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REVIEW ARTICLE

Clinical pharmacology considerations and drug–drug interactions with long-acting cabotegravir and rilpivirine relevant to sub-Saharan Africa

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Long-acting injectable (LAI) cabotegravir and rilpivirine for HIV treatment and LAI cabotegravir for pre-exposure HIV prophylaxis are being rolled out in a multitude of countries worldwide. Due to the prolonged exposure, it can be challenging to undertake 'traditional' pharmacokinetic studies and current guidance is derived from their oral equivalents or physiologically based pharmacokinetic studies. This review aims to consider pharmacokinetic characteristics of cabotegravir and rilpivirine and describe anticipated drug–drug interactions (DDIs) with frequent concomitant medications in African settings. Relevant co-medications were identified from the WHO 2021 List of Essential Medicines. All original human and physiologically based pharmacokinetic studies published in English on PubMed, discussing DDIs with LAI cabotegravir and rilpivirine prior to April 2023, were reviewed. The Liverpool HIV interaction database was also reviewed (https://www.hiv-druginteractions.org/checker). LAI cabotegravir and rilpivirine have half-lives of 6–12 and 13–28 weeks, respectively. Cabotegravir is primarily metabolized by UDP-glucuronyltransferase (UGT)-1A1 and rilpivirine by cytochrome P450 (CYP)-3A4. LAI cabotegravir and rilpivirine themselves exhibit low risk of perpetrating interactions with co-medications as they do not induce or inhibit the major drug metabolizing enzymes. However, they are victims of DDIs relating to the induction of their metabolizing enzymes by concomitantly administered medication. Noteworthy contraindicated co-medications include rifamycins, carbamazepine, phenytoin, flucloxacillin and griseofulvin, which induce CYP3A4 and/or UGT1A1, causing clinically significant reduced concentrations of rilpivirine and/or cabotegravir. In addition to virologic failure, subtherapeutic concentrations resulting from DDIs can lead to emergent drug resistance. Clinicians should be aware of potential DDIs and counsel people receiving LAI cabotegravir/rilpivirine appropriately to minimize risk.

KEYWORDS
antiretroviral, cabotegravir, HIV, interaction, long-acting, rilpivirine

1 | INTRODUCTION

HIV continues to be a major global health concern, with an estimated 39 million people living with the virus worldwide and 29 million people accessing antiretroviral therapy (ART) in 2022.[1] The burden of HIV is particularly high in sub-Saharan Africa, which accounted for approximately two-thirds of all new HIV infections in 2022.[2] Treatment fatigue and poor adherence to ART causes treatment failure and favours the emergence of drug-resistant viral strains and thus constitutes an important impediment to reaching the UNAIDS goal of ending the HIV/AIDS epidemic worldwide by 2030.[3]

Suboptimal adherence to HIV prevention and treatment has motivated the search for alternatives to daily oral medicines, and among the most promising novel approaches is long-acting injectable (LAI) therapy, which has leveraged nanotechnology to modify the pharmacokinetics of the existing compounds. The frontrunner LAI regimen for HIV treatment consists of a combination of the integrase strand transfer inhibitor (INSTI) **cabotegravir** (CAB) together with the non-nucleotide reverse transcriptase inhibitor (NNRTI) **rilpivirine** (RPV), given monthly or every 2 months by intramuscular (IM) injection, and demonstrated comparable efficacy to standard oral therapy in maintaining viral suppression in a number of clinical trials.[4,5] Rollout of this injectable regimen is now underway in Europe, the United States and Australia, and licensing applications are in process in several African countries. In Europe, CAB and RPV are marketed as two separate injectable medicines under the brand names VOCABRIA®[6] and REKAMBYS®,[7] respectively, while in Canada and the United States the regimen is marketed as a combined pack called CABENUVA®.

LAI CAB has also been examined for prevention of HIV infection and is superior to standard oral pre-exposure prophylaxis (PrEP). A global coalition is currently accelerating the rollout of LAI CAB PrEP in many high HIV burden countries.[8]

The use of LAI ART in sub-Saharan settings presents a promising advancement in HIV prevention and treatment, as it is discreet and convenient. However, this novel LAI preventive and therapeutic option brings new clinical pharmacology challenges. Firstly, it is critical to ensure that the drug is deposited into muscle and not adipose tissue, which is less vascular and can result in poor absorption and distribution of the drug. As a result, body mass index (BMI) > 30 kg/m^2 is known to be an independent risk factor for virological failure and longer needles (2-in.) are required in people with high BMI.[9] Secondly, due to the nature of the LAI formulation, the drug is slowly cleared from the body after administration.[10] This means, that should a dose be missed, or treatment discontinued, there is a resultant long pharmacokinetic (PK) 'tail'. During this prolonged period of terminal decay, ART plasma concentrations steadily decline, eventually reaching non-suppressive concentrations, and leading to a risk of viral replication together with selection of drug-resistant variants.[11] Thirdly, in addition to LAI ART, individuals in sub-Saharan countries may require treatment with other medications, including antitubercular, antimalarial or psychotropic agents, to manage comorbidities, some of which come with clinically significant pharmacokinetic or pharmacodynamic drug–drug interactions (DDIs).[12] Healthcare professionals may be unfamiliar with the numerous potential DDIs between LAI CAB and RPV and frequently prescribed concomitant medicines. In addition, many drugs are available over the counter in lower-income settings, meaning DDIs may go unchecked, so patient counselling is important.

DDIs with CAB or RPV have the potential to lead to catastrophic HIV treatment failure, through the lowering of the drugs' plasma concentration with ensuing viral rebound.[3] The evolution and spread of INSTI resistance has significant consequences for the individual and societies, as it requires management with protease-inhibitor-based ART, which is toxic, costly and also plagued with further DDI risk.[13] Therefore, avoiding DDIs that add to the risk of viral rebound and drug resistance is of key importance during use of LAI ART.

Due to the long terminal half-life of LAI CAB and RPV, the associated long dosing interval and the high consequence of low drug exposures causing virological failure, it is challenging to perform DDI studies in people on LAI ART. For this reason, to date, DDI studies have been performed in silico with a virtual clinical population (with physiological parameters that are important for the prediction of drug disposition), using an approach called physiologically based pharmacokinetic (PBPK) modelling.[14] PBPK uses known mechanistic and physiologic properties such as organ-specific blood flow, tissue partition coefficients, specificity and capacity of metabolic enzymes to create whole-body profiles of drug disposition. It then combines in vitro data and clinically observed data to simulate pharmacokinetics and DDIs in the virtual population, an approach that is essential in understanding LAI CAB/RPV pharmacokinetics in the context of DDIs or complex and difficult to study populations.[14]

This literature review aims to raise awareness among healthcare professionals of the pharmacokinetics of LAI CAB and RPV, dosing schedules and the risk of DDIs with commonly used medications in sub-Saharan Africa. This will enable clinicians to adequately counsel patients and to make informed decisions regarding the use of concomitant medications in people receiving LAI ART for HIV prevention or treatment, ultimately improving patient care and reducing the risk of virological failure.

2 | METHODS

The co-medications included in this review concern diseases with a high prevalence or occurrence, and those commonly associated with HIV/AIDS and considered critical for patient care in sub-Saharan Africa. The WHO 2021 Model List of Essential Medicines was consulted to identify drugs of interest to our review.[15]

Once the list of co-medications was identified, a literature search was conducted on PubMed using a predefined Boolean search strategy. The search strategy described in Table 1 was used to identify relevant studies published up until April 2023. The search was limited to studies conducted in humans or PBPK simulation, published in English. All potentially related designs, including trials, observational studies, experimental and in silico studies, were considered in the literature search. Studies were not restricted to a particular geographical area.

TABLE 1 Search terms and strategy for literature review on drug–drug interactions between cabotegravir/rilpivirine and concomitant medications of interest.

Search	Search term	Number of articles
Context	PubMed articles published in English	
1	(cabotegravir OR rilpivirine OR GSK1265744 OR TMC278) [all fields]	1263
2	(interaction* OR anti-tuberculosis OR antipsychotic OR antimalarial OR contraception OR antibacterial OR antifungal OR rifampicin OR rifapentine OR rifabutin OR isoniazid OR pyrazinamide OR ethambutol OR quinolone OR artemether OR dihydroartemisinin OR artesunate OR amodiaquine OR piperaquine OR primaquine OR mefloquine OR quinine OR ciprofloxacin OR ofloxacin OR levofloxacin OR moxifloxacin OR azithromycin OR erythromycin OR clarithromycin OR flucloxacillin OR metronidazole OR ketoconazole OR fluconazole OR amphotericin OR griseofulvin OR flucytosine OR levonorgestrel OR oestradiol OR ethinyl oestradiol OR DMPA OR medroxyprogesterone acetate OR azole) [all fields]	3 865 130
3	1 AND 2; filter from 2005/1/1 to 2023/4/30	338
	Articles reviewed and included if addressing drug–drug interactions with cabotegravir and/or rilpivirine	31

In addition to the literature search, the Liverpool HIV drug interaction database (www.hiv-druginteraction.org) was consulted to identify additional studies on DDIs between CAB or RPV and the predefined co-medications.[16] This database provides a comprehensive resource for healthcare professionals, researchers and patients to identify potential drug interactions between antiretrovirals and other medications used in clinical practice. By consulting this database, we aimed to supplement the literature search and ensure that all relevant information on potential DDIs was captured.

3 | RESULTS

3.1 | CAB pharmacokinetics

CAB, a second-generation INSTI, binds to the active site of HIV integrase enzyme and inhibits the cDNA strand transfer step. Trough concentration (C_{trough}) is the most common efficacy surrogate for INSTIs.[17] LAI CAB for HIV prevention is dosed at 600 mg/3 mL with the first two injections administered 4 weeks apart, followed thereafter by an injection every 8 weeks. This is the same dosing schedule for 2-monthly HIV treatment in combination with LAI RPV. Dosing can be administered within a window ±7 days of the planned date of injection.[6] A 4-week oral lead-in (OLI) of daily oral CAB 30 mg and RPV 25 mg is offered, but not essential, to ensure tolerability before transitioning to injections.

IM CAB has a median time to maximal plasma concentration (T_{max}) of 7 days and reaches steady state after 44 weeks.[18] CAB is highly protein bound (>99.8%) with a volume of distribution of 12.3 L.[6] Both oral and IM CAB are largely metabolized hepatically by **UDP-glucuronyltransferase (UGT)-1A1** with a minor contribution from cytochrome P450 (CYP) 1A9 and are excreted largely in the urine and small amounts in bile/faeces.[19] CAB does not inhibit or induce CYP isoforms, glucuronidation enzymes, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATPs) 1B1/1B3, organic cation transporter (OCT) or other enzymes/transporters. CAB inhibits the renal transporter OAT1 and OAT3, increasing exposures of OAT1 and OAT3 substrates such as ciprofloxacin, tenofovir disoproxil fumarate and cefuroxime, however to a non-clinically significant level.[20] IM CAB has an elimination half-life of 6–12 weeks, compared to 41 h for oral CAB. As with other IM long-acting drugs, CAB exhibits 'flip-flop' pharmacokinetics, with its slow absorption rate contributing to the prolonged elimination half-life.[21] Due to the very long half-life of LAI CAB, some individuals have detectable levels a year after a single injection. If injections are missed or HIV treatment stopped, oral ART must be re-initiated a maximum of 2 months after the last injection to prevent drug resistance. There is no dose adjustment in renal impairment and no dose adjustment in mild–moderate hepatic impairment.[6]

3.2 | RPV pharmacokinetics

RPV is a second-generation NNRTI. An optional 1-month oral lead-in phase (25 mg once daily) is also part of the product label advice prior to use of the injectable formulation. For 2-monthly dosing, 900 mg/3 mL is administered as an IM injection, followed by a second 900 mg injection a month later and thereafter 2-monthly. Injections must be given within 7 days of the planned injection date to avoid subtherapeutic exposures.[7] Oral RPV bioavailability is affected by food intake and it should be taken with a high fat meal to increase total exposures. Oral RPV absorption is also affected by gastric pH and proton pump inhibitors can significantly reduce total exposure.[22] Therefore, it is important to provide adequate counselling to people initiating oral RPV. The peak plasma concentration is at 4 h for oral RPV compared to 3–4 days for IM RPV. LAI RPV reaches 80% of steady-date after 48 weeks.[18] RPV is highly protein (albumin)-bound (99.7%) and is hepatically metabolized with the main clearance pathway being **CYP3A4**. It does not cause any major induction or inhibition of transporters or enzymes.[23] Elimination half-life of the LAI formation is also driven by 'flip-flop' pharmacokinetics and the half-life is 13–28 weeks, compared to 45 h for oral RPV.[7,24] The resistance risks associated with the prolonged pharmacokinetic tail also apply to RPV and an alternative antiretroviral must be considered to avoid monotherapy during a tail period.[25] No dose adjustment is needed in renal impairment or mild–moderate hepatic impairment.[7]

3.3 | DDIs

At clinically relevant concentrations, CAB and RPV exhibit low risk of affecting the concentrations of other co-administered drugs as they do not cause any major induction or inhibition of transporters or enzymes. However, they are susceptible to DDIs when co-administered with medications that are inducers/inhibitors of CYP3A4 or UGT1A1.[6] A summary of potential DDIs with LAI CAB/RPV and their mechanisms are summarized in Figure 1 and Table 2. Furthermore, RPV has been shown, in a randomized, placebo-controlled study of 60 healthy adults,

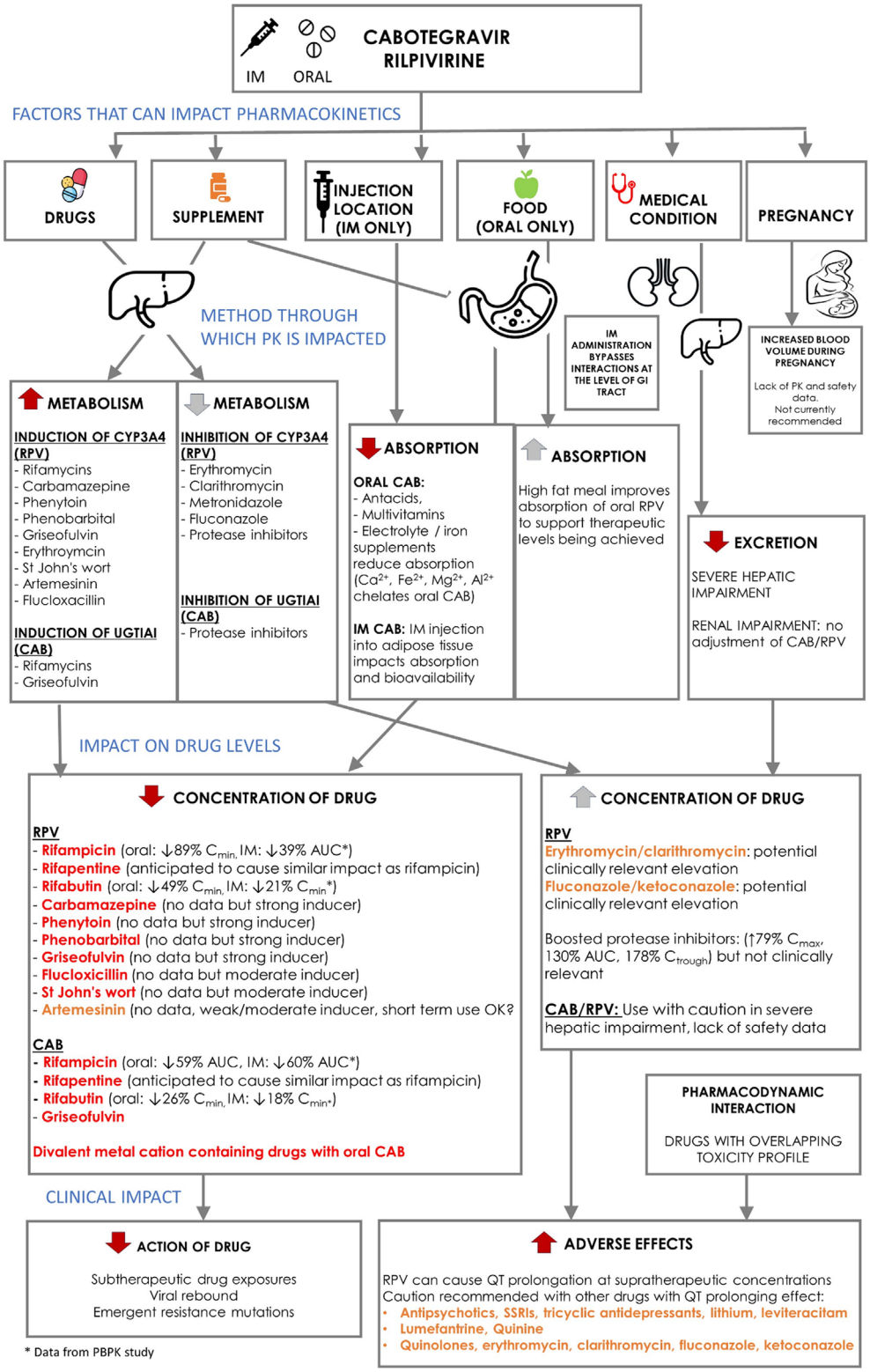

FIGURE 1 Mechanisms of drug–drug interactions with cabotegravir/rilpivirine and expected impact on the drugs concentration.

TABLE 2 Summary of clinically significant effects of frequent co-medications on LA CAB and LA RPV and clinical recommendations.

Concomitant medications	Effects on LA CAB	Effects on LA RPV
Antitubercular agents		
Rifampicin	CAB AUC ↓ by 61% Co-administration contraindicated	RPV AUC ↓ by 38% Co-administration contraindicated
Rifapentine	CAB ↓ Co-administration contraindicated	RPV ↓ Co-administration contraindicated
Rifabutin	CAB ↓ Increased frequency of injections is recommended	RPV ↓ Co-administration contraindicated
Isoniazid	—	—
Pyrazinamide	—	—
Ethambutol	—	—
Quinolones	—	Risk of QT prolongation with both quinolones and RPV
Antipsychotics and antiepileptics		
Carbamazepine	CAB ↓ Co-administration contraindicated	RPV ↓ Co-administration contraindicated
Phenytoin	CAB ↓ Co-administration contraindicated	RPV ↓ Co-administration contraindicated
Haloperidol	—	Risk of QT prolongation with both haloperidol and RPV
Valproate	—	—
Olanzapine	—	—
Lithium	—	—
SSRIs (citalopram and escitalopram)	— —	— Risk of QT prolongation with both citalopram/escitalopram and RPV
Tricyclic antidepressants	—	—
Antimalarials		
Artemisinin	—	RPV ↓ Low risk of clinically significant reduction with short duration of artemisinin treatment
Lumefantrine	—	Risk of QT prolongation with both haloperidol and RPV
Atovaquone/proguanil	—	—
Primaquine	—	Risk of QT prolongation with both primaquine and RPV
Quinine	—	Risk of QT prolongation with both quinine and RPV
Antibacterials		
Penicillins (Flucloxacillin)	— CAB ↓ No significant decrease	— RPV ↓ Use with caution if used at higher doses for a prolonged course (i.e., >10–14 days)
Metronidazole	—	Potential RPV ↑ Risk of QT prolongation with both metronidazole and RPV
Fluoroquinolones	—	Risk of QT prolongation with both fluoroquinolones, especially moxifloxacin, and RPV
Macrolides (Azithromycin)	— —	RPV ↑ Risk of QT prolongation with both Macrolides and RPV No adjustments with azithromycin
Gentamicin	—	No adjustment required
Cephalosporins	—	No adjustment required
Carbapenem	—	No adjustment required

(Continues)

TABLE 2 (Continued)

Concomitant medications	Effects on LA CAB	Effects on LA RPV
Antifungals		
Azoles	—	RPV ↑ Risk of QT prolongation with both Azoles and RPV
Amphotericin	—	—
Griseofulvin	Potential CAB ↓ Co-administration contraindicated	Potential RPV ↓ Co-administration contraindicated
Contraceptives		
Combined oral	—	—
DMPA	—	—
Levonorgestrel implant	—	—

Abbreviations: AUC, area under the curve, the drug concentration as a function of time; DMPA, depot medroxyprogesterone acetate; LA CAB, long-acting cabotegravir; LA RPV, long-acting rilpivirine.

to prolong the QTc interval at supratherapeutic doses of RPV (75 and 300 mg once daily), an effect not observed at the recommended dose of 25 mg orally once daily or 900 mg IM.[26]

When considering impacts of co-administered medications on CAB/RPV, it is crucial to define a concentration target to aim for, to avoid treatment failure of ART. Many definitions have been used, including trough concentration (C_{trough}), inhibitory concentration (IC) for 50% inhibition (IC_{50}), or 90% inhibition (IC_{90}), of viral replication, protein-adjusted inhibitory concentration (PA-IC_{90}) and inhibitory quotient. C_{trough} is often used because, for most drugs with linear pharmacokinetics, it can be a reasonable surrogate for AUC (or exposure over the dosing interval).[17] While C_{trough} may be an appropriate endpoint to quantify changes in drug exposure, it does not inherently link to drug efficacy. PA-IC_{50} and PA-IC_{90} are typically determined from in vitro studies, while appropriately adjusting for differences in protein binding between culture media and blood. When interpreting these, it is important to consider the viral isolate(s) used to obtain the values; frequently these assays are performed early in the drug development process using wild type virus which may not be representative of the true clinical situation. Testing a range of clinical HIV isolates will often lead to a range of IC_{90}.[6] Inhibitory quotients, the ratio between drug concentration and IC_{50} or IC_{90}, have also been used.[27] Importantly, for antiretrovirals, the risk of selection of drug-resistant mutants and therapeutic failure is associated with low C_{trough} concentrations, and the minimum acceptable target concentration is usually defined in relation to the C_{trough}, either as an X-fold increase, or as a 'minimum effective concentration'. Another commonly used target is 4 × PA-IC_{90}. In this paper, change in these drug exposure parameters are assessed in determining the potential clinical significance of a DDI.

3.4 | DDI risk during oral lead-in phase

IM administration of CAB and RPV has the advantage of eliminating first pass metabolism and DDIs occurring at the gastrointestinal level. However, there are a number of drug interactions for CAB and RPV that are clinically relevant during the oral lead-in phase. Divalent metal cations (e.g., Ca^{2+}, Al^{2+}, Mg^{2+}, Fe^{2+} and Zn^{2+}), for example, calcium containing antacids and some multivitamins, chelate with CAB in the gut, can decrease absorption, and therefore dosing with oral CAB must be separated by at least 2 h before or 4 h after such medications.[6,28,29]

RPV requires an acidic gastric environment to facilitate absorption and therefore proton pump inhibitors decrease RPV exposure when taken orally and are contraindicated.[22] H2-receptor antagonists are also expected to impact RPV absorption, due to their impact on gastric acidity, and thus must be given at least 12 h before or 4 h after oral RPV.

3.5 | Tuberculosis (TB) drugs

TB/HIV co-infection is common among people living with HIV (PLWH) in TB-endemic settings, often requiring initiation of TB treatment alongside ART.[30,31] Early initiation of ART within 2 weeks of initiating TB treatment is recommended among PLWH.[30] Isoniazid and rifampicin constitute the backbone of TB treatment regimens, usually combined with ethambutol and pyrazinamide in a 2 month 'intensive phase' as part of a 6-month regimen. More recently a 4-month regimen including rifapentine and moxifloxacin has been shown to be non-inferior to the standard 6-month regimen and may become part of WHO guidelines.[32,33] However, rifampicin and rifapentine are potent inducers of many metabolic pathways and transporters, including CYP3A4 and UGT1A1, which complicates co-administration with many antiretrovirals, including CAB and RPV.[34]

3.6 | Rifamycins with CAB

Pharmacokinetic studies have shown that rifampicin reduces oral CAB exposures, potentially leading to treatment failure and risking emergence of drug resistance.[34] The study by Ford et al. revealed that

rifampicin dosed at 600 mg daily increased the apparent clearance of oral CAB by 2.4-fold, effectively decreasing systemic exposure (area under the plasma concentration–time curve, AUC_{inf}) by 59%.[35]

No in-human pharmacokinetic studies of rifampicin with IM CAB have been conducted for the reasons described above. However, PBPK models, developed and validated using clinical data from oral CAB studies, have predicted similar reductions in exposure with the LAI formulation. A decrease of 41% in both $AUC_{0\text{-}28days}$ and $C_{min,\ 0\text{-}28days}$ was observed following simulations of interaction between IM CAB 400 mg monthly maintenance dose and 600 mg daily oral rifampicin.[36] Bettonte et al. predicted a similar decrease in AUC and C_{min} of 60% and 63%, respectively.[37]

In silico simulations of dose adjustment scenarios aimed at maintaining effective target therapeutic CAB exposure (concentrations above 4 × PA-IC_{90} target) suggested that the interaction with rifampicin cannot be overcome with dose adjustment.[37] The current evidence supports the recommendation that co-administration of rifampicin with oral or LAI CAB should be avoided due to significant reduction in CAB exposure. Rifampicin, and by extension strong CYP inducers, for example, rifapentine, are expected to substantially reduce exposure to IM CAB and increase the risk of treatment failure, thus co-administration is contraindicated.[37] This expected interaction has already been confirmed in clinical settings.[38]

Rifabutin, a moderate inducer of CYPs compared to rifampicin, is reported to result in a more modest reduction in systemic exposure to oral CAB. The oral clearance of CAB is increased by 27% when administered with rifabutin, resulting in a decrease of 21%, 17% and 26% in $AUC_{0\text{-}\tau}$, C_{max} and C_{min}, respectively.[39] These findings are reinforced by PBPK modelling of the interaction between rifabutin 300 mg and LAI CAB 600 mg that predicted similar reductions of 16% and 18% in AUC and C_{min} of LAI CAB, respectively.[37] However, the overall CAB trough concentration and $AUC_{0\text{-}t}$ (2.5 mg/mL and 81.7 mg * h/mL, respectively) were observed to be above 1.35 mg/mL and 45.7 mg * h/mL, exposures achieved with administration of oral CAB 10 mg once daily.[39] Oral CAB 10 mg once daily was previously shown in a phase 2 dose-ranging study to be safe and efficacious in combination with RPV at maintaining viral suppression in HIV patients, thus the reduction in CAB exposure by rifabutin is considered not clinically important.[40] To ensure efficacy, the Apretude product label recommends increasing the frequency of LA CAB for PrEP during concomitant treatment with rifabutin, for example, administering the first two injections 2 weeks apart, followed thereafter by an injection every 4 weeks.[41]

3.7 | Rifamycins with RPV

Pharmacokinetic interaction studies between oral RPV and rifampicin and rifabutin have reported a decrease in RPV exposure.[42,43] Co-administration of rifampicin 600 mg with oral RPV 150 mg daily reduced the AUC_{24h}, C_{max} and C_{min} of oral RPV by 80%, 69% and 89%, respectively.[43] There is no in-human data on the interaction with LAI RPV, but PBPK modelling predicted a 39% decrease in AUC of LAI RPV in the presence of rifampicin. Increasing the dosing frequency of LAI RPV was unable to compensate for the interaction.[37] The significant reduction in exposure to RPV poses a risk of subtherapeutic concentrations, therefore, co-administration of oral and LAI RPV with rifampicin is contraindicated.[16]

In another study, co-administration of oral RPV 150 mg once daily together with rifabutin 300 mg daily was found to reduce the AUC_{24h}, C_{max} and C_{min} of oral RPV by 46%, 35% and 49%, respectively.[42] Similarly, PBPK modelling predicted rifabutin to decrease the AUC and C_{min} of monthly LAI RPV 600 mg by 18% and 19%, respectively. With bimonthly administration of LAI RPV 900 mg, the decrease in AUC and C_{min} was 20% and 21%, respectively.[37] The reduction in RPV exposure resulted in a prediction of only 20% of individuals achieving the minimum effective concentration (>50 ng/mL) with monthly dosing, and none of the individuals on the bimonthly dose achieved concentrations above this limit. Just as the interaction of oral RPV with modest CYP inducers can be overcome by increasing the dose of oral RPV to 50 mg daily, simulations of dose adjustment by addition of oral RPV 25 mg daily to the monthly injection of RPV was shown to overcome the interaction with rifabutin. The increased RPV dosing would be required for the duration of rifabutin and for 2 weeks afterwards. Rifabutin is, however, not widely available in TB-endemic areas and thus the utility of this approach is limited. Co-administration of moderate inducers with LAI CAB and RPV is not currently recommended where alternatives exist, thus a switch back to suitable oral ART would usually be required in this context.[16]

3.8 | Antipsychotics and antiepileptics

Several antipsychotics may interact with ART. First-generation antipsychotics such as chlorpromazine, levomepromazine, fluphenazine and haloperidol are not anticipated to have pharmacokinetic interaction with LAI CAB and RPV.[16] However, since these antipsychotics have potential to cause QTc prolongation[44] and given the potential RPV has to cause QTc prolongation at supratherapeutic doses (≥75 mg daily), there is need to consider this potential pharmacodynamic interaction. This is also applicable to second-generation antipsychotics, which include olanzapine, aripiprazole, clozapine, paliperidone, quetiapine, risperidone, and are not anticipated to have any significant pharmacokinetic interaction with LAI CAB and RPV, though the potential for overlapping QTc prolongation effect exists.[44] Both first- and second-generation antipsychotics are mainly metabolized by CYP enzymes (3A4 and 2D6) and also by glucuronidation. Both CAB and RPV have no clinically relevant impact on these PK pathways.[6]

No studies have been conducted for the selective serotonin reuptake inhibitors (SSRIs) sertraline, fluvoxamine, fluoxetine and paroxetine. These are mostly metabolized by CYP enzymes, predominantly CYP2D6. Clinically relevant drug interactions with CAB and RPV are not anticipated.[16] Citalopram and its therapeutically active isomer escitalopram are SSRIs predominantly metabolized by CYP2C19 and, while no clinically relevant interactions are anticipated, caution is advised due to the risk of QT prolongation with both citalopram and escitalopram.[45] The tricyclic antidepressants amitriptyline,

clomipramine and imipramine have similar metabolic pathways to SSRIs and are anticipated to have no clinically relevant interactions, but imipramine has a potential for QTc prolongation.[46] Lithium carbonate is commonly used as a mood stabilizer. It is anticipated to have no pharmacokinetic interaction as it is mainly eliminated by renal filtration. However, caution is advised due to a risk for QT prolongation through a pharmacodynamic interaction.[47]

The antiepileptics carbamazepine, oxcarbazepine, phenobarbitone and phenytoin are potent inducers of CYP enzymes.[48] Based on clinically significant interactions between rifampicin, which is also a potent inducer, and RPV as described above, significant reduction of both oral and LAI RPV are anticipated, and co-administration is therefore contraindicated. Lamotrigine undergoes glucuronidation while sodium valproate undergoes both glucuronidation and metabolism by CYP 2C9 and 2C19. No clinically significant interactions are anticipated. Levetiracetam does not undergo CYP metabolism; however, due to its potential for QT prolongation, there is risk for pharmacodynamic interaction.

Prior to initiating LA RPV, if the individual is already receiving a drug with the potential to prolong QTc, an electrocardiogram (ECG) should be performed to determine pre-treatment QTc. If QTc already exceeds 450 ms, then addition of RPV should be avoided where possible, to reduce the risk of further QTc prolongation and Torsades de Pointes. Where pre-treatment QTc is within range and co-administration of RPV is possible, no explicit guidance is given on the required monitoring of QTc during co-administration of two QTc-prolonging drugs, so clinical judgement should be used.

Non-oral formulations of benzodiazepines are indicated for status epilepticus and include diazepam, midazolam and lorazepam. Co-administration of midazolam (3 mg) and oral CAB (30 mg once daily) was studied in 12 subjects. Midazolam C_{max} and AUC increased by 9% and 10%; however, this was not clinically relevant. A similar effect is expected between parenteral midazolam and the LAI formulations. Neither lorazepam nor diazepam are anticipated to have significant interactions.[6,16,20]

3.9 | Antimalarials

Treatment of malaria in PLWH is complicated by the risk of overlapping drug toxicities and potential drug interactions. Induction of CYP3A4 and/or CYP2C19 enzymes by artemisinin-based combinations of antimalarial agents is expected to potentially result in a decrease in RPV exposure.[16] Pharmacokinetic studies of artemether have shown an increase in the metabolic ratio of its active metabolite (dihydroartemisinin) over repeated doses, an effect attributed to auto-induction of CYP3A4 by artemether.[49,50] Based on these observations, artemether is expected to potentially interact with RPV, inducing its metabolism. The clinical significance of this potential interaction is yet to be evaluated in a clinical study. The Liverpool Drug Interactions database suggests close monitoring of CAB and RPV plasma concentrations, and that dose adjustment may be necessary in the event of co-administration with artemisinins.[16] Monitoring of plasma CAB and RPV concentrations is not readily available in most settings; therefore, the ability to dose-adjust will be limited. Given that artemisinin-based combination therapy is usually only given for 3–5 days for the treatment of malaria, we believe that this is unlikely to result in a clinically significant and sustained reduction in RPV exposure. However, repeated courses of artemisinin-based combination antimalarial in quick succession would increase the risk of this interaction becoming clinically significant.

In addition, the risk of overlapping toxicity is also a concern for concurrent use of LAI antiretroviral therapy in patients with malaria. Many antimalarial drugs have been associated with the risk of cardiac toxicity. Specifically, halofantrine, lumefantrine and quinoline derivatives (e.g., quinine and chloroquine) have been associated with delayed cardiac repolarization due to prolongation of the QT interval.[51–53] Similarly, RPV can also prolong the QT interval in a dose-dependent fashion.[26] The potential pharmacodynamic interaction between RPV and certain antimalarial drugs predisposes to QTc interval prolongation, a risk for development of ventricular tachyarrhythmias and sudden death.[52] Thus 3–5 days of artemisinin-based combination therapy would be preferable to quinine in people receiving RPV.[6,16]

3.10 | Contraceptives

Hormones used in hormonal contraception can also interact with antiretrovirals due to overlapping metabolism via CYP450 enzymes and/or glucuronidation.[54] Women of child-bearing potential make up a significant portion of the population living with, or at risk of, HIV, and, therefore, DDIs between ART and hormonal contraceptives are of significant relevance. In HPTN 077, a phase 2a trial of the safety, tolerability and pharmacokinetics of two doses of long-acting CAB, 79 of the 85 cisgender women in the trial were on hormonal contraception.[55] In a secondary analysis, oral contraception was associated with a 25% lower peak concentration of CAB, compared to women not on hormonal contraception. Importantly, trough concentration (and other pharmacokinetic parameters AUC, $t_{1/2}$ and time to unquantifiable concentrations) were not affected and this small difference in peak concentrations is unlikely to be clinically significant. Notably, this analysis did not look at hormone concentrations but significant changes in hormone exposures are not anticipated given that neither CAB nor RPV act as metabolic inducers. Daily oral CAB increased levonorgestrel peak concentrations by about 12%, with no effect on ethinyloestradiol.[56] No effects were found on CAB pharmacokinetics, nor on contraception pharmacodynamic endpoints such as luteinizing hormone, follicle-stimulating hormone or progesterone concentrations.

Daily oral RPV has also been studied with ethinyloestradiol and norethindrone oral contraceptive and was found to increase peak ethinyloestradiol by only 17%, with no effect on norethindrone concentrations.[57]

Other data assessing LAI ART and hormonal contraception is limited. Of the other common hormonal contraceptive methods, including depot medroxyprogesterone acetate (DMPA) or progestin-based

implants, no significant DDIs are expected. Extrapolating from oral RPV and CAB, modest interactions may be expected but unlikely to result in clinically significant changes.[56,57]

In summary, all hormonal oral and long-acting contraception can be used without concern in people receiving LAI CAB and/or RPV.

3.11 | Antifungals

To date, very few studies have been performed to evaluate potential interactions between LAI ART and antifungal medications. Among antifungals, azoles are both substrates and potent inhibitors of the CYP3A4 system and are therefore prone to drug interactions. One study which used a supratherapeutic dose of 400 mg/day of RPV with ketoconazole reported a ~50% increase in RPV AUC concentrations when the two agents were co-administered.[26] Due to the potent induction properties of griseofulvin and its potential to reduce therapeutic effect of CAB and/or RPV, co-administration is contraindicated, although no clinical data exists. No interactions are expected for amphotericin or flucytosine, as those compounds do not undergo significant hepatic metabolism. Pharmacodynamic interaction potential exists between RPV and fluconazole and given that both have a potential to prolong the QT interval, caution and monitoring is recommended with this combination.

3.12 | Antibiotics

Commonly used antibiotics in sub-Saharan Africa include penicillins, cephalosporins, aminoglycosides, sulfamethoxazole-trimethoprim, tetracyclines, metronidazole, macrolides and fluoroquinolones. Co-administration of these antibiotics with LAI CAB/RPV are yet to be investigated but based on known drug metabolic pathways, it is unlikely that clinically significant interactions will occur with most antibiotics.[16] Potential interactions that are worth highlighting are discussed here.

3.12.1 | Penicillins

Potential interactions with LAI CAB/RPV are expected to be minimal and of less clinical relevance, except in the case of flucloxacillin. Flucloxacillin has been shown to be a moderate inducer of UGT enzymes,[58,59] but unlikely to cause a significant decrease in CAB concentrations. Flucloxacillin is also a weak–moderate inducer of CYP3A4,[60,61] and would be at risk if administered at higher doses for a duration of more than 10–14 days.

3.12.2 | Macrolides

Erythromycin is a known CYP3A4 inhibitor.[62] A clinically relevant interaction is possible with co-administration of erythromycin and LAI CAB/RPV due to potentially increased levels of RPV, a CYP3A4 substrate. As mentioned previously, supratherapeutic RPV dosing has been associated with prolongation of the cardiac repolarization cycle (QT interval).[6] Macrolides are also associated with a QT prolonging effect.[63,64] Thus, caution should be exercised with co-administration of older macrolides and LAI CAB/RPV. A pre-treatment ECG is advisable to ensure that the QTc is <450 ms prior to the addition of a second QT prolonging drug. Azithromycin may be considered as an alternative due to its low propensity for CYP3A4 inhibition and can be safely co-administered with CAB and RPV.[6]

3.12.3 | Quinolones

The fluoroquinolones (e.g., ciprofloxacin, ofloxacin and moxifloxacin) have long been associated with cardiotoxic adverse effects due to QT interval prolongation.[65] Although QT prolongation is a class effect, proarrhythmic potential varies widely among individual agents, with moxifloxacin being the most likely to cause QT prolongation.[65] The potential additive/synergistic interaction of quinolones with RPV on QT interval prolongation requires caution when the drugs are to be co-administered, and additional ECG monitoring may be needed with higher risk agents such as moxifloxacin.[6,16]

3.12.4 | Metronidazole

Metronidazole is thought to inhibit CYP3A4[66]; however, co-administration with several CYP3A4 probes (e.g., midazolam) did not result in increased plasma concentrations of these substrates.[67] Considering that the precise mechanism of metronidazole inhibition of CYP450 enzyme machinery is yet to be fully elucidated, an interaction with RPV cannot be ruled out.[16,68] More data is required on metronidazole's CYP3A4 inhibitory effects.

There are no anticipated interactions with cephalosporins, carbapenems and aminoglycosides such as gentamicin.[16]

4 | DISCUSSION

Our review aimed to discuss potential DDIs between LAI CAB and RPV and common concomitant medications in sub-Saharan African healthcare settings. Although the potential for DDIs caused by CAB or RPV is low, a certain number of CYP3A4- and/or UGT1A1-inducing medications can reduce the exposure of CAB and/or RPV and create a risk of treatment failure. Notable concomitant medications that are contraindicated due to a pharmacokinetic interaction include rifamycins, carbamazepine, phenytoin, griseofulvin and flucloxacillin. The only notable pharmacodynamic interaction relates to RPV, which is associated with a risk of QT prolongation at supratherapeutic dosing.[6] Patients already receiving a co-medication with QT prolongation potential (e.g., citalopram or erythromycin) may benefit from ECG prior to initiation of LA RPV and further ECG

monitoring can be considered if the use of two QT prolonging medications is sustained, or symptoms arise.

With the current rollout of LAI CAB and LAI RPV for HIV treatment and prevention, it is crucial to raise awareness on potential DDIs. The impact of DDIs in people receiving LAI CAB and RPV is magnified by the fact that is a two-drug, rather than a three-drug regimen, thus both drugs must be fully active. NNRTI resistance is highly prevalent in many African countries, and higher RPV concentration may be required to suppress viral replication.[69] Inadvertent co-administration of a CYP3A4 inducer over a sustained period would be more likely to result in viral rebound where drug susceptibility is already compromised. As discussed above, the long pharmacokinetic tail linked to the slow clearance of the drug, as well as its irreversibility, create a risk of resistance development in the case of treatment discontinuation (Figure 2).[10,11] Awareness of the risks must be present at multiple levels. Healthcare professionals and HIV clinicians in particular must take the risk of DDIs into account when initiating LAI ART and ask about prescribed or over-the-counter medicines being used at every appointment. Likewise, patients, as well as community pharmacies and drug vendors, must also be aware of potential DDIs and their implications. This is particularly essential in settings where medications can be bought without requiring prescriptions.

The optional CAB/RPV oral lead-in may give rise to interactions that are specific to the oral formulation as they affect drug absorption rather than drug metabolism. For example, proton pump inhibitors that decrease absorption of oral RPV or antacids that decrease absorption of oral CAB.[22,29] In such cases, omitting the oral lead-in by opting for the direct-to-injection approach may be preferable to discontinuing or altering the dosing schedule of their co-medications.[6]

In addition to DDIs, appropriate administration of the drug itself is critical. Healthcare professionals may want to consider injecting LAI CAB/RPV with longer (2 in.) needles in patients with BMI > 30 kg/m^2, to avoid administering the drug in adipose tissue. Injection into adipose tissue alters the pharmacokinetics and can lead to nodule formation. Virological failure has been associated with BMI > 30 kg/m^2 (adjusted incidence rate ratio 1.09, 95% confidence interval 1.00–1.19, $P = .044$), highlighting the importance of injection placement.[9]

Few studies have been conducted on specific drug classes and their possible interactions with LAI ART. Notably, the evidence on antimalarials and antifungals, including PBPK studies, is scarce, and some of the recommendations outlined in this review, along with part of the Liverpool HIV Interaction database guidance,[16] have been based on theoretical predictions, derived from established induction or inhibition effects with other drugs. Furthermore, the need for well-established therapeutic targets that accurately correlate to clinical

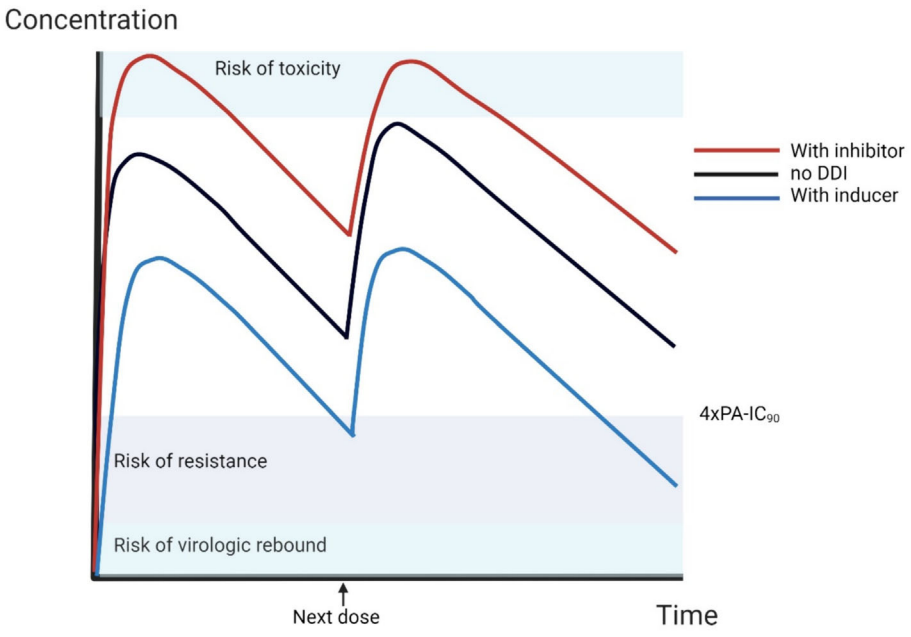

FIGURE 2 Time concentration curve illustrating the impact of enzyme inducers and inhibitors on a drug concentration. As substrates of metabolizing enzymes, cabotegravir and/or rilpivirine concentrations can be increased or decreased when co-administered with drugs that either inhibit or induce those enzymes. The black line shows a theoretical concentration *vs.* time profile of a drug given in the absence of an enzyme inhibitor or inducer. It would be anticipated that concentrations would be maintained above 4 × PA-IC$_{90}$ prior to the next dose being given. However, in the presence of an enzyme inducer (blue line), concentrations would be expected to fall more rapidly and may fall below the 4 × PA-IC$_{90}$ prior to the next scheduled dose. The areas highlighted in grey represents the window of concentrations where selection for mutant drug-resistant virus is most at risk as concentrations may be effective against susceptible strains, but not resistant strains. The bottom blue area represents where concentrations are expected to be ineffective, and risk of viral rebound occurs. Conversely, when given with an enzyme inhibitor (top red line), concentrations are expected to persist or perhaps accumulate to higher concentrations, increasing the risk of toxicities or adverse events, for example, QTc prolongation with rilpivirine. Created with BioRender.com.

endpoints, such as viral suppression in the absence of resistance, are needed to accurately interpret the clinical significance of DDI studies, either measured or predicted. Additional research is required to provide comprehensive guidance to healthcare providers and patients.

The limited number of DDI studies and their complexity is partly due to the magnitude of the extended half-life, and irreversibility, of long-acting agents. Therefore, the field is increasingly relying on alternative predictive modelling and simulation to estimate impact of co-administration. PBPK studies are one tool that has been applied and has allowed the modelling of DDIs with increasing precision.[14]

LAI ART is a promising treatment option for PLWH and other regimens in the development pipeline could prove invaluable for patients for whom the use of CAB/RPV may be contraindicated (e.g., those with underlying NNRTI resistance).

5 | CONCLUSION

In conclusion, our review highlights the significance of potential DDIs involving LAI CAB and RPV and frequently used concomitant medications, particularly in sub-Saharan African countries. Awareness is crucial, spanning healthcare providers, PLWH and dispensing outlets, especially where prescription-free medication access exists.

5.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2023/24.[70]

AUTHOR CONTRIBUTIONS

All authors (Adrian Steulet, Bonniface Obura, Catriona Waitt, Eva Laker, Melanie R. Nicol and Fiona V. Cresswell) contributed to the literature review, the drafting of the original manuscript and the revision of subsequent versions.

CONFLICT OF INTEREST STATEMENT

The authors report no conflicts of interest.

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