the effective drug permeability. The effective drug permeability was either calculated from the polar surface area (PSA) and number of hydrogen bond donors (HBD) of the drug or with the apparent permeability of the drug across caco-2 cells [31].

The release of the LAI drug formulation from the IM depot compartment was modelled as a first-order reaction [32], shown in equation 1 and the rates of drug release were fitted to available clinical data [33, 34].

$$\frac{A_{\text{muscle}}}{\text{dt}} = K_{\text{IM}} \times A_{\text{IM depot, muscle}} (1)$$

where $K_{IM,}$ is the release rate of drug (hr^{-1}) from the IM depot; $A_{IM\ depot,muscle}$ is the amount of the drug (mg) in the IM depot within the muscle; and A_{muscle}/dt is the amount of drug released from the IM depot into the systemic circulation per time (mg/hr).

Intestinal clearance of RPV (Clgut) by CYP3A4 was determined using the in vitro intrinsic clearance [35] and abundance of CYP3A4 [36] in the intestine as previously described in literature [31]. Thus, the fraction of the drug escaping intestinal metabolism into the liver was modelled using equation 2:

$$Fg = \frac{\text{Qgut}}{Qgut + (fu,gut \times Clgut)} (2)$$

where Qgut is the rate of blood flow to the gut (L/h) and fu,gut is the unbound fraction of the drug in the gut. Fu,gut was considered to be 1 in the model [37].

2.3 Model distribution

An illustration of the pregnancy PBPK model is shown on Figure 1. A fetal component within the female reproductive organ was not included within this pregnancy PBPK model as the main focus on this study was the PK in the pregnant woman and not fetal exposure. Major assumptions in the PBPK model include perfusion-limited drug distribution, well-stirred distribution model, and no drug reabsorption from the colon. The volume of drug distribution (V_d) was calculated from the volume and tissue-to-plasma ratio of each compartment as previously described [38]. Pregnancy effect on the fraction of the unbound drug was also modelled using equations previously described in literature [23, 39]. Lastly, activity of drug transporters were not included in the model due to inadequate data for such characterisation.

2.4 Liver metabolism

The clearance of the drug by the liver was calculated from the intrinsic clearance of the drug by CYP3A4 enzyme for RPV and by UGT1A1 and UGT1A9 enzymes for cabotegravir [40]. The intrinsic clearance of the drug by each enzyme were scaled to the whole of liver using the microsomal protein content per gram of liver (MPPGL) and the weight of the liver. The intrinsic clearance for RPV and CAB were calculated using equations 3 and 4 respectively: z

$$\text{Cl}_{\text{CYP3A4,liver}} = \text{Cl}_{\text{int,CYP3A4,liver}} \times \text{Abundance} \times \text{MPPGL} \times \text{Weig}ht_{\text{liver}} (3)$$

$$\text{Cl}_{\text{UGT,liver}} = \text{Cl}_{\text{int,UGT,liver}} \times \text{MPPGL} \times \text{Weig}ht_{\text{liver}} (4)$$

where $Cl_{CYP3A4,liver}$ is the hepatic clearance by CYP3A4 enzyme in L/hr; $Cl_{int,CYP3A4,liver}$ in µL/min/pmol, is the intrinsic clearance by a CYP enzyme; $Cl_{UGT,liver}$ is the hepatic clearance by a UGT enzyme in L/hr; $Cl_{int,UGT,liver}$ in µL/min/mg, is the intrinsic clearance per milligram of microsomal protein; Abundance is the enzyme abundance of CYP3A4 per milligram of microsomal protein (pmol/mg); MPPGL is the milligram of microsomal protein per gram of liver (mg/g) and $Weight_{liver}$ is the weight of the liver [32].

The total hepatic clearance of the drug in the liver (Cl_h) was used to calculate the fraction of the drug reaching the systemic circulation from the liver as described in equation 5:

$$F_h = \frac{Q_h}{Q_h + (Cl_h \times \frac{fup}{R})} (5)$$

where F_h is the fraction of the drug escaping hepatic metabolism and entering the systemic circulation from the liver, Q_h is the rate of blood flow to the liver, Cl_h is the total hepatic clearance of the drug in the liver, f_{up} is the fraction of the unbound drug in plasma and R is the tissue-to-plasma partition of the drug in the liver.

2.5 Drug parameters

Raltegravir (RAL) was included in this study as a probe substrate for the activity of UGT1A1 in pregnancy. RAL is solely metabolised by UGT1A1 and can be used to validate the ontogeny pf UGT1A1 in both pregnant and non-pregnant populations. Similarly, clinical PK data of RAL in both populations are available. Unlike CAB, clinical PK data for oral RPV in pregnancy are available [20, 21, 41]. However, there are no available PK data for LAI RPV in pregnancy. Physicochemical properties and in vitro data for the drugs modelled in this study (RPV, RAL and CAB) are listed in Table 1. Renal drug clearance was not implemented in the model as all three drugs are mainly cleared by the liver.

2.6 Adult PBPK model validation against available clinical data

The oral regimens tested in adults included: 30 mg CAB single dosing and 30 mg CAB repeated dosing for CAB [34, 42]; 25 mg RPV and 150 mg RPV repeated dosing [43-46]; and 400 mg RAL single and repeated dosing [47, 48]. Similarly, the LAI regimens tested in adults included: 800 mg IM CAB followed by 200 mg IM CAB monthly, 800 mg IM CAB followed by 400 mg IM CAB monthly, and 800 mg IM CAB every 3 months; and 1200 mg IM RPV followed by 600 mg IM RPV monthly and 1200 mg IM RPV followed by 900 mg IM RPV monthly [34].

PK parameters of each drug were simulated and compared with the corresponding adult data from clinical studies available in literature to validate the adult PBPK model. The doses, regimens and routes of drug administration were modelled to mimic the clinical studies used to validate the model. The model validation process was conducted in line with the European Medicines Agency (EMA) guidelines for PBPK model qualification [49]. Each model was considered validated when the summary statistics (mean or median) of the simulated PK parameters such as AUC, C_{min} and C_{max} were less than two-fold of the reported clinical values and the absolute average fold error (AAFE) was also less than two.

2.7 Model Modifications to develop a pregnancy PBPK model

Following successful validation of the non-pregnant adult model, the adult PBPK model was feminised by limiting the values for gender-specific parameters (e.g. organ weights) to female only [27]. The adult female PBPK model was later modified to represent a pregnant population. Pregnancy-induced anatomical, physiological, and metabolic changes, known to influence PK, were incorporated into the adult female model to generate a pregnancy PBPK model [17, 50]. Blood-flow rates to different organs and tissues during pregnancy were computed as fractions of the cardiac output and were obtained from literature [50]. Key pregnancy-related biological changes that were implemented in the model have been listed in Table 2.

The varying levels of plasma proteins was also modelled using previously established equations [23, 39] to capture the effect on the unbound fraction of drug in plasma. The clinical PK data of oral 400 mg RAL [51, 52] and oral 25 mg RPV [21, 41] in pregnancy were used to validate the pregnancy PBPK model. By

extension, the activity of UGT1A1 and CYP3A4 respectively, during pregnancy as represented within the pregnancy PBPK model, were also validated in the process.

2.8 Predictions of the pharmacokinetics of LAI CAB and LAI RPV in pregnancy

The two approved dosage regimens for LAI CAB comprise of 600 mg CAB administered intramuscularly followed by 400 mg IM CAB every month (LAI CAB monthly dosing of CAB) or 600 mg IM CAB every 2 months (LAI CAB bimonthly dosing). Like CAB, approved dosage regimens for LAI RPV include 900 mg IM RPV for one month followed by 600 mg IM RPV every month (LAI RPV monthly dosing of RPV) or 900 mg IM RPV every 2 months (LAI RPV bimonthly dosing). In all the cases, the administration of the LAI doses is preceded by their respective oral lead-in doses for one month.

Simulations were performed to predict the disposition of both the monthly and bimonthly LAI CAB and LAI RPV for a total period of 12 weeks (i.e. 3 months) without the oral lead-in components. Results from a recent study suggest comparable plasma trough concentrations (C_{trough}) after the first LAI dose with or without an oral lead-in though the study reported data for only CAB [53]. The simulations in pregnancy PBPK model were initiated at first (week 1-13), second (week 14-26), and third (week 28-40) trimesters of pregnancy. In addition, the female adult PBPK model was used to run similar simulations for a non-pregnant adult female. The simulations were performed to explore any differences in the disposition of both drugs if they were initiated in the first, second or third trimesters of pregnancy as compared to non-pregnant women. Predicted C_{trough} were also compared against clinical target concentrations for RPV and CAB.

3 Results

3.1 Adult PBPK model verification

The comparison between the simulated PK of orally administered CAB, RPV and RAL in adults against their respective observed clinical data are shown in table 3. The absolute average fold error (AAFE) values of the simulated vs observed PK parameters were all less than 2-fold which was the accepted threshold for this study. Likewise, the simulated PK of LAI CAB and LAI RPV in adults were compared against their corresponding clinical data as shown in table 4 with the AAFE yielding values below 2-fold. Thus, the adult PBPK models were considered qualified and suitable for investigating the PK of oral CAB, RPV and RAL in novel clinical scenarios. The same also applied for the suitability of the adult PBPK model to evaluate the PK of LAI CAB and LAI RPV in adults.

3.2 Pregnancy PBPK model verification

A comparison of the simulated PK of oral RAL and RPV in different trimesters of pregnancy against clinical PK data has been summarised in Table 5. The pregnancy PBPK model adequately predicted the PK parameters for oral RAL and oral RPV in pregnancy with AAFE values less than 2.

3.3 Predictions of LAI CAB and LAI RPV in pregnancy

The predicted PK parameters for the monthly and bimonthly dosing regimens of LAI CAB and LAI RPV in pregnant populations are shown in Figure 2. For both dosing regimens of LAI, the $C_{trough}$of CAB at the end of 12 weeks were predicted to be higher than 4*$PAIC_{90}$ (0 .664 µg/ml) throughout pregnancy. Likewise, the C_{trough} of RPV at the end of 12 weeks were predicted to be higher than 50 ng/ml (standard RPV C_{trough} target) [19]. However, the C_{trough} of RPV at the end of 12 weeks were predicted to be lower than 70 ng/ml in 3.3, 5.8, 5.5 and 1.8% of the pregnant populations in first, second and third trimester and the non-pregnant adult female population respectively (Table S1).

Unlike the LAI RPV monthly dosing, the C_{trough} for the bimonthly dosing of LAI RPV was lower than 50 ng/ml (˜4*$PAEC_{90}$ = 48 ng/ml) in 1, 0.5, 2.3 and 0.8% and lower than 70 ng/ml (newly recommended C_{trough} target) in 81.5, 89.3, 81 and 33.3% of the pregnant populations in first, second and third trimester and the non-pregnant adult female population respectively (Table S1). However, C_{trough} was above the

protein-adjusted EC_{90} for RPV (12 ng/ml) throughout pregnancy for both the monthly and bimonthly dosing regimen of RPV.

4 Discussion

We successfully developed a pregnancy PBPK model to predict the disposition of the approved monthly and bimonthly dosing regimens of LAI CAB and LAI RPV in pregnancy without the oral lead-in components. An earlier study had shown that C_{trough} after the first LAI CAB dose with or without an oral lead-in were comparable though the target C_{trough} could be achieved faster with the LAI CAB dose if given with the oral lead-in component [53]. The pregnancy PBPK model was developed from a validated adult PBPK model by incorporating pregnancy-induced biological changes that are known to influence PK such as changes in body weight, relevant enzyme activities and cardiac output defined by gestational age [17]. The adult PBPK model was validated with PK data of LAI CAB and LAI RPV in adults [34]. Similarly, available clinical PK data of oral RPV in pregnancy were used to validate the pregnancy PBPK model for RPV PK and by extension, the CYP3A4 activity in pregnant women. The absence of clinical PK data for oral CAB in pregnancy led to the adoption of a probe substrate (RAL) to validate UGT1A1 activity in pregnancy. RAL was a suitable probe substrate in this instance as it is solely metabolised by UGT1A1 and clinical PK data of oral RAL in pregnancy are available [52]. The use of a probe substrate to validate enzyme activity for a different drug with inadequate data has been previously reported in another study [54].

The model predictions suggest that both dosing regimens of LAI CAB were predicted to maintain efficacy throughout pregnancy. In contrast, whilst the monthly dosing regimen of RPV could maintain antiviral efficacy throughout pregnancy for majority of the population, the model suggests the need for caution in introducing the bimonthly regimen of RPV to the pregnant population. Use of the bimonthly regimen therefore requires careful clinical evaluation, including viral load monitoring and potentially therapeutic drug monitoring.

In the PBPK model, a simple first-order equation was used to characterise the absorption/release rate of the drug into the systemic circulation from the IM depot in the muscle. The mathematical expression was independent of the size of the patient's muscle mass which could explain why the predicted PK of LAI CAB did not vary significantly between virtual patients with different body mass indices (BMI). Unlike the predicted PK of LAI CAB, studies in humans have reported that BMI is a significant covariate for the PK of LAI CAB [55]. The size of muscle mass might affect the available depot space for the drug in the muscle which could lead to a faster release of the drug into the systematic circulation and contribute to a faster decline of the LAI CAB concentrations in patients with low BMI [55, 56]. Patel et al (2020) reported higher maximal levels of LAI CAB in the plasma of a study volunteer with lower BMI compared to two others with higher BMI [56]. However, the release rates of LAI CAB and LAI RPV used in this study were fitted into the model with available clinical data [33, 34]. Sensitivity analyses of the plasma concentrations of cabotegravir and rilpivirine to variations of their release rates are shown in Figure S1. The PK of monthly and bimonthly LAI CAB and LAI RPV were also simulated for non-pregnant adult females for comparison with the pregnant population because LAI CAB PK has been reported to differ between males and females [55].

Drug transporter activity was not incorporated into the PBPK model primarily due to lack of data. RPV is not a known substrate of any drug transporter. On the other hand, CAB is a substrate of Multidrug resistance protein 1 (P-glycoprotein 1) and breast cancer resistance protein (BCRP) in vitro [57]. Though pregnancy has been reported to influence the activity of P-glycoprotein 1 and BCRP in rodents [58, 59], data in humans are not available. Regardless, the influence of drug transporter activity on the PK of oral CAB appear to be minimal [57].

A fetal compartment was not included in the female reproductive of the pregnancy PBPK model. As such, fetal exposure to the LAI CAB and LAI RPV in pregnancy could not be evaluated. UGT1A is not

likely expressed in fetal liver [60]. Though fetal liver has been reported to express CYP3A, however, the contribution of the fetal liver clearance to the overall drug clearance of LAI RPV in the mother are expected to be minimal [61].

The administration of LAI drugs in pregnancy is not a new paradigm. LAI antipsychotic drugs have been administered in pregnancy for over two decades. Despite this long duration, PK data on the use of LAI antipsychotics in pregnancy has been very limited [62]. Similarly, outcomes on the safety of LAI antipsychotics in pregnancy have been inconsistent. Where poor outcomes have been reported in pregnancy after the use of LAI antipsychotics, there have been insufficient data to determine if the poor outcomes are due to the illness, class of the drug or the long-acting formulation [63]. Nonetheless, there have been strong arguments for LAI antipsychotic use during pregnancy owing to improved adherence, reduced risk of overdose, and less psychiatric rehospitalisation compared to oral antipsychotics [64]. Adherence to antipsychotics is particularly important during pregnancy to prevent relapses which might lead to poor birth outcomes [64].

In a similar vein, adherence to antiretrovirals in pregnancy is highly necessary to reduce the risk of vertical transmission of HIV. LAI antiretrovirals might be a preferred choice throughout pregnancy to support adherence and to reduce psycho-social challenges relating to disclosure of HIV status. In addition, the new option of LAI antiretrovirals might be particularly important in early pregnancy for women living with HIV that may prefer a non-oral route of drug administration due to nausea and vomiting. However, there is a need to frequently monitor pregnant women on LAI antiretrovirals towards improving available data on safety and efficacy. PBPK modelling readily overcomes many ethical and logistic challenges associated with randomised clinical trials in complex populations. It could also prove useful in exploring PK in complex clinical scenarios and complex populations.

Since the approval of LAI RPV and LAI CAB for the general adult population, there have been limited clinical data to guide the dosing of both LAIs in pregnant women. In this study, we developed a pregnancy PBPK model to describe plasma concentrations of LAI CAB and LAI RPV in pregnancy. Based on the model predictions, both the monthly and bimonthly dosing regimen of LAI CAB could maintain antiviral efficacy throughout pregnancy without need for adjustments. However, bimonthly dosing regimen of LAI RPV might be introduced in pregnancy with caution and adequate monitoring. Future clinical studies in humans are needed to confirm these model predictions.

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Conflict of interest statement

Marco Siccardi has received research grant funding from Janssen and ViiV unrelated to this work. M.S. is currently employed by Labcorp. All other authors have no potential conflicts of interest to declare.

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Data Availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Tables

Table 1: Input drug parameters for the CAB, RAL and RPV models.

Drug parameter	**CAB**	**RAL**	**RPV**
Molecular weight	405	444	366
pKa	10.04 [40]	6.67 [32]	3.26 [40]
R	0.441 [40]	0.6 [32]	0.67 [40]
Log $P_{o:w}$	1.04 [40]	0.58 [32]	4.32 [40]
f_{up}	0.007 [40]	0.17 [32]	0.003 [40]
HBD	2 [40]		
PSA	99.2 [40]		
Caco-2 P_{app} (cm/s)		6.6×10^{-6} [32]	12×10^{-6} [40]
CYP3A4 CL_{int} (µL/min/pmol)			2.04 [40]
UGT1A1 CL_{int} (µL/min/mg)	4.5 [40]	12.4[a] [32]	
UGT1A9 CL_{int} (µL/min/mg)	2.2 [40]		
IM drug release rate[b] (h^{-1})	3.406×10^{-4}		4.5×10^{-4}

CAB – cabotegravir, RAL – raltegravir, RPV - rilpivirine, pKa - acid dissociation constant, R - blood-to-plasma drug ratio, Log $P_{o:w}$ - partition coefficient between octanol and water, f_{up} - fraction of drug unbound in plasma, HBD - number of hydrogen bond donors, PSA - polar surface area, P_{app}- apparent permeability coefficient, Cl_{int} - intrinsic clearance, CYP - cytochrome P450, UGT - uridine diphosphate-glucuronosyltransferase.

[a]µL/min/10^6 hepatocytes.

[b]value fitted in the model using available clinical PK data.

Table 2: Key pregnancy-induced anatomical, physiological, and metabolic changes implemented in the pregnancy model

Parameter	**Equation**	**Reference**
Body weight (kg)	Body weight = 61.1 + 0.2409GA + $0.0038GA^2$	[17]
Cardiac output (L/h)	Cardiac output = 301 + 5.916GA - $0.088GA^2$	[17]
Plasma proteins (g/L)	Plasma proteins = 69.7 + 0.2085GA - $0.0305GA^2$ + $0.0006GA^3$	[17]

Parameter	Equation	Reference
CYP3A4 enzyme activity	CYP3A4 activity = 100 + 2.9826GA - 0.0741GA^2	[17]
UGT1A1 enzyme activity	UGT1A1 activity = 100 + 2.9826GA - 0.0741GA^2	[17, 18]

CYP - cytochrome P450, UGT - uridine diphosphate-glucuronosyltransferase, GA – gestational age in pregnancy (weeks).

Table 3: Qualification of adult PBPK model for oral PK of CAB, RPV and RAL (simulated vs observed)

PK parameter	Observed	Simulated	AAFE
30 mg CAB (single dose)# [42]			
C_{max} (µg/ml)	3.61	3.07	1.18
$AUC_{0\text{-}inf}$ (µg.h/ml)	146	98.2	1.49
30 mg CAB (repeated doses)# [34]			
C_{trough} (µg/ml)	4.9	4.6	1.06
C_{max} (µg/ml)	8.3	7.8	1.06
$AUC_{0\text{-}24}$ (µg.h/ml)	147	154	1.05
25 mg RPV (repeated doses)ˆ [43]			
C_{min} (ng/mL)	89.85	68.9	1.30
C_{max} (ng/mL)	203.8	219.75	1.08
$AUC_{0\text{-}24}$ (ng.h/mL)	2589	3304.9	1.28
25 mg RPV (repeated doses)ˆ [45]			
C_{trough} (ng/mL)	67.3	62.2	1.08
C_{max} (ng/mL)	180.9	189.60	1.05
$AUC_{0\text{-}24}$ (ng.h/mL)	2528	2895.7	1.15
25 mg RPV (repeated doses)# [44]			
C_{trough} (ng/mL)	74.5	62.7	1.19
C_{max} (ng/mL)	148	176.01	1.19
$AUC_{0\text{-}24}$ (ng.h/mL)	2227	2779.8	1.25
25 mg RPV (repeated doses)# [44]			
C_{trough} (ng/mL)	87.4	66.7	1.31
C_{max} (ng/mL)	171	177.68	1.04
$AUC_{0\text{-}24}$ (ng.h/mL)	2473	2860.3	1.16
150 mg RPV (repeated doses)ˆ [46]			
C_{trough} (ng/mL)	478	400.6	1.19
C_{max} (ng/mL)	1123	1296	1.15
$AUC_{0\text{-}24}$ (ng.h/mL)	16051	19398	1.21
400 mg RAL (repeated doses)# [47]			
C_{trough} (ng/ml)	48.84	44.71	1.09
C_{max} (ng/ml)	1203	1749	1.45
$AUC_{0\text{-}12}$ (ng.h/ml)	4440	8530	1.92
400 mg RAL (single dose)# [48]			
C_{trough} (ng/ml)	35.79	65.65	1.83
C_{max} (ng/ml)	1279	1631	1.28
$AUC_{0\text{-}inf}$ (ng.h/ml)	4884	8406	1.72

Data presented are Geometric mean values, ˆData presented are arithmetic mean values,

AAFE – absolute average fold error, CAB – cabotegravir, RAL – raltegravir, RPV - rilpivirine, C_{trough} –

plasma concentration at the end of the dosing interval, C_{max} – maximum plasma concentration, $AUC_{0\text{-}inf}$ – area under the plasma plasma concentration time curve till infinity, $AUC_{0\text{-}12}$ – area under the plasma plasma concentration time curve within 12 hours.

Table 4: Qualification of adult PBPK model for PK of LAI CAB and LAI RPV (simulated vs observed)

Regimen	C_τ (μγ/μλ)	C_τ (μγ/μλ)	C_{max} (μγ/μλ)	C_{max} (μγ/μλ)	C_{max} (μγ/μλ)
	Observed*	Simulated	Simulated	AAFE	Observed#
CAB					
800 mg IM + 200 mg IM monthly	1.61	1.68	1.68	1.04	2.2
800 mg IM + 400 mg IM monthly	3.27	2.71	2.71	1.21	4.4
800 mg IM quarterly	1.1	1.4	1.4	1.26	3.3
	C_τ (νγ/μλ)	**C_τ (νγ/μλ)**	**C_{max} (ng/ml)**	**C_{max} (ng/ml)**	**C_{max} (ng/ml)**
	Observed*	Simulated	Simulated	AAFE	Observed#
RPV					
1200 mg IM + 600 mg IM monthly	78.9	109.4	109.4	1.39	126
1200 mg IM + 900 mg IM monthly	79.1	132.8	132.8	1.68	168

Data presented as geometric mean values.# Clinical data observed by Spreen et al 2014 [34]. AAFE – absolute average fold error; C_τ – plasma concentration at the end of the dosing interval, C_{max} – maximum plasma concentration, $AUC_{0\text{-}\tau}$ – area under the plasma concentration time curve within the dosing interval, IM – intramuscular.

Table 5: Qualification of pregnancy PBPK model for oral PK of RAL and RPV in pregnant women (simulated vs observed)

PK parameter	**Observed**	**Simulated**	**AAFE**
RAL			
2nd trimester++a			
C_{12} (ng/ml)	62.1	34	1.81
C_{max} (ng/ml)	2250	1386	1.62
$AUC_{0\text{-}12}$ (ng.h/ml)	6600	6622	1.00
3rd trimester++a			
C_{12} (ng/ml)	64	36	1.78
C_{max} (ng/ml)	1770	1458	1.21
$AUC_{0\text{-}12}$ (ng.h/ml)	5400	7084	1.31
3rd trimester^b			
C_{12} (ng/ml)	77	42	1.84
C_{max} (ng/ml)	1430	1515	1.06
$AUC_{0\text{-}inf}$ (ng.h/ml)	5000	7366	1.47
RPV			
2nd trimester#c			
C_{min} (ng/ml)	54.3	30.2	1.80
C_{max} (ng/ml)	121	166	1.37
$AUC_{0\text{-}24}$ (ng.h/ml)	1792	2226	1.24
3rd trimester#c			
C_{min} (ng/ml)	52.9	36.5	1.45
C_{max} (ng/ml)	123	177	1.44
$AUC_{0\text{-}24}$ (ng.h/ml)	1762	2456	1.39
3rd trimester^d			

PK parameter	Observed	Simulated	AAFE
C_{min} (ng/ml)	50	33	1.50
C_{max} (ng/ml)	110	170	1.57
$AUC_{0\text{-}24}$ (ng.h/ml)	1710	2400	1.39

$^{++}$ Median values. ˆGeometric mean values. $^{\#}$Arithmetic mean values. RAL – raltegravir, RPV - rilpivirine, AAFE – absolute average fold error, C_{12} – plasma concentration 12 hrs after dose administration, C_{min} – minimum plasma concentration, C_{max} – maximum plasma concentration, $AUC_{0\text{-}inf}$ – area under the plasma plasma concentration time curve till infinity, $AUC_{0\text{-}12}$ – area under the plasma plasma concentration time curve within 12 hours, $AUC_{0\text{-}24}$ – area under the plasma plasma concentration time curve within 24 hours.

[a]Watts et al 2014 [52]; [b]Blonk et al 2015 [51]; [c]Osiyemi et al 2018 [21];[d]Schalkwijk et al 2017 [41]

Table S1: Simulated PK parameters for monthly and bimonthly dosing of LAI CAB and LAI RPV (without oral lead-in component) at week 12 in pregnant and non-pregnant women.

		CAB 600mg then 400mg monthly^{++} (n=400)	CAB 600mg then 400mg
		$\hat{}_{\tau\rho\upsilon\upsilon\gamma\eta}$ *(μγ/μλ)*	$\hat{}_{\mu\alpha\xi}$ *(μγ/μλ)*
Non-pregnant Adults	*Geometric mean*	2.20	2.65
	SD	0.37	0.44
	% $\hat{}_{\tau\rho\upsilon\upsilon\gamma\eta}$ *<0.664 μγ/μλ*	0	-
First trimester	*Geometric mean*	1.83	2.29
	SD	0.30	0.36
	% $\hat{}_{\tau\rho\upsilon\upsilon\gamma\eta}$ *<0.664 μγ/μλ*	0	-
Second trimester	*Geometric mean*	1.71	2.07
	SD	0.30	0.35
	% $\hat{}_{\tau\rho\upsilon\upsilon\gamma\eta}$ *<0.664 μγ/μλ*	0	-
		CAB 600mg then 400mg monthly^{++} (n=400)	CAB 600mg then 400mg
		$\hat{}_{\tau\rho\upsilon\upsilon\gamma\eta}$ *(μγ/μλ)*	$\hat{}_{\mu\alpha\xi}$ *(μγ/μλ)*
Third trimester	*Geometric mean*	2.12	2.36
	SD	0.37	0.40
	% $\hat{}_{\tau\rho\upsilon\upsilon\gamma\eta}$ *<0.664 μγ/μλ*	0	-

$^{++}$ PK parameters between week 9-12 of drug administration; #PK parameters between week 5-12 of drug administration; C_{trough} – plasma concentration at the end of the dosing interval, C_{max} – maximum plasma concentration within the dosing interval, $AUC_{0\text{-}inf}$ – area under the plasma plasma concentration time curve till infinity,$AUC_{0\text{-}672}$ – area under the plasma plasma concentration time curve within the last dosing interval period of 1 month (672 hrs), $AUC_{0\text{-}1344}$ – area under the plasma concentration time curve within the last dosing interval period of 2 months (1344 hrs), SD – standard deviation.

Figure legends

Figure 1: Schematic pregnancy PBPK model diagram illustrating organs and tissues as compartments, and blood flows as (blue/red) arrows. IM – intramuscular.

Figure 2. Predicted average plasma concentration-time profile of approved dosing regimens of LAI cabotegravir LAI rilpivirine without oral lead-in in pregnant and non-pregnant adults. A – Monthly LAI cabote-

gravir; B - Bimonthly LAI cabotegravir; C - Monthly LAI rilpivirine; and D - Bimonthly LAI rilpivirine. C_{trough}– plasma concentration at the end of the dosing interval.

Figure S1: Sensitivity analyses of plasma concentrations of (A) rilpivirine and (B) cabotegravir to variations (± 37.5 and 75%) of their respective release rates from the long-acting injectable formulations in the PBPK model. The sensitivity analysis was performed for single doses of 900 mg long-acting rilpivirine and 600 mg long-acting cabotegravir.

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