Physiologically-Based Pharmacokinetic Modeling to Support the Clinical Management of Drug–Drug Interactions With Bictegravir

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Bictegravir is equally metabolized by cytochrome P450 (CYP)3A and uridine diphosphate-glucuronosyltransferase (UGT)1A1. Drug–drug interaction (DDI) studies were only conducted for strong inhibitors and inducers, leading to some uncertainty whether moderate perpetrators or multiple drug associations can be safely coadministered with bictegravir. We used physiologically-based pharmacokinetic (PBPK) modeling to simulate DDI magnitudes of various scenarios to guide the clinical DDI management of bictegravir. Clinically observed DDI data for bictegravir coadministered with voriconazole, darunavir/cobicistat, atazanavir/cobicistat, and rifampicin were predicted within the 95% confidence interval of the PBPK model simulations. The area under the curve (AUC) ratio of the DDI divided by the control scenario was always predicted within 1.25-fold of the clinically observed data, demonstrating the predictive capability of the used modeling approach. After the successful verification, various DDI scenarios with drug pairs and multiple concomitant drugs were simulated to analyze their effect on bictegravir exposure. Generally, our simulation results suggest that bictegravir should not be coadministered with strong CYP3A and UGT1A1 inhibitors and inducers (e.g., atazanavir, nilotinib, and rifampicin), but based on the present modeling results, bictegravir could be administered with moderate dual perpetrators (e.g., efavirenz). Importantly, the inducing effect of rifampicin on bictegravir was predicted to be reversed with the concomitant administration of a strong inhibitor such as ritonavir, resulting in a DDI magnitude within the efficacy and safety margin for bictegravir (0.5–2.4-fold). In conclusion, the PBPK modeling strategy can effectively be used to guide the clinical management of DDIs for novel drugs with limited clinical experience, such as bictegravir.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Bictegravir is a novel integrase inhibitor against HIV with limited clinical experience in drug–drug interactions (DDIs). Its exposure might be altered by inhibitors and inducers of cytochrome P450 (CYP)3A and uridine diphosphate-glucuronosyltransferase (UGT)1A1.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ The aim of this modeling study was to investigate the change of bictegravir exposure mediated by moderate inhibitors and inducers and multiple drugs that might interact mutually by our previously developed and verified physiologically-based pharmacokinetic (PBPK) model.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ Bictegravir can be coadministered with moderate inhibitors and inducers of CYP3A and UGT1A1 based on our PBPK simulation results. Furthermore, the combination of strong inhibitors and inducers (e.g., ritonavir + rifampicin) were predicted to mitigate the DDI magnitude within the safety margin for bictegravir; however, the safety of such a coadministration was not established in a clinical study.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ The PBPK modeling strategy can effectively be used to support the clinical management of DDIs for novel drugs with limited clinical experience such as bictegravir.

Bictegravir is a novel integrase inhibitor that was approved in 2018 in the Unites States and Europe.[1,2] The combination of bictegravir with the two nucleoside/nucleotide reverse transcriptase inhibitors tenofovir alafenamide and emtricitabine (Biktarvy) is recommended as an initial treatment regimen for most people living with HIV (PLWH) by the US and European guidelines.[3,4]

One general concern with HIV treatment is drug–drug interactions (DDI) with other concomitant drugs, which can lead to

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drug adverse events or loss of efficacy. Bictegravir has no known inhibitory or inducing effect on drug metabolizing enzymes. Coadministration of bictegravir with substrates of the active organic cation transporter 2 (OCT2) and the multidrug and toxin extrusion transporter 1 (MATE1) may increase their plasma concentration as bictegravir was shown to inhibit both transporters *in vitro*.[5] The metabolism of bictegravir is mediated by cytochrome P450 (CYP)3A and uridine diphosphate-glucuronosyltransferase (UGT)1A1,[6] and therefore bictegravir exposure can be altered by inhibitors and inducers of both enzymes.[5] Only limited DDI studies were conducted during the clinical development of bictegravir, including the typical strong paradigm inhibitors (e.g., voriconazole and atazanavir) and inducers (e.g., rifampicin) to investigate the "worst case" scenarios. However, the effect of weak or moderate inhibitors or inducers of CYP3A and UGT1A1 on bictegravir exposure is difficult to extrapolate from the existing DDI data. Furthermore, the effect of concomitant drugs with mutually interacting effects on bictegravir exposure is unknown. However, it is of tremendous importance to assess the likelihood and magnitude of any DDI to understand the clinical significance of a given DDI and whether the DDI can be safely managed by dose modifications.

Physiologically-based pharmacokinetic (PBPK) modeling has demonstrated the predictive power to simulate DDI scenarios[7,8] and is recommended by the health authorities.[9–12] The ability of PBPK modeling to predict the magnitude of DDIs and potential dose adjustments of the victim drug to overcome a given DDI are valid strategies to support the clinical management of DDIs. Virtual individuals inform the PBPK model, which are generated based on clinically observed organ weights, blood flows, the glomerular filtration rate, and other physiological parameters that are important to predict drug pharmacokinetics.[13] A combination of measured *in vitro* and clinically observed *in vivo* data are used to correctly simulate drug disposition in the virtual human body.[14]

The aim of the present modeling study was to utilize our previously developed and verified PBPK framework[14] to simulate different DDI scenarios with bictegravir to guide its clinical DDI management.

METHODS

To ensure a safe and efficacious coadministration of bictegravir with drugs that can inhibit or induce CYP3A and UGT1A1, we took three steps to analyze DDIs involving bictegravir by our PBPK modeling framework.[14] Firstly, we developed and verified a PBPK model for bictegravir.[15] Secondly, the potential of our developed PBPK framework to predict DDIs involving bictegravir was verified against clinically observed data of strong paradigm inhibitors and inducers of CYP3A and UGT1A1 (voriconazole, boosted darunavir, unboosted and boosted atazanavir, and rifampicin). Lastly, the fully verified bictegravir model was used to simulate bictegravir DDIs of clinical interest.

PBPK modeling

A whole-body PBPK model constructed in Matlab 2017a (MathWorks, Natick, MA) was used.[14] Virtual individuals aged 20 to 50 years were generated to inform the PBPK model structure under the consideration of observed demographical (e.g., body weight), physiological (e.g., organ volume), and biological (e.g., hepatic enzyme abundance) variability. The age was distributed according to the demographic data. Variability was considered for all population parameters using normal distribution.[13]

The development of the PBPK model for bictegravir and its ability to predict "real-life" plasma concentrations of Swiss HIV Cohort Study participants aged 20 to 85 years has been described in an accompanied paper.[15]

Two drug models for voriconazole and cobicistat were developed to verify the predictive potential of the used PBPK framework[14] to simulate DDI scenarios of bictegravir with strong paradigm inhibitors and inducers of CYP3A and UGT1A1 (**Table S1**). The voriconazole PBPK model was taken from the literature, modified, and verified for our used PBPK framework.[16] The cobicistat model was newly developed based on published *in vitro* and *in vivo* data. Cobicistat is metabolized and eliminated mainly via CYP3A and to a lesser extent via CYP2D6, the bile, and the kidney.[17,18] We performed a retrograde calculation of the intrinsic clearance of CYP2D6 from clinically observed cobicistat clearance after a high single cobicistat dose (400 mg), assuming that CYP3A was fully inhibited.[19] The intrinsic clearance of CYP3A was calculated from a single cobicistat dose of 50 mg, accounting for the autoinhibition of CYP3A at lower cobicistat doses.[19] The renal and biliary clearance were taken from the report of the European Medicine Agency.[18] All cobicistat model parameters are detailed in **Table S1**.

All other used drug models were previously developed and verified for our PBPK framework.[20–22]

Model verification against clinically observed data from DDI studies

Verification of drug models followed the best practice approach, whenever clinically observed data were available.[23] In the case of voriconazole and cobicistat, several doses were used to verify the concentration-dependent clearance (published clinical studies, used for model verification, are detailed in **Table S2**). These published concentration-time profiles for voriconazole and cobicistat model verification were digitized using GetData Graph Digitizer V. 2.26 (www.getdata-graph-digitizer.com), which demonstrated an excellent accuracy.[24] The predictive performance of the model to simulate DDIs with bictegravir was verified against clinically observed data, using the perpetrators voriconazole, cobicistat, atazanavir/ritonavir, and darunavir/ritonavir. These clinically observed DDI study data were provided by Gilead Sciences. Successful predictions were judged by overlaying clinically observed data with the simulation results, and pharmacokinetic parameters had to be predicted within twofold of clinically observed data, which is considered best practice for modeling and simulation by the regulatory agencies.[11] The absolute average fold error (AAFE) was calculated for each drug, whenever clinically observed data were available. Simulations were matched closely to the published clinical studies regarding dose and dosing regimens.

Simulations of DDI scenarios without clinically observed data

DDI scenarios were predicted for pairwise and multiple drug combinations. Simulations were performed with the CYP3A inhibitors voriconazole, ketoconazole, clarithromycin, and cobicistat, the combined CYP3A and UGT1A1 inhibitors atazanavir and nilotinib, the CYP3A inhibitor and UGT1A1 inducer ritonavir, and the CYP3A and UGT1A1 inducers rifampicin and efavirenz. Bictegravir is combined with the two nucleoside/nucleotide reverse transcriptase inhibitors tenofovir alafenamide and emtricitabine in clinical practice and would in principle not be combined with an additional antiretroviral drug.[5] However, in clinical situations where an intensification of HIV treatment is needed, HIV protease inhibitors (with the exception of atazanavir or atazanavir/cobicistat) and other HIV drug classes could be combined.[25] Thus, it is of interest to evaluate the used anti-HIV agents not only because they have a well-known interaction profile and are representative for other inhibitors and inducers of CYP3A and UGT1A1 but also because some of them could be combined with bictegravir/emtricitabine/tenofovir alafenamide for instance in individuals with multiple resistances to HIV.

However, it needs to be highlighted that the safety of combining bictegravir and other antiretroviral drugs (despite tenofovir alafenamide and emtricitabine) was not investigated in a clinical study.

We simulated scenarios of drugs that might interact mutually, especially the combination of inhibitors and inducers as HIV patients often receive multiple concomitant non-HIV medications. In clinical practice, it is often difficult to estimate the net effect of an interaction particularly when concomitant medications have opposite effects on drug-metabolizing enzymes. Simulated scenarios included the combination of voriconazole or ritonavir with nilotinib, rifampicin, and efavirenz as well as nilotinib with rifampicin and efavirenz. Altogether, these drugs allow for simulating all the possible DDI scenarios (i.e., association of moderate or strong inhibitors or inducers of CYP3A4 or UGT1A1) which can be encountered in clinical practice with bictegravir in the presence of the large list of comedications that HIV individuals are likely to receive.

In each case, we simulated the DDI in 100 virtual individuals (50% women, 10 trials with 10 individuals in each). The inhibitors and inducers were simulated for 14 days at dosages commonly used in clinical practice (**Table S3**). Bictegravir dosing (50 mg once daily) was started on the seventh day and was given until the end of the simulations. DDI magnitudes were calculated for the first day of bictegravir dosing and on the seventh day. Data are presented as the mean with the [95% confidence interval].

RESULTS

Firstly, we developed PBPK models for voriconazole and cobicistat to verify the predictive potential of the used PBPK framework to replicate clinical DDI studies with bictegravir. Both drugs exhibit nonlinear pharmacokinetics, and thus several single and multiple doses were simulated.

Clinically observed data for voriconazole were usually simulated within the 95% confidence interval of the PBPK model predictions (**Figure S1–S4**). Pharmacokinetic parameters for different routes of administration (intravenous and oral), doses (50–400 mg), and dosing regimens (single and multiple) were predicted within 1.25-fold in 57%, within 1.5-fold in 81%, and within 2-fold in 95% cases of clinically observed data (**Table S4**). The only value, which was predicted outside of the twofold margin was the peak concentration of the 200 mg single oral dose. The AAFE for voriconazole predictions was −0.50. Voriconazole is metabolized by CYP3A and CYP2C19. To verify the fraction metabolized for both enzymes, DDI studies with ritonavir in enhanced and poor metabolizers of CYP2C19 were simulated, which were predicted in accordance with clinically observed data (**Figure S5**; **Table S5**; AAFE = 0.90). The predicted CYP3A inhibition of voriconazole was verified against clinically observed data with midazolam. DDIs with intravenous and oral midazolam were well predicted by our developed PBPK framework (**Figure S6**; **Table S5**; AAFE = 1.74).

Most clinically observed data for cobicistat were within the 95% confidence interval of the PBPK simulations apart from the single 50-mg dose (**Figure S7–S8**). The clinically relevant 150 mg once-daily dose was well predicted by our PBPK model also using therapeutic drug monitoring data from the Swiss HIV Cohort Study. Pharmacokinetic parameters were predicted within 1.25-fold in 60%, within 1.5-fold in 77%, and within 2-fold in 97% cases of clinically observed data (**Table S6**). Only the drug exposure of the 50-mg single cobicistat dose was overpredicted within threefold. The AAFE for cobicistat was 1.86. To verify the implemented inhibition of CYP3A, darunavir/cobicistat (800/150 mg once daily) and atazanavir/cobicistat (300/150 mg once daily) were simulated.

Those clinically observed data were predicted within the 95% confidence interval of the PBPK model simulations (**Figure S9**). All pharmacokinetic parameters were predicted within 1.25-fold of clinically observed data for both boosted protease inhibitors apart from the terminal half-life of atazanavir/cobicistat, which was underpredicted (ratio predicted:observed: 0.65; **Table S6**; AAFE = 0.69).

Model verification against clinically observed data from DDI studies

The predictive performance to simulate bictegravir DDIs by our PBPK model was verified against clinical DDI studies with voriconazole and darunavir/cobicistat to investigate CYP3A inhibition, atazanavir and atazanavir/cobicistat to investigate the combined inhibition of the CYP3A and UGT1A1 pathway, and rifampicin to investigate the effect of CYP3A and UGT1A1 induction on bictegravir pharmacokinetics. Clinically observed data of the DDI studies were always contained within the 95% confidence interval of the PBPK model predictions (**Figure 1**). Furthermore, all AUC ratios were predicted within 1.25-fold of the clinically observed data (**Table 1**). The AAFEs for bictegravir in the absence and presence of perpetrators were 0.34 and 1.47, respectively.

Simulations of DDI scenarios without clinically observed data

After verifying the predictive potential of the used PBPK approach to simulate DDIs involving bictegravir, several DDI scenarios were investigated. The strong competitive and mechanism-based CYP3A inhibitors ketoconazole, voriconazole, clarithromycin, and cobicistat inhibited bictegravir metabolism to the same extent with a predicted AUC ratio of 1.21 (1.04; 1.60) on day 1 and 1.68 (1.14; 2.63) on day 7 (**Figure 2**; Supplementary **Table S7**). Ritonavir, which has inhibitory and inducing properties, led to simulated DDI magnitudes of 1.02 (0.84; 1.29) on day 1 and 1.08 (0.62; 1.84) on day 7. In contrast, atazanavir and nilotinib, which inhibit CYP3A and UGT1A1, led to AUC ratios of 1.37 (1.14; 1.68) and 1.39 (1.15; 1.67) on day 1, and 2.53 (1.92; 3.36) and 2.85 (1.77; 3.82) on day 7. Boosted darunavir and boosted atazanavir showed no differences compared with ritonavir or atazanavir alone. The strong and moderate inducers of both pathways, rifampicin and efavirenz, led to predicted AUC ratios of 0.50 (0.37; 0.68) and 0.77 (0.63; 0.89) on day 1, and 0.30 (0.20; 0.42) and 0.56 (0.37; 0.74) on day 7, respectively. When nilotinib was combined with a strong CYP3A inhibitor (e.g., voriconazole and ritonavir), the AUC ratios were simulated to be 1.52 (1.14; 2.13) on day 1 and 3.53 (2.00; 5.04) on day 7 (**Figure 3**). However, if both strong CYP3A inhibitors were combined with the dual inducers rifampicin and efavirenz, the resulting predicted DDI magnitudes (1.05 (0.85; 1.41) on day 1 and 1.14 (0.71; 1.92) on day 7) indicated no DDI according to the FDA classification.[26] The combination of nilotinib with rifampicin reduced the AUC ratio to 1.06 (0.70; 1.37) on day 1 and 1.31 (0.55; 2.27) on day 7. In combination with the moderate inducer efavirenz, the AUC ratio of bictegravir in the presence of nilotinib was predicted to be 1.29 (1.05; 1.58) on day 1 and 2.13 (0.96; 3.23) on day 7.
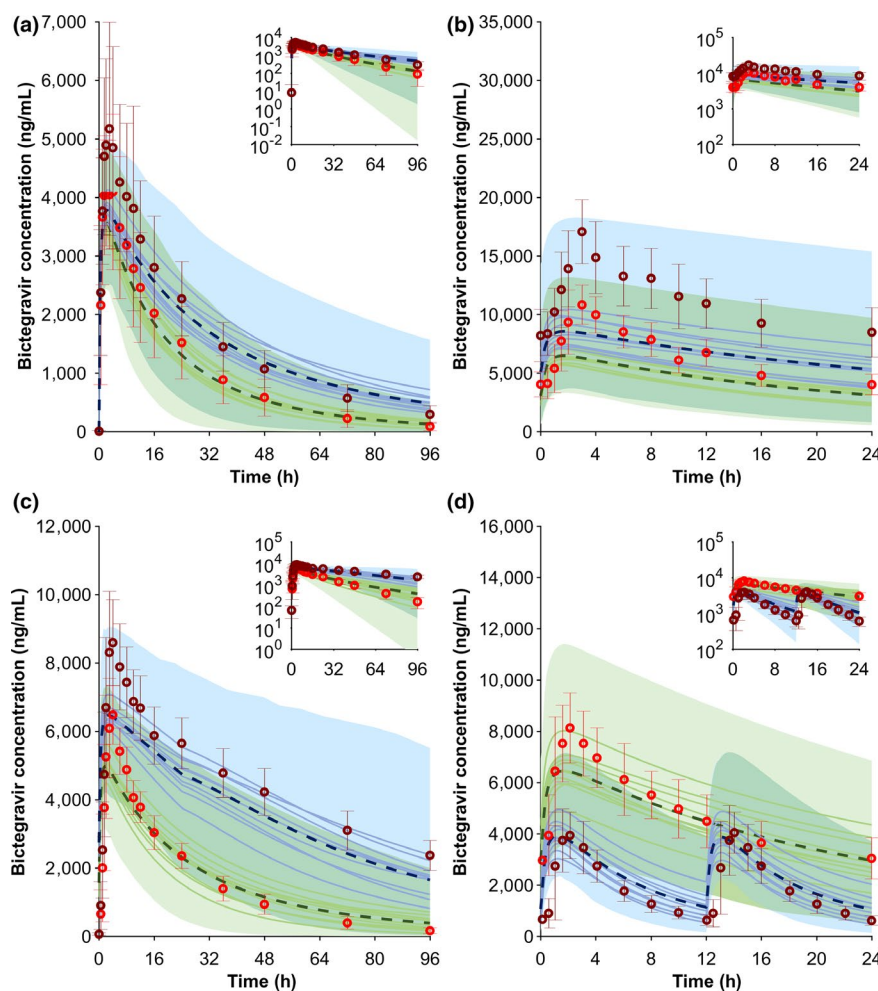
Figure 1 Predicted vs. observed concentration-time profiles for bictegravir in the (green) absence and the (blue) presence of **(a)** 300 mg once-daily voriconazole, **(b)** 800/150 mg once-daily darunavir/cobicistat, **(c)** 300/150 mg once-daily atazanavir/cobicistat, and **(d)** 600 mg once-daily rifampicin. The red and the dark red markers show the clinically observed data (mean ± standard deviation) for the control and DDI scenario, respectively (**Table S2**). The solid lines, the dashed line, and the shaded area represent the mean of each virtual trial, the mean, and the 95% confidence interval of all virtual individuals. DDI, drug–drug interaction; h, hour. [Colour figure can be viewed at wileyonlinelibrary.com]

DISCUSSION

Clinical DDI studies are usually only conducted for strong paradigm inhibitors and inducers; however, in clinical practice drugs are also combined with moderate-to-weak inhibitors and inducers and often several concurrent drugs are coadministered that might interact mutually. The present simulation study investigated DDI scenarios for the novel integrase inhibitor bictegravir by PBPK modeling. This modeling work suggests that bictegravir may be able to be administered with other medications apart from dual strong perpetrators that inhibit or induce CYP3A and UGT1A1 as summarized in **Table 2**.

Before exploring unknown scenarios of interest, PBPK models must be verified against existing clinically observed data.[14] DDI studies were performed for the strong competitive and mechanism-based CYP3A inhibitors voriconazole and darunavir/cobicistat, the CYP3A and UGT1A1 inhibitor atazanavir, and the CYP3A and UGT1A1 inducer rifampicin. In all cases, the clinically observed data were predicted within the 95% confidence interval of the PBPK model (**Figure 1**); however, the predicted shape of the

darunavir/cobicistat simulation (**Figure 1b**) was not overlaying the predicted mean of the PBPK simulation. One reason could be that the implemented fraction metabolized by CYP3A of bictegravir might not be correct; however, in this case, the DDI with voriconazole (**Figure 1a**) would also be wrongly predicted. Another reason is that our PBPK model is not able to predict the CYP3A inhibition of cobicistat; however, clinically observed data of darunavir and atazanavir boosted with cobicistat (**Figure S9**) were predicted within the 95% confidence interval of the PBPK model simulations, excluding this possibility. A more likely explanation could be interindividual variability, which might have not been captured in the clinical DDI study with 15 individuals, but is well captured by the model as shown by our previous predictions of 50 mg bictegravir against clinically observed therapeutic drug monitoring data of the PLWH enrolled in the Swiss HIV Cohort Study.[15] Taken together, the used modeling approach demonstrated its predictive power to simulate clinical scenarios with the novel integrase inhibitor bictegravir. In general, the PBPK modeling strategy is commonly used to predict DDI scenarios and is used to inform drug labels.[9,10]

Table 1 Observed vs. predicted pharmacokinetic parameters

	Control scenario			DDI scenarios			DDI ratio		
	Observed	Predicted	Ratio P/O	Observed	Predicted	Ratio P/O	Observed	Predicted	Ratio P/O
Bictegravir + voriconazole									
C_{max} (ng/mL)	4,092 ± 1,326	3,714 ± 689	0.91	5,171 ± 1,822	3,874 ± 698	0.75	1.26	1.04	0.83
AUC_t (ng*h/mL)	98,774 ± 39,162	91,489 ± 54,044	0.93	148,890 ± 63,483	143,235 ± 74,839	1.13	1.51	1.57	1.04
$t_{1/2}$ (h)	17.6 ± 7.0	17.1 ± 15.9	0.97	25.0 ± 10.7	26.4 ± 24.3	1.06	1.42	1.55	1.09
Bictegravir + darunavir/c									
C_{max} (ng/mL)	10,827 ± 1,680	6,578 ± 2,962	0.61	17,069 ± 2,731	8,667 ± 4,445	0.51	1.58	1.32	0.84
AUC_t (ng*h/mL)	152,480 ± 35,190	145,231 ± 127,342	0.95	265,330 ± 58,176	237,125 ± 208,175	0.89	1.74	1.63	0.94
$t_{1/2}$ (h)	17.4 ± 4.0	20.2 ± 12.6	1.16	26.6 ± 5.8	32.3 ± 24.6	1.21	1.53	1.6	1.04
Bictegravir + atazanavir									
C_{max} (ng/mL)	6,748 ± 1,136	5,051 ± 1,386	0.75	8,579 ± 1,262	6,643 ± 1,613	0.77	1.27	1.32	1.03
AUC_t (ng*h/mL)	149,500 ± 55,644	146,658 ± 108,680	0.98	424,410 ± 151,214	448,985 ± 273,708	1.06	2.84	3.06	1.08
$t_{1/2}$ (h)	18.9 ± 7.0	17.6 ± 9.4	0.93	58.1 ± 20.7	45.1 ± 37.1	0.78	3.07	2.56	0.83
Bictegravir + atazanavir/c									
C_{max} (ng/mL)	6,479 ± 858	5,062 ± 1,269	0.78	8,591 ± 1,259	6,526 ± 1,459	0.76	1.33	1.29	0.97
AUC_t (ng*h/mL)	149,640 ± 51,040	157,448 ± 100,792	1.05	422,590 ± 111,754	354,894 ± 156,143	0.84	2.82	2.25	0.8
$t_{1/2}$ (h)	19.0 ± 6.5	21.6 ± 14.4	1.14	57.7 ± 15.2	39.0 ± 37.1	0.68	3.04	1.81	0.59
Bictegravir + rifampicin									
C_{max} (ng/mL)	8,130 ± 1,365	10,617 ± 7,404	1.31	4,043 ± 803	3,978 ± 1,880	0.98	0.5	0.37	0.75
AUC_t (ng*h/mL)	113,850 ± 26,387	115,840 ± 96,317	1.02	22,751 ± 7,835	28,219 ± 23,418	1.24	0.2	0.24	1.22
$t_{1/2}$ (h)	18.6 ± 4.3	20.2 ± 23.8	1.09	3.8 ± 1.3	5.1 ± 3.8	1.36	0.2	0.25	1.25

Observed vs. predicted pharmacokinetic parameters of the control and the DDI scenario and the DDI ratio (DDI scenario / control scenario).

AUC_t, area under the curve to tau; C_{max}, peak concentration; h, hour; O, observed; P, predicted; $t_{1/2}$, elimination half-life.
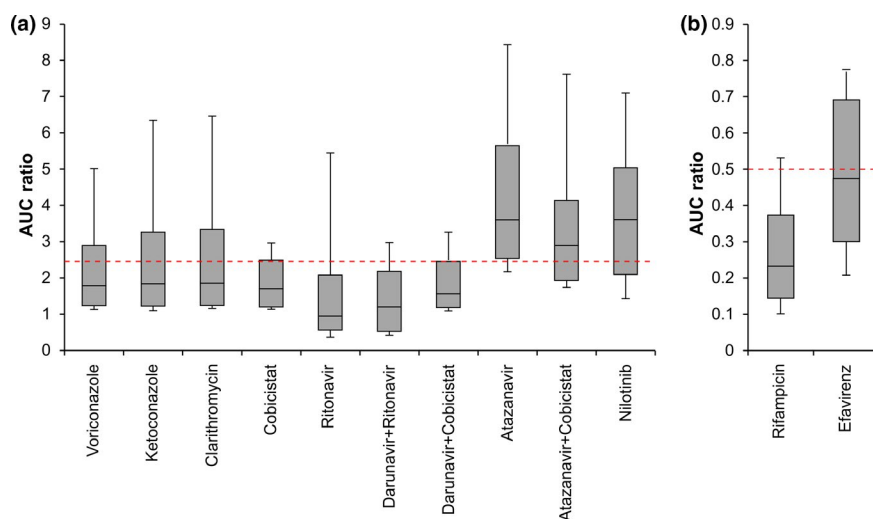
Figure 2 AUC ratios for bictegravir in the presence of one (a) inhibitor or (b) inducer of CYP3A and UGT1A1. Box and whisker plots show the median and 95% confidence interval. The red dashed line represents the efficacy-safety margin of bictegravir (2.4-fold for inhibitors and 0.5-fold for inducers). AUC, area under the curve; CYP, cytochrome P450; UGT, uridine diphosphate-glucuronosyltransferase. [Colour figure can be viewed at wileyonlinelibrary.com]
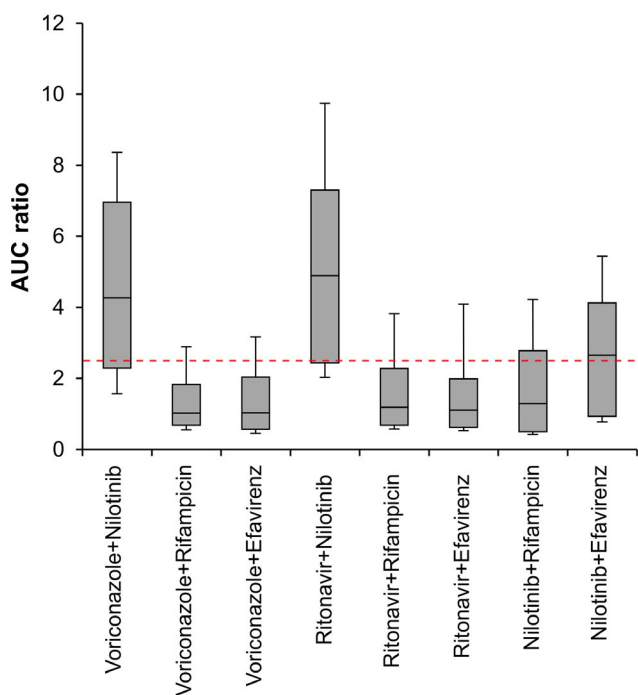

Figure 3 AUC ratios for bictegravir in the presence of multiple inhibitors and inducers of CYP3A and UGT1A1. Box and whisker plots show the median and 95% confidence interval. The red dashed line represents the efficacy-safety margin of bictegravir (2.4-fold). AUC, area under the curve; CYP, cytochrome P450; UGT, uridine diphosphate-glucuronosyltransferase. [Colour figure can be viewed at wileyonlinelibrary.com]

After the successful model verification, we simulated different DDI scenarios for CYP3A and UGT1A1 inhibitors and inducers (**Figures 2** and **3**). The modeling approach allowed for simulating the victim drug (in our case bictegravir) under steady-state conditions, which is usually not done in clinical studies for cost reasons. It is commonly believed that for drugs with linear pharmacokinetics

in respect to dose and time, the single-dose design provides DDI data of equal quality to steady-state conditions that are common in clinical practice.[27] However, for drugs with a long half-life, such as bictegravir, the AUC ratio might be increased under steady-state conditions.[28] Our simulation results indicated that DDI magnitudes are on average 40% higher on day 7 of bictegravir coadministration with inhibitors and inducers compared with day 1. The highest increase is shown for the moderate CYP3A and strong UGT1A1 inhibitor nilotinib, which led to a 2.4-fold higher DDI magnitude on day 7 compared with day 1. In contrast, coadministration of bictegravir and ritonavir for seven days led only to a 6% increase in the DDI magnitude. A possible explanation is that ritonavir is a strong inhibitor of CYP3A but is also an inducer of UGT1A1,[29,30] and both opposite effects might mitigate the DDI magnitude under steady-state conditions.

Data from bictegravir phase III clinical trials have shown a good safety profile with up to a 2.4-fold increase in bictegravir exposure.[31,32] Our PBPK simulations showed that this limit is only reached for dual strong inhibitors of CYP3A and UGT1A1 (e.g., atazanavir and nilotinib). If CYP3A and UGT1A1 are both moderately induced (e.g., efavirenz), our predictions suggest that this drug can be safely coadministered with bictegravir, because the decrease in bictegravir exposure was simulated within the accepted safety margin of 0.5-fold for inducers.[33]

One advantage of the used PBPK approach is that population simulations are conducted, covering the physiological variability of the "true" patient population (e.g., regional blood flows and enzyme abundance) better than clinical studies with small numbers of participants. However, prediction can only be made with absolute certainty for characterized pharmacokinetic mechanisms. Our model demonstrated previously that it was able to predict "real-life" plasma concentrations, sampled within the general therapeutic drug monitoring program of the Swiss HIV Cohort Study.[15,21] On day 1 of coadministration of bictegravir and various perpetrators, 2.4-fold higher bictegravir exposure was only predicted to

Table 2 Summary of the predicted magnitude of interactions between bictegravir and perpetrators

Association with	Predicted effect on bictegravir AUC[a]	Examples of perpetrators	Model-based coadministration prediction[b]
Dual CYP3A4/UGT1A1 inhibitor	2.5–2.9-fold	Atazanavir Atazanavir/cobicistat Nilotinib	Avoid
Strong CYP3A4 inhibitor	1.7-fold	Clarithromycin Erythromycin Cobicistat HIV protease[c] Itraconazole Ketoconazole Posaconazole Voriconazole	Possible
Strong CYP3A4 inducer	0.3-fold	Carbamazepine Enzalutamide Phenytoin Rifampicin Rifapentine St John's Wort	Avoid
Moderate CYP3A4 inducer	0.6-fold	Bosentan Dexamethasone Efavirenz Etravirine Primidone Thioridazine	Possible
Dual CYP3A4/UGT1A1 inhibitor + strong CYP3A4 inhibitor	3.5-fold	See corresponding examples above	Avoid
Dual CYP3A4/UGT1A1 inhibitor + strong CYP3A4 inducer	1.3-fold	See corresponding examples above	Possible
Dual CYP3A4/UGT1A1 inhibitor + moderate CYP3A4 inducer	2.1-fold	See corresponding examples above	Possible
Strong CYP3A4 inhibitor + strong CYP3A4 inducer	1.1-fold	See corresponding examples above	Possible
Strong CYP3A4 inhibitor + moderate CYP3A4 inducer	1.3-fold	See corresponding examples above	Possible

Summary of the predicted magnitude of interactions between bictegravir and perpetrators characterized by different inhibitory/inducing effects considering various key combinations. Examples of perpetrators with similar inhibitory/inducing strength (as per classification of the FDA[39]) are provided in the table to allow translation to other drug combinations that could present in clinical practice.

[a]Predicted effect after coadministering drugs for 7 days. [b]The safety of many of these combinations was not investigated in clinical studies. [c]Except atazanavir.

be achieved when nilotinib and an additional CYP3A inhibitor (e.g., voriconazole or ritonavir) was administered with bictegravir. However, the safety threshold of 2.4-fold was simulated to be almost always achieved for bictegravir under steady-state conditions. The only exceptions were predicted for ritonavir and the combination of rifampicin and voriconazole or ritonavir. However, it should be highlighted that high DDI magnitudes were only predicted in a minority of individuals (**Table S7**), notably those with certain hepatic conditions such as a high CYP3A activity. This assumption is supported by the overall good tolerability of bictegravir in patients of the Swiss HIV Cohort, receiving concomitantly strong CYP3A inhibitors such as itraconazole.

Of interest, the inducing effect of rifampicin on bictegravir was simulated to be reversed when adding a strong inhibitor of CYP3A (e.g., ritonavir).[26] This finding suggests that the interaction between bictegravir and rifampicin might be managed when using concomitantly a strong CYP3A4 inhibitor. Similarly, the coadministration of etravirine (UGT1A1 and CYP3A4 inducer) and dolutegravir (substrate of UGT1A1 and CYP3A4) requires the concomitant use

of a strong CYP3A4 inhibitor (i.e., boosted protease inhibitor) to mitigate the DDI magnitude.[34] As bictegravir is coformulated with tenofovir alafenamide and emtricitabine, the effect of ritonavir and rifampicin on these two antiretroviral drugs needs to be considered as well. Rifampicin was shown to have no effect on emtricitabine. Plasma exposure of tenofovir (administered as tenofovir alafenamide) was reduced by 55% when coadministered with rifampicin; however, the intracellular tenofovir diphosphate concentration (active entity) was still more than fourfold higher compared with intracellular diphosphate tenofovir levels administered as disoproxil fumarate.[35] The efficacy of once-daily tenofovir alafenamide with rifampicin still needs clinical validation. Furthermore, it is unclear whether the approach of adding ritonavir would be suitable from a tolerability standpoint. It should be highlighted that the label contraindicates the coadministration of bictegravir with rifampicin due to the substantial decrease in bictegravir plasma concentrations.[5]

It is important to highlight some limitations of a modeling approach. PBPK models can only account for known metabolism and transport pathways, using reliable *in vitro* data as the input for the

drug model prediction.[14] The modeling approach can be used to test hypotheses about unknown distribution and elimination pathways to fit clinically observed concentration-time data; however, this would require verification by *in vitro* experiments. Pharmacokinetic interactions can only be predicted with absolute certainty when metabolism and active transport processes are fully characterized. Furthermore, pharmacodynamic interactions cannot be accounted for.

Our modeling study used drugs that are representative for all drugs with equal inhibitory and inducing properties and therefore supports the rationalization with interactions with similar underpinning mechanisms. Examples of perpetrators which may be encountered in HIV clinical practice are listed in **Table 2**. Based on our simulation results, it would be possible, for instance, to administer the strong inhibitor posaconazole for the treatment of a fungal infection in a patient on bictegravir therapy (bictegravir AUC is predicted to increase by 70%) or to coadminister both posaconazole and the moderate inducer thioridazine with bictegravir in a psychotic patient with a fungal infection (bictegravir AUC is predicted to increase by 30%).

The number of aging PLWH is growing, and thus the combination of geriatric and HIV care will become more important in the future.[36] Age-related comorbidities and consequently polypharmacy are highly prevalent in the elderly, thereby increasing the risk for DDIs. We previously demonstrated that DDI magnitudes are not modified with aging;[22] thus, the results of this simulation study might be extrapolated to elderly PLWH.

The development and verification of a predictive PBPK model takes time and requires strong expertise and is therefore not intended for the daily management of DDI queries in the clinic. DDI magnitudes can be estimated between drug pairs based on the degree of metabolism by a specific enzyme and the strength of an inhibitor or inducer without considering physiological variability.[37,38] They provide a more straightforward supportive tool to evaluate the clinical relevance of DDIs and whether a dose adjustment is needed to overcome a given DDI.

In conclusion, we present a predictive PBPK model to simulate DDI scenarios with the novel integrase inhibitor bictegravir as the victim drug. Combinations of bictegravir with strong inhibitors and inducers of CYP3A and UGT1A1 (e.g., atazanavir, nilotinib, and rifampicin) were predicted to be contraindicated. However, the coadministration of bictegravir with moderate inhibitors and inducers of CYP3A and UGT1A1 and the combination of strong inhibitors with strong inducers (e.g., ritonavir + rifampicin) led to DDI magnitudes within the efficacy-safety margin for bictegravir in our simulations. The PBPK modeling strategy can guide the clinical DDI management of novel drugs with limited clinical experience, such as bictegravir.

Supporting Information

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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