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

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March 25, 2024

Abstract

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 comedications 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. LAI cabotegravir and rilpivirine have half-lives of 6-12 and 13-28 weeks, respectively. Cabotegravir is primarily metabolised by UDP-glucuronyltransferase (UGT)-1A1 and rilpivirine by cytochrome P450 (CYP)-3A4. LAI cabotegravir and rilpivirine themselves exhibit low risk of perpetrating interactions with comedications as they do not induce or inhibit the major drug metabolising enzymes. However, they are victims of DDIs relating to the induction of their metabolising enzymes by concomitantly administered medication. Noteworthy contraindicated comedications 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 minimise risk.

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. The burden of HIV is particularly high in sub-Saharan Africa, which accounted for approximately two-thirds of all new HIV infections in 2022 . 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 .

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 two months by intramuscular (IM) injection, and demonstrated comparable efficacy to standard oral therapy in maintaining viral suppression in a number of clinical trials. Roll out of this injectable regimen is now underway in Europe, USA 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® and REKAMBYS®respectively, while in Canada and the United States the regimen is marketed as a combined pack called CABENUVA®.

LAI cabotegravir 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 roll out of LAI cabotegravir PrEP in many high HIV burden countries.

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 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-inch) are required in people with high BMI . Secondly, due to the nature of the LAI formulation, the drug is slowly cleared from the body after administration. 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), leading to a risk of viral replication together with selection of drug-resistant variants . 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 drug-drug interactions (DDIs). Healthcare professionals may be unfamiliar with the numerous potential DDIs between LAI cabotegravir and rilpivirine 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 cabotegravir or rilpivirine have the potential to lead to catastrophic HIV treatment failure, through the lowering of the drugs' plasma concentration with ensuing viral rebound . 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 . 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. 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.

This literature review aims to raise awareness amongst 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.

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 .

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 below (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.

In addition to the literature search, the Liverpool HIV drug interaction database was consulted to identify additional studies on DDIs between cabotegravir or rilpivirine and the predefined co-medications. 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.

Results

Cabotegravir pharmacokinetics

Cabotegravir, 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. LAI cabotegravir for HIV prevention is dosed at 600mg/3ml with the first 2 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 rilpivirine. Dosing can be administered within a window +/-7 days of the planned date of injection . A 4-week oral lead-in (OLI) of daily oral cabotegravir 30 mg and rilpivirine 25 mg is offered, but not essential, to ensure tolerability before transitioning to injections.

Intramuscular cabotegravir has a median time to maximal plasma concentration (T_{max}) of 7 days and reaches steady state after 44 weeks . Cabotegravir is highly protein bound (>99.8%) with a volume of distribution is 12.3 L. Both oral and intramuscular cabotegravir are largely metabolised hepatically by UDP-glucuronyltransferase (UGT)-1A1 with a minor contribution from Cytochrome P450 (CYP) 1A9 and are excreted largely in the urine and small amount in bile/faeces . Cabotegravir 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. However, cabotegravir inhibits the renal transporter OAT1 and OAT3 and can increase exposures of OAT1 and OAT3 substrate such as ciprofloxacin, tenofovir disoproxil fumarate, cefuroxime, however this is to a non-clinically significant level. Intramuscular cabotegravir has an elimination half-life 6-12 weeks, compared to 41 hours for oral cabotegravir. As with other intramuscular long-acting drugs cabotegravir exhibits 'flip-flop' pharmacokinetics, with the slow absorption rate contributing to the prolonged elimination half-life . Due to the very long half-life of LAI cabotegravir some individuals have detectable levels a year after a single injection. If injections are missed or HIV treatment is 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 is needed in mild-moderate hepatic impairment .

Rilpivirine pharmacokinetics

Rilpivirine is a second-generation NNRTI. An optional 1-month oral lead in phase (25 mg once daily) is also part of the product label prior to use of the injectable formulation. For two-monthly dosing, 900mg/3ml is administered as an IM injection, followed by a second 900mg injection a month later and thereafter two-monthly. Injections must be given within 7 days of the planned injection date to avoid subtherapeutic exposures . Oral rilpivirine bioavailability is affected by food intake and it should be taken with a high fat

meal to increase total exposures. Oral rilpivirine absorption is also affected by gastric pH and proton pump inhibitors can significantly reduce total exposure . Therefore, it is important to provide adequate counselling to people initiating oral rilpivirine. The peak plasma concentration is at 4 hours for oral rilpivirine compared to 3-4 days for IM rilpivirine. LAI rilpivirine reaches steady-date after 48 weeks. Rilpivirine is highly protein (albumin)-bound (99.7%) and is hepatically metabolised with the main clearance pathway being CYP3A4 and does not cause any major induction or inhibition of transporters or enzymes . Elimination half-life of the LAI formation is also driven by "flip-flop" pharmacokinetics and half-life is 13-28 weeks, compared to 45 hours for oral rilpivirine . The resistance risks associated with the prolonged pharmacokinetic tail also apply to rilpivirine and appropriate cover with an alternative antiretroviral must be used. No dose-adjustment is needed in renal impairment or mild-moderate hepatic impairment .

Drug-Drug Interactions

At clinically relevant concentrations, cabotegravir and rilpivirine 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 . A summary of potential DDIs with LAI CAB/RPV and their mechanisms are summarized in Figure 1 and Table 2.

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 C_{trough}, inhibitory concentration (IC) IC_{50}, IC_{90}, 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). While C_{trough} may be an appropriate endpoint to quantify changes in drug exposure, it does not inherently link to drug efficacy. Protein-adjusted IC_{50} or IC_{90}(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}s. Inhibitory quotients, the ratio between drug concentration and IC_{50} or IC_{90}, have also been used. 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 4x-PAIC_{90}. In this paper, change in these drug exposure parameters are assessed in determining the potential clinical significance of a DDI.

DDI risk during oral lead in phase

Intramuscular administration of cabotegravir and rilpivirine has the advantage of eliminating first pass metabolism and DDIs occurring at the gastrointestinal level. However, there are a number of drug interactions for cabotegravir and rilpivirine that are clinically relevant during the oral lead-in phase. Divalent metal cations (e.g. Ca^{2+}, Al^{2+}, Mg^{2+}, Fe^{2+}, Zn^{2+}) for example calcium containing antacids and some multivitamins chelate with cabotegravir in the gut and can decrease absorption and therefore dosing with oral cabotegravir must be separated by at least 2 hours before or 4 hours after such medications . Rilpivirine requires an acidic gastric environment to facilitate absorption and therefore proton-pump inhibitors decrease rilpivirine exposure when taken orally .

Tuberculosis drugs

Tuberculosis/HIV co-infection is common among people living with HIV (PLWH) in TB endemic settings, often requiring initiation of TB treatment alongside ART. Early initiation of ART within two weeks of initiating TB treatment is recommended among people living with HIV. Isoniazid and rifampicin constitute the backbone of TB treatment regimens, usually combined with ethambutol and pyrazinamide in a two 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 . However, rifampin and rifapentine are potent inducers of many metabolic pathways and transporters including CYP3A4 and UGT1A1 which complicates coadministration with many antiretrovirals, including cabotegravir and rilpivirine .

Rifamycins with cabotegravir

Pharmacokinetic studies have shown that rifampicin reduces oral cabotegravir exposures, potentially leading to treatment failure and risking emergence of drug resistance . The study by Ford et al., revealed that rifampicin dosed at 600mg daily increased the apparent clearance of oral cabotegravir by 2.4-fold, effectively decreasing systemic exposure (area under the plasma concentration-time curve, AUC_{inf}) by 59% .

No in-human pharmacokinetic studies of rifampicin with IM cabotegravir have been conducted due to the reasons described above. However, PBPK models, developed and validated using clinical data from oral cabotegravir 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 cabotegravir 400mg monthly maintenance dose and 600 mg daily oral rifampicin . Bettonte et al. predicted a similar decrease in AUC and C_{min} of 60% and 63% respectively .

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

Rifabutin, a moderate inducer of CYPs compared to rifampicin, is reported to result in a more modest reduction in systemic exposure to oral cabotegravir. The oral clearance of cabotegravir is increased by 27% when coadministered with rifabutin resulting in a decrease of 21%, 17% and 26% in $AUC_{0\text{-}\tau}$, C_{max} and C_{min}, respectively . These findings are reinforced by PBPK modelling of the interaction between rifabutin 300 mg and LAI cabotegravir 600 mg that predicted similar reductions of 16% and 18% in AUC and C_{min} of LAI cabotegravir respectively . However, the overall cabotegravir 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 respectively, exposures achieved with administration of oral cabotegravir 10mg once daily . Oral cabotegravir 10mg once daily was previously shown to be safe and efficacious in combination with rilpivirine at maintaining viral suppression in HIV patients, thus the reduction in cabotegravir exposure by rifabutin is not clinically important .

Rifamycins with rilpivirine

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

In another study, coadministration of oral rilpivirine 150 mg once daily together with rifabutin 300 mg daily was found to reduce the AUC_{24h}, C_{max}, and $C_{min}$of oral rilpivirine by 46%, 35%, and 49% respectively . Similarly, PBPK modelling predicted rifabutin to decrease the AUC and C_{min} of monthly LAI rilpivirine 600 mg by 18% and 19% respectively. With bimonthly administration of LAI rilpivirine 900 mg, the decrease in AUC and C_{min} was 20% and 21% respectively . The reduction in rilpivirine 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 rilpivirine with modest CYP inducers can be overcome by increasing the dose of oral rilpivirine to 50 mg daily, simulations of dose adjustment by addition of oral rilpivirine 25 mg daily to the monthly injection of rilpivirine was shown to overcome the interaction with rifabutin. Rifabutin is however not widely available in TB endemic areas and thus the utility of this approach is limited. Also, co-administration of moderate inducers with LAI cabotegravir and rilpivirine is not currently recommended where alternatives exist.

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 cabotegravir and rilpivirine . However, since these antipsychotics have potential to cause QTc prolongation and given the potential rilpivirine has potential to cause QTc prolongation at supratherapeutic doses, there is need to monitor for 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 cabotegravir and rilpivirine, though the potential for overlapping QTc prolongation effect exists . Both first- and second-generation antipsychotics are mainly metabolised by CYP enzymes (3A4 and 2D6) and also by glucuronidation. Both cabotegravir and rilpivirine have no clinically relevant impact on these pathways .

No studies have been conducted for the selective serotonin reuptake inhibitors (SSRIs) sertraline, fluvoxamine, fluoxetine, and paroxetine. These are mostly metabolised by CYP enzymes, predominantly CYP2D6. Clinically relevant drug interactions with cabotegravir and rilpivirine are not anticipated . Citalopram and its therapeutically active isomer escitalopram are SSRIs predominantly metabolised 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 . The tricyclic antidepressants amitriptyline, clomipramine and imipramine have similar metabolic pathways to SSRIs and are anticipated to have no significant interactions, but imipramine has a potential for QTc prolongation . Lithium carbonate is commonly used as a mood stabiliser. It is anticipated to have no significant pharmacokinetic interaction as it is mainly eliminated by renal filtration. However, caution is advised due to a risk for QT prolongation .

The antiepileptics carbamazepine, oxcarbazepine, phenobarbitone and phenytoin are potent inducers of CYP enzymes . Based on clinically significant interactions between rifampicin which is also a potent inducer and rilpivirine as described above, significant reduction of both oral and LAI rilpivirine 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.

Non-oral formulations of benzodiazepines are indicated for status epilepticus and include diazepam, midazolam, and lorazepam. Coadministration of midazolam (3 mg) and oral cabotegravir (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 .

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 combination antimalarial agents is expected to potentially decrease in rilpivirine exposure . Pharmacokinetic studies of artemether have shown increase in the metabolic ratio of its active metabolite (dihydroartemisinin) over repeated doses, an effect attributed to autoinduction of CYP3A4 by artemether . Based on these observations, artemether is expected to potentially interact with rilpivirine, 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 cabotegravir and rilpivirine plasma concentrations and that dose adjustment may be necessary in the event of coadministration with artemisinins . Monitoring of plasma cabotegravir and rilpivirine concentrations is not readily available in most settings therefore the ability to dose-adjust will be limited.

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, chloroquine) have been associated with delayed cardiac repolarization due to prolongation of the QT interval . Similarly, rilpivirine also prolongs the QT interval in a dose-dependent fashion. In a randomised, placebo-controlled study of 60 healthy adults, supra-therapeutic doses of rilpivirine (75mg and 300mg once daily) was shown to prolong the QTc interval, an effect not observed at the recommended dose of 25 mg orally once daily or 900 mg IM . The potential pharmacodynamic interaction between rilpivirine and antimalarial drugs predisposes to QTc interval prolongation, a risk for development of ventricular tachyarrhythmias and sudden death . Caution is advised for concurrent use of LAI rilpivirine in patients on treatment with QT-prolonging antimalarial and ECG monitoring advised.

Contraceptives

Hormones used in hormonal contraception can also interact with antiretrovirals due to overlapping metabolism via CYP450 enzymes, and/or glucuronidation . 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 cabotegravir, 79 of the 85 cisgender women in the trial were on hormonal contraception . In a secondary analysis, oral contraception was associated with a 25% lower peak concentration of cabotegravir, compared to women not on hormonal contraception. Importantly, trough concentration (and other pharmacokinetic parameters AUC, $t_{\frac{1}{2}}$, 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 cabotegravir nor rilpivirine act as metabolic inducers. These results were corroborated by a similar sub-study in HPTN 084 noting a lack of clinically relevant interaction.

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 rilpivirine and cabotegravir, modest interactions may be expected but unlikely to result in clinically significant changes. Daily oral rilpivirine has been studied with ethinylestradiol and norethindrone oral contraceptive, for example, and was found to increase peak ethinylestradiol by only 17% with no effect on norethindrone concentrations . In another study, daily oral cabotegravir increased levonorgestrel peak concentrations by about 12% with no effect on ethinylestradiol . No effects were found on cabotegravir pharmacokinetics, nor on contraception pharmacodynamic endpoints such as luteinizing hormone, follicle-stimulating hormone, or progesterone concentrations.

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

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. In particular, given that both rilpivirine and fluconazole have potential to prolong QT interval, caution and monitoring is recommended with this combination. One study which used a supratherapeutic dose of 400 mg/day of rilpivirine with ketoconazole reported a ˜50% increase in rilpivirine AUC concentrations when the two agents were co-administered .While no dose adjustments arerecommended, monitoring of breakthrough fungal infections may be warranted when rilpivirine is coadministered with azoles, including fluconazole. Due to the potent induction properties of griseofulvin and

its potential to reduce therapeutic effect of cabotegravir and/or rilpivirine 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.

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 cabotegravir/rilpivirine are yet to be investigated but based on known drug metabolic pathways, it is unlikely that clinically significant interactions will occur with most antibiotics . Potential interactions that are worth highlighting are discussed here.

Penicillins

Potential interactions with LAI cabotegravir/rilpivirine 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 both CYP3A4 and UGT enzymes, an effect likely to result in increased clearance and subtherapeutic concentrations of both rilpivirine and cabotegravir. Consequently, subtherapeutic concentrations pose a risk of loss of drug effectiveness and development of resistance and co-administration is not recommended .

Macrolides

Erythromycin is a known CYP3A4 inhibitor . A clinically relevant interaction is possible with co-administration of erythromycin and LAI cabotegravir/rilpivirine due to potentially increased levels of rilpivirine, a CYP3A4 substrate. High steady-state $C_{max}$of oral rilpivirine (4.4-fold higher than that observed (116 ng/mL) with the recommended 600 mg monthly dose of injectable rilpivirine) has been associated with prolongation of the cardiac repolarization cycle (QT interval) . A further risk for QT prolongation, resulting from a potential pharmacodynamic interaction, is the fact that macrolides are also associated with a QT prolonging effect . Prolongation of the QT interval is a risk factor for development of ventricular arrhythmias, particularly torsade de pointes, a rare but life-threatening event. Caution should, therefore, be exercised with co-administration of older macrolides and LAI cabotegravir/rilpivirine. Azithromycin may be considered as an alternative due to its low propensity for CYP3A4 inhibition and can be safely co-administered with cabotegravir and rilpivirine .

Quinolones

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

Metronidazole

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

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

Discussion

Our review aimed to discuss potential DDIs between LAI cabotegravir and rilpivirine and common concomitant medications in sub-Saharan African healthcare settings. Although the potential for DDIs caused by

cabotegravir or rilpivirine is low, a certain number of CYP3A4- and/or UGT1A1-inducing medications can reduce the exposure of cabotegravir and/or rilpivirine and create a risk of treatment failure. Notable concomitant medications that are contraindicated include rifamycins, carbamazepine, phenytoin, griseofulvin, and flucloxacillin. Rilpivirine is associated with a risk of QT prolongation at supratherapeutic dosing . Patients receiving co-medications with QT prolongation risk may require ECG monitoring with rilpivirine.

With the current roll-out of LAI cabotegravir and LAI rilpivirine for HIV treatment and prevention, it is crucial to raise awareness on potential DDIs. 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) . 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 new prescribed, herbal 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 rilpivirine or antacids that decrease absorption of oral cabotegravir. 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.

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 inch) 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=0.044) highlighting the importance of injection placement .

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, 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 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 to model drug-drug interactions with increasing precision .

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

Conclusion

In conclusion, our review highlights the significance of potential drug-drug interactions involving LAI cabotegravir and rilpivirine 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.

Bibliography

Figure 1: Mechanisms of drug-drug interactions with cabotegravir/rilpivirine, and expected impact on the drugs concentration

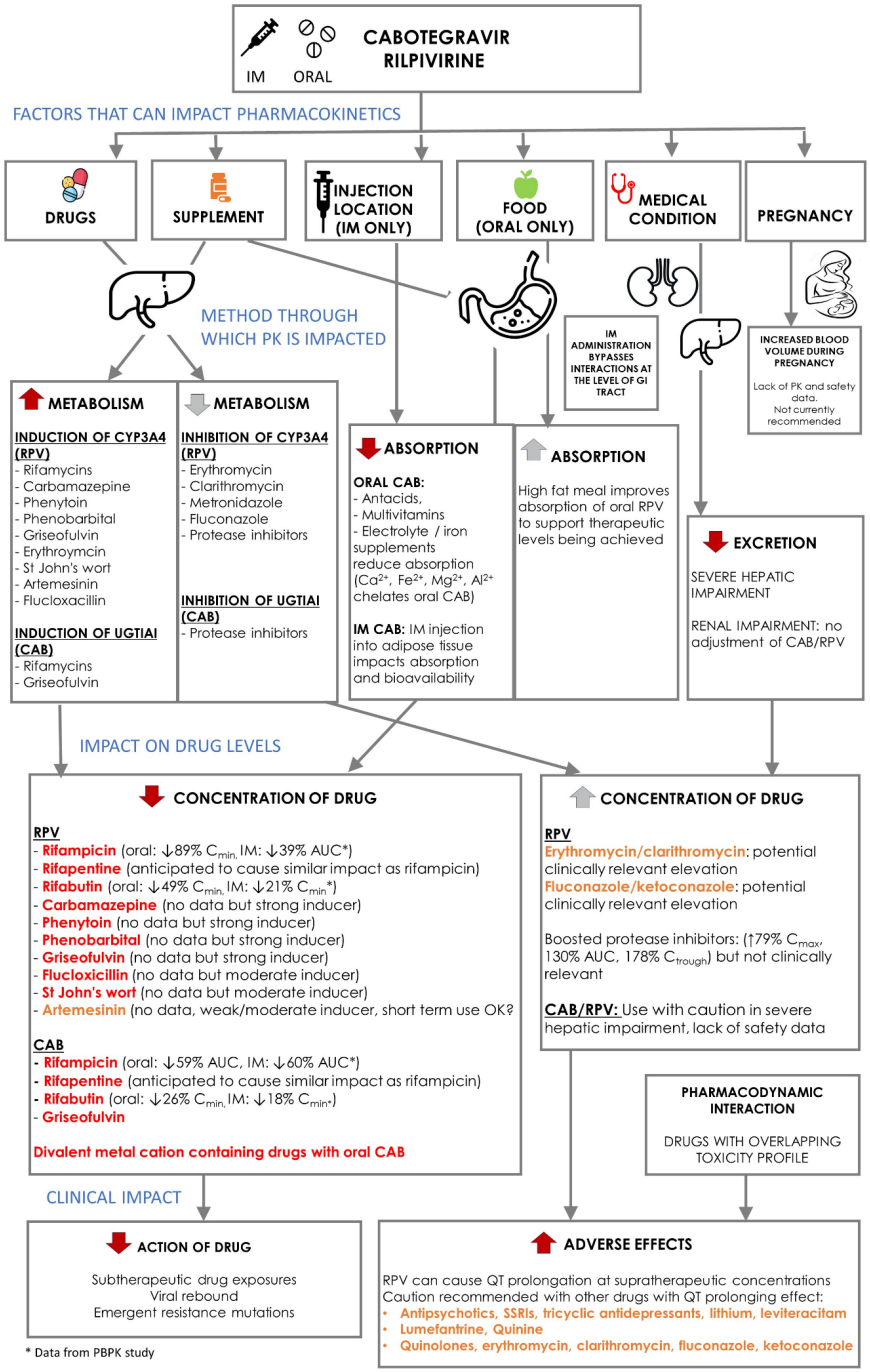
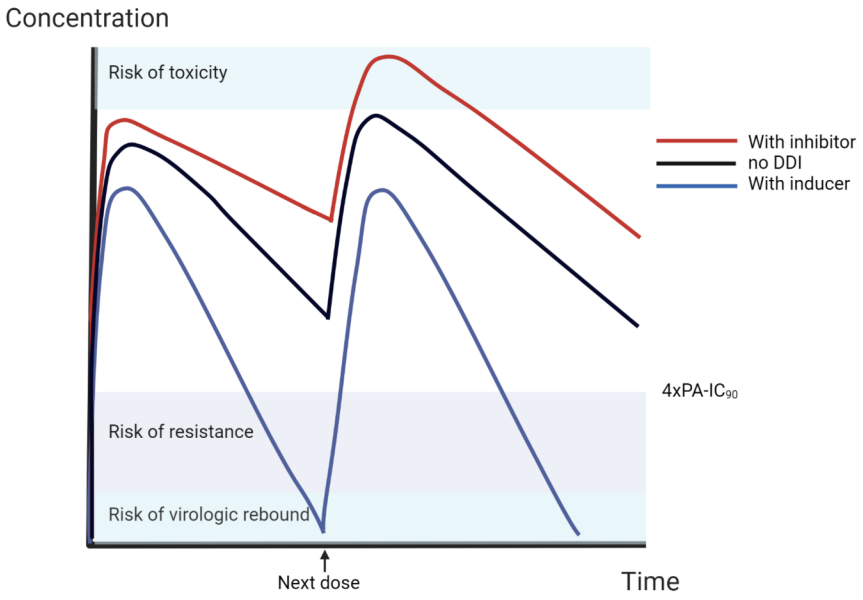


Figure 2: Time concentration curve illustrating the impact of enzyme inducers and inhibitors on a drug concentration



Legend: 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 4xPAIC$_{90}$ 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 4xPAIC$_{90}$ 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 blue line) concentrations are expected to persist or perhaps accumulate to higher concentrations, increasing the risk of toxicities or adverse events, e.g. QTc prolongation with rilpivirine.

Table 1: Search terms and strategy for literature review on drug-drug interactions between cabotegravir/rilpivirine and concomitant medications of interest

Search	**Search Term**
Context	PubMed articles published in English
1	(cabotegravir OR rilpivirine OR GSK1265744 OR TMC278) [all fields]
2	(interaction* OR anti-tuberculosis OR antipsychotic OR antimalarial OR contraception OR antibacterial OR ant
3	1 AND 2 ; filter from 2005/1/1 – 2023/4/30

Table 2: Summary of clinically significant effects of frequent co-medications on LA CAB/RPV[*1] in Sub-Saharan settings and clinical recommendations

Concomitant Medications	**Effects on LA CAB/RPV**	**Clinical recommendations**
Antitubercular agents	Antitubercular agents	Antitubercular agents
Rifampicin	CAB AUC[*2]	**Co-administration contrain**
Rifapentine		**Co-administration contrain**
Rifabutin	(non-clinically significant reduction in CAB AUC)	**Co-administration contrain**
Isoniazid	–	No adjustment required

Pyrazinamide	–	No adjustment required
Ethambutol	–	No adjustment required
Quinolones	–	Risk of QT prolongation with b
Antipsychotics and Antiepileptics	Antipsychotics and Antiepileptics	Antipsychotics and Antiepilepti
Carbamazepine		**Co-administration contrain**
Phenytoin		**Co-administration contrain**
Haloperidol	–	Risk of QT prolongation with b
Valproate	–	No adjustment required
Olanzapine	–	No adjustment required
Lithium	–	No adjustment required
SSRIs (citalopram and escitalopram)	– –	No adjustment required Risk of
Tricyclic antidepressants	–	No adjustment required
Antimalarials	Antimalarials	Antimalarials
Artemisinin		**Co-administration contrain**
Lumefantrine	–	Risk of QT prolongation with b
Atovaquone/proguanil	–	No adjustment required
Primaquine	–	Risk of QT prolongation with b
Quinine	–	Risk of QT prolongation with b
Antibacterials	Antibacterials	Antibacterials
Penicillins (Flucloxacillin)	– CAB— RPV—	No adjustments required **Co-a**
Metronidazole	Potential RPV —	Risk of QT prolongation with b
Fluoroquinolones	–	Risk of QT prolongation with b
Macrolides (Azithromycin)	RPV — –	Risk of QT prolongation with b
Gentamicin	–	No adjustment required
Cephalosporins	–	No adjustment required
Carbapenem	–	No adjustment required
Antifungals	Antifungals	Antifungals
Azoles		Monitor for QT prolongation
Amphotericin	–	No adjustment required
Griseofulvin		**Co-administration contrain**
Contraceptives		
Combined oral	–	No adjustment required
DMPA	–	No adjustment required
Levonorgestrel implant	–	No adjustment required

[*1] LA CAB/RPV=Long acting cabotegravir/rilpivirine

[*2] AUC= Area under the curve, the drug concentration as a function of time

[*3] DMPA= depot medroxyprogesterone acetate

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`2. Figure 1 - Summary of DDIs.docx` available at https://authorea.com/users/759168/articles/733588-clinical-pharmacology-considerations-and-drug-drug-interactions-with-long-acting-cabotegravir-and-rilpivirine-relevant-to-a-sub-saharan-africa

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`3. Figure 2 - Time curve of DDI.docx` available at https://authorea.com/users/759168/articles/733588-clinical-pharmacology-considerations-and-drug-drug-interactions-with-long-acting-cabotegravir-and-rilpivirine-relevant-to-a-sub-saharan-africa