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First Author: Darren M. Moss
Corr. Author: Darren M. Moss

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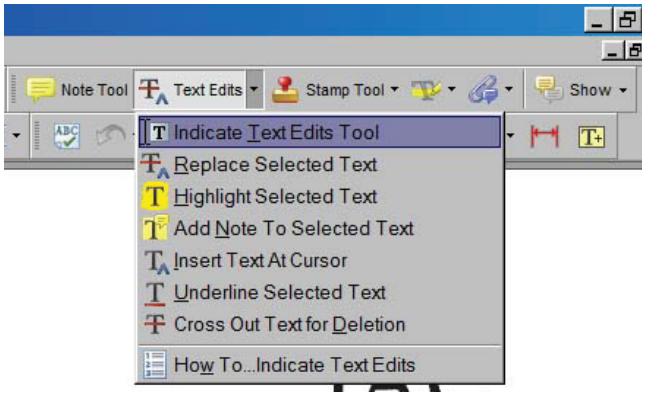

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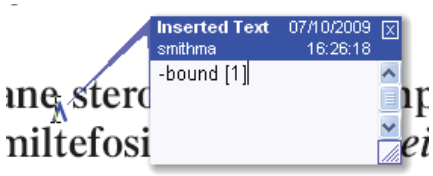

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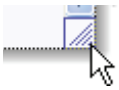

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Predicting intestinal absorption of raltegravir using a population-based ADME simulation

Darren M. Moss[1]*, Marco Siccardi[2], David J. Back[2] and Andrew Owen[2]

[1]*Molecular and Biochemical Parasitology Group, Liverpool School of Tropical Medicine, Liverpool, UK;* [2]*Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, UK*

*Corresponding author. Tel: +44-(0)151-705-3350; Fax: +44-(0)151-794-5656; E-mail: darren.moss@liverpool.ac.uk

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Objectives: Raltegravir pharmacokinetics (PK) show high intra- and inter-patient variability and are also influenced by co-administered substances that alter the gastrointestinal tract environment, such as pH-altering or metal-containing agents. The aim of this investigation was to develop a population-based absorption, distribution, metabolism and excretion (ADME) model to investigate the effects of gastrointestinal pH and ingested magnesium on raltegravir PK.

Methods: *In vitro* data describing the disposition of raltegravir were obtained from literature sources or generated by standard methods. Raltegravir (400 mg single dose) PK were simulated in healthy volunteers (50 subjects per group, 20–50 years old, 0.5 proportion female subjects) over a 12 h period.

Results: Simulated raltegravir PK correlated well with data from clinical trials, with a mean deviation in C_{max}, $AUC_{0\text{-}12}$ and C_{trough} of <20%. Solubility of raltegravir in the gastrointestinal tract was increased at higher luminal pH. Increased intestinal pH and transit time both correlated with higher raltegravir absorption ($P<0.001$). Magnesium ingestion reduced raltegravir exposure in simulated subjects, with mean C_{trough} reduced by 32% ($P<0.001$).

Conclusions: The *in vitro–in vivo* extrapolation model developed in this study predicted raltegravir PK in virtual individuals with different gastrointestinal pH profiles. The main PK variables were predicted with good accuracy compared with reference data, and both luminal pH and magnesium were able to influence drug absorption. This modelling system provides a tool for investigating the absorption of other drugs, including HIV integrase inhibitors currently in development, which have also shown interactions with food and metal-containing products.

Keywords: HIV, pharmacokinetics, integrase inhibitors, permeability, IVIVE

Introduction

Raltegravir shows marked variability in pharmacokinetics (PK) both between patients and in the same patient over time. High variability in raltegravir C_{trough}, with median coefficients of variation (CV%) of 128% and 245% for inter- and intra-patient variability, respectively, has been observed in a clinical cohort.[1] Similar high variability has been observed when assessing raltegravir plasma AUC.[2] High intra-individual variability in plasma raltegravir concentrations and inconsistent concentration–response relationships have complicated the use of therapeutic drug monitoring and predictive PK modelling of raltegravir.

The primary route of raltegravir elimination is glucuronidation via the liver, with around 30% being excreted in urine.[3] Metabolism is achieved by UDP-glucuronosyltransferase 1A1 (UGT1A1) and the drug is neither a substrate for nor an inhibitor of major cytochrome P450 enzymes.[3,4] Atazanavir inhibits UGT1A1, causing an increase in raltegravir exposure, and rifampicin mediates induction of UGT1A1, causing a decrease in raltegravir exposure.[5,6] In addition, raltegravir is a weak substrate for the drug transporters ABCB1, SLC22A6 and SLC15A1 and also inhibits SLC22A6 *in vitro*.[7] Raltegravir shows uneven distribution in tissues, with a 2.3-fold higher concentration in vaginal fluid and a 17-fold lower concentration in CSF compared with plasma.[8,9] These factors do not fully explain the high intra-patient variability in raltegravir PK, and recent clinical studies suggest that variation in raltegravir absorption may be more relevant.[10]

The PK of raltegravir are influenced by co-administered agents that raise gastrointestinal (GI) tract pH, such as omeprazole and

famotidine.[11] The rate of disintegration of standard 400 mg raltegravir tablets increases when dissolved at higher pH.[12] High-fat food has been shown to increase raltegravir exposure, which may be attributable to a fat-induced increase in raltegravir solubility, although in the same study low-fat food decreased raltegravir exposure by an unknown mechanism.[13] Furthermore, antacids containing divalent metals have been shown to reduce raltegravir C_{trough} in healthy subjects, which is believed to be the result of reduced raltegravir absorption caused by magnesium binding in the lumen.[14] These factors may contribute to the high variability observed in raltegravir PK.

Two drug efficacy studies found that 18% (2 of 11) and 33% (2 of 6) of patients who failed raltegravir therapy had no evidence of HIV integrase mutations.[15,16] These studies suggest that raltegravir therapy failure may occur independently of HIV resistance mutations. Raltegravir exposure may be an influencing factor; however, this was not investigated in the studies. Non-adherence to treatment may have also contributed to therapy failure without known resistance mutations. A statistically significant correlation between raltegravir exposure and virological response was recently demonstrated in patients taking 800 mg raltegravir once a day, where C_{trough} was a predictor of raltegravir treatment failure.[17] These data suggest that raltegravir exposure contributes to treatment failure, although high HIV RNA at baseline is the strongest correlate.

A population PK model has been published based on data from six fasted healthy volunteers given a single 400 mg dose of raltegravir, and another model has been published based on the data from 145 HIV-infected patients and 19 healthy volunteers.[10,18] The PK data used in these studies were highly variable and both concluded that the lack of information on factors with a potential effect on raltegravir absorption limits the interpretation of the results. Our previous investigations set out to determine the impact of drug transporters, pH, cationic metals, raltegravir tablet breakdown rate and various other factors on raltegravir disposition *in vitro*.[7,12,19] By incorporating these mechanistic data into physiologically based PK (PBPK) models describing physiological parameters, predictions of potential interactions between raltegravir and co-administered agents may be made *a priori*.

In vitro–in vivo extrapolation (IVIVE) is the process of using *in vitro* physicochemical, permeability and metabolic parameters to predict *in vivo* drug characteristics using PK simulation modelling. The Simcyp population-based absorption, distribution, metabolism and excretion (ADME) simulator utilizes a 'bottom-up' approach that integrates demographic, anatomical, physiological and drug-specific factors.[20] These data are included in PBPK models, based on physiological compartments that mimic ADME processes in the human body. This approach can be used to investigate drug disposition in drug discovery and development, such as PK profiling, drug–drug interactions, bioavailability and drug exposure in special populations.[21–23] Moreover, design of a clinical trial can be optimized using IVIVE by determining how factors such as sample size, sex ratio and age may influence PK.[24] Oral absorption of a drug can be simulated using different approaches and taking into account the dynamic interplay of tablet disintegration, dissolution, solubility, intestinal permeation and, for some drugs, metabolism. The advanced dissolution, absorption and metabolism (ADAM) model within Simcyp represents the GI tract as compartments based upon their physiological and anatomical characteristics, and the relationship between permeability, metabolism and dissolution, amongst other factors, can be simulated.[25] The aim of this investigation was to develop an IVIVE

Table 1. Input parameters detailing raltegravir properties

Input parameters	Value	Reference
Physical chemistry		
mol. wt	445.16	42
$LogP_{O:W}$	0.58	19
pKa	6.67	19
B/P	0.6	43
fu	0.17	43
Absorption		
P_{app} pH 7.4, $\times 10^{-6}$ cm/s	6.6	19
tablet release rate	increased at higher pH	12
solubility–pH profile	see Figure S1, available as Supplementary data at *JAC* Online	ACD/PhysChem Suite predicted
Distribution		
V_{ss}, L/kg	0.308	Simcyp predicted
Elimination		
hepatic CL_{int}, μL/min/10^6 hepatocytes	12.4	18
CL_R, L/h	3.6	32

$LogP_{o:w}$, log partition coefficient between octanol and water (pH 7); B/P, blood to plasma drug ratio; fu, free drug fraction in plasma; P_{app} pH 7.4, apical to basolateral apparent permeability in Caco-2 monolayer at pH 7.4; V_{ss}, volume of distribution; CL_{int}, intrinsic clearance; CL_R, renal clearance.

Table 2. Values for GI pH, raltegravir solubility and raltegravir PK values in each population group after a single 400 mg dose of raltegravir

	Group 1 (very low pH)	Group 2 (low pH)	Group 3 (medium pH)	Group 4 (high pH)	Group 5 (very high pH)
Stomach					
Mean pH	1	2.5	3	5	6
Raltegravir solubility, mg/mL	0.04	0.04	0.04	0.12	0.98
Duodenum					
Mean pH	4	4.5	5	6	6.4
Raltegravir solubility, mg/mL	0.04	0.08	0.12	0.98	2.4
Jejunum					
Mean pH	4.4	5	5.5	6.8	7
Raltegravir solubility, mg/mL	0.07	0.12	0.33	5.8	8.9
Ileum					
Mean pH	6.4	6.8	7.4	7.6	8
Raltegravir solubility, mg/mL	2.4	5.8	20.3	30.0	37.3
Colon					
Mean pH	5	5.5	6	6.2	6.5
Raltegravir solubility, mg/mL	0.12	0.33	0.98	1.6	2.9
C_{max}, ng/mL	1491	1980	2094	2541	2545
(5th–95th percentile)	(821–2836)	(1376–3403)	(1416–3657)	(1676–4383)	(1645–4148)
$AUC_{0\text{-}12}$, ng h/mL	5756	7285	8165	10137	11046
(5th–95th percentile)	(2486–12335)	(3770–14645)	(4308–16231)	(5321–18916)	(6169–19691)
T_{max}, h	3.7	3.3	3.2	2.3	2.1
(range)	(1.3–5.3)	(1.4–4.4)	(1.3–4.3)	(1.3–3.1)	(1.2–2.9)
C_{trough}, ng/mL	30.9	51.4	113.2	153.2	188.2
(5th–95th percentile)	(8.4–60.9)	(21.6–93.6)	(58.4–210.1)	(87.3–254.7)	(95.4–312.8)
fa	0.39	0.49	0.55	0.69	0.75
(5th–95th percentile)	(0.16–0.60)	(0.26–0.67)	(0.34–0.73)	(0.45–0.86)	(0.54–0.91)

GI pH values are the mean for each group and had a CV% set at 2% when determining pH variation for individuals within a group. Raltegravir solubility values in each GI segment are the mean for each group and were determined using the ACD/PhysChem Suite (see Figure S1, available as Supplementary data at *JAC* Online). Groups 1–5 each contained 50 individuals and represented very low (Group 1) to very high (Group 5) GI pH. Geometric mean values for C_{max}, $AUC_{0\text{-}12}$, C_{trough} and fa are given with 5th and 95th percentiles. Median T_{max} is given with range.

model for simulating raltegravir PK and to investigate the role of GI pH and ingested magnesium using the ADAM model. The model detailed in this investigation includes data from previous clinical trials and also *in vitro* data from previous studies.[7,12,19] This combined approach provides a system to determine which physiological and drug-based attributes are important in explaining high raltegravir PK variability.

Methods

In vitro–in vivo extrapolation: drug parameters

Raltegravir PK properties were simulated using the full PBPK model implemented in the Simcyp population-based simulator (Version 11.0, Simcyp Ltd, UK). Data describing raltegravir physiochemical and pharmacological properties were added to the model and are summarized in Table 1.

Raltegravir logP, pKa and apparent permeability (P_{app}) have previously been determined in-house.[19] The dissolution rate of standard 400 mg film-coated raltegravir tablets was previously determined in a physiological range of pH buffers, and a higher dissolution rate was observed with increased pH.[12] The intrinsic solubility of raltegravir at pH 1–9 was predicted using the ACD/PhysChem Suite (Toronto, Canada) and data were added to the IVIVE model (Figure S1, available as Supplementary data at *JAC* Online). The volume of distribution and penetration into tissues were predicted with the full PBPK model within Simcyp using tissue:plasma partition coefficients predicted using the method of Poulin and Theil.[26] All other factors were obtained from published literature.

In vitro–in vivo extrapolation: system parameters

All system parameters were taken from the North European Caucasian population library within Simcyp, with the exception of patient GI pH values, the ranges of which were obtained from the literature.[27–30] All simulations were performed in five separate population groups, named Group 1, 2, 3, 4 and 5. These groups contained individuals with the same physiological attributes as each other (allowing for variation around the mean) except for mean GI pH values, which increased from Group 1 to Group 5 (Table 2). All simulated groups consisted of 50% female subjects. The mean transit times of drug in the different sections of the GI tract were 0.4, 3.3 and 12 h in the stomach, intestine and colon, respectively. Each transit time is the mean for a population representative

and each segment had a CV% of 30% when determining GI transit time for individuals in a group.

In vitro–in vivo extrapolation: simulation design

Raltegravir (400 mg single dose) PK were simulated in healthy volunteers (20–50 years old, 0.5 proportion female subjects) over a 12 h period. Fifty subjects per population group were chosen as the number to use in all subsequent simulations. Simulated PK results were compared with actual PK results in published data and were used to calculate simulated geometric mean values for C_{max} (ng/mL), $AUC_{0\text{-}12}$ (ng h/mL), C_{trough} (ng/mL) and fa (fraction of dose absorbed), which were given with 5th and 95th percentiles. Median T_{max} (h) was calculated and given with range. The transit time of raltegravir through the small intestine was collected from all simulated subjects and any correlation between transit time and fraction of raltegravir absorbed was determined.

A parallel trial was performed as described above to simulate the impact of elevated GI magnesium concentrations on raltegravir PK values. Drug parameters were altered so that the Caco-2 monolayer P_{app} of raltegravir was reduced from 6.6 to 3.4 cm/s, which was taken from previously published data, simulating the impact of 25 mM magnesium salt on raltegravir P_{app}.[19]

Statistical analyses

Data were analysed using SPSS 19.0 for Windows. All data were tested for normality using the Shapiro–Wilk test. An independent *t*-test was used to determine the significance of normally distributed data and the Mann–Whitney *U*-test was used for non-normal data. A two-tailed *P* value of <0.05 was accepted as being statistically significant. The correlation between simulated raltegravir intestinal transit time (h) and fraction of drug absorbed was assessed using linear regression analysis. The regression coefficient (β) was calculated from the linear regression plot and given with 95% CI.

Results

Impact of GI pH on raltegravir solubility

The impact of pH on raltegravir solubility in the GI tract is shown in Table 2. A general trend towards increased raltegravir solubility in all GI segments can be observed by progressing from Group 1 to 5. Between groups the subjects differ only in mean GI pH values (subjects in Group 1 have very low GI pH, progressing to Group 5 subjects with very high GI pH); therefore the increase in raltegravir solubility is likely to be a direct effect of increased GI pH.

Impact of GI pH and drug intestinal transit time on raltegravir PK parameters

The impact of GI pH on raltegravir PK parameters in subject Groups 1 to 5 is also shown in Table 2. Using linear regression analysis, a general trend towards increased raltegravir exposure can be observed by progressing from Group 1 (very low GI pH) to Group 5 (very high GI pH) ($\beta=0.088$ for each group progression (95% CI = 0.077–0.099, $R^2=0.496$, $P<0.001$). Median T_{max} decreased as GI pH increased, which may be influenced by decreased tablet disintegration time and higher drug solubility during the earlier stages of the GI tract. Raltegravir intestinal transit time data were collated from subjects in all groups tested (50 subjects from each group, 250 subjects in total) and ranged from 68 to 350 min. Linear regression analysis using intestinal transit time (independent variable) and fraction of drug absorbed (dependent variable) gave a β-value of 0.099 (95% CI = 0.085–0.113, $R^2=0.427$), which equates to a 9.9% increase in fraction of drug absorbed for every 1 h increase in intestinal transit time ($P<0.001$).

The fraction of raltegravir absorbed from each GI segment is shown for subjects in Groups 1, 2, 3, 4 and 5 (Figure 1). Raltegravir absorption via the jejunum was low in subjects from Groups 1, 2 and 3 but became a more substantial route of absorption in subjects from Groups 4 and 5. Similarly, raltegravir absorption via the colon was greater in subjects from Groups 4 and 5. Group 5 subjects showed a mean drug fraction absorbed via the colon of 20% compared with small intestine. A fraction absorbed of 28% was observed for the hydrophilic drug cefradine in a separate study using rats.[31] As subjects differ only in their mean GI pH values between groups, the differences in absorption profiles between groups are likely to be pH related.

Comparison between reference and simulated raltegravir PK values

Reference PK values (mean ± SD) for C_{max} (2519 ± 1930 ng/mL), $AUC_{0\text{-}12}$ (7076 ± 4071 ng h/mL) and C_{trough} (71 ± 50 ng/mL) in Table 3 are the mean of geometric mean values for fasted, healthy volunteers in selected previous studies.[3,11,13,14,18,32] All reference values displayed high inter-study variability, as shown by the large standard deviations. Simulated PK values obtained from subjects in Groups 1 to 5 fell within the range obtained for reference PK values. Group 2 displayed the best match with the reference value for $AUC_{0\text{-}12}$ (+3% deviation) and C_{trough} (−28% deviation), although the reference C_{max} value was most closely predicted in Group 4 (+1% deviation). Groups 2 and 4 represent populations with 'low' and 'high' GI pH values, respectively (Table 2). When simulated data from all groups were combined, reference data matched well with simulated geometric mean C_{max} (2091 ± 801 ng/mL; −17% deviation), $AUC_{0\text{-}12}$ (8255 ± 4214 ng h/mL; 17% deviation) and C_{trough} (77 ± 79 ng/mL; 8% deviation).

Impact of magnesium on raltegravir exposure

The impact of magnesium binding on raltegravir PK values in subject Groups 1 to 5 is shown in Table 4. Geometric mean ratios (GMRs) were generated that were the ratios of raltegravir PK values in the presence of elevated GI magnesium concentrations and PK values under the standard conditions given in Table 2. Simulated C_{max}, AUC and C_{trough} were all significantly ($P<0.008$) reduced by the presence of magnesium in the GI tract. Raltegravir T_{max} was not significantly altered by magnesium in Groups 1 ($P=0.49$), 2 ($P=0.29$) or 3 ($P=0.34$) but was significantly increased in Groups 4 (2.6 h versus 2.3 h, $P=0.003$) and 5 (2.5 h versus 2.1 h, $P=0.001$). The increased T_{max} in Groups 4 and 5 are likely a result of an inhibited rate of raltegravir absorption, caused by reduced tablet breakdown and lower drug solubility. Data from all groups were combined and are shown in Figure 2.

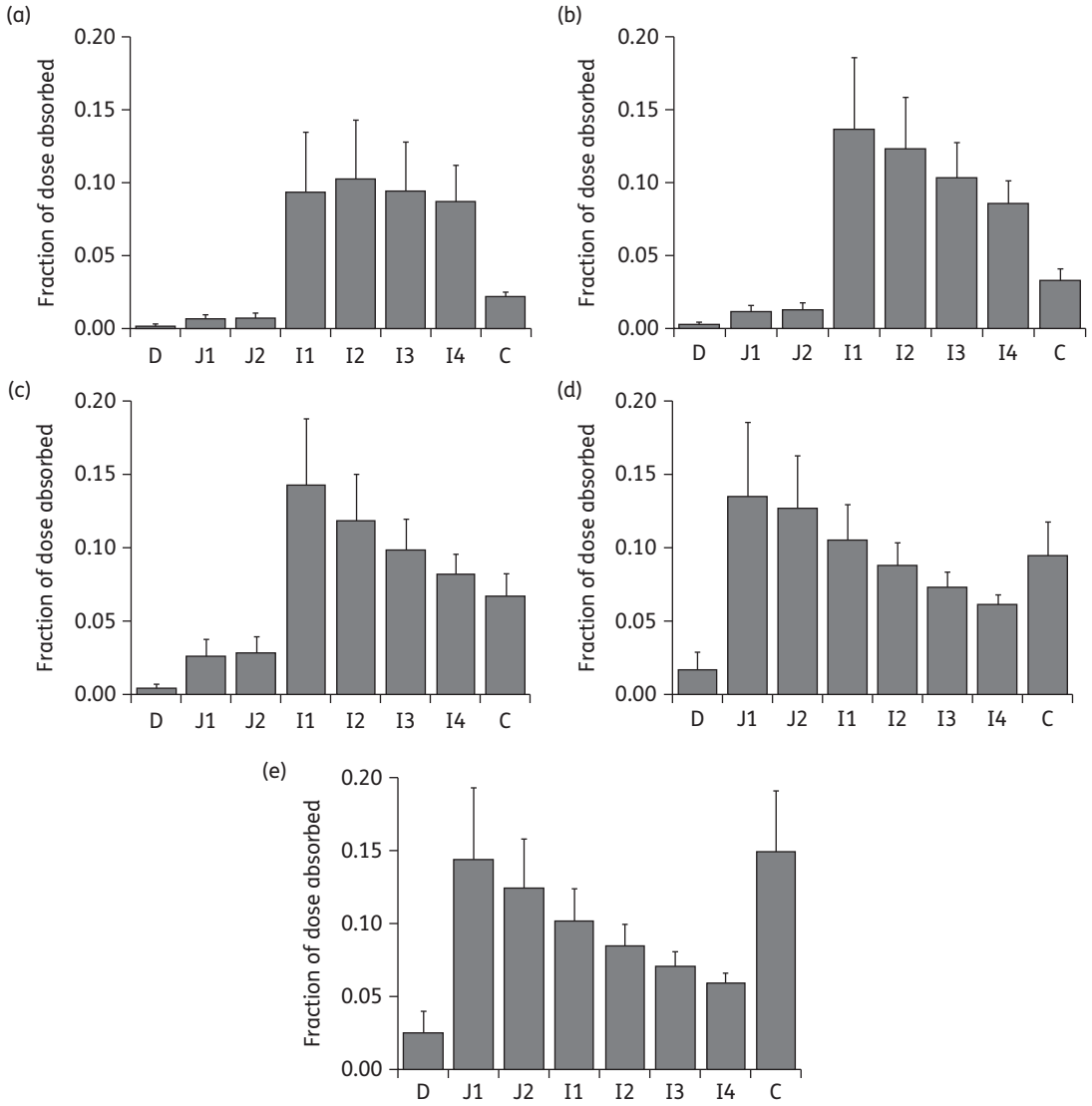

Figure 1. Mean simulated fraction of raltegravir absorbed (drug absorbed in segment/drug administered) ± SD in each GI segment from 50 individuals from Group 1 (a; very low pH), Group 2 (b; low pH), Group 3 (c; medium pH), Group 4 (d; high pH) and Group 5 (e; very high pH). Table 2 gives details of GI pH values for each group. D, duodenum; J1, jejunum section 1; J2, jejunum section 2; I1, ileum section 1; I2, ileum section 2; I3, ileum section 3; I4, ileum section 4; C, colon.

Table 3. Comparison of reference raltegravir PK values obtained from the literature with simulated PK values

	C_{max} (ng/mL)	Difference from reference (%)	$AUC_{0\text{-}12}$ (ng h/mL)	Difference from reference (%)	C_{trough} (ng/mL)	Difference from reference (%)
Reference value	2519 ± 1930	—	7076 ± 4071	—	71 ± 50	—
Group 1	1491 ± 582	−41%	5756 ± 3092	−19%	31 ± 27	−56%
Group 2	1980 ± 623	−21%	7285 ± 3399	3%	51 ± 31	−28%
Group 3	2094 ± 665	−17%	8165 ± 3618	15%	113 ± 48	59%
Group 4	2541 ± 808	1%	10137 ± 4300	43%	153 ± 60	115%
Group 5	2545 ± 792	1%	11046 ± 4335	56%	188 ± 78	164%
Combined data	2091 ± 801	−17%	8255 ± 4214	17%	77 ± 79	8%

Reference PK values for C_{max}, $AUC_{0\text{-}12}$ and C_{trough} are the mean ± SD values of geometric mean values for fasted, healthy volunteers in selected previous studies.[3,11,13,14,18,32] Each simulated population group contained 50 individuals and geometric mean ± SD values are presented for C_{max}, $AUC_{0\text{-}12}$ and C_{trough}. The percentage difference of each simulated result to the reference value is given.

Table 4. Raltegravir PK values in the presence of elevated magnesium GI concentrations

	Group 1 (very low pH)	Group 2 (low pH)	Group 3 (medium pH)	Group 4 (high pH)	Group 5 (very high pH)
C_{max}, ng/mL	842	1215	1301	1604	1616
5th–95th percentile	447–1611	831–2114	858–2331	1014–2842	1028–2672
GMR	0.56	0.61	0.62	0.63	0.63
P value	<0.001	<0.001	<0.001	<0.001	<0.001
$AUC_{0\text{-}12}$, ng h/mL	3435.7	4635	5208	6712	7359
Range	1394–7542	2215–9767	2623–10698	3306–13023	3769–13570
GMR	0.60	0.64	0.64	0.61	0.67
P value	<0.001	<0.001	<0.001	<0.001	<0.001
T_{max}, h	3.8	3.5	3.3	2.6	2.5
Range	1.4–5.7	1.4–4.7	1.4–4.5	1.3–3.5	1.3–3.4
Median ratio	1.03	1.06	1.03	1.13	1.19
P value	0.49	0.29	0.34	0.003	0.001
C_{trough}, ng/mL	21.9	33.3	66.2	90.3	152.1
5th–95th percentile	4.6–58.2	11.8–63.2	32.5–119.8	48.4–153.5	88.9–253.6
GMR	0.71	0.65	0.58	0.59	0.81
P value	0.008	<0.001	<0.001	<0.001	0.005
fa	0.23	0.31	0.35	0.45	0.50
5th–95th percentile	0.09–0.38	0.15–0.46	0.20–0.50	0.27–0.64	0.31–0.67
GMR	0.59	0.63	0.64	0.65	0.67
P value	<0.001	<0.001	<0.001	<0.001	<0.001

Each simulated population group contained 50 individuals. Geometric mean values for C_{max}, $AUC_{0\text{-}12}$, C_{trough} and fa are given with 5th and 95th percentiles. Median T_{max} (h) is given with range. Values in Table 6 have been divided by corresponding values in Table 4 to calculate the GMRs (C_{max}, $AUC_{0\text{-}12}$, C_{trough} and fa) or median ratios (T_{max}). *P*-values were calculated by comparing values between Table 4 and Table 2.

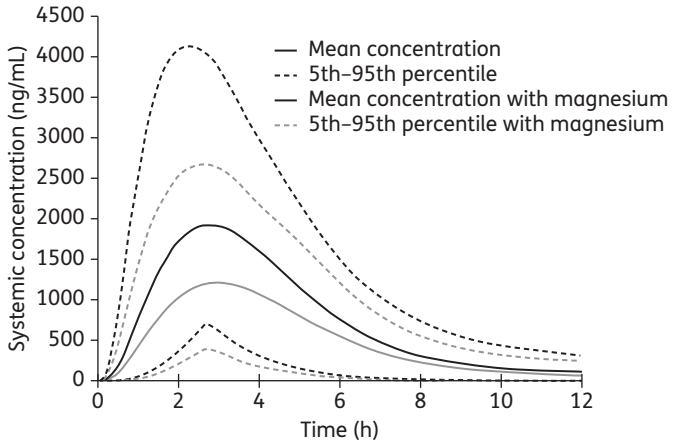

Figure 2. Mean simulated raltegravir plasma concentration–time profile (black continuous line) with 5th and 95th percentiles (black broken lines) using combined data from Groups 1–5 (50 subjects from each group, 250 subjects in total). Also shown is the mean simulated raltegravir plasma concentration–time profile (grey continuous line) with 5th and 95th percentiles (grey broken lines) using combined data from Groups 1–5 following co-ingestion of magnesium (50 subjects from each group, 250 subjects in total).

Discussion

The IVIVE model developed in this study predicted the PK of raltegravir in individuals with different GI pH profiles. The main PK variables were predicted with good accuracy when compared with reference data. In simulated subjects, increased GI pH and small intestinal transit time were both associated with improved raltegravir exposure. Importantly, both factors are capable of causing intra-patient PK variability *in vivo* under certain conditions.[33,34]

HIV-infected patients, particularly those with advanced disease progression, have both higher gastric pH and higher prevalence of gastric microbe colonization than in uninfected individuals.[35,36] The higher gastric pH in HIV-infected patients may explain why co-administration of omeprazole with raltegravir shows less impact on raltegravir PK in HIV-infected patients (40% increase in AUC) compared with healthy volunteers (210% increase in AUC).[11,37] However, this hypothesis needs empirical confirmation as GI pH was not directly measured in either study and there are no published data showing the effect of pH on raltegravir solubility *in vivo*. A recent study found a statistically significant 65% increase ($P=0.01$) in raltegravir bioavailability in females compared with males.[10] Females have higher gastric pH and longer GI transit time than males and the results from our simulations suggest both of these factors could potentially increase raltegravir exposure.[20] However, conflicting reports suggest no increased raltegravir exposure in females and factors other than GI pH, such as lower hepatic blood flow and reduced intestinal P-glycoprotein expression in females, may better explain any difference in bioavailability.[16,32]

The simulations showed evidence of decreased raltegravir exposure when individuals were exposed to magnesium in the GI

tract. Previously determined permeability values were used in the simulations, where 25 mM magnesium chloride significantly reduced raltegravir P_{app} through Caco-2 monolayers.[19] It must be acknowledged that the concentration of GI magnesium in real subjects would fluctuate depending on compartment volume and magnesium absorption, therefore the intestinal permeation of raltegravir would also fluctuate. However, it can be seen from the model that the rate of raltegravir absorption is a limiting factor in ultimate exposure. The data from these simulations support the hypothesis that the combined effect of increased solubility and reduced intestinal permeability could explain the interaction observed *in vivo*, where raltegravir T_{max} and C_{trough} were lower in subjects co-administered raltegravir and a magnesium-containing antacid.[14]

The model created in this study has limitations and the inclusion of further *in vitro* data could potentially improve the model's predictive ability. Elimination of raltegravir from virtual subjects was determined by whole organ clearance obtained from published literature: information about the role of individual metabolic enzymes was not included.[18,32] The metabolism of raltegravir involves enzymes UGT1A1, UGT1A3 and UGT1A9.[4] A model that included the clearance of raltegravir by these individual enzymes, combined with known phenotypic variations and expression levels in the virtual population, could provide a more accurate model for determining raltegravir elimination. Similarly, the impact of drug transporters on raltegravir exposure *in vivo* is not fully understood and was not included in the final model. The simulated population in our model used physiological parameters based on data from healthy adults, and the model at present does not contain a population representing HIV-infected individuals. Consequently, we could not investigate the influence of the disease on raltegravir exposure in our model. Most raltegravir PK data predicted by our model were within the range of those found in clinical data; however, the volume of raltegravir distribution is substantially lower than in previously published models.[10,18] This discrepancy may be due to the differences in modelling strategy, where our model utilized *in vitro* data in PBPK simulations (bottom-up) and the previously published models used patient PK data (top-down).

A relationship between raltegravir exposure and treatment outcome has yet to be conclusively established in the clinic. There is evidence from studies that raltegravir exposure, when combined with virological parameters, may play a role in treatment success and drug resistance development.[15,17,38] Raltegravir PK profiles occasionally contain multiple peaks or delayed (>8 h after dosing) peaks and, in an attempt to explain these peaks, it has been suggested that raltegravir is able to undergo enterohepatic recirculation via conversion of the raltegravir glucuronide metabolite back to the parent form in the intestine, leading to subsequent reabsorption.[10] However, a study in healthy subjects using radiolabelled raltegravir did not support the theory, as there was no evidence of drug reabsorption.[15] Enterohepatic recirculation of raltegravir was therefore not included in the final model. Tablet disintegration rate, which has been shown to increase in higher pH solutions *in vitro*, may help explain unusual raltegravir PK profiles.[12,39] Also, preferential absorption of raltegravir from particular sections of the GI tract depending on GI pH, as demonstrated in our model (Figure 1), may further explain delayed/multiple drug concentration peaks. These data remain theoretical as no study has investigated raltegravir absorption via different sections of the gut *in vivo*. Further investigation is needed to determine the extent of raltegravir enterohepatic recirculation and these data would have the potential to further improve our model.

In conclusion, the Simcyp population-based ADME simulator has been used to create a model simulating raltegravir PK parameters with acceptable accuracy to ~~real-life~~ data. The most useful feature of this model is to investigate 'what-if' scenarios by directly altering subject physiological parameters such as GI pH and drug absorption rate and observing the effect on raltegravir PK. This also provides a tool for investigating the absorption of other drugs, such as the second-generation HIV integrase inhibitors elvitegravir and dolutegravir, which have also shown interactions with food and metal-containing products.[40,41]

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Supplementary data

Figure S1 is available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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