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A population pharmacokinetics analysis assessing the exposure of raltegravir once-daily 1200mg in pregnant women living with HIV

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Abstract

Once-daily two 600mg tablets (1200mg QD) raltegravir offers an easier treatment option compared to the twice-daily regimen of one 400mg tablet. No pharmacokinetic, efficacy or safety data of the 1200mg QD regimen have been reported in pregnant women to date as it is challenging to collect these clinical data. This study aimed to develop a population pharmacokinetic (popPK) model to predict the pharmacokinetic profile of raltegravir 1200mg QD in pregnant women and to discuss the expected pharmacodynamic properties of raltegravir 1200mg QD during pregnancy based on previously reported concentration-effect relationships. Data from 11 pharmacokinetic studies were pooled (n=221). A two-compartment model with first-order elimination and absorption through three sequential transit compartments best described the data. We assessed that the bio-availability of the 600mg tablets was 21% higher as the 400mg tablets, and the bio-availability in pregnant women was 49% lower. Monte-Carlo simulations were performed to predict the pharmacokinetic profile of 1200mg QD in pregnant and non-pregnant women. The primary criteria for efficacy was that the lower bound of the 90% confidence interval (CI) of the concentration before next dose administration (C_{trough}) geometric mean ratio (GMR) of simulated pregnant/non-pregnant women had to be >0.75. The simulated raltegravir C_{trough} GMR (90%CI) was 0.51 (0.41-0.63), hence not meeting the primary target for efficacy. Clinical data from two pregnant women using 1200mg QD raltegravir showed a similar C_{trough} ratio pregnant/non-pregnant. Our pharmacokinetic results support the current recommendation of not using the raltegravir 1200mg QD regimen during pregnancy until more data on the exposure-response relationship becomes available.

Introduction

Antiretroviral treatment is particularly important in pregnant women living with HIV, because adequate antiretroviral drug (ARV) therapy dramatically reduces the risk of mother-to-child-transmission of HIV (1, 2). However, physiological changes during pregnancy often decrease the ARV exposure, as a result of hampered absorption, increased volume of distribution and/or increased metabolism and elimination (3, 4). To ensure adequate ARV efficacy and safety, the pharmacokinetics of every ARV has to be examined in pregnant women living with HIV. Generally, it takes around 6 years to fill this knowledge gap after drug registration, during which pregnant women and their unborn babies are at risk for inadequate antiviral therapy (5).

In 2017, a novel raltegravir formulation was granted market authorization. This once-daily (QD) regimen of two 600mg tablets (1200mg QD) offers an easier treatment option compared to the twice-daily (BID) regimen of one 400mg tablet (400mg BID). The raltegravir 1200mg QD regimen demonstrated non-inferior efficacy and similar safety to the 400mg BID regimen at 96 weeks (6, 7). The 600mg formulation can be dosed once-daily because of the less erratic absorption, higher bioavailability, higher loading dose and decreased influence of concomitant food intake (8). When dosed as 1200mg QD the mean raltegravir C_{trough} is 38% lower compared to dosing as 400mg BID, making this regimen theoretically more sensitive for possible concentration lowering influences such as drug-drug interaction and pregnancy (8). No clinical pharmacokinetic, efficacy or safety data of the 600mg formulation in pregnant women exists up to date, and therefore this formulation is not recommended to be used during pregnancy (9).

The raltegravir 400mg BID regimen is among the preferred regimens for pregnant women in high-income settings, as it produces rapid viral load decline, has low potential for drug-drug-interactions and the experience with its use in pregnancy is growing (1, 10). Pharmacokinetic data showed that the raltegravir exposure decreases on average by 29%-54% in pregnant women treated with raltegravir 400mg BID (11, 12). The sufficient rate of virologic response, large pharmacokinetic variability and debatable concentration-efficacy relationship led to the conclusion that the decreased exposure of the BID-regimen during pregnancy would not be of clinical relevance (11, 12).

The concentration-efficacy relationship is debatable for raltegravir; no relationship could be observed for the 400mg BID and 1200mg QD regimen up to date (13). However, a relationship has been observed for the raltegravir 800mg QD regimen. This regimen demonstrated inferiority in achieving HIV RNA <50 copies/mL compared to the 400mg BID regimen (14). Logistic regression models and a receiver operating characteristic (ROC) curve showed that individuals with a C_{trough} <0.020mg/L had a greater chance of failing to achieve viral suppression, although the sensitivity was low (45%) and the specificity moderate (75%) (13). The mean C_{trough} of patients treated with raltegravir 800mg QD (0.018 mg/L) was lower as the observed mean C_{trough} of pregnant patients treated with 400mg BID (0.064 and 0.077 mg/L), indicating efficacy of this regimen during pregnancy (11, 12, 14). This also suggests no concentration-effect relationship could be observed for the 400mg BID because the pharmacokinetic parameters remain above the minimum concentration needed for efficacy (13).

The availability of multiple proven effective and safe alternative ARVs makes it challenging, or even impossible, to timely collect clinical pharmacokinetic data of the raltegravir 1200mg QD regimen in

pregnant women. As the formulation, dosage and dosing schedule differ for the 1200mg QD we cannot directly apply the findings from the pharmacokinetic studies in pregnant women treated with 400mg BID raltegravir. A population pharmacokinetic (popPK) model can be used to characterize the concentration-time course of a drug for individual subjects, and to simulate concentration-time profiles under varying conditions as different dosing regimens and populations. This approach enables a timely assessment of the applicability a new formulation in pregnant women without putting a variety of women at risk. This study aims to i) develop a popPK model for raltegravir in individuals with and without HIV-infection (400mg and 600mg formulations), including pregnant women (400mg formulation), ii) to predict the pharmacokinetic profile of raltegravir 1200mg QD in pregnant women, and iii) to discuss the expected pharmacodynamic characteristic of raltegravir 1200mg QD in pregnancy based on the published concentration-effect relationship.

Methods:

Pharmacokinetic data

Data from 11 pharmacokinetic studies with raltegravir and rich sampling schedules were pooled (8, 11, 15-22). These studies include a combination of healthy and HIV-infected subjects taking 400mg and 600mg raltegravir tablets, and pregnant subjects taking the 400mg tablets. The study protocols and subject characteristics are summarized in Table 1, and detailed information can be found in the original publications (8, 11, 15-22). Twenty-two European, HIV-infected, pregnant women treated with a 400mg BID raltegravir-based regimen were included to determine the effect of pregnancy on the pharmacokinetics of raltegravir. These women underwent intensive pharmacokinetic sampling during the third trimester (preferably at 33 weeks gestation) and postpartum (4-6 weeks after giving birth). *The exclusion criteria* are described in the Supporting Information.

Development population pharmacokinetic model

A population pharmacokinetic model was developed using NONMEM 7.4 (ICON Development Solutions, Hanover, MD, USA). The first-order conditional estimation method with eta-epsilon interaction was used. Pirana 2.9.7 (Certara, Princeton, NJ, USA) was used as an interface to NONMEM and to structure and document model development, R 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria) for data management, graphical visualization and evaluation, and Perl speaks NONMEM (PsN) for automation of a diverse range of processes related to model development (23).

Several population pharmacokinetic models have previously been developed for healthy or HIV-infected children and adults treated with raltegravir 400mg tablets (24-27). However, visual predictive checks (VPCs) showed none of these models were able to directly describe the absorption and elimination profile adequately in our larger dataset. Model development was conducted in a step-wise fashion (28). We started with the pharmacokinetic data of healthy subjects using raltegravir 1200mg QD, because this regimen has a less variable absorption and a longer dosing interval, facilitating estimation of the primary pharmacokinetic parameters. Subsequently the data of healthy subjects using raltegravir 400mg BID, patients living with HIV using raltegravir 1200mg QD, patients living with HIV using raltegravir 400mg BID and pregnant women living with HIV using raltegravir 400mg BID were added stepwise. The model structure was re-evaluated after each round including new data.

One, two and three compartment models were evaluated. First- and zero-order (dual) absorption models, entero-hepatic recirculation, mixture and transit absorption models were evaluated to describe the variable absorption of raltegravir. Model selection was based on maximum likelihood statistics (quantified by the objective function value [OFV]), with a 5% significance level (dOFV 3.84), physiological plausibility, precision in parameters estimates, standard goodness-of-fits plots and visual predictive checks.

The typical bioavailability (F) value was set to 1, because no intravenous data was available to allow for estimation of the absolute bioavailability. For the stochastic component of the model, log-normal and box-cox transformed distributions for the interindividual variability (IIV) and interoccasion variability (IOV) between doses were tested (29, 30). Normally distributed additive, proportional and combined residual error model structures were tested, next to a dynamic transform-both-sides approach which allows estimation of both the shape and scedasticity parameters (30). Also, a time-varying approach to empirically account for model errors resulting from the erratic and highly variable absorption of raltegravir was tested with a different proportional error for the time before and after 3h (the average timepoint for C_{max}) (2, 31). The lower limit of quantification (LLOQ) of the different studies are shown in Table 1. Below LLOQ (BLOQ) values were included as LLOQ divided by 2 (1% of the total samples). The consecutive BLOQ values in the elimination phase and the predose BLOQ samples of single-dose studies were excluded (2% of the total samples).

All flow and volume parameters were scaled with body weight according allometric theory, with fixed allometric exponents of 0.75 for flow parameters and 1 for volumes of distribution (32). For pregnant women, postpartum weight was used since applicability of allometric scaling for pregnant women has not

been established and could confound the potential pregnancy effect (32). In the case of missing postpartum weight (n=4), the weight was calculated from the third trimester weight times the mean difference between third trimester and postpartum weight (-7%).

Covariate testing was based on physiological plausibility and results from previous population pharmacokinetic models. Sex was tested as covariate on F, and Caucasian ethnicity as covariate on central volume of distribution (Vc) (25). We tested atazanavir and efavirenz co-administration as covariates on F and CL (20, 21, 33). Pregnancy was tested as a dichotomous covariate on CL, mean absorption time (MAT), F, Vc and absorption rate (Ka) (3). Covariates-parameter relations were evaluated using a forward inclusion and backward elimination approach. The selection was based on biological plausibility, previous models and maximum likelihood statistics (quantified by a 5% significance level (dOFV 3.84) applied for likelihood ratio testing of nested models. Because the pregnancy covariate was the most defining covariate, this covariate was evaluated extensively. A sensitivity analysis was performed for all significant covariates effects of pregnancy separately. This means that separate simulations were carried out and that we evaluated whether the choose for a covariate pregnant defined the conclusion based on our primary endpoint.

Different meal types have considerable and variable effect on the pharmacokinetic profile of raltegravir (8, 34). A low-fat meal compared to fasted conditions decreases raltegravir exposure for the 400mg and 600mg tablets in a similar matter (8). The pharmacokinetic profile of raltegravir is not meaningfully altered by a moderate-fat meal, while the exposure is increased with a high-fat meal and this effect is more pronounced for the 400mg formulation than the 600mg formulation (8, 34). Only data of the 600mg formulation across different meal types was available to us. The effect of food (irrespective of meal type), a low-fat meal (389 kcal, 6.9% fat) and a moderate-fat meal (650-844 kcal, 48% fat) as a covariate on F and MAT in subjects using the 600mg formulation was tested, assuming a similar food effect for the 400mg formulation. The studies examining the 400mg raltegravir formulation were performed under fasted or moderate fat conditions, as shown in Table 1.

Simulations

To predict the pharmacokinetic profile of raltegravir 1200mg QD in pregnant and non-pregnant individuals simulations with the final model were performed. Monte-Carlo simulations with 3000 individuals with multi-level of random effect (parameter uncertainty, inter-occasion variability and inter-individual variability) were conducted. The procedure was repeated 1000 times using Stochastic

Simulation and Estimation (SSE) from PsN to account for parameter uncertainty. The parameter uncertainty was obtained from a sampling importance resampling (SIR) procedure (35). The covariate distribution in the simulation dataset was derived from 186 pregnant and postpartum women of the European Pharmacokinetics of newly developed ANtiretroviral agents in HIV-infected pregNAnt women (PANNA) study (www.pannastudy.com). These covariates were resampled, maintaining the covariate structure, 3000 times with 10% noise. Simulations were conducted without residual error.

Six scenarios were evaluated: the concentration-time curve of pregnant and non-pregnant women treated with raltegravir 1200mg QD at steady-state under fasted, low-fat and moderate-fat conditions. High-fat conditions were not simulated because the model did not perform sufficiently under these conditions and it was not believed to be a commonly occurring meal type (~1000 kcal and 50% fat). We assumed that postpartum weight was similar to non-pregnant weight. The same 3000 individuals were simulated under the six different conditions. The $AUC_{0\text{-}24h}$ was derived from the model and the C_{trough} was defined as the individual predicted concentration on 24h after drug intake.

Target values simulation

As a proxy for efficacy, the C_{trough} of pregnant women on the 1200mg QD raltegravir dosing regimen was compared to the same metric in non-pregnant women. The lower bound of the 90%CI of the GMR C_{trough} of pregnant / non-pregnant women was defined to be >0.75, similarly to the target established in drug-drug interaction studies with the raltegravir 1200mg regimen by the manufacturer and regulatory authorities (22, 36). A secondary outcome parameter was the proportion of individuals with a C_{trough} <0.020 mg/L among pregnant compared to non-pregnant women using 1200mg QD. This target was derived from the receiver operating characteristic (ROC) curve from the pharmacokinetic data of the inferior 800mg once-daily regimen (converted from 45nM by calculating with a raltegravir molar mass of 0.0004444 mg/nmol) (13).

Additionally, the simulated GMRs were compared with the clinical data of two women included in the PANNA study. This European, open-label, multi-center, within-patient, pharmacokinetic phase-IV study includes pregnant women living with HIV using raltegravir 1200mg QD. At third trimester (approximately 33 weeks) and postpartum (preferably 4-6 weeks), EDTA blood samples were collected at 0, 0.5, 1, 2, 3, 4, 6, 8, 12 and 24h after observed intake of raltegravir with moderate-fat food (650 kcal; 30 g fat). Plasma concentrations were centrally analyzed using a validated liquid chromatography based assay (LLOQ 0.01

mg/L) (37). Pharmacokinetic parameters were determined using non-compartmental analysis (Phoenix 64 version 8.1, Certara). The detailed protocol of this study has been described in an earlier publication (11).

Results

Data from 11 studies with 226 individuals and 5,772 sampling points were pooled. In the following order, we excluded 1164 samples due to interacting co-medication, 99 BLOQ values (while 70 were imputed as LLOQ/2) and 493 non-evaluable samples as defined in the methods. Ultimately, the popPK model was built with 221 individuals and 4,016 sampling points as showed in Table 1.

A two-compartment model with first-order elimination and absorption through three sequential absorption compartments best described the data. The structure of the model is depicted in Figure 1. The transit rate constant (k_{tr}) was estimated and MAT was based on Eq.1:

ktr = n +1 / MAT

with *n* equals the number of transit compartments. We included log-normally distributed IIV on CL, Vc, Q, Vp and the residual error, as well as log-normally distributed IOV between doses on F and MAT. IIV correlations on CL with Q, and Q with Vp were included (dOFV –62.5). A time-varying and log-normally distributed proportional error structure with one proportional error for first 3 hours after drug intake and one for more than 3 hours after drug intake was included to empirically account for the larger observed variability during the absorption phase compared to the disposition phase (dOFV -112.7) (2).

The following covariate-parameter relationships were included: a dichotomous covariate for intake with food (irrespective of meal type) on MAT (dOFV -46.76, 160% increase with food), a dichotomous covariate for atazanavir co-administration on CL (dOFV -12.43, 17% decrease with atazanavir), a dichotomous covariate for the 600mg formulation on F (dOFV -5.88, 21% increase with 600mg formulation vs 400mg formulation), a dichotomous covariate for intake with a low-fat meal on F (dOFV -46.98, 45% decrease with a low-fat meal), a dichotomous covariate for the 600mg formulation on the magnitude of IOV in F (dOFV -127.31, 72% decrease with 600mg formulation vs 400mg formulation), a dichotomous covariate for efavirenz co-administration on F (dOFV -5.28, 17% decrease with efavirenz), and a dichotomous covariate for being pregnant on F (dOFV -17.82, 49% decrease during pregnancy). The sensitivity analysis for the pregnancy covariate is included in the Supporting Information. The final population estimates are shown in Table 2.

A VPC based on 1000 samples and stratified for pregnancy and tablet formulation, is shown in Figure 2. This VPC indicated an adequate model fit to the observed concentration-time data. Standard goodness-of-fit plots indicated no bias in the structural model or unaccounted data heterogeneity (Supporting information).

A 21% higher bioavailability (relative standard error [RSE] 26%) was estimated for the 600mg tablets in comparison to the 400mg tablets, and a 49% lower bioavailability (RSE 14%) was estimated in pregnant compared to non-pregnant women. Predictions of raltegravir $AUC_{0\text{-}24h}$ and C_{trough} in pregnant women treated with 1200mg QD raltegravir are shown in Table 3. The predicted GM (95%CI) raltegravir C_{trough} was 0.024 (0.002-0.133), 0.014 (0.001-0.086), 0.027 (0.003-0.160) mg/L in pregnant women treated with 1200mg QD raltegravir in fasted, low-fat and moderate-fat conditions, respectively. Simulations of non-pregnant and pregnant women treated with 1200mg QD raltegravir showed that the GMR (90%CI) was 0.51 (0.41-0.63) (Table 3). The lower bound of the 90%CI GMR was not >0.75, hence the primary efficacy target was not fulfilled.

The predicted proportion with a C_{trough} <0.020 mg/L was substantially higher in pregnant women compared to non-pregnant women using 1200mg QD. Under fasted conditions 36.5% of the simulated pregnant women had a C_{trough} < 0.020 m/L, compared to 17.1% of the simulated non-pregnant women. This was 58.6 vs. 31.7%, and 33.7% vs. 15.2% for low-fat and moderate-fat conditions, respectively.

These results were similar compared to the clinical data of two pregnant women from the PANNA study, as depicted in Figure 3. Woman 1 was co-treated darunavir/ritonavir 800/100mg QD. At 33 weeks gestational age, raltegravir $AUC_{0\text{-}24h}$ and C_{trough} were 16.25 mg*h/L and 0.012 mg/L, respectively. At 4 weeks postpartum, raltegravir $AUC_{0\text{-}24h}$ and C_{trough} were 22.72 mg*h/L and 0.027 mg/L, respectively. This corresponds to a C_{trough} ratio pregnant/non-pregnant of 0.52. The second woman was co-treated with emtricitabine/tenofovir disoproxil fumarate 200/245mg and an $AUC_{0\text{-}24h}$ of 13.09 mg*h/L and C_{trough} of < 0.01 mg/L was estimated at 32 weeks gestational age. At 5 weeks postpartum, we assessed an $AUC_{0\text{-}24h}$ of 27.24 mg*h/L and C_{trough} of 0.015 mg/L. Although BLOQ during third trimester, the C_{trough} was measurable and we calculated an approximate C_{trough} ratio pregnant/non-pregnant of 0.46. Although these women had a C_{trough} <0.020 mg/L at third trimester, both women had an HIV RNA viral load <50 copies/mL at third trimester and at postpartum visit. Woman 1 delivered a healthy boy of 4010 gram at 40 weeks gestational age. The boy had a negative HIV viral load at delivery. The healthy boy of woman 2 was born at 39 weeks of gestational age, was 2886 gram and also had a negative HIV viral load at delivery.

Discussion:

With this popPK model we performed a first evaluation of the drug exposure with the 1200mg QD raltegravir regimen in pregnant women. We estimated that physiological changes during third trimester of pregnancy decrease the bioavailability of raltegravir with 49% compared to non-pregnant women. The predetermined primary target was not met, and simulations predicted that a substantial part of the pregnant women treated with 1200mg QD had an anticipated C_{trough} <0.020 mg/L.

The primary target was set on the basis of the criteria of the 1200mg QD regimen used in interaction studies from the manufacturer and the submission to the European regulatory authority (22, 36). No pharmacokinetic target has been established for the raltegravir 1200mg QD regimen, as no clear relationship between plasma concentrations and virologic response has been established up until now for this regimen (7). Therefore, we believe that a conservative approach is suitable, aiming at a marginal deviation from the general population for which efficacy has been demonstrated. The efficacy of the 1200mg QD regimen was shown in a non-inferiority trial in a population of treatment-naïve adults (n=797) with HIV RNA >1000 copies/mL with a median (interquartile range) raltegravir C_{trough} of 0.050 (0.028-0.094) mg/L (7).

We predicted that a substantial proportion of the pregnant women using raltegravir 1200mg QD will have a C_{trough} <0.020 mg/L. This C_{trough} target was derived from a study with raltegravir 800mg QD in treatment-naïve patients with a high viral HIV load at baseline, so this target may not be applicable to our population (13). Also, the C_{trough}, C_{max} and AUC relate differently to each other for the 1200mg QD dosing regimen compared to the 400mg BID and 800mg QD regimens, and it remains unclear whether this C_{trough} target can be applied to other dosing regimens. Clinical data suggests that the C_{trough} target is not applicable to the 1200mg QD regimen since no direct relationship between a low C_{trough} (median C_{trough} of 0.019 mg/L in the lowest quartile) and virologic failure could be observed in 797 participants during the phase 3 study with the 1200mg QD regimen (14).

The current popPK modelling and simulating approach has several limitations. Raltegravir plasma concentrations show high variability between and within individuals due to the erratic absorption, making model development and derivation of significant covariates challenging. Various tested absorption models were not able to well describe the variable absorption with multiple peaks of raltegravir, an empirical time-varying residual error model was included (2). Furthermore, we assumed that physiological changes

during pregnancy had a similar effect on the 400mg as on the 600mg formulation. This is theoretically expected for the pregnancy effects such as the possible increased volume of distribution and increased clearance. However, the possibly increased gastric pH, decreased gastric emptying and increased intestinal transit time in pregnant women could impact both formulations differently (38, 39). The 600mg tablet is believed to disintegrate and dissolute faster as the 400mg tablet, and a diminished influence of concomitant high-fat food intake has been observed for the 600mg tablet(8). Since research indicates that the gastrointestinal changes during pregnancy have an overall minimal effect on the bio-availability of drugs (40), and since the absorption of raltegravir is multi-factorial and highly variable, we expect that the different gastro-intestinal pregnancy effect on both formulations are likely to be negligible. The influence of physiological changes during pregnancy can also differ for the divergent food conditions and we based our conclusion on pregnancy data with moderate-fat food conditions only. We were also not able to test the effect of a moderate-fat meal on raltegravir pharmacokinetics separately, because this individual data was not available to use. We based the absence of a moderate-fat meal effect on F on earlier pharmacokinetic research (34). Total raltegravir concentrations were predicted with our popPK model, while the unbound raltegravir concentration functions as the active motion. The unbound drug fraction can change during pregnancy because the plasma protein concentration decrease (3, 41). No data of unbound raltegravir concentration was available to us, but the difference in raltegravir unbound fraction is expected be marginal as raltegravir is modestly bound to plasma proteins (~83%) (36).

Adequate performance of our simulations with the 1200mg QD regimen are indicated by comparisons to earlier data. A historical, small, multiple-dose, pharmacokinetic study determined an GM $AUC_{0\text{-}24h}$ and C_{trough} of 26.46 mg*h/L and 0.036 mg/L in non-pregnant women in fasted state, which are similar to our predictions of 25.45 mg*h/L and 0.047 mg/L, respectively (8). The predicted pharmacokinetic parameters of pregnant women using 1200mg QD were also similar to the clinical data of two pregnant women from the PANNA study. The C_{trough} ratio pregnant / postpartum of these two women fell in the 90%CI of our predicted C_{trough} GMR. These subjects had an adequate virological response and no MTCT occurred.

Simulations with a popPK model of raltegravir 1200mg QD in pregnant women suggested inadequate raltegravir exposure during the third trimester of pregnancy. There is, however, a limited knowledge on the concentration-efficacy relationship of the 1200mg QD regimen. Therefore, it is difficult to establish whether the inadequate exposure results in inadequate response. Although the limited, available clinical data (with lower raltegravir exposures) suggested an adequate virologic response, data of two cases are not powered to support clinical efficacy of raltegravir 1200mg QD during pregnancy. A conservative

approach restraining the use of the QD regimen in pregnant women seems reasonable until additional research confirms that approximately 50% lower raltegravir exposures for the raltegravir 1200mg QD regimen remain effective. The raltegravir 400mg BID regimen demonstrated adequate efficacy and safety during pregnancy and is a good alternative for these women. When treatment with raltegravir 1200mg is believed to be necessary in a pregnant woman, intensive viral load monitoring and opportunistic collection of clinical and pharmacokinetic data is advised.

Study highlights:

- What is the current knowledge on the topic?

The twice-daily regimen of one 400mg raltegravir tablet is among the preferred regimens for pregnant women and adequate clinical, pharmacokinetic and safety data is available. However, such data do not exist for the once-daily regimen of two 600mg raltegravir tablets.

- What question did this study address?

Is the 1200mg once-daily raltegravir regimen an effective treatment option during pregnancy based on the estimated pharmacokinetic profile and the expected pharmacodynamic properties of this regimen?

- What does this study add to our knowledge?

Simulations with the developed popPK model suggested inadequate raltegravir exposure in third trimester women using raltegravir 1200mg once-daily.

- How might this change clinical pharmacology or translational science?

This popPK model serves as an *in silico* prediction tool to predict raltegravir exposure in various populations using the 400mg and 600mg tablet formulations. Predictions showed restraining the once-daily raltegravir regimen for now in pregnant women seems reasonable until more data becomes available.

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Author Contributions:

T.P., E.S., A.C., V.B. and D.B. designed the research . V.B., E.S. and T.P. analyzed the data and performed the research. V.B., E.S. and T.P. wrote the manuscript.

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Figure legends

Figure 1: Final model structure. *Ktr, first-order transit rate; Ka, first-order absorption rate; Vc central volume of disbribution; Vp peripheral volume of distribution; Q, intercompartmental clearance; CL, clearance.*

Figure 2: Visual predictive check of the final model (simulations n=1000). The *observations are indicated by black dots. The median (continuous line) and 2.5th and 97.5th percentiles (dashed lines) of the observations are shown. The gray shaded areas indicate the 95% confidence interval around the median, 2.5th and 97.5th percentile of the simulated data. Vertical markers are sampling points*

Figure 3: Comparison of the simulated GMR pregnant /non-pregnant C_{trough} with the ratio derived from the clinical data of two pregnant women. *The median (solid line) and 5th and 95th (dashed line) percentile of the simulated GMR C_{trough} are shown. The ratio third trimester /postpartum C_{trough} of the two clinical cases are indicated by the dot-dashed line. GMR: geometric mean ratio; C_{trough}: concentration before next dose administration.*

Supplemental Information

Supplemental Material

Table 1: Patient and study characteristics summarized by study

	Number of patients	Number of samples	Number of patients included	Number of samples included	Population	Female sex, %	Age, years [median (range)]	Weight, kg [median (range)]	Raltegravir Regimen	Fed status at drug intake	Sampling design, hours postdose	Lower limit of quantification, mg/L
(12)	24	564	24	515	Healthy	54%	31 (18-55)	67 (48-99)	400mg BID	Fasted	0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12 at steady state	0.014
(13)	18	432	16	176	Healthy	50%	43 (22-55)	71 (52-93)	400mg BID	Fasted	0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12 after single dose	0.014
(20)	24	528	23	228	Healthy	52%	35 (20-53)	70 (49-103)	400mg BID	Fasted	0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 at steady state	0.014
(15)	24	528	22	379	Healthy	53%	47 (18-53)	74 (59-95)	400mg BID	Fasted	0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 at steady state	0.014
(16)	18	393	18	321	HIV-infected	17%	45 (37-75)	76 (67-110)	400mg BID + 800mg QD	Moderate fat [a]	0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 /24 at steady state	0.014
(9)	22	353	22	313	HIV-infected, pregnant	100%	33 (23-44)	65 (43-89)	400mg BID	Moderate fat [a]	0, 0.5, 1, 2, 3, 4, 6, 8, 12 at steady state	0.014
(7)	18	594	18	561	Healthy	89%	41 (25-55)	64 (49-97)	1200mg QD	Fasted + Low-fat + high-fat [a]	0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48 after single dose	0.002
(7)	23	532	23	460	Healthy	30%	42 (25-55)	77 (60-96)	1200mg QD	Fasted	0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24 at steady state	0.002
(17)	21	560	21	507	Healthy	10%	32 (21-52)	83 (59-111)	1200mg QD	Fasted	0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 167.5 after single dose	0.002

(18)	14	364	14	336	Healthy	64%	40 (21-55)	72 (59-95)	1200mg QD	Moderate fat [a]	0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 48, 72, 263 after single dose	0.002
(19)	20	924	20	220	HIV-infected	10%	53 (29-62)	75 (54-108)	1200mg QD	Fasted	0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24 at steady-state	0.002

a lowfat: 389 kcal, 6.9% fat; moderate-fate: 650-844 kcal, 48% fat; high-fat: 997 kcal, 51% fat

Abbreviations: BID twice-daily; QD once-daily

Table 2: Final population estimates

Parameter	Parameter estimate	RSE (%) from SIR
K_a (h^{-1})	0.741	2
MAT (h), fasted	0.336	8
- factor change in MAT fed [a]	1.6	19
V_c/F (L) [b]	44.3	7
CL/F (L/h) [b]	55.8	5
- factor change in CL with atazanavir [a]	-0.17	25
Q/F (L/h) [b]	5.68	7
V_p/F (L) [b]	92.8	9
F [c]	1 (fixed)	
- factor change in F 600mg formulation [a]	0.209	26
- factor change in F low-fat meal [a]	-0.459	9
- factor change in F pregnancy [a]	-0.487	14
- factor change in F efavirenz co-administration [a]	-0.167	37
IIV V_c/F (%)	69.7 [d]	14 [e]
IIV CL/F (%)	28.6 [d]	6 [e]
- Correlation coefficient with Q/F	0.18	41
IIV Q/F (%)	71.5 [d]	12 [e]
- Correlation coefficient with V_p/F	0.59	10
IIV V_p/F (%)	115.2 [d]	22 [e]
IIV residual error (%)	25.6 [d]	5 [e]
IOV F (%), 400mg formulation	112.1 [d]	17 [e]
- factor change in IOV in F 600mg formulation [f]	-0.718	4
IOV MAT (%)	140.5 [d]	21 [e]
Proportional residual error ≤ 3 hours after drug intake (%)	43.5 [d]	3 [e]
Proportional residual error > 3 hours after drug intake (%)	29.0 [d]	2 [e]

a the covariate effects of fed conditions on MAT, atazanavir on CL, 600mg formulation on F, low-fat meal on F, pregnancy on F, efavirenz on F and 600mg formulation on IOV F were obtained with: MAT in fed conditions = MAT fasted * (1 + factor

change in MAT fed); CL when atazanavir co-administration = clearance * (individual weight / 70) $^{0.75}$ * (1 + factor change in CL with atazanavir); F in pregnancy, 600mg formulation, low-fat meal and efavirenz co-administration = 1 * (1 + factor change in F 600mg formulation) * (1 + factor change in F low-fat meal) * (1 + factor change in F pregnancy) * (1 + factor change in F efavirenz-co-administration)

b for the typical individual weighing 70kg

c the reference case for F is non-pregnant, the 400mg formulation, other food conditions as low-fat, and no efavirenz co-administration.

d transformed from log normal variance to %CV with √(exp(variance)-1)

e transformed individual SIR results from log normal variance to %CV with √(exp(variance)-1) for calculation of the relative standard error.

f the covariate effect of 600mg formulation on the IOV F was obtained with: (1 + factor change in IOV in F 600mg formulation) * IOV F 400mg formulation

Abbreviations: Ka, first-order absorption rate; MAT, mean absorption time; Vc/F apparent central volume of disbribution; CL/F apparent clearance; Q/F, apparent intercompartmental clearance; Vp/F apparent peripheral volume of distribution; F, bioavailability; IIV, inter-individual variability; IOV, inter-occasion variability; RSE, relative standard error; SIR, sampling importance resampling

Table 3: Simulated pharmacokinetic parameters of pregnant and non-pregnant women treated with 1200mg QD (two tablets of 600mg). *AUC: area under the curve; Ctrough: concentration before next dose administration; GMR: geometric mean ratio; GM: geometric mean; NA: not applicable.*

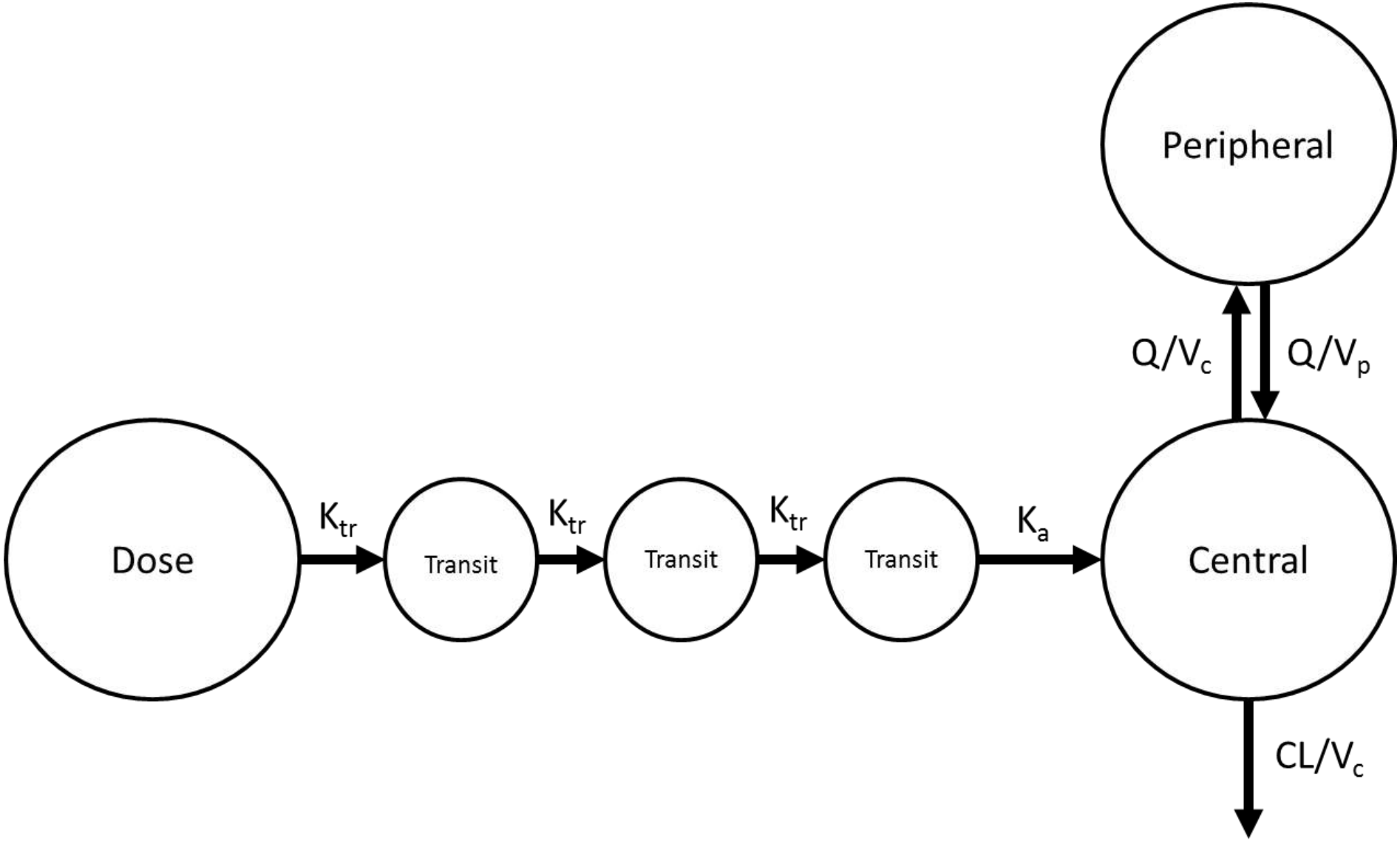
		Simulations repeated 1000 times with alternative parameters estimates (n individuals = 3000)			**Simulations with typical parameter estimates (n individuals = 3000)**		**Historical reference**
Condition	**Parameter**	**Pregnant vs. non-pregnant, GMR (90%CI)**	**% Pregnant women with C_{trough} < 0.020 mg/L GM (95%CI)**	**% Non-pregnant women with C_{trough} < 0.020 mg/L, GM (95%CI)**	**Pregnant, GM (95%CI)**	**Non-pregnant, GM (95%CI)**	**Non-pregnant, GM (95%CI)**
Fasted	$AUC_{0\text{-}24h}$, mg *h/L	0.51 (0.41-0.63)	36.5 (25.9-50.2)	17.1 (12.5-22.2)	13.06 (5.69-28.53)	25.45 (11.09-55.60)	26.46 (22.83-30.66) [a,b]
	C_{trough}, mg/L				0.024 (0.002-0.133)	0.047 (0.004-0.250)	0.036 (0.027-0.047) [a,b]
Lowfat	$AUC_{0\text{-}24h}$, mg *h/L		58.6 (45.2-72.3)	31.7 (24.7-40.2)	7.06 (3.08-15.43)	13.76 (6.00-30.08)	14.62 (12.69-16.85) [a,c,d]
	C_{trough}, mg/L				0.014 (0.001-0.086)	0.028 (0.003-0.169)	0.021 (0.016-0.039) [a,c]
Modfat	$AUC_{0\text{-}24h}$, mg *h/L		33.7 (23.6-47.3)	15.2 (11.0-20.2)	13.06 (5.69-28.53)	25.45 (11.09-55.60)	NA
	C_{trough}, mg/L				0.027 (0.003-0.160)	0.052 (0.005-0.312)	NA

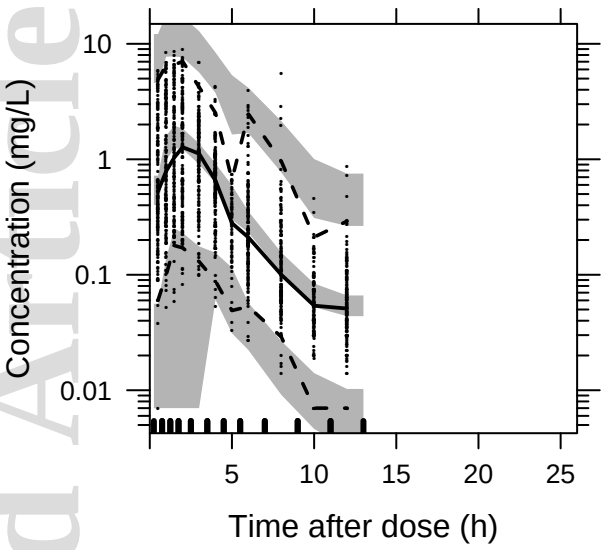
a calculated from nM to mg/L and h*nM to mg*h/L by multiplying with molar mass of raltegravir of 0.0004444 mg/nmol

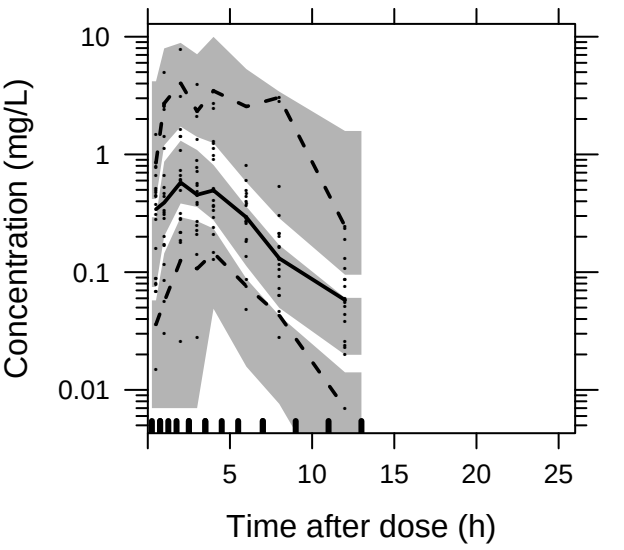
b multiple-dose pharmacokinetic study (n=23) (7)

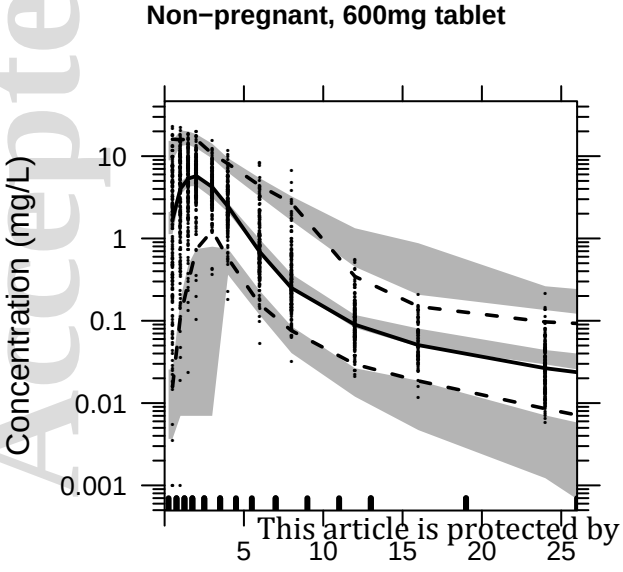
c single-dose pharmacokinetic study (n=16) (7)

d $AUC_{0\text{-}48h}$ reported









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