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PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELING OF LONG-ACTING CABOTEGRAVIR AND RILPIVIRINE IN SPECIAL POPULATIONS AND DRUG–DRUG INTERACTION SCENARIOS

Dr. Anand Srinivasan[1*], Dr. Surulivel Rajan M.[2], Dr. Pinaki Sengupta[3]

[1*]Department Department of Pharmacology, AIIMS Bhubaneswar, dranandsrinivasan123@gmail.com

[2]Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, Manipal.

[3]National Institute of Pharmaceutical Education and Research (NIPER), Ahmedabad

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ABSTRACT-

This study compared physiologically based pharmacokinetic (PBPK) models of long acting cabotegravir (CAB) and rilpivirine (RPV) to describe exposure at regular dosing, special population conditions and clinically relevant drug–drug interaction scenarios. The modeling framework included the modeling of intramuscular depot release, the modeling of the physicochemical and metabolic properties of the drugs, population physiology, and enzyme-mediated interactions. Model verification results indicated good agreement with the observed pharmacokinetic parameters with 73% of simulated parameters within 1.25-fold, 83% within 1.5-fold and 100% within twofold of observed values. Predicted RPV reduction was less than that predicted for progressive reductions in CAB, with the greatest reduction seen for greater BMI categories. The exposure of the CAB and RPV generally increased with age. Drug-drug interaction simulations showed that the strongest inducer was rifampicin, for which the fold reduction in the AUC of CAB and RPV was around 61% and 38%, respectively, while the fold reduction for rifabutin was moderate. The decreases in exposure were small and brief with residual induction with efavirzen. Alternative dosing simulations indicated that some loss of activity with rifabutin was countered with dosing changes; induction by rifampicin was potentially problematic. Sensitivity analysis revealed that solubility, viscosity, thickness of the diffusion layer and related depot properties were found to be significant factors for the long-acting pharmacokinetics. Overall, PBPK modeling was used to provide a mechanistic framework to assess exposure variability and to support tailored dosing strategies for CAB/RPV.

Keywords: Cabotegravir; Rilpivirine; PBPK modeling; Drug–drug interactions; Long-acting antiretroviral therapy

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1. Introduction

Long-acting antiretroviral therapy (LAART) is a major step forward in HIV care that means that people can take fewer pills that are injected into the skin rather than taken orally every day.Long-acting antiretroviral therapy (LAART) is an important new treatment development that allows people to receive fewer pills that are injected into the skin instead of taking them daily orally, potentially enhancing treatment convenience and adherence. Bares and Scarsi developed two long-acting injectable agents that are complementary, Cabotegravir (CAB), an integrase strand transfer inhibitor, and rilpivirine (RPV), a non-nucleoside reverse transcriptase inhibitor (NNRTI), to suppress viral levels (Bares & Scarsi, 2021). For individuals living with HIV (HIViLs), sustained drug delivery from intramuscular CAB/RPV formulations allows for extended dosing intervals as a therapeutic strategy (Flexner et al., 2021). Long-acting administration has shown clinical pharmacokinetic activity and antiviral effects (Letendre et al., 2020). Cabotegravir exposure has also been determined in both oral and injectable formulations to inform effective long-acting dosing regimens (Han et al., 2024). There has been more recent evidence of the possibility of achieving effective pharmacokinetics with and without an oral lead-in period.

Although the therapeutic benefits can be considerable, long-acting drugs are associated with unique pharmacokinetic problems, as the drug absorption can occur over a period of weeks or months after being administered intramuscularly. This means that plasma concentrations can be affected by the variability in absorption, distribution, metabolism, and injection characteristics (Hodge et al., 2021). Changes in cabotegravir exposure may also be a result of individual physiological factors, which have been shown in pharmacokinetic studies of women using hormonal contraception (Blair et al., 2020). It is therefore crucial that sufficient levels of antiviral are maintained during the dosing interval to minimize the risk of subtherapeutic exposure.

Long-acting drug disposition can greatly vary from person to person. BMI is especially pertinent as obesity influences intramuscular deposition and systemic exposure to CAB and RPV (Bettonte et al., 2024). Efficacy, safety, and pharmacokinetics have also been studied in BMI groups in phase 3/3b trials (Elliot et al., 2024). Physiological changes can also occur with age that can alter drug distribution and clearance, which must be evaluated especially in older individuals with HIV (Bettonte, Berton, Battegay, et al., 2024). Another physiologically dynamic population is pregnant women whose drug disposition can be altered, and PBPK approaches can characterize this alteration (Atoyebi et al., 2025; Dallmann et al., 2018).

UGT1A1 and UGT1A9 are the primary enzymes responsible for the metabolism of cabotegravir while CYP3A4 is the primary enzyme responsible for the metabolism of rilpivirine, with enzyme induction being a significant source of drug–drug interactions (Hodge et al., 2021). These pathways can be affected by the use of rifampicin, rifabutin and efavirenz. In studies conducted to date, cabotegravir has been found to affect the pharmacokinetics (PK) of rifabutin, and PBPK-

based studies suggest that inducing comedications can significantly alter the exposure to long-acting CAB/RPV (Bettonte et al., 2023; Ford et al., 2019).

Physiologically based pharmacokinetic modeling uses a combination of the properties of the drug and physiological properties to simulate concentration–time profiles under specific clinical conditions. More recently, PBPK models have been developed to account for the intramuscular disposition of antiretroviral drugs and the depot-release processes (Bettonte, Berton, Stader, et al., 2024). These are especially helpful in special patient populations and/or complex DDI situations where clinical studies are not easily conducted.

The objectives of this study are to develop and evaluate PBPK models of long acting CAB and RPV, assess the pharmacokinetic exposure in special populations, and simulate clinically relevant DDI and alternative dosing scenarios to aid in the use of individualized and evidence-based long acting antiretroviral therapy.

2. Materials and Methods

2.1 Study Design

A computational physiologically-based pharmacokinetic (PBPK) modelling and simulation framework approach was used to characterize long-acting cabotegravir (CAB) and rilpivirine (RPV) under standard treatment conditions, special populations and clinically relevant drug–drug interaction (DDI) scenarios. The workflow comprised model implementation, representation of long-acting intramuscular depot, model verification, special-population simulation, DDI assessment, evaluation of alternative dosing, and sensitivity analysis.

2.2 Dataset and Data Sources

Three data sets were employed. The first included PBPK model parameters, physicochemical properties and metabolic data, verification inputs and sensitivity-analysis settings for CAB and RPV (Marzolini & Bettonte, 2024). The second included observed and literature pharmacokinetic data for long-acting CAB/RPV in obese and elderly patients. The third described DDI scenarios with rifampicin, rifabutin and efavirenz. Elderly analyses were based on model-based simulations as there were no publicly available individual-level elderly pharmacokinetic observations.

2.3 PBPK Model Development

The physicochemical and metabolic parameters in the dataset were used to develop drug-specific PBPK models. CAB disposition included molecular properties, plasma protein binding, tissue distribution, renal elimination and metabolism primarily via UGT1A1 and UGT1A9. RPV modeling included its physicochemical properties, distribution, elimination and metabolism

mediated by CYP3A4. These drug-specific parameters were combined with the physiological compartments to obtain systemic concentration–time profiles.

2.4 Long-Acting Intramuscular Formulation Modeling

An intramuscular depot model of drug dissolution, diffusion, local muscle blood flow, formulation characteristics, and injection site processes was used to represent long-acting CAB and RPV administration. CAB regimens consisted of a 600-mg loading dose followed by a 400-mg Q4W or 600-mg Q8W maintenance dose. RPV regimens were either a 900-mg loading dose followed by 600-mg Q4W or 900-mg Q8W. These schedules are simulations based on the scenarios found in the data set.

2.5 PBPK Model Verification

Model performance was tested against observed (or referenced) pharmacokinetic data provided in the supplied workbooks. Maximum plasma concentration (Cmax), area under the concentration–time curve (AUC) and trough concentrations were key endpoints. For four-week simulations, AUC over four weeks (AUC4wk) and the concentration at week 4 (C4wk) were emphasized. Agreement was assessed using predicted-to-observed ratios and concentration–time profiles.

2.6 Special-Population Simulations

Simulations for special populations were based on obesity and older age. Body size and physiological differences that affect intramuscular depot behavior, distribution, and systemic exposure were included in obesity scenarios. The level of CAB and RPV exposure in BMI-related conditions was compared to the reference adult population. Physiological changes associated with older age on body composition, organ function, blood flow and drug disposition were included in older-adult simulations. These analyses were interpreted as predictive simulations, as raw elderly observations were not available.

2.7 Drug–Drug Interaction Simulations

DDI simulation assessed the impacts on CAB and RPV exposure by rifampicin, rifabutin and efavirenz. Rifampicin was modeled as a strong enzyme inducer at the dose of 600 mg QD and rifabutin was modeled as a moderate enzyme inducer at 300 mg QD. The interactions of CAB were simulated largely by induction of UGT1A1/UGT1A9, while interactions of RPV were evaluated by induction of CYP3A4. The recovery of CAB and RPV exposure was also assessed after Efavirenz discontinuation, in the various scenarios modeled.

2.8 Alternative Dosing Scenarios

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Alternative dosing strategies were examined to see if a change in dosing frequency or supplemental dosing decreased inducer-induced loss of drug exposure. CAB simulations were conducted with Q4W and Q3W modifications during the time of exposure to rifampicin and with further loading during the time of exposure to rifabutin. Supplementary oral dosing with selected Q4W and Q8W dosing regimens was included as RPV scenarios. The trough and systemic exposure with each alternative strategy was compared to the standard strategy.

2.9 Sensitivity and Model Evaluation

Sensitivity analysis was carried out for the depot parameters to determine those with the highest effect on the CAB pharmacokinetics. For the predefined dataset, the dose of CAB was 800mg as a 2×400 mg depot. The diffusion-layer thickness, solubility, drug density, viscosity, inflammation factor and muscle blood flow were varied one at a time. Cmax, AUC4wk, and C4wk were used to evaluate effects. The overall model outputs were summarized by means of predicted exposure, percentage change from reference exposure, predicted-to-observed ratio, and graphical concentration time profile.

3. Results

3.1 Overall PBPK Model Performance

The constructed intramuscular PBPK model was able to sufficiently simulate the pharmacokinetic characteristics of long-acting CAB and RPV. Finally, 73%, 83% and all simulated pharmacokinetic endpoints were within 1.25-fold, 1.5-fold and 2-fold of clinically observed values, respectively, which suggests that the verified framework can be applied for future simulations for special populations and DDIs. As seen in Table 1, the verification regimens of principal long-acting CAB and RPV remained within the prespecified range of 2-fold acceptance criterion when compared to observations.

Table 1. Verification performance of long-acting cabotegravir and rilpivirine PBPK models

Intramuscular scenario	Cmax P/O ratio	Trough/C4wk P/O ratio	AUC P/O ratio
CAB 400 mg, single dose	1.04	1.68	1.52
CAB 800 mg, single dose	1.14	0.89	1.13

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CAB 800 mg followed by 400 mg multiple doses	0.80	0.86	0.84
RPV 600 mg, single dose	0.62	0.62	0.78
RPV 1200 mg, single dose	1.20	0.86	1.06

P/O, predicted-to-observed; CAB, cabotegravir; RPV, rilpivirine.

3.2 Verification of Long-Acting CAB and RPV

CAB predictions were very close to the observed data after the 800-mg injection of the imformable dose, as the P/O ratios were 1.14, 0.89, and 1.13 for Cmax, C4wk, and AUC, respectively. The Cmax was well-predicted with the 400-mg CAB dose; moderate over-prediction of C4wk and AUC was observed. Exposures were generally lower in RPV 600-mg simulations, whereas they were closer to each other in the 1200-mg regimen. However the evaluated endpoints were still within the two-fold verification boundary. The distribution of the verification ratios is shown in Figure 1, and it is seen that all ratios were below the preset value of two.

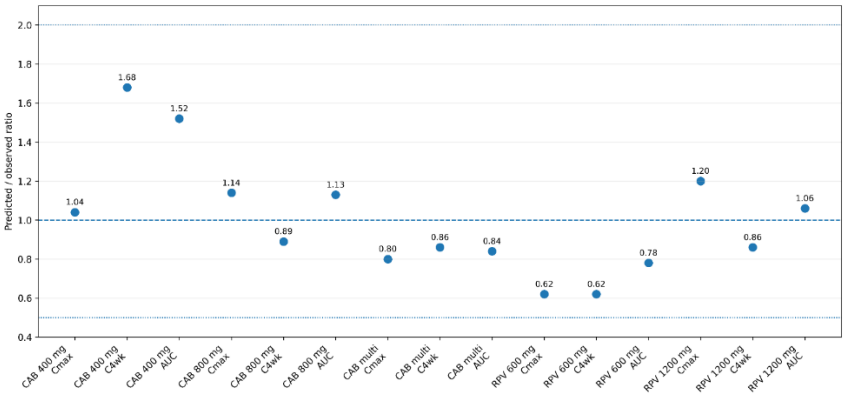


Figure 1. Predicted-to-observed ratios for selected long-acting CAB and RPV pharmacokinetic endpoints

3.3 Effect of Obesity on CAB and RPV Exposure

Obesity caused less CAB exposure reduction as compared to RPV exposure. With monthly CAB administration, Cmin and AUC decreased by 14% at BMI 25–30 kg/m², 19% at 30–35 kg/m², 35% at 35–40 kg/m², 48% at 40–50 kg/m², and 62% at 50–60 kg/m². The same decrease was anticipated

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in the Q8W regimen with the highest BMI group having approximately 63%. RPV did not change as much, even though clinically significant decreases were observed at BMI ≥40 kg/m². The greatest exposure decreases were in morbid obesity as indicated in Table 2.

Table 2. Predicted influence of BMI on steady-state long-acting CAB/RPV exposure

BMI (kg/m²)	CAB Q4W Cmin/AUC change	CAB Q8W Cmin/AUC change	RPV Q4W finding
25–30	−14%	−10%	Within bioequivalence range
30–35	−19%	−12%	Within bioequivalence range
35–40	−35%	−35%	Within bioequivalence range
40–50	−48%	−47%	Cmin −18%; AUC −21%
50–60	−62%	−63%	Cmin −22%; AUC −27%

Changes are relative to normal-weight virtual individuals with BMI 18.5–25 kg/m².

3.4 Effect of Older Age on Long-Acting Exposure

Exposure to the drugs was predicted to be higher at older ages, not lower. Older adults exhibited 29% higher Cmin and 26% higher AUC compared with young adults after Q8W administration of CAB. With Q4W dosing, RPV demonstrated increases of 28% and 25% in Cmin and AUC, respectively, and 46% and 41% with Q8W dosing. The monthly CAB variations were within the normal range (0.8–1.25 fold). The age-related effect was most evident for bimonthly RPV as shown in Figure 2.

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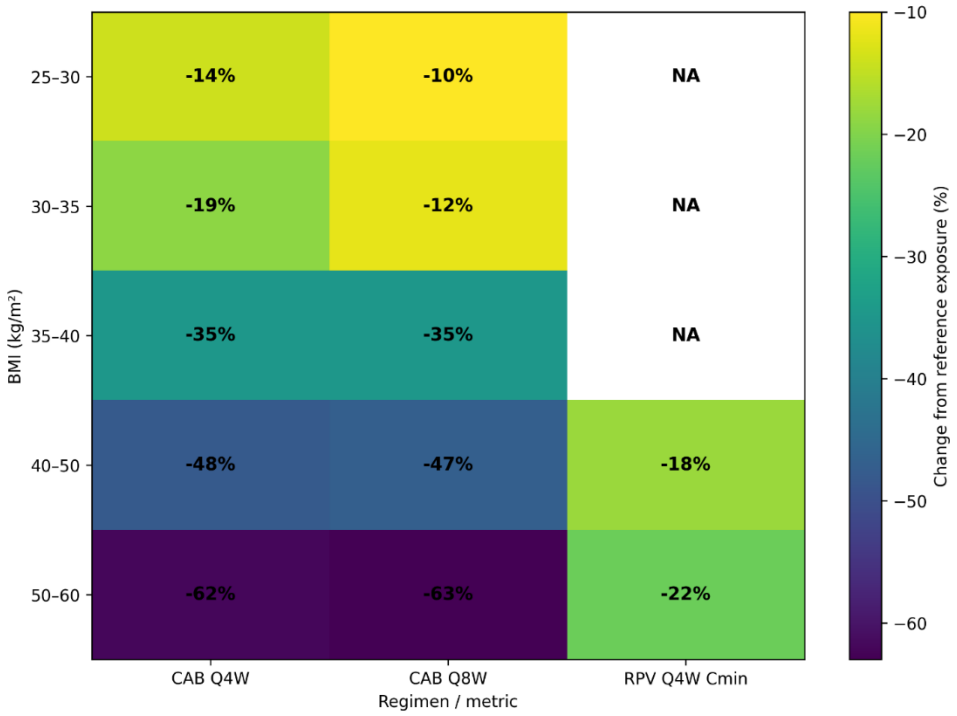


Figure 2. Predicted percentage increase in CAB and RPV exposure in older versus young adults

3.5 Drug–Drug Interaction and Efavirenz-Switching Results

There was a distinct difference in the effects of strong and moderate enzyme induction. Rifampicin caused the greatest decrease in systemic exposure and rifabutin caused lesser changes that could be managed by modifying the regimen. The simulations of the efavirenz-switching showed that the temporary decreases occurred following discontinuation, and CAB was also above the specified efficacy limit. The key interaction findings are in Table 3.

Table 3. Predicted effects of rifampicin, rifabutin, and residual efavirenz induction

Interaction scenario	**CAB result**	**RPV result**	**Main finding**
Rifampicin at steady state	AUC −61%	AUC −38%	Strong clinically important induction

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Rifabutin at steady state	AUC −16%	AUC −18%	Moderate induction
Rifabutin management	Monthly CAB feasible	Monthly RPV + oral RPV 25 mg/day	Exposure could be compensated
Efavirenz discontinuation	−11% day 1; −13% day 7; −8% day 14	Maximum reported decrease ≈10% at day 7	Transient residual induction

3.6 Comparison of Strong and Moderate Induction and Dosing Strategies

The variation between rifampicin and rifabutin was significant. The CAB AUC was decreased by rifampicin by 61 per cent in comparison with 16 per cent in rifabutin administration; the corresponding decreases in RPV were 38 and 18 per cent. To completely overcome strong induction of rifampicin, increasing CAB injection frequency to Q4W or Q3W was not enough. Conversely, interactions with rifabutin may be avoided with monthly CAB/RPV with 25 mg oral RPV/day. The significant decrease in exposure is evident in Figure 3, which shows a substantial decrease in exposure with rifampicin.

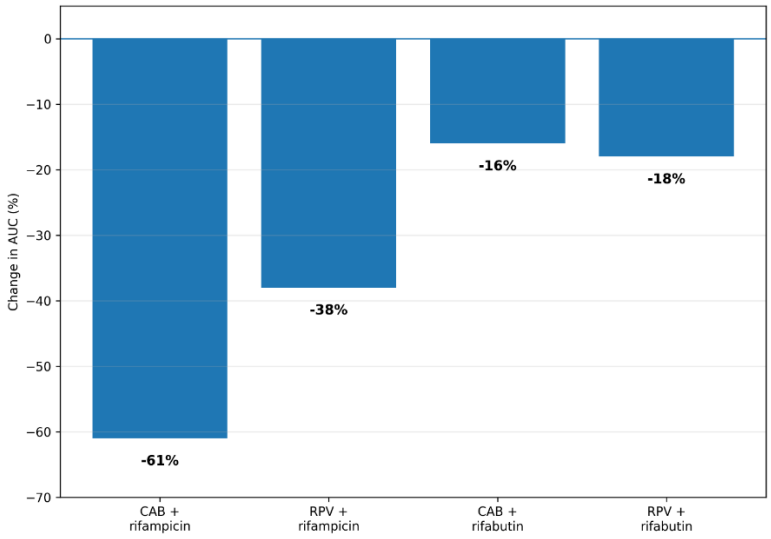


Figure 3. Predicted steady-state AUC reduction of long-acting CAB and RPV during rifampicin and rifabutin coadministration

3.7 Sensitivity Analysis

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Formulation and depot-release properties were found to be important factors in the long-acting CAB pharmacokinetics through local sensitivity analysis. Parameters that had the largest effect on Cmax, AUC and trough concentration were media viscosity, drug solubility and diffusion-layer thickness. A higher viscosity, drug density, and diffusion-layer thickness were found to have an inverse relationship with exposure metrics, while a higher drug solubility had positive effects. The trough concentration was inversely related to the inflammation factor, whereas Cmax and AUC were directly related. Table 4 shows a summary of these relationships.

Table 4. Direction and relative importance of depot parameters in the CAB sensitivity analysis

Parameter	**Cmax**	**AUC**	**Ctrough**	**Interpretation**
Media viscosity	Negative	Negative	Negative	Higher-impact parameter
Drug solubility	Positive	Positive	Positive	Higher-impact parameter
Diffusion-layer thickness	Negative	Negative	Negative	Higher-impact parameter
Drug density	Negative	Negative	Negative	Exposure-sensitive parameter
Inflammation factor	Positive	Positive	Negative	Influenced depot release
Muscle blood flow	Evaluated	Evaluated	Evaluated	Not highlighted among dominant parameters

3.8 Integrated Sensitivity and Pharmacokinetic Interpretation

The results overall suggest that the overall exposure to long-acting CAB/RPV is dependent on the interaction between depot-release properties, dosing interval, and metabolic induction. Increased solubility increases drug release while increased parameters to retard dissolution/diffusion generally decrease systemic exposure. The special-population effect with the highest risk of reduced concentrations was obesity (particularly following Q8W); older patients tended to have higher concentrations. DDIs showed the greatest exposure reduction with rifampicin, followed by

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a considerable exposure reduction with rifabutin, and minimal and temporary exposure reductions with etravirine induction. Figure 4 shows the directions of the main depot-related sensitivity effects.

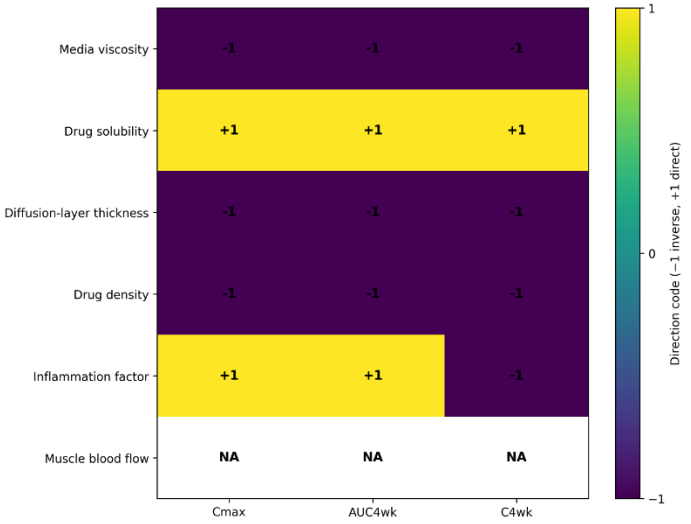


Figure 4. Direction of local sensitivity effects of intramuscular depot parameters on CAB Cmax, AUC, and trough concentration

4. Discussion

Within the context of the present PBPK analysis, a mechanistic model that includes a depot model for cabotegravir (CAB) and rilpivirine (RPV), systemic disposition, patient physiology, and enzyme-mediated drug interactions was found to be sufficient to represent the two drugs. Predicted values of pharmacokinetic parameters generally agreed with observed values; obesity, ageing, dosing interval, and enzyme-inducing comedications were found to affect drug exposure. These results are also consistent with clinical experience showing long-term antiviral activity of long-acting CAB/RPV over long courses of treatment (Orkin et al., 2020; Swindells et al., 2021).

Model verification indicated that the exposure (Cmax, AUC and trough) predictions from CAB and RPV were within the acceptable prediction boundaries. This is consistent with the fact that PBPK modelling is suitable for extrapolation of long-acting pharmacokinetics beyond direct studies. Population pharmacokinetic analyses have also shown that the disposition of CAB after injection is predictable over time and RPV has been shown to have prolonged absorption and interindividual variability (Neyens et al., 2021; Yu et al., 2022). The use of a therapeutic drug monitoring level in the real world also helps to further reinforce the need to understand the trough level in the context of long-acting exposure and potential treatment failure (Thoueille et al., 2024).

Physiological changes due to obesity and ageing were postulated to modify the exposure to CAB and RPV, but in different ways and to different extents across populations and regimens. The

results emphasize the need to account for the characteristics of the body, the site of injection, and the changes of the body with age when interpreting concentrations of long-acting drugs. Analyses of clinical trials have demonstrated CAB/RPV efficacy in a variety of treated populations, with the risk of pharmacokinetic variability potentially responsible for some variation in individual exposure (Orkin et al., 2023). Thus, PBPK simulations are useful in identifying patients that require more PK monitoring.

The most intense interaction was reported with rifampicin, which is known for its strong enzyme-inducing property. Similarly, prior studies with PBPK models predicted large decreases in CAB and RPV exposures with coadministration of rifampicin (Rajoli et al., 2019). A long acting CAB/RPV treated patient with clinical evidence also supports the need to carefully interpret concentrations in strong induction (Sunagawa et al., 2023). Rifabutin had smaller effects and the residual effects of induction by efavirenz were more short-lived. The results highlight the need to take into account the magnitude of the induction and de-induction current when changing therapy.

Both the Q4W and Q8W simulations suggested that the dose interval had an impact on the level of exposure reduction. The clinical feasibility of extended dosing is supported by ATLAS-2M which demonstrated efficacy for Q8W CAB/RPV over 48 weeks, 96 weeks, and 152 weeks (Jaeger et al., 2021; Overton et al., 2020, 2023). In DDI conditions or physiological changes, shorter dosing period or additional doses may be needed. DTI has also demonstrated similar effectiveness compared to oral lead-in treatment, which ensures treatment flexibility (Orkin, Oka, et al., 2021).

The results of the present study are consistent with the results of FLAIR, which showed sustained efficacy and tolerability of long-acting CAB/RPV for 96 weeks (Orkin, Morell, et al., 2021). They are also consistent of previous phase 3 data that demonstrated the long acting CAB/RPV is also effective for viral suppression after oral induction (Orkin et al., 2020). These current PBPK findings, when combined with these clinical observations, provide mechanistic understanding of variability in exposure in more difficult-to-test scenarios.

Some of the key benefits are mechanistic PBPK model, multiple DDI scenarios, evaluation of Q4W and Q8W regimens and special populations. The analysis, however, was partly dependent on published and model-derived parameters and patient-level data were limited for some special populations, especially older adults. Therefore, simulated predictions should be used in conjunction with, not instead of, clinical evidence.

Further studies are needed to validate the data in patients with renal or hepatic impairment, larger BMI and age groups, other enzyme-inducing and inhibiting medications, and prospective therapeutic drug monitoring groups. Additional integration of clinical PK data with PBPK models may facilitate optimization of long-acting CAB/RPV dosing in individual patients and enhance the evidence base for complicated clinical scenarios.

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5. Conclusion

The results of this study show the usefulness of physiologically based pharmacokinetic modeling in describing the disposition of long-acting cabotegravir and rilpivirine during typical dosing conditions, special populations, and clinically relevant drug-drug interaction scenarios. The constructed framework exhibited adequate predictive ability for the key pharmacokinetic parameters' (Cmax, AUC, trough concentration) under the Q4W and Q8W dosing regimens. The simulations showed that obesity led to decreased systemic exposure, especially at higher BMI categories, while ageing led to increased exposure to cabotegravir and rilpivirine due to physiological changes in distribution and clearance. Of the assessed drug interactions, rifampicin resulted in the highest decrease in exposure, rifabutin had a more moderate effect, and exposure to the drug was minimally affected by the induction effect of residual efavirenz, which seemed to be more short-lived. Clinically relevant reductions in some inducer-related effects were partly overcome by alternative dosing approaches, but strong induction should be taken into account. In addition, sensitivity analysis revealed how the properties of the intramuscular depot, such as depot solubility, viscosity, thickness of the depot diffusion layer, and local physiological conditions, affect the long-acting pharmacokinetics. In summary, PBPK modeling offers a clinically relevant and mechanistic tool to predict exposure variability, investigate dosing adaptations, and guide individualization of long-acting CAB/RPV use. Additional prospective validation of the results in larger special populations and multidrug settings is needed.

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