Clinical Infectious Diseases

MAJOR ARTICLE

Management of Drug-Drug Interactions Between Long-Acting Cabotegravir and Rilpivirine and Comedications With Inducing Properties: A Modeling Study

Sara Bettonte,[1,2] Mattia Berton,[1,2] Felix Stader,[3] Manuel Battegay,[1,2] and Catia Marzolini[1,2,4]

[1]Division of Infectious Diseases and Hospital Epidemiology, Departments of Medicine and Clinical Research, University Hospital Basel, Basel, Switzerland; [2]Faculty of Medicine, University of Basel, Basel, Switzerland; [3]PBPK Research and Development, Certara UK Limited, Sheffield, UK; and [4]Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, United Kingdom

Background. Long-acting (LA) intramuscular cabotegravir and rilpivirine are prone to drug-drug interactions (DDI). However, given the long dosing interval, the conduct of clinical DDIs studies with LA antiretrovirals is challenging. We performed virtual clinical DDI studies using physiologically based pharmacokinetic (PBPK) modeling to provide recommendations for the management of DDIs with strong or moderate inducers such as rifampicin or rifabutin.

Methods. Each DDI scenario included a cohort of virtual individuals (50% female) between 20 and 50 years of age with a body mass index of 18–30 kg/m^2. Cabotegravir and rilpivirine were given alone and in combination with rifampicin or rifabutin. The predictive performance of the PBPK model to simulate cabotegravir and rilpivirine pharmacokinetics after oral and intramuscular administration and to reproduce DDIs with rifampicin and rifabutin was first verified against available observed clinical data. The verified model was subsequently used to simulate unstudied DDI scenarios.

Results. At steady state, the strong inducer rifampicin was predicted to decrease the area under the curve (AUC) of LA cabotegravir by 61% and rilpivirine by 38%. An increase in the dosing frequency did not overcome the DDI with rifampicin. The moderate inducer rifabutin was predicted to reduce the AUC of LA cabotegravir by 16% and rilpivirine by 18%. The DDI with rifabutin can be overcome by administering LA cabotegravir/rilpivirine monthly together with a daily oral rilpivirine dose of 25 mg.

Conclusions. LA cabotegravir/rilpivirine should be avoided with strong inducers but coadministration with moderate inducers is possible by adding oral rilpivirine daily dosing to the monthly injection.

Keywords. drug-drug interaction; long-acting cabotegravir; long-acting rilpivirine; PBPK modeling; inducer.

Over the years, antiretroviral treatments have become more efficacious, safer, and simpler with lower pill burden. Another major milestone has been achieved with the approval of the first long-acting (LA) injectable drugs cabotegravir/rilpivirine allowing infrequent dosing. After an optional oral lead-in phase (cabotegravir/rilpivirine 30/25 mg daily for 1 month), followed by an intramuscular loading dose (cabotegravir/rilpivirine 600/900 mg), cabotegravir/rilpivirine can be administered for treatment at a maintenance intramuscular dose of 400/600 mg monthly or of 600/900 mg every 2 months [1–3]. LA cabotegravir has also been approved by the Food and Drug Administration (FDA) for use as pre-exposure prophylaxis (PrEP) [4]. In this indication, cabotegravir with or without oral lead-in is given at a loading dose of 600 mg followed by a maintenance dose of 600 mg every 2 months.

Although LA cabotegravir and rilpivirine represent an exciting advance, a number of questions related to their use remain unresolved including the management of drug-drug interactions (DDIs). Cabotegravir is primarily metabolized by uridine diphosphate-glucuronosyltransferase (UGT)1A1 and to a lesser extent by UGT1A9, whereas rilpivirine undergoes metabolism by cytochrome P450 (CYP)3A4; therefore, their exposure can be impacted notably by comedications with inducing properties [5]. DDI data have only been generated with oral cabotegravir and rilpivirine as, given the long dosing interval, the conduct of clinical DDIs studies with LA antiretrovirals is challenging [5]. However, the magnitude of DDIs may differ based on the route of administration because intestinal

Received 24 August 2022; editorial decision 09 November 2022; published online 15 November 2022

Correspondence: S. Bettonte, Division of Infectious Diseases and Hospital Epidemiology, Departments of Medicine and Clinical Research, University Hospital Basel, Petersgraben 4, 4031 Basel, Switzerland (sara.bettonte@unibas.ch).

Clinical Infectious Diseases® 2023;76(7):1225–36

https://doi.org/10.1093/cid/ciac901

metabolism is bypassed with the intramuscular administration, thereby potentially mitigating DDIs.

Physiologically based pharmacokinetic (PBPK) modeling has demonstrated its predictive power to simulate clinically relevant yet unstudied DDI scenarios [6, 7]. In recent years, PBPK guided dose recommendations have been approved in several drug labels as an alternative to real-world studies [8–10]. PBPK modeling combines in vitro data and clinically observed data to simulate pharmacokinetics in virtual individuals [11]. The virtual population used to inform the PBPK model is generated based on observed organ weights, blood flows, and other physiological parameters that are important for the prediction of drug disposition [12]. To date, one PBPK modeling study has investigated the DDI between the strong inducer rifampicin and LA cabotegravir/rilpivirine [13]. However, this study did not evaluate the effect of moderate inducers and did not determine whether a dose or frequency adjustment of cabotegravir and rilpivirine could overcome the interaction with strong/moderate inducers. This is an important clinical gap given that the intramuscular release of drugs cannot be interrupted which becomes an issue when individuals on LA antiretrovirals present an inaugural disease (eg, epilepsy, tuberculosis) requiring treatment with an inducer.

To address this conundrum, we performed virtual DDI studies using PBPK modeling. LA cabotegravir and rilpivirine were coadministered with either a strong or moderate inducer and dosing adjustment strategies were investigated to provide recommendations for the management of DDIs with LA antiretrovirals.

METHODS

We took 3 steps to analyze DDIs between LA cabotegravir/rilpivirine and inducers. First, we developed and verified drug models for the oral and intramuscular administration of cabotegravir and rilpivirine. Second, we verified the performance of our PBPK framework to predict DDIs against clinically observed data with the strong (rifampicin) and moderate (rifabutin) paradigm inducers of CYP3A4 and UGTs. Third, the fully verified PBPK model was used to simulate unstudied DDI scenarios. Each DDI scenario included 50–100 virtual individuals (50% female) representative of people with human immunodeficiency virus (HIV, PWH) between 20 and 50 years of age with a body mass index of 18–30 kg/m^2.

PBPK Model Implementation and Drug Model Development

Details on our whole-body PBPK model [11], adapted to mechanistically describe the release of LA cabotegravir and rilpivirine from the depot injected in the ventrogluteal muscle [14], are provided in the Supplementary Material. The model verification was carried out both for cabotegravir and rilpivirine, the parameters used for the drug model development are summarized in Supplementary Table 1. For each drug, the available clinical data were compared with the PBPK model simulations generated by matching the clinical trial participants with our virtual cohort (eg, age range, proportion of female). Furthermore, drug dosing regimens were matched to the design of the corresponding clinical trial. The clinical observed data were digitalized using GetData Graph Digitizer V.2.26 [15], additionally missing pharmacokinetic parameters (eg, area under the curve [AUC]) were calculated using non-compartmental analysis in Matlab®2020a. The clinical studies used for the cabotegravir and rilpivirine intramuscular and oral model development are shown in Supplementary Table 2. As per regulatory agencies guidance [10, 16, 17], the PBPK models were considered qualified if the ratio between the predicted versus observed pharmacokinetic parameters and the absolute average fold error (AAFE) were within 2-fold.

Before running DDIs simulations, the drug models for the strong inducer rifampicin [18–20] and the moderate inducer rifabutin [21, 22] were developed and their predictive performance verified against clinically observed data. The drug parameters used to develop the models are detailed in Supplementary Table 1. As before, the verification step consisted in generating simulations where the virtual individuals and the dosing regimens matched those of the clinical studies summarized in Supplementary Table 4. The models were qualified if the predictions were within 2-fold of the observed data [10, 16, 17].

Model Qualification Against Clinically Observed DDI Data

After verifying the drug models, the PBPK framework was qualified against clinically observed DDI data. The simulated scenarios included the oral DDI between cabotegravir (30 mg single dose) or rilpivirine (150 mg once daily [QD]) and rifampicin (600 mg QD) [23, 24] as well as the oral DDI between cabotegravir (30 mg QD) or rilpivirine (25 mg QD) with rifabutin (300 mg QD) [25, 26] (Supplementary Table 6). The predictions were qualified if the ratio between predicted and observed pharmacokinetic parameters was within 2-fold [10, 16, 17].

Simulations of Unstudied DDI Scenarios With Strong and Moderate Inducers

For each scenario presented in Table 1, a cohort of 50–100 virtual individuals (aged 20–50 years (50% female) was generated to inform the PBPK model.

Several dosing adjustments were simulated to evaluate the management of DDIs between intramuscular cabotegravir or rilpivirine with rifampicin or rifabutin (Table 1). In order to cover various scenarios that may present in clinical practice, DDI simulations were performed both when cabotegravir/rilpivirine are at steady state (maintenance dose) or after the first injection (loading dose). Furthermore, we reproduced the FDA dosing adjustment recommendations to overcome the DDI between LA cabotegravir (PrEP) and moderate inducers [4] to further verify the predictive performance of our model.

Table 1. Study Design for the Simulated Unstudied DDI Scenarios

Victim	Perpetrator	Study Design
DDI with strong inducer: rifampicin		
Cabotegravir loading dose 600 mg	Rifampicin 600 mg steady state	Rifampicin (600 mg QD) at steady state. Administration first cabotegravir intramuscular loading dose (600 mg) for PrEP or for HIV treatment.
Rilpivirine loading dose 900 mg	Rifampicin 600 mg steady state	Rifampicin (600 mg QD) at steady state. Administration first rilpivirine intramuscular loading dose (900 mg) for HIV treatment.
Cabotegravir steady-state treatment Q4W	Rifampicin 600 mg steady state	Cabotegravir for HIV treatment (600 mg loading dose, 400 mg maintenance dose Q4W) at steady state. Administration of rifampicin (600 mg QD) started 7 d before the last injection of cabotegravir at steady state.
Rilpivirine steady-state treatment Q4W	Rifampicin 600 mg steady -state	Rilpivirine for HIV treatment (900 mg loading dose, 600 mg maintenance dose Q4W) at steady state. Administration of rifampicin (600 mg QD) started 7 d before the last injection of rilpivirine at steady state.
Cabotegravir steady-state PrEP Q8W	Rifampicin 600 mg steady state	Cabotegravir for PrEP (600 mg Q8W) at steady state. Administration of rifampicin (600 mg QD) started 7 d before the last injection of cabotegravir at steady state.
Evaluated dosing adjustment to overcome DDI with strong inducer		
Cabotegravir steady-state PrEP Q4W	Rifampicin 600 mg steady state	Rifampicin (600 mg QD) is administered 7 d before the last injection and is given concomitantly to cabotegravir for PrEP dosed Q4W.
Cabotegravir steady-state PrEP Q3W	Rifampicin 600 mg steady state	Rifampicin (600 mg QD) is administered 7 d before the last injection and is given concomitantly to cabotegravir for PrEP dosed Q3W.
DDI with moderate inducer: rifabutin		
Cabotegravir loading dose 600 mg	Rifabutin 300 mg steady state	Rifabutin (300 mg QD) at steady state. Administration first cabotegravir intramuscular loading dose (600 mg) for PrEP or for HIV treatment.
Rilpivirine loading dose 900 mg	Rifabutin 300 mg steady state	Rifabutin (300 mg QD) at steady state. Administration first rilpivirine intramuscular loading dose (900 mg) for HIV treatment.
Cabotegravir steady-state treatment Q4W	Rifabutin 300 mg steady state	Cabotegravir for treatment (600 mg loading dose, 400 mg maintenance dose Q4W) at steady state. Administration of rifabutin (300 mg QD) started 7 d before the last injection of cabotegravir at steady state.
Rilpivirine steady-state treatment Q4W	Rifabutin 300 mg steady state	Rilpivirine for treatment (900 mg loading dose, 600 mg maintenance dose Q4W) at steady state. Administration of rifabutin (300 mg QD) started 7 d before the last injection of rilpivirine at steady state.
Cabotegravir steady-state PrEP Q8W	Rifabutin 300 mg steady state	Cabotegravir for treatment or PrEP (600 mg Q8W) at steady state. Administration of rifabutin (300 mg QD) started 7 d before the last injection of cabotegravir at steady state.
Rilpivirine steady-state treatment Q8W	Rifabutin 300 mg steady state	Rilpivirine for treatment (900 mg Q8W) at steady state. Administration of rifabutin (300 mg QD) started 7 d before the last injection of rilpivirine at steady state.
Evaluated Dosing Adjustment to Overcome DDI With Moderate Inducer		
Cabotegravir 600 mg Q2W	Rifabutin 300 mg steady state	Rifabutin (300 mg QD) at steady state. Administration first loading dose of cabotegravir intramuscular injection (600 mg) for PrEP or for HIV treatment followed by a second injection (600 mg) after 15 d.
Rilpivirine 900 mg Q2W	Rifabutin 300 mg steady state	Rifabutin (300 mg QD) at steady state. Administration first loading dose of rilpivirine intramuscular injection (900 mg) for HIV treatment followed by a second injection (900 mg) after 15 d.
Rilpivirine steady-state treatment Q8W + 25 mg PO	Rifabutin 300 mg steady state	Rilpivirine for treatment (900 mg Q8W) at steady state. Administration of rifabutin (300 mg QD) started 7 d before the last injection of rilpivirine at steady state concomitantly to 25 mg oral RPV.
Rilpivirine steady-state treatment Q4W + 25 mg PO	Rifabutin 300 mg steady state	Rilpivirine for treatment (900 mg loading dose, 600 mg maintenance dose Q4W) at steady state. Administration of rifabutin (300 mg QD) started 7 d before the last injection of rilpivirine at steady state concomitantly to 25 mg oral RPV.
Rilpivirine steady-state treatment Q4W + 50 mg PO	Rifabutin 300 mg steady state	Rilpivirine for treatment (900 mg loading dose, 600 mg maintenance dose Q8W) at steady state. Administration of rifabutin (300 mg QD) started 7 d before the last injection of rilpivirine at steady state concomitantly to 50 mg oral RPV.
Cabotegravir steady-state PrEP Q4W	Rifabutin 300 mg steady state	Rifabutin (300 mg QD) is administered 7 d before the last injection and is given concomitantly to cabotegravir for PrEP (600 mg) dosed Q4W as per FDA dosing recommendation [4].

Abbreviations: DDI, drug-drug interaction; FDA, Food and Drug Administration; HIV, human immunodeficiency virus; IM, intramuscular administration; PO, oral administration; PrEP, pre-exposure prophylaxis; QD, once daily; Q2W, administration every 2 weeks; Q3W, administration every 3 weeks; Q4W, administration every 4 weeks; Q8W, administration every 8 weeks; RPV, rilpivirine.

RESULTS

PBPK Model Implementation and Drug Model Development

The PBPK model implemented with the intramuscular framework correctly predicted drug pharmacokinetics (Supplementary Table 3). For oral cabotegravir, the peak concentration (C_{max}), AUC, and trough concentration (C_τ) ratios (ie, predicted/observed data) were within 1.25-fold after single and multiple doses administration. When cabotegravir was injected in the muscle, the AUC and C_τ ratios were 0.81, 0.89 (single injection) and 0.84, 0.86 (multiple injections). For rilpivirine, the predictions were within 1.5-fold of observed data for oral single and multiple doses. After intramuscular administration, the AUC and C_τ ratios were 0.95 and 0.92 (single injection), and the C_τ ratio was 0.63 for rilpivirine administered every

Table 2. Pharmacokinetic Parameters of LA Cabotegravir in Presence and in Absence of Rifampicin and Rifabutin

Victim	Perpetrator	Pharmacokinetic Parameter	Absence Perpetrator Predicted	Presence Perpetrator Predicted	DDI Ratio Predicted
DDI with strong inducer: rifampicin					
Cabotegravir loading dose 600 mg	Rifampicin 600 mg steady state	C_τ (ng/mL)	887 (64)	331 (55)	0.37
		AUC_τ (ng h/mL)	684 948 (56)	270 706 (53)	0.40
Cabotegravir steady-state treatment Q4W	Rifampicin 600 mg steady state	C_τ (ng/mL)	2543 (53)	982 (41)	0.39
		AUC_τ (ng h/mL)	1 844 732 (52)	711 130 (42)	0.39
Cabotegravir steady-state PrEP Q8W	Rifampicin 600 mg steady state	C_τ (ng/mL)	1671 (66)	627 (50)	0.38
		AUC_τ (ng h/mL)	3 081 079 (61)	1 173 287 (49)	0.38
Evaluated dosing adjustment to overcome DDI with strong inducer					
Cabotegravir steady-state PrEP Q4W	Rifampicin 600 mg steady state	C_τ (ng/mL)	2462 (63)	935 (48)	0.38
		AUC_τ (ng h/mL)	2 076 609 (57)	803 147 (47)	0.39
Cabotegravir steady-state PrEP Q3W	Rifampicin 600 mg steady state	C_τ (ng/mL)	3257 (64)	1227 (47)	0.38
		AUC_τ (ng h/mL)	2 012 694 (57)	788 422 (47)	0.39
DDI with moderate inducer: rifabutin					
Cabotegravir loading dose 600 mg	Rifabutin 300 mg steady state	C_τ (ng/mL)	947 (60)	780 (57)	0.82
		AUC_τ (ng h/mL)	729 069 (51)	612 883 (50)	0.84
Cabotegravir steady-state treatment Q4W	Rifabutin 300 mg steady state	C_τ (ng/mL)	2563 (61)	2143 (57)	0.84
		AUC_τ (ng h/mL)	1 859 887 (59)	1 555 392 (55)	0.84
Cabotegravir steady-state PrEP Q8W	Rifabutin 300 mg steady state	C_τ (ng/mL)	1671 (66)	1387 (61)	0.83
		AUC_τ (ng h/mL)	3 081 079 (61)	2 571 910 (57)	0.83
Evaluated dosing adjustment to overcome DDI with moderate inducer					
Cabotegravir 600 mg Q2W	Rifabutin 300 mg steady state	C_τ (ng/mL)	2246 (63)	1863 (60)	0.83
		AUC_τ (ng h/mL)	1 916 933 (58)	1 603 379 (57)	0.84
Cabotegravir steady-state PrEP Q4W	Rifabutin 300 mg steady state	C_τ (ng/mL)	2462 (63)	2051 (58)	0.83
		AUC_τ (ng h/mL)	2 076 609 (57)	1 741 089 (54)	0.84

AUC_τ and C_τ are represented as geometric mean (CV).

Abbreviations: AUC_τ, area under the curve to tau; C_τ, trough concentration; DDI, drug-drug interaction; PrEP, pre-exposure prophylaxis; Q2W, administration every 2 weeks; Q3W, administration every 3 weeks; Q4W, administration every 4 weeks; Q8W, administration every 8 weeks.

other month. The rifampicin and rifabutin drug models were also qualified as their simulated pharmacokinetic parameters were all within 2-fold of observed data (Supplementary Table 5).

Model Verification Against Clinically Observed DDI Data

The PBPK framework was used afterward to simulate oral DDIs between cabotegravir or rilpivirine and rifampicin or rifabutin for which observed clinical data are available (Supplementary Figure 3). For cabotegravir, DDI predictions with rifampicin and rifabutin were within 1.5-fold and 2-fold, respectively (Supplementary Table 7). For rilpivirine, predictions were within 2-fold (rifampicin) and 1.5-fold (rifabutin).

Simulations of Unstudied DDI Scenarios With Strong and Moderate Inducers

The fully validated PBPK framework was used to simulate unstudied DDI scenarios of interest.

Cabotegravir and Rifampicin

Rifampicin was predicted to reduce the C_τ and AUC of the first intramuscular cabotegravir loading dose (600 mg) by 63% and 60%, respectively (Table 2; Figure 1*A*). A similar decrease in C_τ and AUC was predicted when cabotegravir was at steady state both for the monthly (loading dose 600 mg, maintenance dose 400 mg) (Figure 1*C*) and bimonthly administration (600 mg loading dose, maintenance dose 600 mg every other month) (Figure 2*A*). After the first injection of cabotegravir, the proportion of individuals with cabotegravir concentrations above the 4-fold protein adjusted 90% inhibitory concentrations (4× PA-IC_{90}) [27] during the dosing interval was 11%; while the proportion was 84% and 36% for cabotegravir (at steady state) administered once monthly and every other month, respectively (Table 3).

Two dosing adjustment scenarios were evaluated to overcome the DDI between cabotegravir (used for PrEP) and rifampicin. First, we increased the dosing frequency of cabotegravir

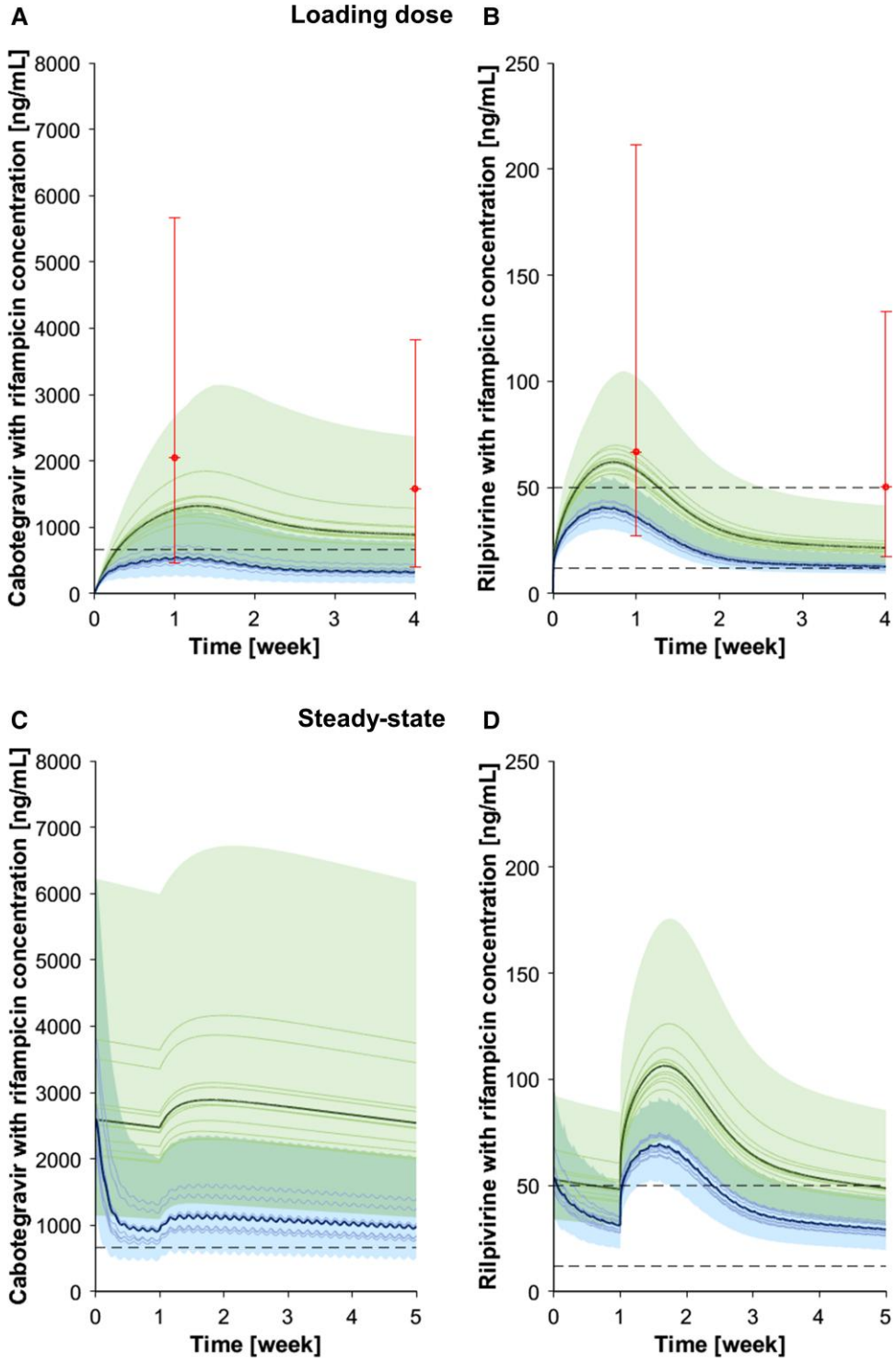

Figure 1. Concentration-time profiles for (*A*) cabotegravir 600 mg loading intramuscular dose, and (*B*) rilpivirine 900 mg loading intramuscular dose in absence (*green*) and presence (*blue*) of 600 mg once daily rifampicin. Concentration-time profiles for (*C*) cabotegravir intramuscular at steady state, and (*D*) rilpivirine intramuscular at steady state in absence (*green*) and presence (*blue*) of 600 mg once daily rifampicin. 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. In panels (*A*) and (*C*) the dashed line represents the 4 × PA-IC_{90} for cabotegravir (664 ng/mL), and the red markers in panel (*A*) represent the median values measured from Orkin et al [34]. together with the 5th percentile and the 95th percentile. In panels (*B*) and (*D*) the dashed lines represent the PA-IC_{90} for rilpivirine (12 ng/mL), the minimal concentration for therapeutic response (50 ng/mL), and the red markers in panel (*B*) represent the median values measured from Orkin et al [34]. together with the 5th percentile and the 95th percentile. The trial design is explained in Table 1. The panels of the profiles at steady state depict the end of the previous intramuscular dosing so that the actual injection occurs at week 1 on the scale of the graph. Abbreviation: PA-IC_{90}, protein adjusted 90% inhibitory concentrations.

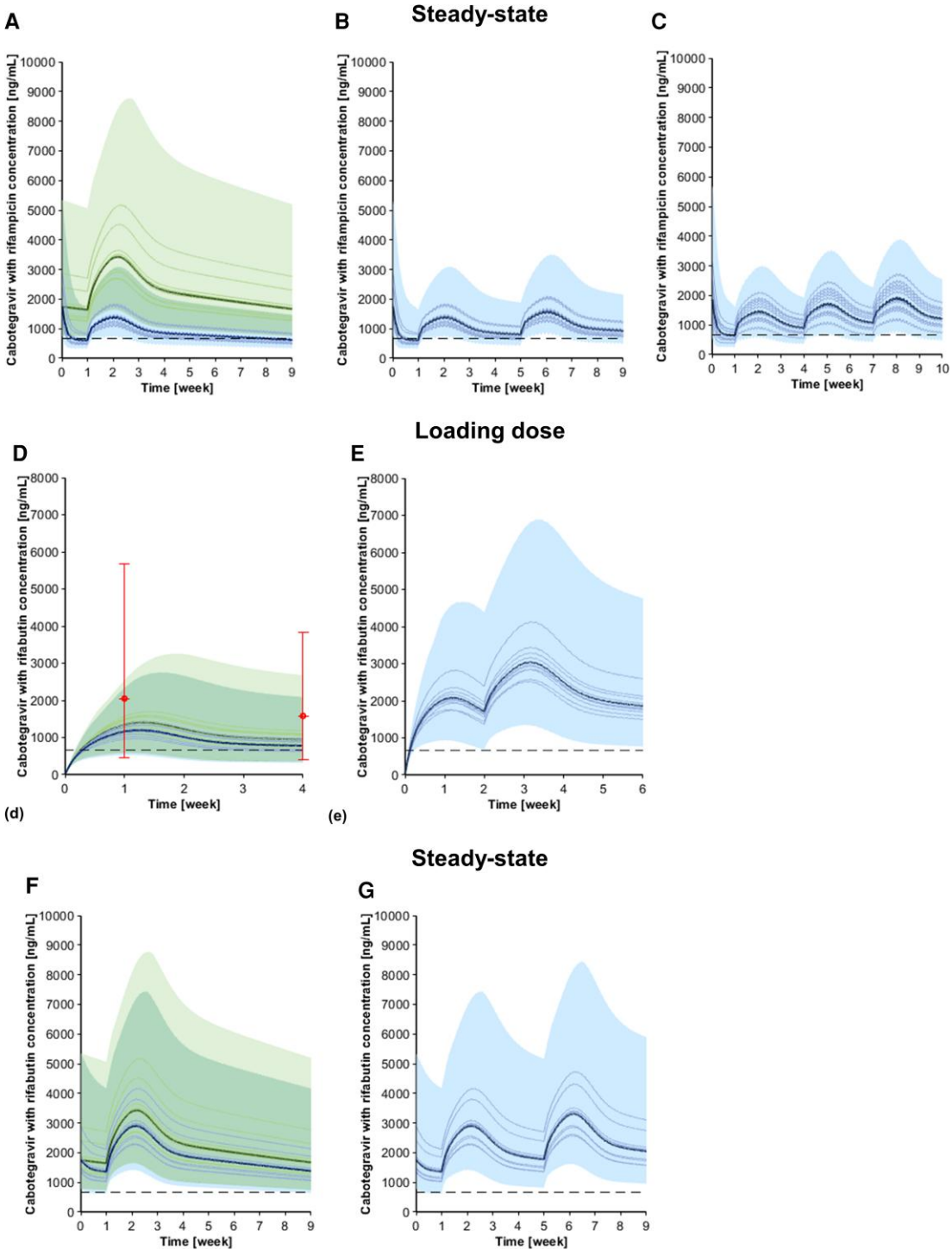

Figure 2. Dosing strategies to overcome DDI with cabotegravir. In panel (*A*) concentration-time profiles for cabotegravir 600 mg (PrEP) at steady state in the absence (*green*) and the presence (*blue*) of 600 mg once daily rifampicin; (*B*) dosing adjustment scenario to overcome the DDI with rifampicin by injecting cabotegravir every 4 wks instead of the recommended 8 wks; (*C*) dosing adjustment scenario to overcome the DDI with rifampicin by injecting cabotegravir every 3 wks instead of the recommended 8 wks. *D*, Concentration-time profiles for cabotegravir loading dose (600 mg) in the absence (*green*) and the presence (*blue*) of 300 mg once daily rifabutin; (*E*) dosing adjustment scenario to overcome DDI by injecting cabotegravir loading dose every 2 wks. *F*, Concentration-time profiles for cabotegravir 600 mg (PrEP) at steady state in the absence (*green*) and the presence (*blue*) of 300 mg once daily rifabutin; in panel (*G*) dosing adjustment scenario to overcome the DDI with rifabutin by injecting cabotegravir every 4 wks instead of the recommended 8 wks. 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 dashed line represents the 4 × PA-IC_{90} for cabotegravir (664 ng/mL). The red markers in panel (*D*) represent the median values measured from Orkin et al [34], together with the 5th percentile and the 95th percentile. The trial design is explained in Table 1. The panels of the profiles at steady state depict the end of the previous intramuscular dosing so that the actual injection occurs at week 1 on the scale of the graph. Abbreviations: DDI, drug-drug interaction; PA-IC_{90}, protein adjusted 90% inhibitory concentrations; PrEP, pre-exposure prophylaxis.

Table 3. Percentage of Virtual Individuals With Predicted Cabotegravir Plasma Concentration Above the 4× PA-IC_{90} (664 ng/mL) Target [27] and Above the Highest Observed Median C_{max} in Long-Term Studies (13 100 ng/mL) (ie, Safety Threshold) [35] for Each Simulated DDI Scenario

Study Design	Percentage Simulated Individuals Above 664 ng/mL in Presence of Inducer	Percentage Simulated Individuals Above 13 100 ng/mL in Presence of Inducer
DDI with strong inducer: rifampicin		
Cabotegravir: loading dose 600 mg Rifampicin: 600 mg steady state	11	0
Cabotegravir: steady-state treatment Q4W Rifampicin: 600 mg steady state	84	0
Cabotegravir: steady-state PrEP Q8W Rifampicin: 600 mg steady state	36	0
Evaluated dosing adjustment to overcome DDI with strong inducer		
Cabotegravir: steady-state PrEP Q4W Rifampicin: 600 mg steady state	84	0
Cabotegravir: steady-state PrEP Q3W Rifampicin: 600 mg steady state	88	0
DDI with moderate inducer: rifabutin		
Cabotegravir: loading dose 600 mg Rifabutin: 300 mg steady state	60	0
Cabotegravir: steady-state treatment Q4W Rifabutin: 300 mg steady state	100	0
Cabotegravir: steady-state PrEP Q8W Rifabutin: 300 mg steady state	94	0
Evaluated dosing adjustment to overcome DDI with moderate inducer		
Cabotegravir: 600 mg Q2W Rifabutin: 300 mg steady state	97	0
Cabotegravir: steady-state PrEP Q4W Rifabutin: 300 mg steady state	100	0

Abbreviations: DDI, drug-drug interaction; PA-IC_{90}, protein adjusted 90% inhibitory concentrations; PrEP, pre-exposure prophylaxis; Q2W, administration every 2 weeks; Q3W, administration every 3 weeks; Q4W, administration every 4 weeks; Q8W, administration every 8 weeks.

to 4 weeks (instead of the recommended 8 weeks in absence of inducer). In this scenario, cabotegravir C_τ and AUC were still reduced by 62% and 61%, respectively (Table 2; Figure 2*B*), with only 84% of individuals having concentrations >4× PA-IC_{90}. Reducing the dosing interval to 3 weeks did not significantly improve cabotegravir exposure as C_τ and AUC were reduced by 62% and 61% (Figure 2*C*), respectively, with only 88% individuals >4× PA-IC_{90} concentration threshold (Table 3).

Cabotegravir and Rifabutin

Rifabutin was predicted to reduce the C_τ and AUC of the first intramuscular cabotegravir loading dose (600 mg) by 18% and 16%, respectively (Table 2; Figure 2*D*). A similar decrease in C_τ and AUC was predicted when cabotegravir was at steady state both for the monthly (loading dose 600 mg, maintenance dose 400 mg) and bimonthly administration (600 mg loading dose, maintenance dose 600 mg every other month; Figure 2*F*). After the first intramuscular dose of cabotegravir, the proportion of individuals with concentrations >4× PA-IC_{90} was 60%; although the proportion was 100% and 94% for cabotegravir (at steady state) administered once monthly and every other month, respectively (Table 3).

We simulated the dosing recommendations of the FDA for cabotegravir (PrEP) in presence of the moderate inducer rifabutin [4]. The dosing interval between the first and second injection of cabotegravir was reduced to 2 weeks (instead of the recommended 4 weeks in absence of inducer). In this scenario, C_τ and AUC was reduced by 17% and 16%, respectively (Table 2; Figure 2*E*), whereas the proportion of individuals with concentrations >4× PA-IC_{90} was 97%. During steady-state conditions, increasing cabotegravir dosing to 4 weeks (instead of the recommended 8 weeks in absence of inducer), resulted in a small decrease in C_τ (17%) and AUC (16%) with 100% individuals being above the efficacy threshold at the end of the dosing interval thereby supporting the FDA dosing recommendations (Table 3; Figure 2*G*).

Rilpivirine and Rifampicin

Rifampicin was predicted to reduce the C_τ and AUC of the first intramuscular rilpivirine loading dose (900 mg) by 41% and

Table 4. Pharmacokinetic Parameters of LA Rilpivirine in Presence and in Absence of Rifampicin and Rifabutin

Victim	Perpetrator	Pharmacokinetic Parameter	Absence Perpetrator Predicted	Presence Perpetrator Predicted	DDI Ratio Predicted
DDI with strong inducer: rifampicin					
Rilpivirine loading dose 900 mg	Rifampicin 600 mg steady state	C_τ (ng/mL)	22 (40)	13 (22)	0.59
		AUC_τ (ng h/mL)	24 199 (34)	14 859 (20)	0.61
Rilpivirine steady-state treatment Q4W	Rifampicin 600 mg steady state	C_τ (ng/mL)	49 (35)	29 (23)	0.60
		AUC_τ (ng h/mL)	48 292 (33)	29 810 (21)	0.62
DDI with moderate inducer: rifabutin					
Rilpivirine loading dose 900 mg	Rifabutin 300 mg steady state	C_τ (ng/mL)	22 (42)	18 (27)	0.80
		AUC_τ (ng h/mL)	24 607 (38)	20 076 (25)	0.82
Rilpivirine steady-state treatment Q4W	Rifabutin 300 mg steady state	C_τ (ng/mL)	49 (35)	40 (26)	0.81
		AUC_τ (ng h/mL)	48 292 (33)	39 673 (24)	0.82
Rilpivirine steady-state treatment Q8W	Rifabutin 300 mg steady state	C_τ (ng/mL)	30 (38)	24 (26)	0.79
		AUC_τ (ng h/mL)	80 214 (34)	64 010 (22)	0.80
Evaluated dosing regimen to overcome DDI with moderate inducer					
Rilpivirine 900 mg Q2W	Rifabutin 300 mg steady state	C_τ (ng/mL)	48 (42)	39 (27)	0.80
		AUC_τ (ng h/mL)	58 595 (37)	47 295 (24)	0.81
Rilpivirine steady-state treatment Q8W + 25 mg PO	Rifabutin 300 mg steady state	C_τ (ng/mL)	69 (35)	52 (26)	0.76
		AUC_τ (ng h/mL)	2276 (30)	1810 (22)	0.80
Rilpivirine steady-state treatment Q4W + 25 mg PO	Rifabutin 300 mg steady state	C_τ (ng/mL)	98 (76)	74 (44)	0.76
		AUC_τ (ng h/mL)	2978 (64)	2329 (37)	0.78
Rilpivirine steady-state treatment Q4W + 50 mg PO	Rifabutin 300 mg steady state	C_τ (ng/mL)	138 (43)	104 (31)	0.75
		AUC_τ (ng h/mL)	4609 (36)	3646 (26)	0.79

AUC_τ and C_τ are represented as geometric mean (CV).

Abbreviations: AUC_τ, area under the curve to tau; C_τ, trough concentration; DDI, drug-drug interaction; PO, oral administration; PrEP, pre-exposure prophylaxis; Q2W, administration every 2 weeks; Q4W, administration every 4 weeks; Q8W, administration every 8 weeks.

39%, respectively (Table 4; Figure 1*B*), with all the individuals predicted to have rilpivirine concentrations below 50 ng/mL (ie, minimal concentration for therapeutic response) [28] (Table 5). Similar predictions were obtained when rilpivirine was at steady state for the monthly treatment (900 mg intramuscular loading dose, 600 mg maintenance dose; Figure 1*D*).

The DDI with rifampicin was not manageable by increasing the dosing frequency given that rilpivirine concentrations were mostly below 50 ng/mL during the dosing interval.

Rilpivirine and Rifabutin

Rifabutin was predicted to reduce the C_τ and AUC of the first intramuscular rilpivirine loading dose by 20% and 18%, respectively (Table 4; Figure 3*A*). However, none of the individuals had concentrations >50 ng/mL. When rilpivirine was at steady state, the decrease in C_τ and AUC was 19% and 18% (monthly administration) and 21% and 20% (bimonthly administration; Figure 3*C*), respectively (Table 4). However, only 20% of the individuals were predicted to have concentrations >50 ng/mL at the end of the monthly dosing interval; although no one was above this limit with the bimonthly administration (Table 5).

To overcome the DDI between rilpivirine and rifabutin, four scenarios were evaluated. First, we reduced the dosing interval between the first and the second injection of rilpivirine (900 mg) to 2 weeks (instead of the recommended 4 weeks in absence of inducer). With this strategy, C_τ and AUC were reduced by 20% and 19%, respectively (Table 4; Figure 3*B*), but the number of individuals with concentrations >50 ng/mL was only 13% (Table 5). Second, we added an oral daily rilpivirine dose (25 mg) to the bimonthly intramuscular administration of rilpivirine (at steady state). With this dose adjustment, C_τ and AUC decreased by 24% and 20%, respectively (Figure 3*D*); however, only 62% of the individuals had concentrations >50 ng/mL at the end of the dosing interval (Table 5). Third, we added an oral daily rilpivirine dose (25 mg) to the monthly intramuscular administration of rilpivirine (600 mg at steady state). C_τ and AUC were still reduced by 24% and 22%, respectively (Figure 3*E*); however, 92% of individuals

Table 5. Percentage of Virtual Individuals With Predicted Rilpivirine Plasma Concentration Above the Minimal Concentration for Therapeutic Response (50 ng/mL) [28] and Above the Concentration Associated With a Higher Risk of QT Prolongation (500 ng/mL) for Each Simulated DDI Scenario

Study Design	Percentage Simulated Individuals Above 50 ng/mL in Presence of Inducer	Percentage Simulated Individuals Above 500 ng/mL in Presence of Inducer
Strong inducer: rifampicin		
Rilpivirine: loading dose 900 mg Rifampicin: 600 mg steady state	0	0
Rilpivirine: steady-state treatment Q4W rifampicin: 600 mg steady state	0	0
Moderate inducer: rifabutin		
Rilpivirine: loading dose 900 mg Rifabutin: 300 mg steady state	0	0
Rilpivirine: steady-state treatment Q4W Rifabutin: 300 mg steady state	20	0
Rilpivirine: steady-state treatment Q8W Rifabutin: 300 mg steady state	0	0
Evaluated dosing adjustment to overcome DDI with moderate inducer		
Rilpivirine: 900 mg Q2W Rifabutin: 300 mg steady state	13	0
Rilpivirine: steady-state treatment Q8W + 25 mg PO Rifabutin: 300 mg steady state	62	0
Rilpivirine: steady-state treatment Q4W + 25 mg PO Rifabutin: 300 mg steady state	92	0
Rilpivirine: steady-state treatment Q4W + 50 mg PO Rifabutin: 300 mg steady state	100	0

Abbreviations: DDI, drug-drug interaction; PO, oral administration; PrEP, pre-exposure prophylaxis; Q2W, administration every 2 weeks; Q4W, administration every 4 weeks; Q8W, administration every 8 weeks.

had concentrations >50 ng/mL. Finally, we increased the oral daily rilpivirine dose to 50 mg given with the monthly injection of rilpivirine (600 mg at steady state). C_τ and AUC decreased by 25% and 21%, respectively (Figure 3*F*), and all individuals were >50 ng/mL.

DISCUSSION

PBPK modeling is increasingly used to predict the potential for DDIs and to support dosing recommendations. This approach is particularly relevant when the conduct of clinical DDIs studies presents challenges like for LA antiretrovirals. Studies evaluating DDI management strategies are of utmost importance considering that PWH on treatment with LA cabotegravir and rilpivirine may require to initiate treatments for comorbidities with a risk of DDI. The evaluation of the DDI and the possibility to overcome the interaction with the antituberculosis drugs rifampicin and rifabutin has indeed been identified as one of the questions to address for the implementation of LA antiretroviral therapy in low- and middle-income countries [29].

To address this conundrum, we developed a PBPK framework to perform virtual clinical DDI studies. Our model was able to predict cabotegravir and rilpivirine pharmacokinetics within 1.25–1.5-fold of observed data. Furthermore, clinically observed oral DDIs for cabotegravir and rilpivirine coadministered with rifampicin or rifabutin were always predicted within 1.5- to 2.0-fold, thereby demonstrating the predictive performance of our PBPK approach.

Of interest, predicted DDI magnitudes were shown to be similar when cabotegravir is administered orally versus intramuscularly. For instance, rifampicin decreased cabotegravir AUC after oral and intramuscular administration (steady state) by 64% and 61%, respectively. Conversely, the DDI was mitigated for rilpivirine as rifampicin decreased rilpivirine AUC by 74% after oral administration and by 48% after intramuscular administration. This difference is explained by the fact that rilpivirine has an absolute oral bioavailability (measured in animals) of 24–54% [30], suggesting high first-pass metabolism, whereas cabotegravir undergoes less intestinal metabolism due to lower intrinsic clearance and UGT abundance in the intestine [31]. Therefore, escaping the first-pass metabolism will not significantly change the DDI magnitude in the case of cabotegravir. To further support this fact, efavirenz was shown to reduce levonorgestrel (bioavailability 95%) AUC by 56% after oral administration and by 57% after subcutaneous administration [32, 33].

The various simulated DDI scenarios suggest that DDIs with the strong inducer rifampicin cannot be overcome to ensure cabotegravir concentrations above the 4× PA-IC_{90} target during the entire dosing interval. Increasing the dosing frequency of cabotegravir (PreP) to every 4 or 3 weeks resulted in only 84% or 88% of individuals above this target. This conservative target was selected as it has been associated with high protective efficacy in vaginal and rectal simian HIV challenge models [27]. Furthermore, this target corresponds to the 5th percentile of LA cabotegravir initial trough concentrations (ie, after the first loading injection) observed in the treatment phase 3 trials [34]. Similarly, increasing the dosing frequency of rilpivirine would not allow to overcome the DDI with rifampicin given that rilpivirine concentrations are mostly below 50 ng/mL (ie, minimal concentration associated with therapeutic response) [28].

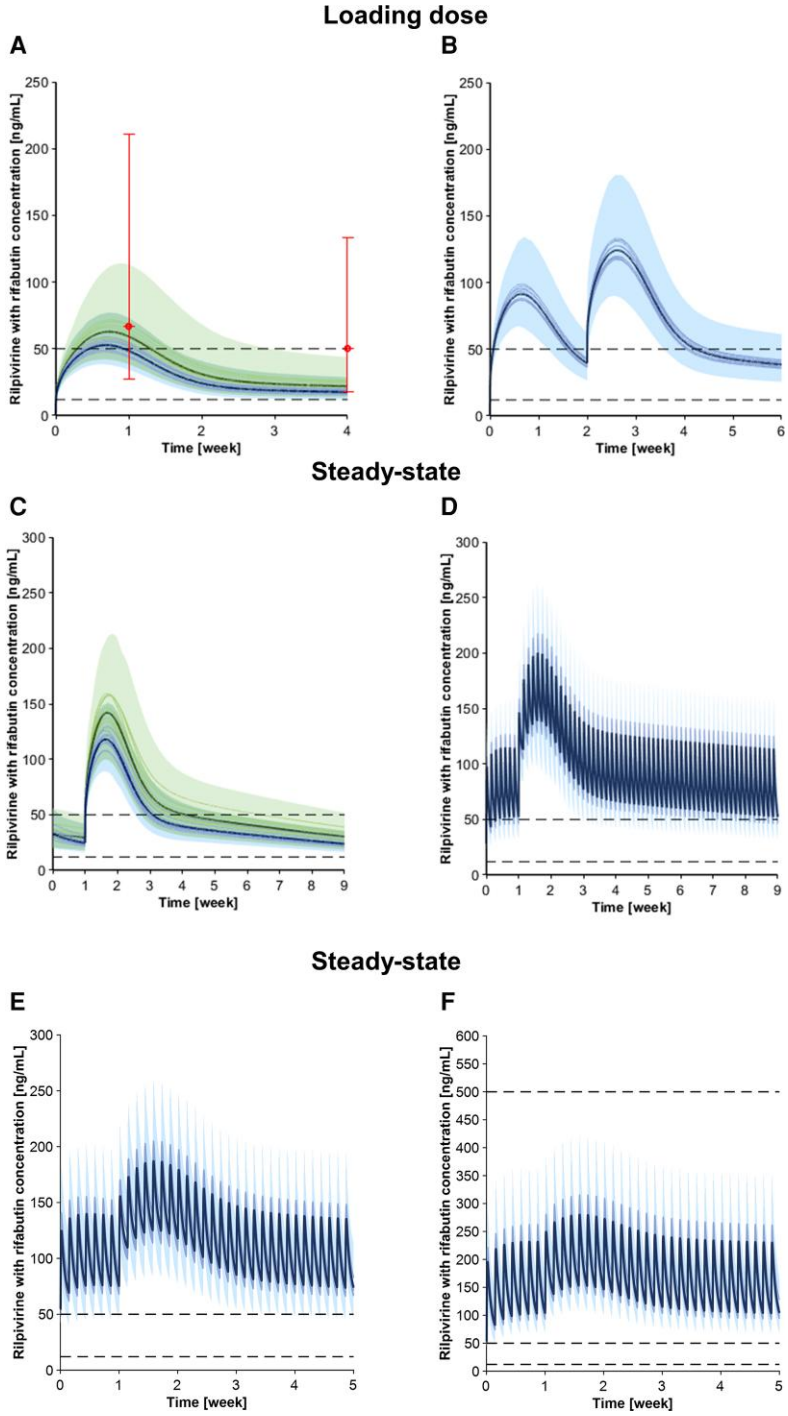

Figure 3. Dosing strategies to overcome DDI with rilpivirine. *A*, Concentration-time profiles for rilpivirine loading dose (900 mg) in the absence (*green*) and the presence (*blue*) of 300 mg once daily rifabutin; (*B*) dosing adjustment scenario to overcome DDI by injecting rilpivirine loading dose every 2 wks. *C*, Concentration-time profiles for rilpivirine at steady state injected every other month in the absence (*green*) and the presence (*blue*) of 300 mg once daily rifabutin; (*D*) dosing adjustment scenario to overcome the DDI with rifabutin by injecting rilpivirine every 8 wks and adding an oral daily rilpivirine dose (25 mg) to the bimonthly intramuscular administration; (*E*) dosing adjustment scenario to overcome DDI with rifabutin by injecting rilpivirine every 4 wks instead of the recommended 8 wks and adding an oral daily rilpivirine dose (25 mg) to the monthly administration; (*F*) dosing adjustment scenario to overcome DDI with rifabutin by injecting rilpivirine every 4 wks instead of the recommended 8 wks and adding an oral daily rilpivirine dose (50 mg) to the monthly administration. 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 dashed line represents the PA-IC_{90} for rilpivirine (12 ng/mL), the minimal concentration for therapeutic response (50 ng/mL), and in (*F*) the concentration associated with a higher risk of QT prolongation (500 ng/mL). The red markers in panel (*A*) represent the median values measured from Orkin et al [34]. together with the 5th percentile and the 95th percentile. The trial design is explained in Table 1. The panels of the profiles at steady state depict the end of the previous intramuscular dosing so that the actual injection occurs at week 1 on the scale of the graph. Abbreviations: DDI, drug-drug interaction; PA-IC_{90}, protein adjusted 90% inhibitory concentrations.

Conversely, the DDI with rifabutin or other moderate inducers can be managed. If a moderate inducer is initiated before or with the first injection of cabotegravir, the second loading injection should be administered 2 weeks after the first injection with subsequent injections given monthly thereafter (at either 400 mg or 600 mg for treatment and 600 mg for PrEP). This same dosing interval applies to rilpivirine (900 mg intramuscular first and second loading dose, 600 mg maintenance dose) with, in addition, an oral rilpivirine daily dose of 25 mg started on the same day as the moderate inducer. After adjustment, rilpivirine and cabotegravir concentrations are predicted to remain below their safety threshold (rilpivirine: 500 ng/mL [28] and cabotegravir: 13 100 ng/mL [35]). These dose adjustments should be maintained another 2 weeks after stopping the moderate inducer as induction persists upon discontinuation of an inducer. Increasing further the rilpivirine dose (ie, 50 mg) does not bring additional advantage in terms of the proportion of individuals maintaining concentrations >50 ng/mL for the entire dosing interval.

Our findings are supported by a population pharmacokinetic model built using cabotegravir plasma concentrations measured in clinical trials. This model evaluated the effect of rifampicin and rifabutin on LA cabotegravir. In this study, rifampicin significantly reduced LA cabotegravir trough concentrations which were not improved by increasing the frequency of administration or cabotegravir dose. However, the interaction with rifabutin was overcome with monthly injection of LA cabotegravir [35].

PBPK modeling allows to capture the inter-individual variability within a population. This strength is critical to ensure that the simulated DDI magnitudes and the related dosing adjustments can apply to most individuals. It is important to highlight some limitations. It was not possible to verify DDIs with LA cabotegravir and rilpivirine; however, the model was able to simulate correctly their pharmacokinetics and to reproduce known DDI studies. The virtual population had BMI from 18 to 30 kg/m^2 therefore the simulations do not reflect the combined effect of obesity and inducers on DDIs. Future studies are needed to address this point.

CONCLUSIONS

DDIs between strong inducers and LA cabotegravir and rilpivirine cannot be overcome. However, DDIs with moderate inducers can be managed by administering LA cabotegravir and rilpivirine monthly together with an oral rilpivirine daily dose of 25 mg.

Supplementary Data

Supplementary materials are available at *Clinical 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.

Notes

Financial support. This work was supported by Schweizerischer Nationalfonds zur Förderung der Wissenschaftlichen Forschung (grant number 188504).

Potential conflicts of interest. C. M. has received speaker honoraria from MSD and ViiV unrelated to this work. F. S. reports grants or contracts and stock or stock options from Certara UK Ltd, Simcyp Division (employee). All other authors report no potential conflicts of interest.

All authors have submitted the ICMJE form for disclosure of potential conflicts of interest. Conflicts that the editor consider relevant to the content of the manuscript have been disclosed.

References

1. U.S. Food and Drug Administration. Vocabria product label. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212887s000lbl.pdf. Accessed August 2022.
2. European Medicines Agency. Rekambys summary of product characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/rekambys-epar-product-information_en.pdf. Accessed August 2022.
3. U.S. Food and Drug Administration. Cabenuva product label. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/212888s005s006lbl.pdf. Accessed August 2022.
4. U.S. Food and Drug Administration. Apretude product label. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215499s000lbl.pdf. Accessed August 2022.
5. Hodge D, Back DJ, Gibbons S, Khoo SH, Marzolini C. Pharmacokinetics and drug-drug interactions of long-acting intramuscular cabotegravir and rilpivirine. Clin Pharmacokinet **2021**; 60:835–53.
6. Rowland Yeo K, Walsky RL, Jamei M, Rostami-Hodjegan A, Tucker GT. Prediction of time-dependent CYP3A4 drug-drug interactions by physiologically based pharmacokinetic modelling: impact of inactivation parameters and enzyme turnover. Eur J Pharm Sci **2011**; 43:160–73.
7. Almond LM, Mukadam S, Gardner I, et al. Prediction of drug-drug interactions arising from CYP3A induction using a physiologically based dynamic model. Drug Metab Dispos **2016**; 44:821–32.
8. Wagner C, Pan Y, Hsu V, et al. Predicting the effect of cytochrome P450 inhibitors on substrate drugs: analysis of physiologically based pharmacokinetic modeling submissions to the US Food and Drug Administration. Clin Pharmacokinet **2015**; 54:117–27.
9. Wagner C, Pan Y, Hsu V, Sinha V, Zhao P. Predicting the effect of CYP3A inducers on the pharmacokinetics of substrate drugs using physiologically based pharmacokinetic (PBPK) modeling: an analysis of PBPK submissions to the US FDA. Clin Pharmacokinet **2016**; 55:475–83.
10. US Food and Drug Administration. Physiologically based pharmacokinetic analyses: guidance for industry. Available at: https://www.fda.gov/files/drugs/published/Physiologically-Based-Pharmacokinetic-Analyses-%E2%80%94-Format-and-Content-Guidance-for-Industry.pdf. Accessed August 2022.
11. Stader F, Penny MA, Siccardi M, Marzolini C. A comprehensive framework for physiologically based pharmacokinetic modelling in Matlab(®). CPT Pharmacometrics Syst Pharmacol **2019**; 8:444–59.
12. Stader F, Siccardi M, Battegay M, Kinvig H, Penny MA, Marzolini C. Repository describing an aging population to inform physiologically based pharmacokinetic models considering anatomical, physiological, and biological age-dependent changes. Clin Pharmacokinet **2019**; 58:483–501.
13. Rajoli RKR, Curley P, Chiong J, et al. Predicting drug-drug interactions between rifampicin and long-acting cabotegravir and rilpivirine using physiologically based pharmacokinetic modeling. J Infect Dis **2019**; 219:1735–42.
14. Bettonte S, Berton M, Stader F, Battegay M, Marzolini C. Cabotegravir pharmacokinetics after oral and intramuscular administration using physiologically based pharmacokinetic modelling [abstract n. IV-06]. In: Population Approach Group Europe conference. Ljubljana June 28-July 1, **2022**.
15. Wojtyniak JG, Britz H, Selzer D, Schwab M, Lehr T. Data digitizing: accurate and precise data extraction for quantitative systems pharmacology and physiologically-based pharmacokinetic modeling. CPT Pharmacometrics Syst Pharmacol **2020**; 9:322–31.
16. European Medicines Agency. Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-reporting-physiologically-based-pharmacokinetic-pbpk-modelling-simulation_en.pdf. Accessed August 2022.
17. Shebley M, Sandhu P, Emami Riedmaier A, et al. Physiologically based pharmacokinetic model qualification and reporting procedures for regulatory submissions: a consortium perspective. Clin Pharmacol Ther **2018**; 104:88–110.

18. Ellis E, Wagner M, Lammert F, et al. Successful treatment of severe unconjugated hyperbilirubinemia via induction of UGT1A1 by rifampicin. J Hepatol **2006**; 44: 243–5.
19. US Food and Drug Administration. Drug development and drug interactions: table of substrates, inhibitors and inducers. Available at: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers. Accessed August 2022.
20. Dawra VK, Sahasrabudhe V, Liang Y, et al. Effect of rifampin on the pharmacokinetics of ertugliflozin in healthy subjects. Clin Ther **2018**; 40:1538–47.
21. Vourvahis M, Davis J, Wang R, et al. Effect of rifampin and rifabutin on the pharmacokinetics of lersivirine and effect of lersivirine on the pharmacokinetics of rifabutin and 25-O-desacetyl-rifabutin in healthy subjects. Antimicrob Agents Chemother **2012**; 56:4303–9.
22. Dyavar SR, Mykris TM, Winchester LC, Scarsi KK, Fletcher CV, Podany AT. Hepatocytic transcriptional signatures predict comparative drug interaction potential of rifamycin antibiotics. Sci Rep **2020**; 10:12565.
23. Ford SL, Sutton K, Lou Y, et al. Effect of rifampin on the single-dose pharmacokinetics of oral cabotegravir in healthy subjects. Antimicrob Agents Chemother **2017**; 61:e00487–17.
24. Van Heeswijk R, Hoetelmans R, Kestens D, et al. The effects of CYP3A4 modulation on the pharmacokinetics of TMC278, an investigational non-nucleoside reverse transcriptase inhibitor (NNRTI) [abstract 74]. In: 7th International Workshop on Clinical Pharmacology of HIV Therapy, Lisbon, Portugal, 20–22 April 2006.
25. Ford SL, Lou Y, Lewis N, et al. Effect of rifabutin on the pharmacokinetics of oral cabotegravir in healthy subjects. Antivir Ther **2019**; 24:301–8.
26. European Medicines Agency. Edurant summary of product characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/edurant-epar-product-information_en.pdf. Accessed August 2022.
27. Landovitz RJ, Li S, Eron JJ, Jr., et al. Tail-phase safety, tolerability, and pharmacokinetics of long-acting injectable cabotegravir in HIV-uninfected adults: a secondary analysis of the HPTN 077 trial. Lancet HIV **2020**; 7: e472–e81.
28. Aouri M, Barcelo C, Guidi M, et al. Population pharmacokinetics and pharmacogenetics analysis of rilpivirine in HIV-1-infected individuals. Antimicrob Agents Chemother **2017**; 61:e00899-16.
29. Cresswell FV, Lamorde M. Implementation of long-acting antiretroviral therapy in low-income and middle-income countries. Curr Opin HIV AIDS **2022**; 17: 127–34.
30. European Medicines Agency. Assessment report Edurant. Available at: https://www.ema.europa.eu/en/documents/assessment-report/edurant-epar-public-assessment-report_en.pdf. Accessed August 2022.
31. Al-Majdoub ZM, Couto N, Achour B, et al. Quantification of proteins involved in intestinal epithelial handling of xenobiotics. Clin Pharmacol Ther **2021**; 109: 1136–46.
32. Scarsi KK, Darin KM, Nakalema S, et al. Unintended pregnancies observed with combined use of the levonorgestrel contraceptive implant and efavirenz-based antiretroviral therapy: a three-arm pharmacokinetic evaluation over 48 weeks. Clin Infect Dis **2016**; 62:675–82.
33. Carten ML, Kiser JJ, Kwara A, Mawhinney S, Cu-Uvin S. Pharmacokinetic interactions between the hormonal emergency contraception, levonorgestrel (Plan B), and Efavirenz. Infect Dis Obstet Gynecol **2012**; 2012:137192.
34. Orkin C, Bernal Morell E, Tan DHS, et al. Initiation of long-acting cabotegravir plus rilpivirine as direct-to-injection or with an oral lead-in in adults with HIV-1 infection: week 124 results of the open-label phase 3 FLAIR study. Lancet HIV **2021**; 8:e668–e78.
35. Han K, Baker M, Margolis D, Spreen W, Ford SL. Impact of UGT induction by rifampin and rifabutin on cabotegravir long-acting pharmacokinetics for HIV pre-exposure prophylaxis (PrEP) using population pharmacokinetic modeling and simulation. In: HIVR4P conference (virtual), January 27-28, **2022**.