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MAJOR ARTICLE

Impact of Obesity on the Drug–Drug Interaction Between Dolutegravir and Rifampicin or Any Other Strong Inducers

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Background. Obesity is increasingly prevalent among people with HIV. Obesity can impact drug pharmacokinetics and consequently the magnitude of drug–drug interactions (DDIs) and, thus, the related recommendations for dose adjustment. Virtual clinical DDI studies were conducted using physiologically based pharmacokinetic (PBPK) modeling to compare the magnitude of the DDI between dolutegravir and rifampicin in nonobese, obese, and morbidly obese individuals.

Methods. Each DDI scenario included a cohort of virtual individuals (50% female) between 20 and 50 years of age. Drug models for dolutegravir and rifampicin were verified against clinical observed data. The verified models were used to simulate the concurrent administration of rifampicin (600 mg) at steady state with dolutegravir (50 mg) administered twice daily in normal-weight (BMI 18.5–30 kg/m^2), obese (BMI 30–40 kg/m^2), and morbidly obese (BMI 40–50 kg/m^2) individuals.

Results. Rifampicin was predicted to decrease dolutegravir area under the curve (AUC) by 72% in obese and 77% in morbidly obese vs 68% in nonobese individuals; however, dolutegravir trough concentrations were reduced to a similar extent (83% and 85% vs 85%). Twice-daily dolutegravir with rifampicin resulted in trough concentrations always above the protein-adjusted 90% inhibitory concentration for all BMI groups and above the 300 ng/mL threshold in a similar proportion for all BMI groups.

Conclusions. The combined effect of obesity and induction by rifampicin was predicted to further decrease dolutegravir exposure but not the minimal concentration at the end of the dosing interval. Thus, dolutegravir 50 mg twice daily with rifampicin can be used in individuals with a high BMI up to 50 kg/m^2.

Keywords. PBPK modeling; dolutegravir; drug–drug interaction; obesity; rifampicin.

Worldwide obesity represents one of the biggest public health challenges, currently affecting more than 1 billion people [1]. Developing countries are not spared by this epidemic; in fact, the prevalence of obesity was reported to range from 14% to 31% in the 10 highest-burden countries [2]. As a result of highly effective antiretroviral drugs (ARVs) and related health improvement, people with HIV (PWH) are affected by obesity at a similar rate as the general population [3].

Obesity is associated with several anatomical, physiological, and biological changes [4], such as increase in adipose tissue weight, hepatic blood flow, glomerular filtration rate, and altered enzyme abundance, which have an impact on volume of distribution, hepatic clearance, renal clearance, and metabolism, respectively [5]. Obesity-related physiological changes have been shown to reduce efavirenz exposure [6, 7]. Due to its superior virologic efficacy, dolutegravir has now replaced efavirenz as first-line therapy for the treatment of HIV in low- and middle-income countries [8]. The effect of obesity on dolutegravir pharmacokinetics has become a question of particular interest following observations from several clinical trials that people on dolutegravir are more likely to gain weight after starting treatment [9, 10]. We previously reported that dolutegravir exposure was lower in obese individuals but to an extent that is not considered clinically relevant [11]. However, the relevance of this decrease has not been evaluated in the context of drug–drug interactions (DDIs) with inducers of drug metabolism.

Tuberculosis (TB) is the most common opportunistic infection among PWH in resource-limited settings [12]. Rifampicin, a cornerstone agent for the treatment of TB, potently induces the enzymes involved in dolutegravir metabolism, namely uridine diphosphate glucuronosyltransferase (UGT) 1A1 and cytochrome P450 (CYP) 3A4. Thus, rifampicin substantially reduces dolutegravir concentrations; however, a supplemental 50 mg dose of dolutegravir, given 12 hours after the standard dose, was shown to compensate the induction by rifampicin in nonobese individuals [13]. Therefore, the current treatment

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guidelines recommend the administration of dolutegravir at a dose of 50 mg twice daily in HIV/TB-coinfected individuals on rifampicin treatment. The same dose adjustment is also recommended with other strong inducers (eg, carbamazepine) [14]. Nevertheless, considering that obesity reduces dolutegravir exposure, it is unknown whether this dose adjustment provides adequate dolutegravir concentrations in individuals with a high body mass index (BMI).

Physiologically based pharmacokinetic (PBPK) modeling is a mathematical technique recognized by regulatory agencies [15–17] that has demonstrated its predictive power to simulate drug pharmacokinetics in special populations [18] as well as DDI scenarios [19, 20]. PBPK modeling combines in vitro data with clinically observed data to simulate pharmacokinetics in virtual individuals [21]. We previously developed a virtual obese population to inform PBPK models by gathering data on organ weights, blood flows, and other physiological parameters of interest for the prediction of drug disposition in this special population [4].

In this study, we performed virtual DDI studies using PBPK modeling to determine whether the currently recommended dolutegravir dose adjustment in the presence of rifampicin (or any other strong inducers) allows to reach adequate concentrations in obese (BMI 30–40 kg/m^2) and in morbidly obese individuals (BMI 40–50 kg/m^2).

METHODS

To correctly interpret the DDI results in obese and morbidly obese individuals, we followed three steps to validate the PBPK model. First, the drug models for dolutegravir and rifampicin were developed and verified against published clinical observed data. Second, the ability of the model to correctly predict the fraction metabolized by UGT1A1 and CYP3A4 was checked by running DDI simulations at steady state in nonobese individuals (BMI 18.5–30 kg/m^2). Third, we simulated the unknown DDI scenarios in obese (BMI 30–40 kg/m^2) and morbidly obese individuals (BMI 40–50 kg/m^2).

Model Validation

Our previously published PBPK model developed in Matlab®2020a [21] was informed with mathematical functions describing the anatomical, physiological, and biological changes occurring in a White obese population with age and BMI ranges of 20–50 and 18.5–60 kg/m^2, respectively [4]. The drug models for dolutegravir and rifampicin were developed using the physicochemical (eg, molecular weight, logP, pKa) and pharmacokinetic properties (eg, plasma protein binding, intrinsic clearance) summarized in Supplementary Table 1. The clinical observed data used to visually compare the simulation results for rifampicin were obtained from the literature (Supplementary Table 2) and, for dolutegravir, from both the literature and the Swiss HIV Cohort Study [11]. The drug models were validated by reproducing the drug dosing used in the published clinical trials and matching the demographic characteristics of the individuals participating in the studies with the virtual individuals generated by the model (ie, proportion of females, age range, and BMI range). Both models were considered validated when the predictions were within 2-fold of clinical observed data as per PBPK guidelines [22, 23].

DDI Simulations in Nonobese Individuals

The verification of the model's ability to correctly predict the DDI magnitude between dolutegravir and rifampicin and the fraction of dolutegravir metabolism by UGT1A1 (major) and CYP3A4 was conducted against available clinical data. The two studies used to verify the simulations were done in nonobese individuals (BMI 18.5–30 kg/m^2) at steady state administration of rifampicin (600 mg) combined with dolutegravir (50 mg) given either once daily [24] or twice daily [13].

DDI Simulations in Obese and Morbidly Obese Individuals

The same DDI scenarios (dolutegravir 50 mg either once or twice daily with rifampicin 600 mg) were simulated in obese (BMI 30–40 kg/m^2) and morbidly obese individuals (BMI 40–50 kg/m^2), without changing any of the drug parameters. A cohort of 100 virtual individuals aged 20–50 years (50% female) was generated to compare the magnitude of the DDIs in obese and morbidly obese individuals with the magnitude observed in the nonobese population. In addition, the simulated dolutegravir trough concentration (C_τ) was compared against the in vitro protein-adjusted 90% inhibitory concentration (PA-IC_{90}) of 64 ng/mL [25] and the alternative conservative clinical target trough concentration of 300 ng/mL (total plasma concentration) [26] to evaluate the need for a dose adjustment.

Patient Consent

This study does not include factors necessitating patient consent.

RESULTS

Model Validation

The PBPK model for rifampicin was developed and successfully verified against clinical observed data since the simulated parameters were within the 2-fold error margin (Supplementary Table 2, Supplementary Figure 1). The dolutegravir PBPK model, developed and presented in our previous work [11], was able to correctly describe the pharmacokinetics of dolutegravir alone both in nonobese and obese individuals.

DDI Simulations in Nonobese Individuals

The first studied scenario was the DDI between dolutegravir 50 mg once daily together with rifampicin 600 mg once daily. The simulation results were in agreement with clinical data,

and the observed data points were all contained in the 90% normal range of the PBPK model predictions. The predicted vs observed area under the curve during the dosing interval ($AUC_{0-\tau}$) and the C_τ were 53 281 vs 52 101 ng*h/mL and 1085 vs 1061 ng/mL for dolutegravir once daily alone, and these values were 17 712 vs 22 750 ng*h/mL and 59 vs 156 ng/mL when combined with rifampicin in nonobese individuals (Figure 1*A*). The simulated DDI ratios for dolutegravir once daily in the absence and presence of rifampicin were all within the 2-fold error margin apart from C_τ, which was underpredicted (Table 1).

The second clinical scenario was the co-administration of rifampicin 600 mg once daily with dolutegravir 50 mg twice daily. The PBPK model was able to reproduce the clinical observed data, and also in this case, all observed data points were within the predicted 90% normal range. The predicted vs observed $AUC_{0-\tau}$ and C_τ were 49 082 vs 46 300 ng*h/mL and 2410 vs 3060 ng/mL for dolutegravir twice daily alone and were 15 900 vs 21 300 ng*h/mL and 528 vs 670 ng/mL when combined with rifampicin (Figure 2*A*). As before, the simulated DDI ratios for dolutegravir twice daily in the absence and presence of rifampicin were within the 2-fold error margin (Table 1).

DDI Simulations in Obese and Morbidly Obese Individuals

After verifying that the PBPK model was able to reproduce the observed clinical data in nonobese individuals, the two DDI scenarios between dolutegravir and rifampicin were simulated both in obese and morbidly obese individuals. The results of the DDI between dolutegravir once daily and rifampicin once daily are reported in Table 2. Of interest, rifampicin decreased the various pharmacokinetic (PK) parameters to a similar extent when considering all three BMI groups, specifically peak concentration (C_{max}) by 37%, 38%, and 40%; C_τ by 95%, 93%, and 90%; and AUC_τ by 66%, 65%, and 64% in nonobese, obese, and morbidly obese individuals, respectively (Figure 1). However, when the DDI ratio for the two obese groups was calculated to take into account the combined effect of induction by rifampicin and obesity (ie, determined as the ratio of the PK parameter in obese individuals with rifampicin relative to the PK parameter in nonobese individuals without rifampicin), the magnitude of the DDI increased. It further reduced C_{max} (by 54% in obese individuals and by 61% in morbidly obese individuals vs 37% in nonobese individuals) and AUC_τ (73% and 76% vs 66%) but not C_τ, whose decrease remained constant across BMI groups (94% and 93% vs 95%) (Table 2). The predicted geometric mean values for C_τ in nonobese, obese, and morbidly obese individuals were 41, 53, and 63 ng/mL, respectively, and therefore slightly below the PA-IC_{90} (64 ng/mL), while the observed C_τ in nonobese individuals was 156 ng/mL and therefore above the PA-IC_{90}.

A similar trend was observed for the DDI scenario between dolutegravir twice daily and rifampicin once daily, as reported in Table 3. The magnitude of the DDI was similar across BMI groups, as indicated by the DDI ratios, which differed by a maximum of 6% for C_τ (85%, 80%, 79% reduction) (Figure 2). However, when the magnitude of the interaction was calculated to take into account both induction by rifampicin and obesity (the PK parameter in obese with rifampicin vs the PK parameter in nonobese individuals without rifampicin), the DDI was more pronounced for C_{max} (decrease by 63% in obese individuals and 71% in morbidly obese individuals vs 53% in nonobese individuals) and AUC_τ (72%, 77% vs 68%) but not for C_τ, which remained mostly unchanged (83%, 85% vs 85%) (Table 3). The simulated geometric mean values for C_τ in nonobese, obese, and morbidly obese individuals were 397, 448, and 387 ng/mL, respectively, and therefore were all above the PA-IC_{90} (64 ng/mL), in agreement with the observed C_τ in nonobese individuals (670 ng/mL). In addition, none of the virtual obese individuals had dolutegravir C_τ lower than PA-IC_{90}, and the proportion of subjects with dolutegravir C_τ above the 300-ng/mL threshold target were not significantly different across the three populations studied (77%, 73%, and 71% in nonobese, obese, and morbidly obese individuals, respectively).

Rifampicin Concentration and Fold Induction

Rifampicin concentrations were slightly different between the three BMI categories (Table 4). C_{max} and AUC_τ were 23% and 15% lower in obese compared with nonobese individuals and 35% and 21% lower in morbidly obese compared with nonobese individuals. Conversely, the elimination half-life ($t_{1/2}$) was found to be about 50% higher in the obese group compared with the nonobese. Nonetheless, when comparing the induction effect on CYP3A4 and UGT1A1, the fold increase in enzyme abundance (calculated as the enzyme levels postinduction relative to the levels at baseline) was similar between the three BMI groups.

DISCUSSION

Obese individuals, including obese PWH, are generally excluded from clinical trials, resulting in limited data on drug pharmacokinetics or on the magnitude of DDIs in this special population. To our knowledge, this study is the first to investigate the impact of obesity on the DDI between the strong inducer rifampicin and dolutegravir administered either once or twice daily. The results of our virtual clinical trials demonstrate that dolutegravir twice daily achieves similar C_τ concentrations in nonobese, obese, and morbidly obese individuals. Thus, the current recommendation to double dolutegravir dose to overcome the DDI with rifampicin can be applied to obese PWH up to a BMI of 50 kg/m^2.

Our PBPK model predicted that rifampicin reduced dolutegravir exposure similarly across the three populations, indicating that the strength of induction is unaltered by

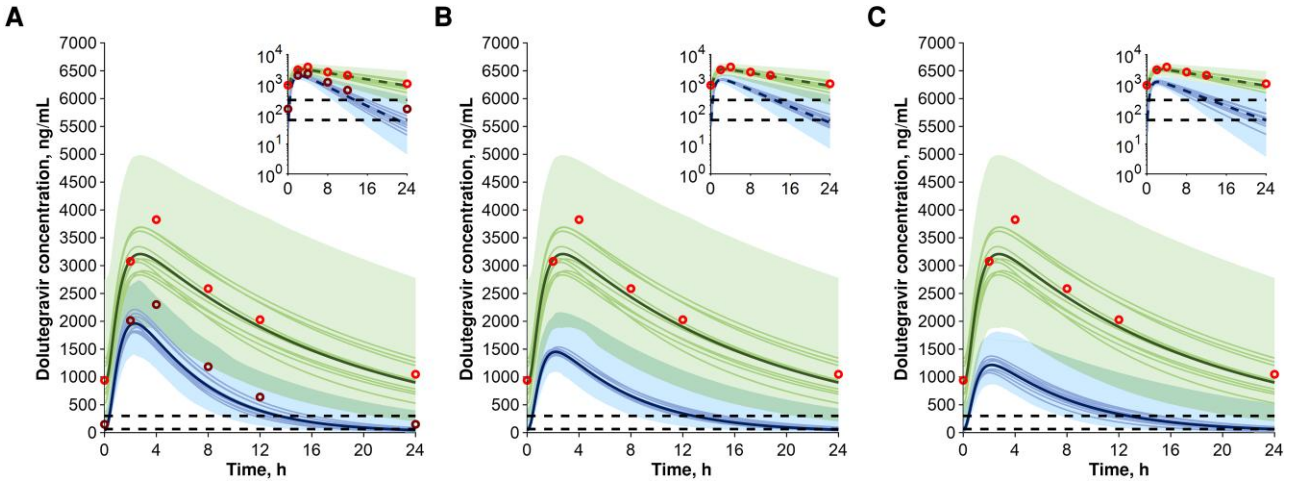

Figure 1. Predicted vs observed concentration-time profile for dolutegravir 50 mg once daily (*A*) in normal-weight individuals (BMI 18.5–30 kg/m^2) in the absence (green or upper concentration-time profile) and presence (blue or lower concentration-time profile) of 600 mg once daily rifampicin, (*B*) concentration-time profile for dolutegravir 50 mg once daily in normal-weight individuals in the absence of rifampicin (green or upper concentration-time profile) and in obese individuals (BMI 30–40 kg/m^2) in the presence of 600 mg once daily rifampicin (blue or lower concentration-time profile), and (*C*) concentration-time profile for dolutegravir 50 mg once daily in normal-weight individuals in the absence of rifampicin (green or upper concentration-time profile) and in morbidly obese individuals (BMI 40–50 kg/m^2) in the presence of 600 mg once daily rifampicin (blue or lower concentration-time profile). The solid lines, the solid bold line, and the shaded area represent the geometric mean of each virtual trial, the geometric mean of all trials, and the 90% normal range of all virtual individuals. The red and dark markers represent clinically observed data for the control and DDI scenarios (BMI 18.5–30 kg/m^2), respectively. The dashed lines represent the PA-IC$_{90}$ for dolutegravir (64 ng/mL) and the target trough concentration (300 ng/mL). Abbreviations: BMI, body mass index; DDI, drug–drug interaction; PA-IC$_{90}$, protein-adjusted 90% inhibitory concentration.

Table 1. Observed vs Predicted DDI Ratio Between Dolutegravir and Rifampicin in Nonobese Individuals (BMI 18.5–30 kg/m^2)

		Dolutegravir Once Daily With Rifampicin Once Daily		Dolutegravir Twice Daily With Rifampicin Once Daily	
		Observed DDI Ratio	Predicted DDI Ratio	Observed DDI Ratio	Predicted DDI Ratio
C_{max}	ng/mL	0.65	0.61	0.56	0.45
C_τ	ng/mL	0.15	0.05	0.28	0.17
AUC_τ	ng*h/mL	0.44	0.33	0.46	0.32

The data are presented as geometric mean.

Abbreviations: AUC_τ, area under the curve to tau; BMI, body mass index; C_{max}, peak concentration; C_τ, trough concentration; DDI, drug–drug interaction.

obesity-related physiological changes. This point was further demonstrated by evaluating the CYP3A4 and UGT1A1 fold induction upon administration of rifampicin, which proved to be similar across the different BMI categories. Conversely, when the DDI ratio was calculated to take into account the combined effect of induction and obesity, dolutegravir C_{max} and AUC_τ (both with the once and twice daily administration) were predicted to be further decreased in obese and morbidly obese compared with nonobese individuals. The negative impact of obesity on dolutegravir exposure was already reported in our recent modeling study, which combined clinical therapeutic drug monitoring data obtained from the PWH in the Swiss HIV Study Cohort [11]. In agreement with our findings, a clinical study evaluating the DDI between ethinylestradiol and the weak inducer topiramate reported a similar induction effect in both nonobese and obese individuals (ie, ethinylestradiol AUC reduced by 3% and C_{max} by 5% and 6% in obese and nonobese individuals). However, when the DDI was calculated to take into account both obesity and the induction effect, AUC and C_{max} further decreased by 25% and 33%, respectively [27].

Conversely to C_{max} and AUC, the combined effect of obesity and induction by rifampicin was predicted to cause no further decrease in dolutegravir C_τ both for once daily and twice daily administration of dolutegravir. This finding is in line with a population pharmacokinetic study reporting a comparable dolutegravir C_τ in the presence of rifampicin for individuals weighting 50 kg compared with those weighting 90 kg [28]. Differences in drug disposition behavior in obese individuals could explain this observation and may possibly relate to the fact that the redistribution phase is prolonged due to the larger volume of distribution, which leads to a longer half-life and an unchanged C_τ.

The predicted dolutegravir C_τ values obtained with twice daily administration in the presence of rifampicin were above the PA-IC$_{90}$ (64 ng/mL), and the proportion of virtual individuals with dolutegravir C_τ above the 300-ng/mL threshold were similar in nonobese, obese, and morbidly obese individuals (77%, 73%, and 71%, respectively). Our finding is consistent with a population pharmacokinetic analysis reporting dolutegravir C_τ concentrations >300 ng/mL in individuals weighing up to 90 kg [28]. Altogether, these data suggest that the recommendation to administer dolutegravir twice daily

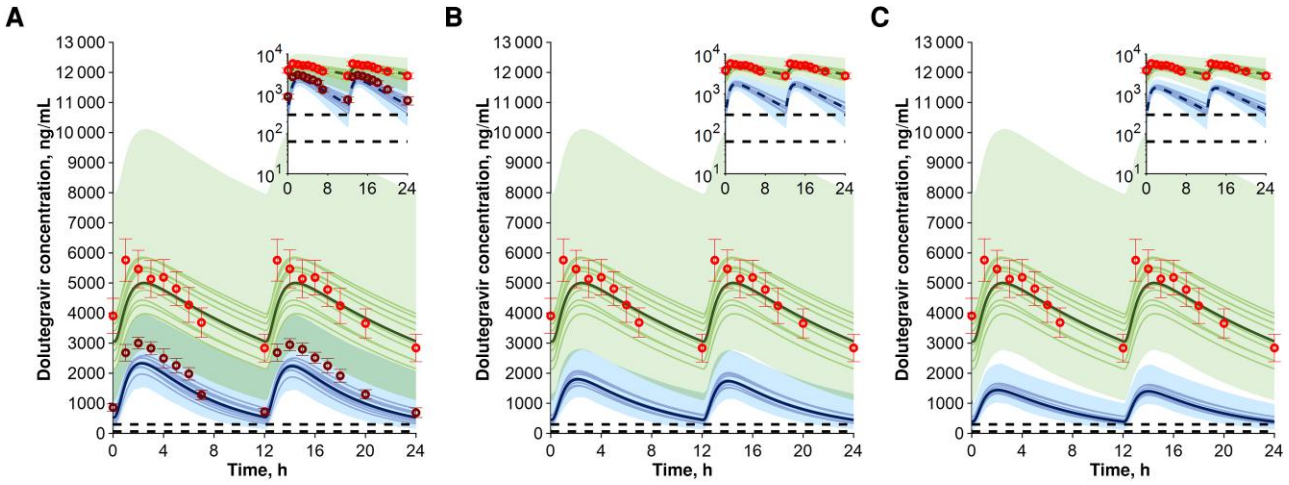

Figure 2. Predicted vs observed concentration-time profile for dolutegravir 50 mg twice daily (*A*) in normal-weight individuals (BMI 18.5–30 kg/m^2) in the absence (green or upper concentration-time profile) and presence (blue or lower concentration-time profile) of 600 mg once daily rifampicin, (*B*) concentration-time profile for dolutegravir 50 mg twice daily in normal-weight individuals in the absence of rifampicin (green or upper concentration-time profile) and in obese individuals (BMI 30–40 kg/m^2) in the presence of 600 mg once daily rifampicin (blue or lower concentration-time profile), and (*C*) concentration-time profile for dolutegravir 50 mg twice daily in normal-weight individuals in the absence of rifampicin (green or upper concentration-time profile) and in morbidly obese individuals (BMI 40–50 kg/m^2) in the presence of 600 mg once daily rifampicin (blue or lower concentration-time profile). The solid lines, the solid bold line, and the shaded area represent the geometric mean of each virtual trial, the geometric mean of all trials, and the 90% normal range of all virtual individuals. The red and dark markers represent clinically observed data for the control and DDI scenarios in normal-weight individuals (BMI 18.5–30 kg/m^2), respectively. The dashed lines represent the PA-IC$_{90}$ for dolutegravir (64 ng/mL) and the target trough concentration (3-00 ng/mL). Abbreviations: BMI, body mass index; DDI, drug–drug interaction; PA-IC$_{90}$, protein-adjusted 90% inhibitory concentration.

Table 2. Predicted DDI Magnitude Between Dolutegravir Once Daily and Rifampicin in Different Obese Groups

		Nonobese (BMI 18.5–30 kg/m^2)			Obese (BMI 30–40 kg/m^2)			Morbidly Obese (BMI 40–50 kg/m^2)			DDI Ratio	
		DTG Alone	DTG With RIF	DDI Ratio	DTG Alone	DTG With RIF	DDI Ratio	DTG Alone	DTG With RIF	DDI Ratio	Obese With RIF/ Nonobese Without RIF	Morbidly Obese With RIF/Nonobese Without RIF
C_{max}	ng/mL	3203	2020	0.63	2405	1482	0.62	2050	1236	0.60	0.46	0.39
C_τ	ng/mL	858	41	0.05	719	53	0.07	653	63	0.10	0.06	0.07
AUC_τ	ng*h/ mL	45 786	15 464	0.34	35 544	12 439	0.35	31 123	11 210	0.36	0.27	0.24

The data are presented as geometric mean.

Abbreviations: AUC_τ, area under the curve to tau; BMI, body mass index; C_{max}, peak concentration; C_τ, trough concentration; DDI, drug–drug interaction; DTG, dolutegravir; RIF, rifampicin.

with rifampicin can be adopted in obese and morbidly obese individuals with a BMI of up to 50 kg/m^2.

In limited-resource settings, where dolutegravir is available as a fixed-dose combination pill together with lamivudine or emtricitabine and tenofovir, dolutegravir twice daily dosing adds complexity to the treatment and adds constraints relative to the availability of the second dose. As a matter of fact, a study conducted in Botswana showed that only 56.4% of HIV/TB-coinfected participants received the supplemental 50 mg dolutegravir dose [29]. Of interest, this same study showed that similar rates of viral suppression were found among PWH on dolutegravir once daily compared with those on dolutegravir twice daily. Similar levels of viral suppression were also observed at weeks 24 and 48 of a randomized, double-blind, placebo-controlled trial evaluating the once vs twice daily administration of dolutegravir in individuals on rifampicin-based treatment [30, 31]. Altogether, these data suggest that dolutegravir once daily dosing with rifampicin may achieve adequate efficacy despite concentrations below the 300-ng/mL threshold (ie, dolutegravir once daily with rifampicin resulted in a C_τ of 156 ng/mL in a clinical DDI study [24]). It should be noted that the 300-ng/mL threshold is derived from a phase 2a study that evaluated the viral load reduction of dolutegravir monotherapy [26]. However, no pharmacokinetic–pharmacodynamic association could be established in the phase 2b SPRING-1 study, in which various dolutegravir doses were evaluated in combination with an NRTI backbone [32]. In this study, all dolutegravir doses (10, 25, 50 mg once daily) resulted in

Table 3. Predicted DDI Magnitude Between Dolutegravir Twice Daily and Rifampicin in Different Obese Groups

		Nonobese (BMI 18.5–30 kg/m^2)			Obese (BMI 30–40 kg/m^2)			Morbidly Obese (BMI 40–50 kg/m^2)			DDI Ratio	
		DTG Alone	DTG With RIF	DDI Ratio	DTG Alone	DTG With RIF	DDI Ratio	DTG Alone	DTG With RIF	DDI Ratio	Obese With RIF/ Nonobese Without RIF	Morbidly Obese With RIF/Nonobese Without RIF
C_{max}	ng/mL	4805	2256	0.47	3713	1754	0.47	2994	1415	0.47	0.37	0.29
C_τ	ng/mL	2650	397	0.15	2223	448	0.20	1819	387	0.21	0.17	0.15
AUC_τ	ng*h/ mL	45 128	14 592	0.32	35 970	12 578	0.35	29 105	10 302	0.35	0.28	0.23

The data are presented as geometric mean.

Abbreviations: AUC_τ, area under the curve to tau; BMI, body mass index; C_{max}, peak concentration; C_τ, trough concentration; DDI, drug–drug interaction; DTG, dolutegravir; RIF, rifampicin.

Table 4. Rifampicin Pharmacokinetics and CYP3A4 and UGT1A1 Fold Induction in Nonobese, Obese, and Morbidly Obese Individuals

		Nonobese (BMI 18.5–30 kg/m^2)	Obese (BMI 30–40 kg/m^2)	Morbidly Obese (BMI 40–50 kg/m^2)
Cmax	ng/mL	10 847	8346	7101
t1/2	h	2.96	4.10	4.88
AUCτ	ng*h/mL	58 218	49 728	45 771
CYP3A4 fold induction		8.6	8.6	9.1
UGT1A1 fold induction		2.6	2.6	2.7

The data are presented as mean.

Abbreviations: AUC_τ, area under the curve to tau; BMI, body mass index; C_{max}, peak concentration; CYP3A4, cytochrome P450 3A4; $t_{1/2}$, half-life; UGT1A1, UDP glucuronosyltransferase 1A1.

comparable rates of virological suppression, suggesting that the 300 ng/mL target could be too conservative.

Based on our model, the administration of dolutegravir once daily with rifampicin was predicted to result in C_τ concentrations slightly below the PA-IC_{90} (64 ng/mL) for all BMI groups. However, when considering the dolutegravir C_τ concentration observed in nonobese individuals (ie, 156 ng/mL), our predictions were slightly underpredicted. The difference between predicted and observed data could possibly relate to the fact that our model does not factor in TB-related physiological changes and does not consider the effect of other TB drugs used in combination with rifampicin, which could have potentially mitigated the effect of rifampicin. The effect of rifampicin on pretomanid exposure was shown indeed to be different in healthy volunteers compared with TB patients [33]. Therefore, considering the limitations of our model and considering that dolutegravir C_τ did not change significantly between the three BMI groups, dolutegravir once daily administration in the presence of rifampicin could possibly result in concentrations above PA-IC_{90} in obese individuals. However, more controlled prospective studies are needed to determine the clinical effectiveness of dolutegravir once daily dosing in the presence of rifampicin both in nonobese and obese individuals.

Another limitation of our model is that the obese population was developed using physiological data from White, obese individuals. However, as highlighted in the findings of an article by Young et al. [34], White and Black study participants had no significant differences in their physiology; also, dolutegravir is metabolized by CYP3A4 and UGT1A1, two enzymes that are not impacted by ethnicity-driven genetic polymorphisms, unlike CYP2B6 for efavirenz [35, 36]. Furthermore, the effect of obesity on dolutegravir 50 mg once daily that we observed and predicted in a White population (reduction of 3% in AUC and 13% in C_{max}) [11] is in agreement with that observed in a clinical study conducted in nonobese and obese Black African PWH (reduction of 9% in AUC and 14% in C_{max}) [37]. Therefore, we believe that our findings can be extrapolated to a Black population.

CONCLUSIONS

The combined effect of obesity and induction by rifampicin was predicted to further decrease the peak concentration and exposure of dolutegravir but not the trough concentration at the end of the dosing interval. Thus, the current recommendation to administer dolutegravir 50 mg twice daily in the presence of rifampicin or any other strong inducers applies also to individuals with a BMI of up to 50 kg/m^2.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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