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ARTICLE

The population pharmacokinetics of dolutegravir co-administered with rifampicin in Thai people living with HIV: Assessment of alternative dosing regimens

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Abstract

Tuberculosis is the most common opportunistic infection in individuals with HIV, and rifampicin is crucial in the treatment of tuberculosis. Drug–drug interactions complicate the use of DTG in HIV/TB co-infection, which makes drug administration more difficult. This study aimed to develop the population pharmacokinetic model of DTG when co-administered with rifampicin. The developed model was further used to investigate different dosing regimens. Forty HIV/TB-co-infected participants receiving DTG 50 mg once daily (OD) with food or DTG 50 mg twice daily (b.i.d.) without food were included in the analysis. Intensive pharmacokinetic samples were collected. The data were analyzed using a nonlinear mixed-effects modeling approach. A total of 332 DTG concentrations from 40 PLWH were analyzed. The pharmacokinetics of DTG co-administered with rifampicin can be best described by a one-compartment model with first-order absorption (incorporating lag time) and elimination. Total bilirubin was the only covariate that significantly affected CL/F. DTG 50 mg b.i.d. results in the highest proportion of individuals achieving in vitro IC_{90} of 0.064 mg/L and in vivo EC_{90} of 0.3 mg/L, while more than 90% of individuals receiving DTG 100 mg OD would achieve the in vitro IC_{90} target. Therefore, DTG 100 mg OD could serve as an alternative regimen by minimizing the difficulty of drug administration. However, its clinical efficacy requires additional evaluation.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

When co-administered with rifampicin, the dosage of DTG must be increased to 50 mg twice a day, necessitating the addition of one extra DTG pill. This could lead to poor compliance and increase the drug stockout burden.

Baralee Punyawudho and Anchalee Avihingsanon contributed equally to this work.

WHAT QUESTION DID THIS STUDY ADDRESS?

Is the DTG 50 mg OD or 100 mg OD dosage adequate for achieving sufficient DTG exposure when taken with rifampicin?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The results confirmed that administering DTG 50 mg b.i.d. resulted in the highest percentage of individuals reaching their target DTG concentration. DTG 100 mg once daily provides adequate DTG levels according to the IC_{90} target.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

DTG 100 mg OD may serve as a possible alternate regimen for PLWH who are co-infected with TB.

INTRODUCTION

Dolutegravir (DTG) is a second-generation integrase strand transfer inhibitor (INSTIs) which is now recommended to be used as a first-line treatment in treatment-naive and treatment-experienced HIV-infected individuals in multiple guidelines including Thai National Guidelines.[1,2] The standard dose of DTG is 50 mg once daily (OD) in INSTI-naïve individuals and 50 mg twice daily for individuals with INSTI-resistant viruses.[3,4] After absorption, DTG is mainly metabolized by uridine 5-diphospho-glucuronosyltransferase 1A1 (UGT1A1) and to a lesser extent by cytochrome P450 3A4 (CYP3A4).[5] It is a substrate for drug efflux pumps including breast cancer resistance protein (BCRP) encoded by ABCG2 and P-glycoprotein (P-gp) encoded by ABCB1.[6] DTG is highly potent and a once-daily dose of 50 mg results in trough concentration (C_{trough}) that are 13 times higher than the in vitro, protein-adjusted IC_{90} of 0.064 mg/L.[7] According to a prior dose ranging study, all DTG doses (10, 25, and 50 mg) exhibited comparable virological responses (10, 25, and 50 mg)[8] Thus, a more conservative target of a C_{trough} >0.3 mg/L, the observed DTG C_{trough} when 10 mg OD was administered, was proposed as an in vivo 90% effective concentration (EC_{90}).[8]

Co-infection with tuberculosis (TB) in people living with HIV (PLWH) is common. People with HIV infection are 15–21 times more likely to develop TB than those without HIV infection.[9] Additionally, TB is the leading cause of death among PLWH, accounting for ~30% of AIDS-related deaths in the world.[9] Rifampicin plays a key role in the treatment of TB as part of the first-line anti-TB regimen. Rifampicin is a potent inducer that stimulates the pregnane X receptor, hence promoting the expression of UGT1A1, CYP3A4, ABCG2, and ABCB1.[10] When DTG is co-administered with rifampicin, a reduced plasma concentration of DTG might be anticipated. Thus, DTG 50 mg twice daily with rifampicin is recommended for individuals requiring concurrent HIV and TB therapy to reduce the possibility of inadequate DTG concentrations.

DTG is available as a generic fixed-dose combination of tenofovir disoproxil fumarate 300 mg/lamivudine 300 mg/dolutegravir 50 mg (TLD) in low- and middle-income countries, including Thailand. Therefore, when DTG 50 mg twice daily is needed, one additional pill of DTG 50 mg single tablet is required to obtain the prescribed dosage. As this regimen deviates from the standard once-daily regimen, the administration of DTG 50 mg twice daily in PLWH on rifampicin may result in poor adherence and increasing drug stockout burden. A previous study from Botswana reported that despite the recommendation for a double dose of DTG in patients with HIV/TB co-infection, only 52.8% were able to receive DTG 50 mg twice daily, while 43.6% received a once-daily DTG dose.[11] When considering a once-daily administration of 100 mg DTG, this regimen may enhance adherence. In addition, previous research has demonstrated a 33-to-66% increase in DTG exposure when the drug is administered with meals, especially high-fat meals as opposed to when the patient is fasting.[12] Therefore, DTG 50 mg OD with meals seems promising and may be adequate to guarantee sufficient DTG exposure when DTG is co-administered with rifampicin.

Even though the population pharmacokinetics of DTG co-administered with rifampicin were previously investigated. One study was conducted in healthy volunteers,[13] and the results clearly indicated a disparity in the pharmacokinetics of DTG between healthy volunteers and actual patients. Another study was performed on African individuals living with HIV and co-infected with tuberculosis[14] who may exhibit different characteristics as a result of diverse ethnic backgrounds. The pharmacokinetic information of DTG in PLWH receiving rifampicin is important for dose optimization in this population. Thus, we assessed the population pharmacokinetics of DTG when co-administered with rifampicin. The developed model was further implemented to evaluate various dosing regimens.

METHODS

Participants and blood samples

This was a cross-sectional analytical study performed at the HIV Netherland Australia Thailand Research Collaboration (HIV-NAT), Thai Red Cross AIDS Research Centre (Bangkok, Thailand) under ClinicalTrials.gov Identifier NCT03731559. Forty Thai PLWH aged >18 years who were newly diagnosed with HIV/TB co-infection were recruited. PLWH on standard rifampicin-based anti-TB therapy (450 mg for PLWH weighing 35–49 kg and 600 mg for PLWH weighing 50 kg or more[15]) were randomized to receive either DTG 50 mg once daily (OD) with food or DTG 50 mg twice daily (b.i.d.) without food. PLWH who are currently taking drugs that can alter the pharmacokinetics of DTG and rifampicin were excluded from the study. At week 4, intensive pharmacokinetic samples were collected at predose, 1, 2, 4, 6, 8, 10, and 12 for the b.i.d. arm. An additional blood sample was collected at 24 h post-dose in the OD arm. Informed consent was obtained from all participants. The study was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, and the Institutional Review Board Committee on human research at the Faculty of Pharmacy, Chiang Mai University, Chiang Mai, Thailand.

Analytical assay

Blood collected during pharmacokinetic sampling was processed within 1 h to attain plasma and was stored at −20°C at the HIV-NAT lab. Stored samples collected for DTG analysis were shipped on dry ice to the Center for Personalized Precision Medicine of Tuberculosis, Inje University College of Medicine, Busan, Republic of Korea. Plasma DTG concentrations were measured by validated LC- MS/MS. The intraday and interday precisions were less than 15% The accuracy ranged between 83.5% and 118.4%. The lower limit of qualification was 0.1 mg/L for DTG.

Population pharmacokinetic analysis

Pharmacokinetic data of DTG were analyzed by nonlinear mixed-effects modeling approach using NONMEM® (version 7.4; Icon Development Solution. Ellicott City, MD) together with Perl-speaks-NONMEM (PsN) toolkit (version 4.7.0: http://psn.sourseforge.net/), Pirana (version 2.9.6). The first-order conditional estimation method with interaction (FOCEI) was used throughout the analysis. The graphical analysis was created by R package (version 4.2.1, R Development Core team; http://www.r-project.org) and Xpose program (version 4.7.2). For the structural model development, one- and two-compartment models with first- and/or zero-order absorption with and without absorption lag time or transit compartment were tested. The inter-individual variability (IIV) and inter-occasion variability (IOV) were assumed to be log-normally distributed. In this study, each occasion was defined as a dosing event with at least one blood sample. As a result, there were two occasions: the pre-dose occasion and the post-dose occasion. IOV was tested either following the inclusion of the IIV or substituting the IIV on absorption parameters (F and absorption rate constant; Ka). The residual unexplained variability (RUV) was characterized by proportional error model. Concentrations below the lower limit of quantification were substituted with LLOQ/2,[16] unless there were consecutive values, which were removed from the dataset. The base model was selected based on the goodness-of-fit (GOF) plots, changes in the objective function value (OFV), successful convergence, and precision of parameter estimates (%RSE). Allometric scaling based on body weight or fat-free mass was incorporated to adjust for the effect of body size on drug disposition. The allometric exponents were fixed to the values of 0.75 and 1 for CL/F and V/F, respectively.

The effects of the following clinically relevant and physiologically plausible covariates were further investigated: sex, age, food, serum creatinine, and total bilirubin. The continuous covariates centered by their medians were investigated with linear, power, and exponential functions. Categorical covariates were investigated with additive, fractional, and exponential model. The covariates were added in a stepwise manner. During forward inclusion, a decrease in OFV of at least 3.84 (χ^2, $p \geq 0.05$, df = 1) was considered statistically significant. An increase in the OFV of at least 6.63 (χ^2, $p \geq 0.01$, df = 1) was used as a cut-off criterion for retaining covariates in the model during backward deletion.

Model evaluation

The nonparametric bootstrapping was used to assess the reliability of the final parameter estimates.[17] One thousand bootstrapped samples were obtained by sampling with replacement from the original dataset. Each of the bootstrapped data was fitted to the final model to provide parameter estimations. The median and 95% confidence interval (CI) for each parameter calculated from the bootstrap data were compared with the values provided by NONMEM. The visual predictive checks (VPC) were performed to assess the predictability of the final model.[18] One thousand simulation datasets were generated using

the parameter estimates from the final model. The 5th, 50th, and 95th percentiles, along with their 95% CI, of the simulated data were plotted against the corresponding percentiles of the observed data.

Observed concentrations were calculated and visually compared with the corresponding percentile predicted by the model.

Simulations for evaluating optimal dosage regimens

Several DTG dosage regimens (DTG 50 mg OD, 50 mg b.i.d., and 100 mg OD) administered in combination with rifampicin were investigated to assess DTG concentrations in Thai PLWH using Monte Carlo simulations. The final model was used to simulate 10,000 DTG trough concentrations (C_{trough}) at steady state with two groups of body weight (41–60 and 60.1–86 kg) for each significant covariate and dosage regimen. Total bilirubin was categorized into five groups: normal (0.1–1.29 mg/dL), grade 1 hyperbilirubinemia (1.3–1.89 mg/dL), grade 2 hyperbilirubinemia (1.9–3.09 mg/dL), grade 3 hyperbilirubinemia (3.1–6.09 mg/dL), and grade 4 hyperbilirubinemia (>6.1 mg/dL).[19] The allocation of weight and total bilirubin value to each individual in each group was performed at random. The simulated DTG C_{trough} were compared with the in vitro protein-adjusted IC_{90} target of 0.064 mg/L and in vivo EC_{90} target of 0.3 mg/L[7,20] across the different dosage regimens. The percentage of simulated individuals achieving target concentrations were calculated.

RESULTS

A total of 332 DTG concentrations from 40 PLWH were analyzed. Data from one participant were consistently below the LLOQ. As a result, data from this individual were removed from the analysis, except for the pre-dose concentration. The concentration–time profiles stratified by treatment group are provided in the Supplementary materials. The participants' characteristics are summarized in Table 1.

Population pharmacokinetic analysis

The pharmacokinetics of DTG co-administered with rifampicin can be best described by a one-compartment model with first-order absorption and elimination. Adding a second compartment did not improve the fit. The addition of lag time for describing the delayed absorption improved the model fit (dOFV = −15.9). The bioavailability (F) was fixed to 1. The IIV of V/F and lag time could not be precisely estimated, thus the V/F and lag time were estimated without its IIV. Allometric scaling with body weight outperformed fat-free mass. The addition of the IOV on the absorption parameters (F and Ka) significantly improved the fit (ΔOFV = 70.071). The results of the covariate analysis showed that total bilirubin was the only covariate that significantly affected CL/F. The pharmacokinetic parameter estimates from the final model are presented in Table 2. The final model of CL/F was described by the following equation:

$$\mathrm{CL/F} = 2.82 \times \left(\frac{\text{body weight}}{60}\right)^{0.75} \times \exp^{-0.297 \times (\text{total bilirubin} - 0.38))}$$

Based on the final model, the estimated CL/F of DTG was 2.82 L/h among PLWH weighing 60 kg and having a total bilirubin of 0.38 mg/dL. An elevation of 1 mg/dL in total bilirubin decreased the CL/F of DTG by 25.7%. The GOF plots of the final model are shown in Figure 1. The model seems to overestimate DTG concentration during

TABLE 1 Summary of demographic characteristics of the study populations stratified by treatment group.

PLWH characteristics	DTG 50 mg once daily with food ($n = 20$)	DTG 50 mg twice daily ($n = 20$)
No. of DTG plasma concentrations	160	140
Sex		
Male (%)	17 (85)	18 (90)
Female (%)	3 (15)	2 (10)
Age (years), median (range)	37.5 ± 17.7 (25.0–60.5)	35.6 ± 19.8 (21.6–53.2)
Weight (kg), median (range)	59.3 ± 13.2 (41.1–78.4)	60.2 ± 18.5 (47.1–86.0)
Serum creatinine (mg/dL), median (range)	0.891 ± 0.310 (0.530–1.23)	0.895 ± 0.105 (0.610–1.73)
Total bilirubin (mg/dL), median (range)	0.380 ± 0.250 (0.140–2.58)	0.350 ± 0.150 (0.170–0.500)

TABLE 2 The final pharmacokinetic parameter estimates and bootstrap results.

Parameter (units)	NONMEM Point estimate	%RSE	95% CI		Bootstrap estimates		
					Median	95% CI	
CL/F (L/h)	2.82	7.2%	2.42	3.22	2.84	2.43	3.20
V/F (L)	19.8	8.2%	16.6	22.9	19.9	17.0	23.5
Ka (h^{-1})	1.41	38.6%	0.344	2.48	1.47	0.344	2.47
F	1 (fixed)	–	–	–	–	–	–
Lag time (h)	0.562	33.6%	0.192	0.932	0.563	0.189	0.854
CL-Bilirubin	−0.297	9.7%	−0.347	−0.240	−0.295	−0.512	−0.118
Inter-individual/Inter-occasion variability (%CV)							
IIV-CL	19.1	14.58%	12.8	23.7	18.9	12.2	24.1
IOV-F1	90.6	20.3%	86.9	94.1	93.3	70.0	134
IOV-Ka	52.0	18.1%	28.1	67.9	48.9	24.9	72.5
Residual variability (%CV)							
RUV prop	15.6	16.4%	9.27	20.0	15.3	9.84	20.3

Abbreviations: %CV, percent coefficient variation; %RSE, relative standard error; CL/F, apparent oral clearance; CL-Bilirubin, the influence of bilirubin on CL/F; F, bioavailability; IIV, inter-individual variability; IOV, inter-occasion variability; Ka, absorption rate constant; RSE defined as: (SEestimate/estimate)×100, where SE is standard error; RUV, residual variability; V/F, apparent volume of distribution.

the first few hours after dose administration (0–5 h), as shown in the conditional weighted residuals (CWRES) versus time. The results from the bootstrap analysis showed that 97.3% of 1000 bootstrap runs were minimized successfully. The bootstrap median and 95% CI of the parameter estimates were comparable to the values obtained from NONMEM (Table 2). The VPC plots stratified by treatment group obtained from 1000 simulations are shown in Figure 2. Despite the fact that the predicted concentrations of the 5th and 95th percentiles seem to be overestimated between 0- and 5-h post-dose, the observed median, 5th, and 95th percentiles at subsequent times fell within the 95% CIs of the simulated medians and respective percentiles. This demonstrated that the final model adequately described the central tendency and variability of the observed data.

Simulations for determining the optimal dosage regimens

Figure 3 shows the results of the DTG C_{trough} in relation to the total bilirubin derived from the various dosage regimens investigated in individuals weighing 41–60 kg and 60.1–86 kg. The percentages of individuals having DTG C_{trough} levels above the in vitro protein-adjusted IC_{90} of 0.064 mg/L and the in vivo EC_{90} of 0.3 mg/L for normal and hyperbilirubinemia individuals taking 50 mg OD, 50 mg b.i.d., and 100 mg OD of DTG are shown in Table 3. Regardless of total bilirubin levels, the administration of DTG 50 mg b.i.d. resulted in the highest proportion of individuals achieving a DTG C_{trough} greater than the in vitro protein-adjusted IC_{90} of 0.064 mg/L (>99%) and in vivo EC_{90} of 0.3 mg/L (>92%) in all weight groups. When DTG 50 mg OD was administered in individuals weighing 41–60 kg and 60.1–86 kg with normal bilirubin levels, 79.2% and 78.4% of individuals achieved the in vitro protein-adjusted IC_{90} of 0.064 mg/L, while 20.9% and 16.2% of individuals reached the in vivo EC_{90} of 0.3 mg/L. When taking DTG 100 mg OD, 92.6% of individuals weighing between 41–60 kg and 92.9% of individuals weighing between 60.1 and 86 kg, who have normal bilirubin levels, would reach a target concentration of 0.064 mg/L. However, using a more conservative target of 0.3 mg/L, 49.7% and 45.7% of individuals were able to achieve concentrations that exceeded the target.

DISCUSSION

In this study, the population pharmacokinetic model of DTG when co-administration with rifampicin was developed. The impact of food and other covariates on the pharmacokinetics of DTG was explored and simulations were carried out to assess DTG exposure across different dosage regimens. The pharmacokinetics of DTG can be best described by a one-compartment model with a first-order absorption which is consistent with previous reports.[14,21–23] Some of the population pharmacokinetics of DTG suggested a two-compartment model to describe DTG pharmacokinetics.[13,24] It is interesting to mention that a two-compartment model could only be identified when the Inter-occasion variability was included for all absorption parameters in a previous study by Kawuma et al.

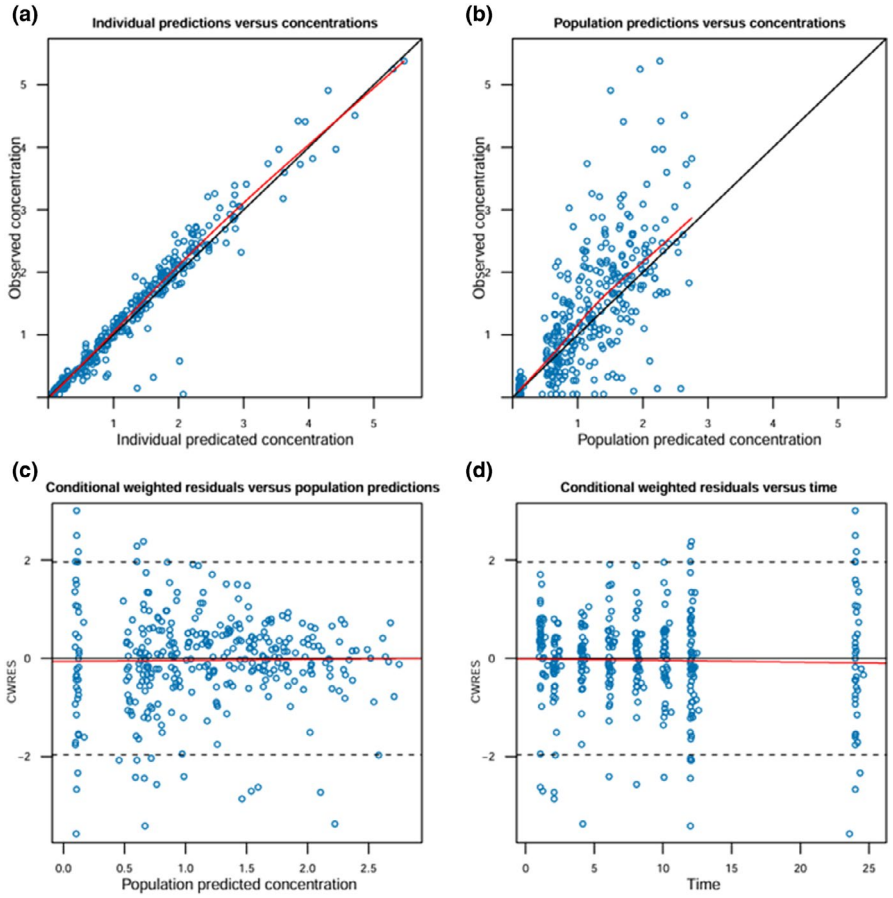

FIGURE 1 Goodness-of-fit plots of the final model: (a) observed concentration (DV) vs. population-predicted concentration, (b) DV vs. individual predicted concentrations (IPRED), (c) conditional weighted residuals (CWRES) vs. PRED, (d) CWRES vs. time after dose.

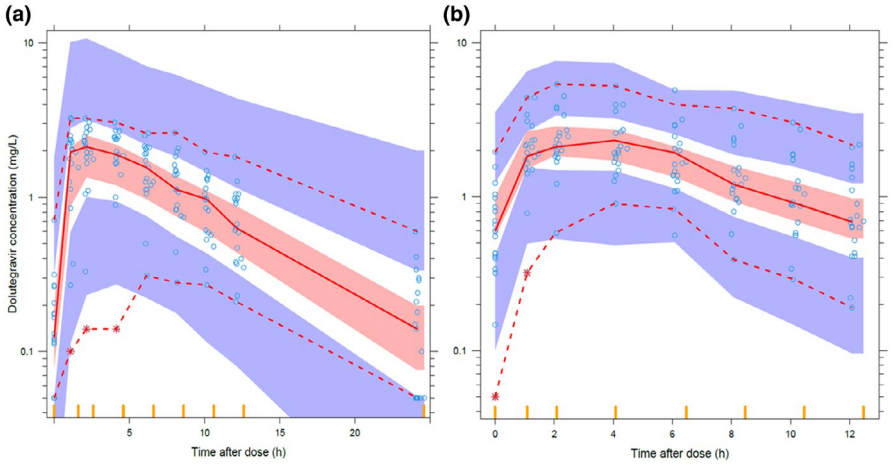

FIGURE 2 The visual predictive check of DTG (VPC) stratified by study group: (a) 50 mg b.i.d. without food and (b) 50 mg OD with food. Open circles represent the observed DTG concentrations. The solid red line represents the 50th percentile of the observed concentration, whereas the dashed lines represent the 5th and 95th percentiles. The shaded areas represent the 95% CI of the respective percentiles predicted by the model.

Despite incorporating the IOV into absorption parameters in our model, a two-compartment model did not improve the fit. With a median total bilirubin level of 0.38 mg/dL, the estimated CL/F of DTG was 2.82 L/h. for 60-kg individuals. It should be emphasized that the estimated DTG CL/F from our study was the CL/F when rifampicin was co-administered. Our estimated DTG CL/F value was comparable to that previously reported by Barcelo et al. but was higher than what was estimated from other previous studies.[13,14,21,23]

Total bilirubin was the only covariate that significantly impacted DTG CL/F. The impact of total bilirubin on DTG pharmacokinetics was previously observed. Zhang et al. found that the CL/F of DTG decreased with total bilirubin through a negative power coefficient.[22] This is in line with the results of our investigation indicating that DTG CL/F was reduced with an increase in total bilirubin. As both DTG and bilirubin are primarily metabolized by UGT1A1, it is likely that there is a competition between bilirubin and DTG for UGT1A1which explains why there is this association.

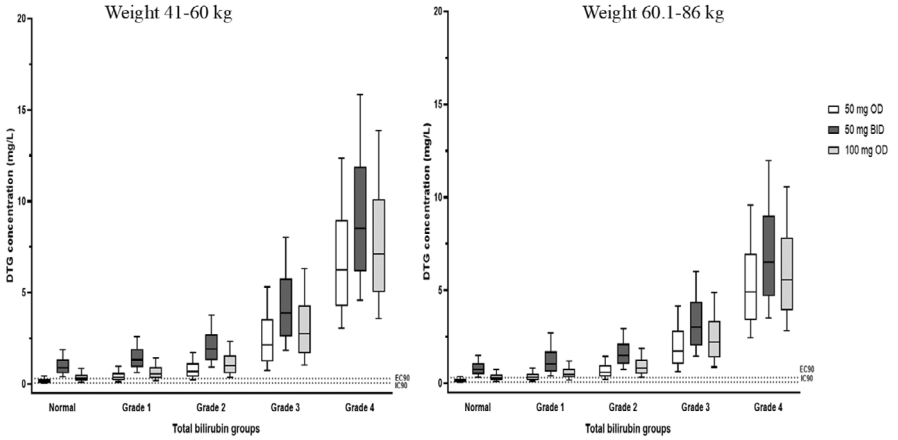

FIGURE 3 Box plots of the simulated trough concentrations of 50 mg once daily (OD), 50 mg twice daily (b.i.d.), and 100 mg OD of DTG in relation to the total bilirubin in individuals weighing 41–60 kg and 60.1–86 kg. The boxes indicate the 25th, 50th, and 75th percentiles, while the whiskers indicate the 5th and 95th percentiles. The in vivo EC_{90} is 0.3 mg/L. Protein-adjusted 90% inhibitor concentration (IC_{90}) is 0.064 mg/L.

TABLE 3 The percentage of simulated individuals achieving in vitro protein-adjusted IC_{90} target of 0.064 mg/L and in vivo EC_{90} target of 0.3 mg/L in different weight group.

	% C_{trough} achieving IC_{90} of 0.064 mg/L					% C_{trough} achieving EC_{90} of 0.3 mg/L				
	Total bilirubin					Total bilirubin				
Regimen	**Normal**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Normal**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Weight 41–60 kg										
50 mg OD	79.2	96.3	99.4	100	100	20.9	58.2	84.1	98.8	100
50 mg b.i.d.	99.9	100	100	100	100	95.5	99.2	99.9	100	100
100 mg OD	92.6	98.9	99.8	100	100	49.7	78.3	93.8	99.7	100
Weight 60.1–86 kg										
50 mg OD	78.4	96.3	99.4	100	100	16.2	53.4	80.7	98.3	100
50 mg b.i.d.	99.9	99.9	100	100	100	92.7	94.8	99.7	99.9	100
100 mg OD	92.9	98.9	99.8	100	100	45.7	74.4	92.1	99.6	100

It was previously shown that the administration of DTG with food increased DTG exposure. The area under the concentration–time curve from 0 to infinity ($AUC_{0-\alpha}$) increased by 33%–66% when DTG was administered with low to high-fat meals, according to a previous study.[12] In addition, a higher maximum concentration of DTG (C_{max}) and duration to maximum concentration of DTG in plasma (T_{max}) was seen with increasing fat content.[12] A previous population pharmacokinetic study of DTG in healthy volunteers demonstrated that the absorption lag time was five times prolonged when DTG was administered with food. Nevertheless, the effect of food on DTG bioavailability has not been identified.[13] Neither the effect of food on bioavailability nor the lag time was found in our study. This absence of association may be attributable to the small number of PLWH in fasting and fed conditions as well as the variability in fat content among foods. Another possible explanation could be the significant fluctuation of DTG during absorption which may disguise the effect of food. Interestingly, despite the delayed absorption was accounted for by adding lag time in the model, the GOF plots demonstrated that DTG concentrations seem to be overestimated between 0 and 5 h. These overestimated concentrations were from 5 PLWH who took DTG with food. Thus, we hypothesized that the delayed absorption by food for some individuals may exceed the estimated lag period. Furthermore, the VPC plots revealed significant variations in absorption among those who took DTG with food. This variability may be attributed to the impact of varying amounts of fat in the meal.

The DTG C_{trough} of 0.3 mg/L is widely used as the target concentration for DTG, as it was determined based on findings from a phase IIb trial. The 0.064 mg/L in vitro target may have limitations when translated to in vivo conditions. Findings from a recent randomized clinical

trial (RADIANT-TB) and a retrospective cohort study in Botswana demonstrated that the efficacy of a double dose of DTG (50 mg b.i.d.) was similar to that of the once-daily dose in PLWH concomitantly receiving rifampicin.[11,25] Additionally, the interim analysis of the clinical efficacy in our study has shown comparable rates of virological suppression between the DTG 50 mg OD and DTG 50 mg b.i.d.[26] While comparable levels of virological suppression were observed in these studies, a greater percentage of patients on the OD regimen had DTG trough concentrations below the in vitro protein-adjusted IC_{90}. This suggests that the in vitro target of 0.064 mg/L is valid and implies that factors other than DTG trough concentrations may also play a role in clinical effectiveness. A potential explanation could be due to a slower dissociation of DTG from a wild-type integrase-DNA complexes, with a half-life of 71 h.[27] Thus, viral suppression is still present, despite having transient DTG concentrations below the in vitro targeted level. However, further investigation is required to confirm this.

When co-administered with rifampicin, DTG CL/F increased by 85.6%–261%.[13,21,23] Thus, doubling the dose of DTG to twice daily is recommended. Our simulation results predicted that DTG 50 mg b.i.d. resulted in the highest proportion of individuals achieving the target trough concentrations of 0.064 and 0.3 mg/mL. This is consistent with the simulation results from previous population pharmacokinetic studies.[13,14] A recent study on population pharmacokinetics compared the pharmacokinetics of DTG when taken with either a standard (10 mg/kg) or high (35 mg/kg) dose of rifampicin. The study demonstrated that regardless of the dose of rifampicin, administering DTG 50 mg b.i.d. provided adequate DTG trough concentrations to attain the target of 0.064 and 0.3 mg/mL.[14] A previous study conducted in a small number of healthy volunteers revealed that DTG 100 mg OD resulted in DTG concentrations that were significantly above the desired in vitro protein-adjusted IC_{90} of 0.064 mg/L. However, it is worth noting that only 5 out of the 14 participants were able to attain the desired in vivo target C_{trough} of 0.3 mg/L.[28] The findings from our study confirmed that although about 50% of individuals with normal bilirubin levels will achieve the more conservative target of 0.3 mg/L with a once-daily dosing regimen of DTG 100 mg, ~93% of individuals with normal bilirubin levels will have C_{trough} >0.064 mg/L. This indicated that a DTG 100 mg once-daily dose provides adequate C_{trough} levels and may improve treatment adherence. However, it will not resolve the problem of potential dolutegravir stockouts of the single pill. Our simulation results indicated that ~80% of individuals with normal bilirubin levels who received a 50 mg OD regimen would achieve the in vitro protein-adjusted IC_{90} of 0.064 mg/L. As a portion of patients receiving DTG 50 mg OD would have DTG concentrations below the target, its efficacy of maintaining viral suppression may be called into question.

Neuropsychiatric adverse events (NP-AEs) are one of the side effects of concern that can result in DTG discontinuation. Previous studies have revealed a correlation between plasma DTG levels and neuropsychiatric adverse events (NP-AEs).[29,30] Although the cutoff values for predicting NP-AEs have not been established, Yagura et al. discovered that subjects with the median DTG C_{trough} greater than 1.34 mg/L had a higher risk of NP-AEs.[29] Moreover, a median DTG C_{trough} of 1.7 mg/L was seen in PLWH who prematurely terminated DTG treatment due to NP-AEs.[31] Based on our simulation results, 0.15%, 25.9%, and 2.91% of individuals weighing 41–60 kg with normal bilirubin would have a DTG C_{trough} >1.34 mg/L when DTG 50 mg OD, 50 mg b.i.d., and 100 mg OD was administered. For individuals weighing 60.1–86 kg with normal bilirubin, 0.05%, 14.5%, and 1.70% of individuals would have DTG C_{trough} >1.34 mg/L (data not shown). When the cutoff value of 1.7 mg/L was used, 0.03%, 13.1%, and 1.26% of individuals weighing 41–60 kg taking DTG 50 mg OD, 50 mg b.i.d., and 100 mg OD, respectively, had DTG C_{trough} levels that exceeded the cutoff value. Individuals weighing 60.1–86 kg with normal bilirubin levels would experience DTG C_{trough} exceeding 1.7 mg/L 0%, 6.02%, and 0.60% when DTG 50 mg OD, 50 mg b.i.d., and 100 mg OD was given, and the percentages increased in individuals with hyperbilirubinemia (data not shown). While administration of DTG 50 mg b.i.d. resulted in the highest number of individuals achieving the target DTG C_{trough}, the higher proportion of the subjects might be also at risk for NP-AEs.

There were some limitations in this study. First, all the participants received DTG with rifampicin. Thus, the pharmacokinetics of DTG in the absence of rifampicin and the effect of rifampicin on the pharmacokinetics of DTG cannot be determined. A recent population pharmacokinetic study conducted by Kengo et al. has shown that an increase in rifampicin exposure leads to a decrease in DTG bioavailability.[14] Due to the unavailability of rifampicin concentrations in our study, we were unable to explore the effects of rifampicin exposure. While the impacts of rifampicin exposure on the pharmacokinetics of DTG were not explicitly studied, our findings support the conclusion of the previous study that DTG 50 mg b.i.d. provides adequate exposure above the target level. Second, the developed model demonstrated an overprediction of DTG concentrations during absorption in some of the individuals who took DTG with food. Despite the fact that the delayed absorption was captured by the lag-time model, these individuals appeared to have a longer delayed absorption. Moreover, our study observed no effect of food on the pharmacokinetics of DTG. Therefore,

the effect of food on the pharmacokinetics of DTG should be further investigated in a larger study. Lastly, the simulations to investigate the alternative doses of DTG when co-administered with rifampicin were based on the C_{trough} target. Therefore, the clinical relevance of these alternative doses requires further investigation. Additionally, the administration of DTG 100 mg OD may result in an increase of the maximum concentration of DTG, potentially leading to the occurrence of toxicities. Nevertheless, this correlation must be confirmed in clinical settings. In conclusion, for PLWH receiving rifampicin as a co-medication, the administration of 50 mg b.i.d. provides highest proportion of patients achieving target concentration, while 100 mg OD provides sufficient DTG concentrations based on the target IC_{90} of 0.064 mg/L. This simplified regimen of 100 mg OD is appealing as an alternate regimen since it may improve adherence while maintaining an adequate DTG exposure. However, its clinical efficacy needs to be further examined.

AUTHOR CONTRIBUTIONS

BP: Design research, analyzed data, wrote manuscript. AC: Analyzed data, wrote manuscript. TU: Design research, performed research. SG: Design research, performed research. SU: Performed research. YSC: Performed research. JGS: Performed research. AA: Design research, performed research, wrote manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declared no competing interests for this work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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