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REVIEW

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Drug-drug interactions potential with the HIV-1 capsid inhibitor lenacapavir

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ABSTRACT

Introduction: Lenacapavir is the first HIV-1 capsid inhibitor administered subcutaneously twice yearly. While lenacapavir is currently only indicated as salvage therapy, it has the potential to become a foundation of future treatments and to revolutionize HIV prevention.

Areas covered: This review summarizes the pharmacology of lenacapavir with particular emphasis placed on its drug–drug interaction (DDI) potential as it is used in treatment-experienced individuals who often present multiple comorbidities and polypharmacy. The effect of lenacapavir on drug metabolizing enzymes and transporters as well as findings of DDI studies are summarized. These data were used to predict DDIs with 1073 comedications. Finally, the management of selected DDIs is discussed. Conferences/workshops abstracts (i.e. CROI, IAS, EACS, HIV Glasgow, PK workshop) were screened using the terms: 'lenacapavir,' 'capsid inhibitor,' 'GS-6207,' and a PubMed search was used to compile data until September 2024.

Expert opinion: Lenacapavir has a favorable DDI profile with 80% of evaluated comedications estimated to have no clinically significant DDIs. More studies are needed to address pharmacological gaps including the pharmacokinetics of lenacapavir in special populations, its transfer across the blood-brain barrier or the placenta as well as the possibility to manage DDIs with moderate/strong inducers by reducing lenacapavir dosing interval.

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Lenacapavir; capsid inhibitor; drug–drug interactions; long-acting; antiretroviral

1. Introduction

Antiretroviral drugs have radically improved over the years with contemporary oral drugs for treatment and prevention of HIV-1 infection which are highly effective and well tolerated. Another outstanding milestone has been the development of long-acting injectable antiretroviral drugs allowing for less frequent dosing with the potential to facilitate treatment adherence and the prospect to reduce HIV transmission.

In 2022, the long-acting injectable antiretroviral treatment armamentarium (i.e. cabotegravir and rilpivirine) was expanded to include lenacapavir, a first-in-class HIV-1 potent capsid inhibitor. Lenacapavir is administered subcutaneously every 6 months following an oral loading dose. Lenacapavir is approved as a therapeutic addition for heavily treatment-experienced adults with multidrug-resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or other safety considerations [1,2]. Clinical trials are undergoing for other indications such as the initial or maintenance treatment of HIV-1 infection with the oral form of lenacapavir in combination with bictegravir (NCT06333808) or islatravir (NCT05052996) or emtricitabine plus tenofovir alafenamide (NCT04143594). The injectable form of lenacapavir is also evaluated in this indication in combination with oral tenofovir alafenamide or bictegravir (NCT04143594). Finally, injectable lenacapavir is being evaluated in various populations that may benefit from pre-exposure prophylaxis (PrEP) to prevent HIV infection (NCT06101329; NCT06513312; NCT04925752; NCT04994509). Remarkably, an interim analysis of the phase 3 randomized PURPOSE 1 trial, evaluating the efficacy of twice-yearly injectable lenacapavir against daily oral PrEP, showed that lenacapavir was superior in preventing HIV infection in cisgender women. Overall, 55 women in the trial newly acquired HIV infection, of those 16 and 39 infections occurred in the daily oral PrEP arms with tenofovir/emtricitabine and tenofovir alafenamide/emtricitabine, respectively, due to the suboptimal adherence observed within the oral PrEP arms of PURPOSE 1. Conversely, no new HIV infections were reported in the lenacapavir arm [3]. Gilead, the manufacturer of lenacapavir, announced in mid-September 2024 the results of an interim analysis of the PURPOSE 2 trial (NCT04925752). This trial investigates twice-yearly injectable lenacapavir against daily oral PrEP in cisgender men, transgender men, transgender women, and gender non-binary individuals who have sex with partners assigned male at birth. Among 2180 people in the trial who received injectable lenacapavir, there were only two cases of HIV infection corresponding to 99.9% of participants not acquiring HIV infection in the lenacapavir group.

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Article highlights

- Lenacapavir, a long-acting first-in-class capsid inhibitor, is currently approved in combination with other antiretroviral drugs for the treatment of multidrug-resistant HIV-1 infection and is undergoing clinical trials for other indications such as therapy for treatment-naïve individuals and pre-exposure prophylaxis.
- Lenacapavir is administered subcutaneously every 6 months following an oral loading dose to achieve efficacious concentrations.
- This agent is minimally metabolized and is primarily cleared unchanged in bile. It is a substrate of CYP3A4, UGT1A1, and P-gp and therefore can be significantly impacted by moderate and strong inducers which are contraindicated.
- Lenacapavir is a moderate inhibitor of CYP3A4 and therefore impacts essentially sensitive and/or narrow therapeutic index CYP3A4 substrates.
- The risk of drug–drug interactions was evaluated for almost 1100 medications, of those 80% did not interact significantly with lenacapavir indicating that this capsid inhibitor has a favorable interaction profile.

Lenacapavir could revolutionize HIV prevention and become a foundation of future HIV treatments. In this review, we summarize the pharmacology of lenacapavir with particular emphasis placed on its drug–drug interaction (DDI) potential as it is licensed for use in treatment-experienced individuals who often present a high burden of comorbidities and related higher use of comedications. The effect of lenacapavir on drug metabolizing enzymes and drug transporters as well as findings of clinical DDI studies are summarized. These data were used to predict DDIs between lenacapavir and close to 1100 commonly used comedications. Finally, the management of selected DDIs of interest is discussed.

2. Pharmacodynamics

Lenacapavir (known previously as GS-6207) inhibits both the early and late stages of the HIV-1 life cycle [4]. The HIV virus is constituted of an encapsulated protein core, known as the capsid, which protects the virus RNA and delivers it to the infected host cells [5]. Lenacapavir binds to monomeric capsid proteins thereby preventing the interaction of the capsid with the host cell. Additionally, it disrupts the capsid disassembly that is required for the reverse transcription. Finally, lenacapavir interferes with the capsid assembly leading to viruses with improperly shaped capsids that can still enter new host cells but that cannot replicate [5].

Lenacapavir has demonstrated high activity *in vitro* against HIV-1 infected macrophages/monocytes and CD4 T-lymphocytes with mean picomolar 50% effective concentrations (EC_{50}) of 56 pM and 32 pM, respectively [4,6]. Furthermore, high virologic efficacy has been demonstrated in people with HIV with up to a 2.3 $\log_{10}$ decline in HIV-1 RNA copies/mL after 10 days following a single subcutaneous dose of lenacapavir (tested doses ranged from 20 to 750 mg) [7]. The maximum effect (E_{max}) was estimated to be a 2.1 $\log_{10}$ decline in HIV-1 RNA with a lenacapavir concentration of ≥4.4 ng/mL predicted to provide near maximal antiviral activity [6,7]. Remarkably, baseline resistances to the other main antiretroviral classes did not affect lenacapavir susceptibility including in individuals with a history of protease inhibitor failure [8,9].

3. Dosing recommendation

Given the delayed onset of subcutaneous lenacapavir, an oral loading dose is critical to achieve efficacious concentrations. There are two recommended dosing regimens for initiating lenacapavir therapy. The first option requires that oral loading doses are administered simultaneously with the injectable form (i.e. day 1: 600 mg (oral) plus 927 mg (subcutaneous); day 2: 600 mg (oral) then 927 mg (subcutaneous) every 6 months or 26 weeks). In the second option, the oral loading doses are given prior to starting the injection (i.e. day 1 and 2: 600 mg (oral); day 8: 300 mg (oral) and starting on day 15: 927 mg (subcutaneous) every 6 months). Both options result in similar drug exposure (Table 1) [10], with concentrations at the end of the dosing interval (C_{trough}) remaining >15.5 ng/mL (corresponding to the 4-fold protein binding adjusted 95% effective concentration) [7].

Delays in the maintenance and loading doses have been evaluated in population pharmacokinetic models to inform dosing recommendations. Subcutaneous maintenance doses can be administered 2 weeks on either side of the due dose (i.e. week 24 or week 28) [11]. However, if more than 28 weeks have elapsed since the last injection, dosing should be reinitiated using either loading option with oral lenacapavir. In the case of the second dosing option, if the day 2 oral dose is missed by <6 days, then a 600 mg dose should be taken as soon as possible with a 300 mg dose on day 8; however, if the oral dose is missed by ≥6 days, then a 600 mg dose should be taken as soon as possible with a 300 mg dose on day 15. If the day 8 oral dose is missed by <6 days, then a 300 mg dose should be taken as soon as possible, and if missed by ≥6 days, then a 300 mg dose should be taken on day 15 [12]. Finally, for individuals unable to receive the subcutaneous injection of lenacapavir at the scheduled time, a weekly oral 300 mg dose can be used to bridge subcutaneous dosing [13].

Product labels recommend injecting lenacapavir into the abdomen. Of interest, a clinical study showed that lenacapavir injection into the thigh or upper arm resulted in similar exposures compared to injection into the abdomen and therefore could be considered as alternate administration sites [14]. Lenacapavir's mode of delivery as a subcutaneous injection, unlike intramuscular injections, gives the option of self-injection which may facilitate uptake.

4. Pharmacokinetics

4.1. Absorption

Oral lenacapavir has a median time to maximal plasma concentration (T_{max}) of 4 hours and plasma half-life is 10–12 days. The single-dose pharmacokinetics of lenacapavir after oral administration are non-linear and less than dose proportional over the dose range of 50 to 1800 mg. The absolute bioavailability of lenacapavir is low (6–10%) and is unaffected by food [15].

Table 1. Simulated pharmacokinetic parameters following simultaneous (option 1) or sequential (option 2) oral and subcutaneous administration of lenacapavir [10].

	Simultaneous dosing regimen (option 1)[a] Day 1: 600 mg (oral) + 927 mg (subcutaneous) Day 2: 600 mg (oral)			Sequential dosing regimen (option 2)[b] Day 1 and 2: 600 mg (oral) Day 8: 300 mg (oral) Day 15: 927 mg (subcutaneous)		
Pharmacokinetic parameters, mean (CV %)	Day 1 to 15	Day 15 to end of month 6	Steady state	Day 1 to 15	Day 15 to end of month 6	Steady state
C_{max} (ng/mL)	80 (56)	87 (72)	97 (70)	70 (56)	87 (72)	97 (70)
AUC_{tau} (h x ng/mL)	18'800 (54)	238'000 (68)	300'000 (69)	15'600 (53)	250'000 (67)	300'000 (69)
C_{trough} (ng/mL)	49 (58)	33 (88)	36 (91)	36 (57)	33 (88)	36 (91)

a = simulated exposures by population pharmacokinetic analysis; b = exposures issued from the phase 3 CAPELLA study. Trough lenacapavir concentrations >15.5 ng/mL, corresponding to the 4-fold in-vitro protein binding adjusted 95% effective concentration, have been associated with high rates of HIV-1 virus suppression [0.7].

Legend: AUCtau, area under the curve to the end of the dosing interval; Cmax, maximal concentration; Ctrough, drug concentration at the end of the dosing interval; CV, coefficient of variation.

Injectable lenacapavir was shown to display two-phase absorption kinetics with an initial fast-release absorption phase followed by a slow-release absorption phase. Injectable lenacapavir is characterized by flip-flop kinetics whereby the elimination rate far exceeds the absorption rate, making the latter the driver of the elimination half-life [16]. Pharmacokinetic studies have shown that after a single 30–450 mg subcutaneous dose of lenacapavir, T_{max} is reached after 77–84 days, and plasma half-life is 8–12 weeks allowing dosing intervals of 26 weeks [17]. Lenacapavir exposure in the injectable form increases dose proportionally over the range of 300 mg to 900 mg [17].

4.2. Distribution

Lenacapavir is highly protein-bound (>99.8%) and the blood-to-plasma ratio is 0.5 to 0.7 [18]. The volume of distribution is 976 L based on population pharmacokinetic analysis [1,2]. The penetration of lenacapavir across the blood-brain barrier has not yet been determined.

4.3. Metabolism and elimination

A human mass balance study performed with a single intravenous 20 mg dose showed that intact lenacapavir was the major entity in plasma (69%) and feces (33%) with 76% of the drug excreted in the feces. This study showed that lenacapavir has no gut metabolism and is minimally metabolized in the liver with most of the drug eliminated unchanged primarily in the feces whereas the renal elimination is negligible [18].

While not extensively metabolized, lenacapavir is a substrate of cytochrome P450 (CYP) 3A4, uridine diphosphate glucuronosyltransferase (UGT) 1A1, and p-glycoprotein (P-gp) [19]. Thus, inducers of these enzymes and P-gp can decrease lenacapavir concentrations whereas inhibitors can increase lenacapavir concentrations. *In vitro* studies have shown that lenacapavir is neither a substrate nor an inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, or CYP2D6 [1,2]. Furthermore, lenacapavir is not a substrate of breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP) 1B1 or OATP1B3 and does not inhibit these transporters or the organic anion transporters (OAT) 1 and OAT3, the organic cation transporters (OCT) 1 and OCT2, or the multidrug and toxin extrusion transporters (MATE) 1 and MATE 2-K in the range of clinically relevant concentrations [1,2]. However, lenacapavir is a moderate inhibitor of CYP3A4 [19]. Due to the long elimination half-life, injectable lenacapavir may increase the exposure of coadministered drugs primarily metabolized by CYP3A4 that are initiated within 9 months after the last dose of lenacapavir [1,2].

4.4. Pharmacokinetics in special populations

4.4.1. Hepatic impairment

The pharmacokinetics of a single dose of lenacapavir 300 mg were studied in a phase I trial comparing healthy volunteers with individuals with moderate hepatic impairment Child-Pugh B: score 7–9) [20]. The area under the curve (AUC) and the maximal concentration (C_{max}) of lenacapavir were shown to be increased by 1.5- and 2.6-fold, respectively, in those with moderate hepatic impairment compared to healthy volunteers. No differences in plasma protein binding, median T_{max}, and elimination half-life were noted between groups. Lenacapavir was deemed generally safe and well-tolerated therefore no *a priori* dose adjustments are needed for individuals with mild-to-moderate hepatic impairment [20]. Lenacapavir has not been studied in individuals with severe hepatic impairment.

4.4.2. Renal impairment

A phase I trial compared the pharmacokinetics of oral lenacapavir 300 mg between healthy volunteers and individuals with severe renal impairment (creatinine clearance <30 mL/min) [20]. The AUC and C_{max} of lenacapavir in patients with severe renal impairment were 1.84- and 2.62-fold higher, respectively, compared to healthy controls. However, given that renal excretion is a minor route of elimination and as lenacapavir exposure was increased less than twofold, no dosage adjustment is needed in individuals with mild, moderate, or severe renal impairment [20].

Although a modest increase in lenacapavir was observed in individuals with organ impairment, it is important to note that lenacapavir was shown in drug development clinical studies to

be well tolerated up to plasma exposures 9-fold higher for C_{max} and 15-fold higher for AUC relative to therapeutic exposures [20].

4.4.3. Obesity

No pharmacokinetic study has formally evaluated the effect of body mass index (BMI) on the pharmacokinetics of lenacapavir. Available pharmacokinetic studies have included individuals with a BMI ranging from 19 to 30 kg/m^2 and within this weight range, no clinically significant differences in lenacapavir exposure were noted in population pharmacokinetic analyses [15,17]. However, it is unknown whether higher BMI affects lenacapavir exposure and warrants any dosing adjustments.

4.4.4. Pregnancy

Lenacapavir has not been studied in pregnant women. In preclinical studies with rats, fertility was not affected at lenacapavir exposures up to 8 times the human exposure, embryo-fetal development was not affected at exposures up to 171 times the human exposure and no significant toxicologic effects were noted during post-natal development [1,2]. However, lenacapavir is not recommended in pregnant women until human data are available unless the benefit outweighs the risk to the fetus. Furthermore, it is not known whether lenacapavir is present in human breast milk or has effects on the breastfed infant. Preclinical studies in rats have demonstrated some transfer of lenacapavir from maternal to neonatal rats; however, it is unclear whether the transfer occurred via the placenta or milk. Until more data are available, breastfeeding is not recommended during lenacapavir treatment [1,2].

4.4.5. Pediatrics

The pharmacology of lenacapavir in the pediatric population is unknown. This is an important gap given the physiological changes that occur throughout adolescence or developmental changes in neonates who, in addition, have maternal lenacapavir exposure.

5. Drug–drug interactions

Mass balance studies indicate that lenacapavir undergoes minimal metabolism [18] and therefore is less subject to DDIs. Drugs impacting lenacapavir and preventing its use are essentially moderate and strong inducers of drug-metabolizing enzymes. On the other hand, *in vitro* studies have shown a low propensity for lenacapavir to induce or inhibit drug transporters or drug-metabolizing enzymes except for moderate inhibition of CYP3A4 [1,2,19]. The labels recommend caution when using lenacapavir with drugs primarily metabolized by CYP3A4 (i.e. sensitive CYP3A4 substrates) and indicate that, upon discontinuation, residual concentrations of lenacapavir may remain in the circulation for prolonged periods and could affect the exposure of sensitive CYP3A4 substrates initiated within 9 months after the last subcutaneous dose [1,2]. The next paragraphs summarize the findings of clinical DDI studies conducted with oral lenacapavir. These clinical data together with data on the clinical pharmacology of almost 1100 comedications were used to predict DDIs with lenacapavir. Finally, selected DDIs of interest are discussed.

5.1. Clinical drug interactions studies

5.1.1. Effect of comedications on the pharmacokinetics of lenacapavir

Clinical DDI studies have been conducted in healthy volunteers using a single 300 mg oral dose of lenacapavir while the perpetrators were dosed to steady state. The dual strong CYP3A4 and P-gp inhibitors cobicistat (150 mg once daily (QD)) and darunavir/cobicistat (800/150 mg QD) were shown

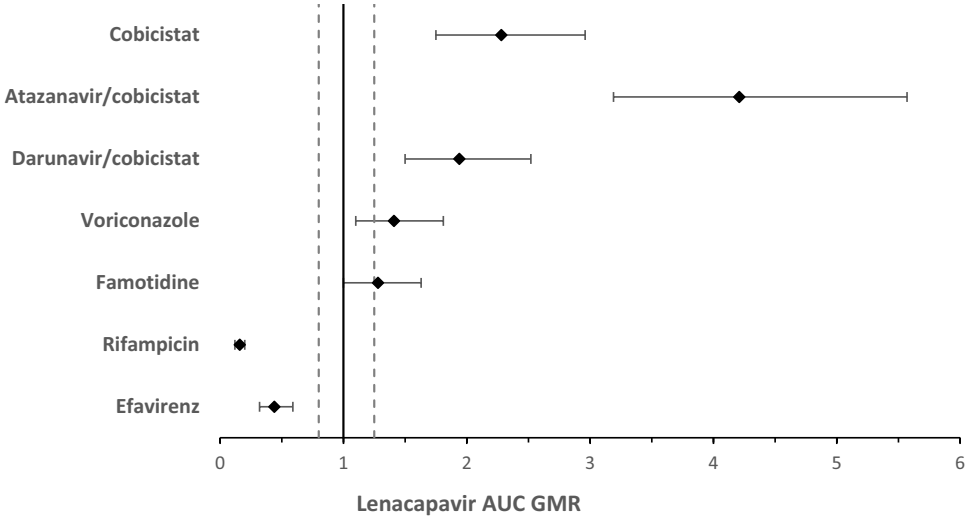

Figure 1. Effect of comedications on oral lenacapavir pharmacokinetics [19].

Legend: lenacapavir was administered at 300 mg (single oral dose) and the perpetrators were dosed to steady-state at the following doses: 150 mg once daily (QD) for cobicistat; 300/150 mg QD for atazanavir/cobicistat; 800/150 mg QD for darunavir/cobicistat; 400 mg twice daily (BID) for one day followed by 200 mg BID for voriconazole; 40 mg QD 2 hours before lenacapavir for famotidine; 600 mg QD for rifampicin and 600 mg QD for efavirenz. Data are expressed as the geometric mean ratio (GMR) + 90% confidence intervals of lenacapavir area under the curve (AUC) in the presence of the perpetrator drug relative to lenacapavir alone. The bioequivalence margin (0.8-1.25) is indicated by dashed vertical lines.

to increase lenacapavir AUC by 2.28-fold and 1.94-fold, respectively. The strong CYP3A4 inhibitor voriconazole (400 mg twice daily (BID) for one day then 200 mg BID) increased lenacapavir exposure by 1.4-fold (Figure 1). However, given the good tolerability of lenacapavir, none of these changes are considered clinically relevant therefore strong CYP3A4 or dual CYP3A4/P-gp inhibitors can be coadministered without the need for a dose adjustment, a recommendation that also applies to subcutaneous lenacapavir [19]. Conversely, the strong CYP3A4, UGT1A1, and P-gp inhibitor atazanavir/cobicistat (300/150 mg QD) substantially increased lenacapavir AUC by 4.21-fold; therefore, lenacapavir is not recommended along with atazanavir alone or atazanavir/ritonavir.

On the other hand, the strong inducer of CYP3A4 and P-gp rifampicin (600 mg QD) and the moderate inducer efavirenz (600 mg QD) were shown to reduce lenacapavir AUC by 84% and 56%, respectively [19]. This substantial reduction in lenacapavir exposure and the related risk of loss of efficacy and development of resistances contraindicates the use of moderate and strong inducers [1,2].

Famotidine (40 mg QD) did not significantly impact lenacapavir absorption kinetics therefore there is no restriction on the co-administration of lenacapavir with acid-reducing agents.

5.1.2. Effect of lenacapavir on the pharmacokinetics of comedications

The clinical DDI studies were done after administering lenacapavir at a dose of 600 mg BID for two days then a single 600 mg dose of lenacapavir was administered with each coadministered drug. Lenacapavir did not significantly alter the exposure of the P-gp substrate tenofovir alafenamide at a dose of 25 mg (AUC increased by 1.3-fold and by 1.4-fold for tenofovir); the OATP substrate pitavastatin dosed at 2 mg (AUC increased by 1.1-fold) and the BCRP/OATP substrate rosuvastatin at a dose of 5 mg (AUC increased by 1.31-fold). However, lenacapavir significantly increased the exposure of the sensitive CYP3A4 substrate midazolam dosed at 2.5 mg by 3.59-fold (simultaneous administration) and by 4.08-fold (one day after lenacapavir administration) [19] (Figure 2). Midazolam administered one day after lenacapavir resulted in a similar magnitude of effect on midazolam concentrations indicating that the effect of lenacapavir on midazolam concentrations is mainly through hepatic CYP3A4 inhibition.

5.2. Prediction of potential drug interactions with lenacapavir

The previously described *in vitro* effects on drug metabolizing enzymes and transporters as well as the clinical interaction studies were used to predict DDIs between lenacapavir and 1073 comedications (i.e. medications listed in the Liverpool HIV drug interaction website as of July 2024 [21]). DDIs with other antiretrovirals were also predicted given that lenacapavir is licensed as a therapeutic addition to antiretroviral regimens in individuals with multidrug-resistant HIV-1 (Table 2).

The identification of the DDI risk was evaluated as described previously [22]. Briefly, data on the clinical pharmacology of individual comedications were extracted from product labels and, where available, published studies on drug metabolism as well as clinical DDI studies or case reports. The propensity of a comedication to cause a clinically significant reduction in lenacapavir exposure was based on its potential to moderately or strongly induce CYP3A4, UGT1A1, or P-gp. The likelihood of a comedication to significantly increase lenacapavir exposure was based on its potential to strongly inhibit both CYP3A4 and UGT1A1; while a moderate or strong inhibition of only one of the two enzymes was predicted to cause a DDI of weak clinical relevance based on the interaction study with darunavir/cobicistat or voriconazole [19]. On the other hand, the clinical relevance of the moderate CYP3A4 inhibition by lenacapavir was

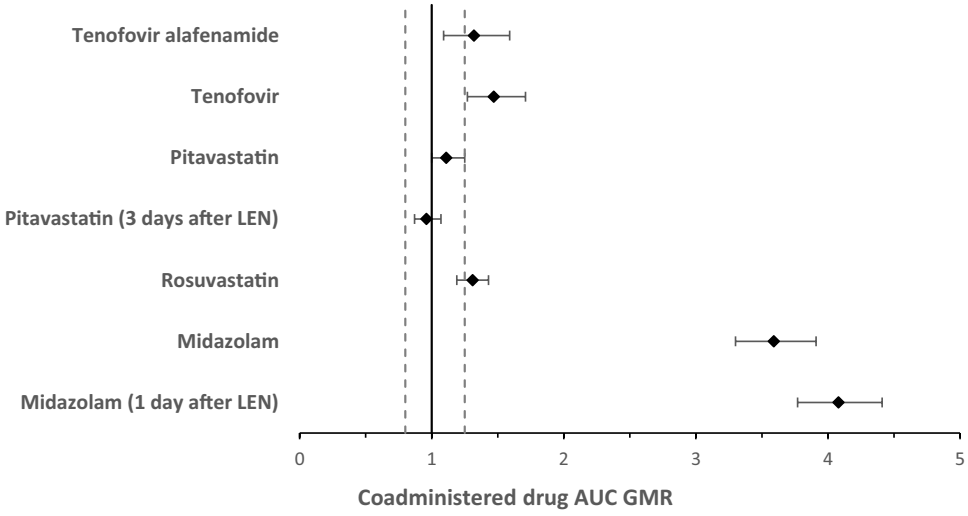

Figure 2. Effect of lenacapavir on comedication pharmacokinetics [19].

Legend: the drug interaction studies were conducted after administering lenacapavir (LEN) at a dose of 600 mg twice daily for two days then a single 600 mg dose of lenacapavir was administered with each coadministered drug, resulting in lenacapavir exposures similar to or higher than those at the recommended dosage regimen. The coadministered drugs were dosed as follows: 25 mg for tenofovir alafenamide (tenofovir alafenamide is converted to tenofovir in vivo); 2 mg for pitavastatin administered simultaneously or 3 days after lenacapavir; 5 mg for rosuvastatin; 2.5 mg for midazolam administered simultaneously or one day after lenacapavir. Data are expressed as the geometric mean ratio (GMR) + 90% confidence intervals of the coadministered drug area under the curve (AUC) in the presence of lenacapavir relative to the drug alone. The bioequivalence margin (0.8-1.25) is indicated by dashed vertical lines.

Table 2. Drug interactions with lenacapavir and other antiretroviral agents [21].

ARVdrug class	ARV drug	Effect on ARV	Dosing recommendations
Integrase Inhibitors	Bictegravir	↑ bictegravir	No dose adjustment needed as potential increase in bictegravir is not clinically relevant.
	Cabotegravir	↔	No dose adjustment needed
	Dolutegravir	↔	No dose adjustment needed
	Elvitegravir/c	↑ lenacapavir AUC by 128%	No dose adjustment needed as increase in lenacapavir is not clinically relevant.
	Raltegravir	↔	No dose adjustment needed
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Dapivirine	↔	No dose adjustment needed
	Doravirine	↑ doravirine	No dose adjustment needed as potential increase in doravirine is unlikely to be clinically relevant.
	Efavirenz	↓ lenacapavir AUC by 56%	Coadministration not recommended due to substantial decrease in lenacapavir.
	Etravirine	↓ lenacapavir	Coadministration not recommended due to potential decrease in lenacapavir.
	Nevirapine	↓ lenacapavir	Coadministration not recommended due to potential decrease in lenacapavir.
	Rilpivirine	↑ rilpivirine	No dose adjustment needed as potential increase in rilpivirine is unlikely to be clinically relevant.
Nucleoside & Nucleotide Analogues (NRTIs)	Abacavir	↔	No dose adjustment needed
	Emtricitabine	↔	No dose adjustment needed
	Islatravir	↔	No dose adjustment needed
	Lamivudine	↔	No dose adjustment needed
	Tenofovir alafenamide	↑ TAF AUC by 32% or tenofovir AUC by 47%	No dose adjustment needed as increase in TAF or tenofovir is not clinically relevant.
	Tenofovir disoproxil fumarate	↑ TDF or tenofovir	No dose adjustment needed as potential increase in TDF or tenofovir is not clinically relevant.
	Zidovudine	↔	No dose adjustment needed
Protease Inhibitors (PIs)	Atazanavir alone	↑↑ lenacapavir	Coadministration not recommended as potential substantial increase in lenacapavir which can lead to adverse effects.
	Atazanavir/r	↑↑ lenacapavir	Coadministration not recommended as potential substantial increase in lenacapavir which can lead to adverse effects.
	Atazanavir/c	↑↑ lenacapavir AUC by 321%	Coadministration not recommended as substantial increase in lenacapavir can lead to adverse effects.
	Darunavir/r	↑ lenacapavir	No dose adjustment needed as increase in lenacapavir is unlikely to be clinically relevant.
	Darunavir/c	↑ lenacapavir AUC by 94%	No dose adjustment needed as increase in lenacapavir is not clinically relevant.
	Lopinavir/r	↑ lenacapavir	No dose adjustment needed as potential increase in lenacapavir is unlikely to be clinically relevant.
Other	Albuvirtide	↔	No dose adjustment needed
	Enfuvirtide	↔	No dose adjustment needed
	Fostemsavir	↔	No dose adjustment needed
	Ibalizumab	↔	No dose adjustment needed
	Maraviroc	↑ maraviroc	No dose adjustment needed for maraviroc in the absence of boosted antiretroviral agents.

Legend: ARV, antiretroviral drug; AUC, area under the curve; ↑, increase; ↓, decrease; ↔, no pharmacokinetic interaction expected;/c, boosting by cobicistat;/r, boosting by ritonavir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.
Green, no drug interaction; yellow, drug interaction of weak clinical relevance; red, deleterious drug interaction.

evaluated by considering the magnitude of the pharmacokinetic change of the comedication in the presence of other moderate CYP3A4 inhibitors, the therapeutic index of the drug, the possibility to monitor the drug effect or to adjust the dosage. Table 3 lists comedications that are contraindicated or not recommended as they may compromise the efficacy of lenacapavir or else result in deleterious adverse effects due to the increase in exposure of the comedication. Given the long elimination half-life of lenacapavir and the related prolonged inhibition of CYP3A4 upon treatment discontinuation, comedications

Table 3. Comedications contraindicated or not recommended with lenacapavir (red flag DDIs). The list was established considering the 1073 medications in the Liverpool HIV drug interaction website as of July 2024 [21].

Therapeutic class	Comedication	Potential consequence of the interaction
Antiarrhythmics	Amiodarone, Disopyramide, Quinidine	Risk of cardiac arrhythmias.
Antibacterials	Rifabutin, Rifampicin, Rifapentine	Potential loss of lenacapavir efficacy.
Antiplatelets	Clopidogrel	Decreased conversion to the active metabolite of clopidogrel leading potential to loss of efficacy.
Anticonvulsants	Carbamazepine, Cenobamate, Eslicarbazepine, Oxcarbazepine, Phenobarbital, Phenytoin, Primidone	Potential loss of lenacapavir efficacy.
Antihistamines	Astemizole, Terfenadine,	Risk of cardiac arrhythmias.
Antimigraine agents	Dihydroergotamine, Ergotamine	Risk of vasospasm leading to cerebral ischemia and/or ischemia of the extremities.
Antiprotozoals	Halofantrine	Risk of cardiac arrhythmias.
Antipsychotics	Cariprazine	Accumulation of cariprazine and its metabolite.
	Pimozide	Risk of QT prolongation and Torsades de Pointes ventricular tachycardia.
	Thioridazine	Potential loss of lenacapavir efficacy.
Antiretrovirals	Atazanavir, Atazanavir/cobicistat, Atazanavir/ritonavir	Significant increase in lenacapavir exposure which can increase the risk of adverse effects.
	Efavirenz, Etravirine, Nevirapine	Potential loss of lenacapavir efficacy.
Cancer therapies	Apalutamide, Bexarotene, Dabrafenib, Enasidenib, Enzalutamide, Ivosidenib, Lorlatinib, Mitotane, Sotorasib, Vemurafenib	Potential loss of lenacapavir efficacy.
	Avapritinib, Bosutinib, Entrectinib, Infigratinib, Neratinib, Pemigatinib, Pexidartinib, Regorafenib	Significant increase in the cancer drug exposure which can result in adverse events.
Gastrointestinal agents	Cisapride, Domperidone	Risk of cardiac adverse events.
Herbals	Guggulsterone, St John's Wort	Potential loss of lenacapavir efficacy.
Hypertension/ Heart failure agents	Bosentan	Potential loss of lenacapavir efficacy.
	Tadalafil	Significant increase in tadalafil exposure which can result in adverse events.
Illicit/recreational	Nitazenes	Increase in nitazene exposure which can result in serious adverse events.
Lipid-lowering agents	Lomitapide	Significant increase in lomitapide exposure which can result in adverse events.
Others	Modafinil, Ursodeoxycholic acid	Potential loss of lenacapavir efficacy.
	Ergometrine, Methylergometrine	Risk of acute ergot toxicity.
	Flibanserin	Risk of severe hypotension and syncope.
Steroids	Betamethasone, Dexamethasone (dose >16 mg)	Potential loss of lenacapavir efficacy.

Table 4. Comedications that can be coadministered with lenacapavir but which may be impacted by lenacapavir residual CYP3A4 inhibition upon treatment discontinuation (amber flag DDIs). The list was established considering the 1073 medications in the Liverpool HIV drug interaction website as of July 2024 [21].

Therapeutic Class	Comedications
Anesthetics and Muscle Relaxants	Ketamine
Analgesics	Alfentanil, Dextropropoxyphene, Fentanyl
Anti-coagulants	Phenprocoumon, Warfarin
Anticonvulsants	Ethosuximide
Antiprotozoals	Quinine
Antipsychotics/Neuroleptics	Lurasidone, Quetiapine
Anxiolytics/Hypnotics/ Sedatives	Alprazolam, Buspirone, Chlordiazepoxide, Clorazepate, Estazolam, Flurazepam, Midazolam, Triazolam
Calcium Channel Blockers	Felodipine, Nifedipine, Nisoldipine, Nitrendipine
Cancer Therapies	Abemaciclib, Acalabrutinib, Bortezomib, Cobimetinib, Cyclophosphamide, Dasatinib, Docetaxel, Encorafenib, Erlotinib, Everolimus, Ibrutinib, Irinotecan, Lapatinib, Paclitaxel, Temsirolimus, Toremifene, Trastuzumab emtansine, Venetoclax, Vinblastine, Vincristine, Vinorelbine
Erectile Dysfunctional Agents	Avanafil, Sildenafil, Tadalafil, Vardenafil
Herbals/Supplements	Red yeast rice
Hypertension/Heart Failure Agents	Doxazosin, Eplerenone, Finerenone, Ivabradine, Lacidipine, Lercanidipine, Macitentan, Ranolazine, Sildenafil
Immunosuppressants	Ciclosporin, Everolimus, Sirolimus, Tacrolimus
Lipid Lowering Agents	Lovastatin, Simvastatin
Other	Alfuzosin, Bromocriptine, Colchicine, Dapoxetine
Overactive Bladder Agents	Darifenacin, Oxybutynin

were also evaluated for their potential to be significantly impacted by residual CYP3A4 inhibition. Such medications are listed in Table 4 and include mostly sensitive CYP3A4 substrates and/or narrow therapeutic index drugs.

It is important to highlight that the interaction study with midazolam was conducted using a higher lenacapavir loading dose (i.e. 600 mg single dose followed by 600 mg twice daily for 2 days and another 600 mg before administering midazolam) than the one used in clinical practice. This resulted in a higher lenacapavir C_{max} (i.e. 202 ng/mL, Gilead data on file) and consequently a more pronounced DDI magnitude with midazolam (i.e. 4-fold) [19]. Considering the contribution of CYP3A4 to midazolam metabolism (i.e. 94%) [23] and considering lenacapavir

C_{trough} at week 26 post administration (i.e. 30 ng/mL) [11], midazolam AUC was predicted to be increased by 30% at the end of the dosing interval using the method developed by Stader et al. [23]. Thus, based on these data, the residual inhibitory effect of lenacapavir is considered to be marginal for nonsensitive CYP3A4 substrates. The method by Stader et al. [23], which considers the fraction of metabolism by a given CYP and the strength of an inhibitor, was applied to estimate the magnitude of the DDI with other CYP3A4 substrates.

DDIs were graded into four levels: red flags for contraindicated drug associations which may have deleterious consequences; amber for potential clinically relevant interactions manageable by close monitoring or dosage adjustment; yellow for interactions of weak intensity with no need of additional monitoring or dosage adjustment; green for no clinically significant interaction expected. The interaction profile of lenacapavir, when considering 1073 comedications, is depicted in Figure 3. Overall, 80% of these comedications were predicted to have no clinically significant interactions with lenacapavir.

5.3. Management of drug interactions of interest within selected therapeutic classes

Antiarrhythmics: antiarrhythmics such as amiodarone, disopyramide, and quinidine are narrow therapeutic index drugs that are not recommended with lenacapavir as an increase in their exposure can expose patients to the risk of arrhythmias or other serious adverse reactions.

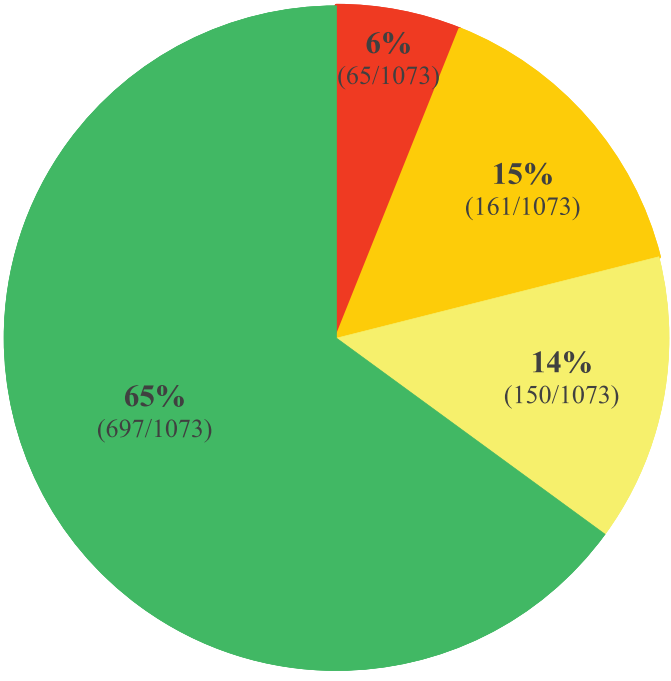

Figure 3. Drug interaction profile of lenacapavir when considering comedications ($n = 1073$) listed in the Liverpool HIV drug interaction website as of July 2024 [21].

Legend: green, no drug interaction; yellow, drug interaction of weak clinical relevance; amber, drug interaction of potential clinical relevance; red, deleterious drug interaction.

Anticoagulants/antiplatelets: anticoagulants include vitamin K antagonists, direct-acting oral anticoagulants (DOACs), and heparin/low molecular weight heparins. The heparin derivatives do not undergo CYP3A4-mediated metabolism and therefore do not interact with lenacapavir. The narrow therapeutic index vitamin K antagonists phenprocoumon and warfarin are partly metabolized by CYP3A4, thus monitoring of the international normalized ratio (INR) is recommended during lenacapavir treatment and in the initial weeks after stopping lenacapavir. Fluctuation in INR could possibly be observed over the 6-month dosing interval given that CYP3A4 inhibition is concentration dependent and given that lenacapavir concentrations after each novel administration are higher (i.e. lenacapavir $C_{max} = 97$ ng/mL) than those at the end of the dosing interval (i.e. $C_{trough} = 36$ ng/mL) (Table 1) [10]. Apixaban and rivaroxaban are substrates of CYP3A4 however no *a priori* dose adjustment is needed based on DDI studies with other moderate CYP3A4 inhibitors. Apixaban exposure was shown to be increased only by 40% in the presence of the moderate inhibitor diltiazem, a change that does not warrant a dose adjustment. However, caution is still warranted in the presence of additional factors such as renal impairment that increases apixaban exposure or may pose an inherent risk of bleeding [24]. Similarly, the CYP3A4 inhibitor fluconazole was shown to increase the exposure of rivaroxaban by 40% [25], an effect that is unlikely to be clinically relevant in most patients, but which could be potentially significant in high-risk patients so that monitoring is warranted.

Other DDIs of interest are with the antiplatelet agents. Clopidogrel is a prodrug that is converted to its active metabolite notably via CYP3A4. Coadministration of clopidogrel with the strong CYP3A4 inhibitor ritonavir reduced the conversion to the active metabolite leading to insufficient inhibition of platelet aggregation, whereas prasugrel's effect has been shown to be unaltered by ritonavir [26]. These data suggest that given the risk of diminished clopidogrel response, prasugrel should be preferred in the presence of lenacapavir unless the patient has a clinical condition that contraindicates its use in which case an alternative antiplatelet agent should be considered. The coadministration of the CYP3A4 substrate ticagrelor and the moderate CYP3A4 inhibitor diltiazem was shown to increase ticagrelor AUC by 2.7-fold whereas the AUC of the active metabolite was unchanged [27]. No *a priori* dose adjustment is needed with lenacapavir however caution is still recommended with monitoring for increased ticagrelor side effects.

Anticonvulsants: some anticonvulsants have inducing properties on drug metabolizing enzymes (i.e. carbamazepine, cenobamate, eslicarbazepine, oxcarbazepine, phenobarbital, phenytoin, primidone) and therefore are contraindicated as they can reduce lenacapavir concentrations which may result in loss of therapeutic effect [1,2]. A minimum of a 2-week but preferably a 4-week cessation period is recommended prior to initiation of lenacapavir due to the persisting inducing effect after discontinuation of a moderate or strong inducer [21,28].

Antipsychotics: some antipsychotics are contraindicated with lenacapavir due to the risk of accumulation and adverse effects (cariprazine and its metabolites (DCAR & DDCAR) have elimination half-lives of 32–68 hours and 30–38 hours &

314–446 hours, respectively [29]); risk of QT prolongation and Torsades de Pointes (pimozide) and loss of lenacapavir efficacy (thioridazine) [21]. However, lenacapavir can be used with other antipsychotic drugs [21]. Moderate CYP3A4 inhibitors were shown to increase the exposure of lurasidone by 2.2-fold [30] and quetiapine by 2.6-fold [31], coadministration with lenacapavir would require halving the dose of the antipsychotic. Caution is also recommended in the initial months after stopping lenacapavir as these antipsychotics may be affected by residual CYP3A4 inhibition [21]. No *a priori* dose adjustment is needed for other antipsychotics.

Antiretrovirals: lenacapavir is contraindicated with efavirenz and atazanavir or boosted atazanavir [19] however all other HIV drugs can be co-administered with no dose adjustment (Table 2).

Anxiolytics: anxiolytics undergoing UGT metabolism (e.g. lorazepam, oxazepam, temazepam) are not impacted by lenacapavir while the impact of lenacapavir on anxiolytics metabolized by CYP3A4 depends on the contribution of CYP3A4 to their metabolism. A dose reduction is recommended for sensitive substrates (i.e. medications predominantly metabolized by CYP3A4) such as alprazolam, buspirone, chlordiazepoxide, clorazepate, estazolam, flurazepam, midazolam and triazolam. For instance, the moderate CYP3A4 inhibitor fluvoxamine has been shown to increase the exposure of both alprazolam and buspirone by 2-fold [32,33]. Thus, their dose should be halved and titration to the lowest effective dose is recommended when coadministering with lenacapavir. Although lenacapavir has been shown to increase midazolam exposure by 4-fold, as mentioned previously, the study was conducted with a higher loading dose of lenacapavir resulting in a larger DDI magnitude than what would be observed with the recommended dosage [19]. A low dose of midazolam is nevertheless recommended with dose adjustment based on the clinical response. No *a priori* dosage adjustment is needed with anxiolytics whose metabolism by CYP3A4 is not predominant (e.g. zolpidem, zopiclone) as moderate inhibitors are anticipated to modestly increase their exposure [23].

Antidepressants: most antidepressants undergo metabolism by CYP2D6 or multiple CYPs contribute to their metabolism therefore clinically relevant DDIs are not anticipated with lenacapavir [21].

Antihypertensives: hypertension can be treated with calcium channel inhibitors (e.g. amlodipine), angiotensin-converting enzyme (ACE) inhibitors (e.g. lisinopril), angiotensin receptor blockers (e.g. losartan), beta-blockers (e.g. metoprolol) or diuretics (e.g. furosemide). Lenacapavir does not interact with agents of these therapeutic classes except for those calcium channel inhibitors which are mainly metabolized by CYP3A4. However, the interaction can be managed by monitoring the blood pressure and adjusting the dose of the calcium channel inhibitor as needed [21].

Cancer drugs: several cancer drugs, notably the kinase inhibitors, which play an increasing role in the treatment of cancer, undergo CYP3A4 metabolism. Due to their toxicity profile, caution is needed when using lenacapavir. DDIs are managed with some tyrosine kinase inhibitors by reducing their dose with close monitoring (e.g. acalabrutinib, encorafenib) or by clinical monitoring with no need for a dose adjustment (e.g. abemaciclib, bortezomib). The reader is referred to individual product labels of tyrosine kinase inhibitors or the University of Liverpool HIV interactions resource (www.hiv-druginteractions.org) [21] for details on the management of drug interactions with moderate CYP3A4 inhibitors. However, some cancer drugs are contraindicated with lenacapavir due to a substantial increase in their exposure and related risk of toxicity (e.g. bosutinib, entrectinib) or due to their inducing properties which can alter lenacapavir efficacy (e.g. enasidenib, lorlatinib).

Erectile dysfunction agents: drugs for erectile dysfunction are sensitive CYP3A4 substrates and should be used at a reduced dose during lenacapavir treatment and in the initial weeks after stopping lenacapavir treatment. The product label for avanafil recommends a maximum dose of 100 mg and not to exceed once every 48 hours in the presence of moderate inhibitors [34]. A starting dose of 25 mg is recommended for sildenafil in the presence of lenacapavir while the dose of tadalafil should not exceed 10 mg every 72 hours or, in case of daily administration, the dose should not exceed 2.5 mg QD [1,2]. Finally, no more than 5 mg vardenafil should be used in a 24-hour period in the presence of lenacapavir [1,2].

Immunosuppressants: ciclosporin, everolimus, sirolimus, and tacrolimus are all sensitive CYP3A4 substrates and are narrow therapeutic index drugs. The coadministration with lenacapavir requires to reduce their dose using therapeutic drug monitoring. The dose adjustment of the immunosuppressant drug may be needed not only during lenacapavir treatment but also during the initial weeks after discontinuing lenacapavir due to the residual CYP3A4 inhibitory effect [21].

Lipid-lowering agents: for HMG-CoA reductase inhibitors, it is recommended to initiate the sensitive CYP3A4 drugs lovastatin and simvastatin with the lowest starting dose, with careful titration and side effects monitoring (i.e. myopathy) in the presence of lenacapavir while there is no dose adjustment needed for atorvastatin or pitavastatin. Lenacapavir is contraindicated with lomitapide as exposure to lomitapide may substantially increase [21].

Steroids: most corticosteroids are substrates of CYP3A4 therefore an increase in their exposure by lenacapavir could possibly increase the risk for Cushing's syndrome and adrenal suppression. It is recommended to initiate with the lowest starting dose and titrate carefully while monitoring for signs of systemic corticosteroid side effects. Betamethasone and dexamethasone (dose >16 mg [35]) are not recommended for coadministration with lenacapavir due to their CYP3A4-inducing effect [21].

Additional information on the management of DDIs can be found in the University of Liverpool HIV interactions resource (www.hiv-druginteractions.org) [21].

6. Conclusion

The licensing of lenacapavir as the first HIV-1 capsid inhibitor and the first subcutaneous antiretroviral drug administered twice a year is an exciting advance for antiretroviral therapy. While lenacapavir is currently only licensed for salvage therapy, it is likely that the indications for use will broaden as more companion agents become available for testing in

combination. The use as PrEP promises new avenues as adherence has been shown to be critical for optimal protection against HIV infection [3]. Besides the reduced pill burden and the long dosing interval, lenacapavir has a favorable DDI profile with 80% out of 1073 evaluated medications having no significant DDIs. Most potentially clinically relevant DDIs are manageable with only 6% being problematic as they may result in loss of lenacapavir efficacy or may lead to toxicities for CYP3A4 sensitive narrow therapeutic index drugs due to the moderate inhibition of CYP3A4 by lenacapavir. When possible, alternative medications should be considered given that lenacapavir is used in individuals with limited HIV treatment options. Importantly, the safe management of DDIs can only be carried out when prescribers are aware of their presence, underlying the importance of a full medicines reconciliation. Screening of DDIs using specialized resources, or prescription review by pharmacists/pharmacologists is advised to ensure safe prescribing.

7. Expert opinion

Long-acting antiretroviral agents are a remarkable advance for the treatment and prevention of HIV infection as they reduce pill burden and have the potential to improve adherence. The pharmacokinetics of subcutaneous administration of lenacapavir is driven by the slow absorption of the drug from the depot resulting in an elimination half-life measured in weeks. While this characteristic allows less frequent dosing, it leads also to a long pharmacokinetic tail, which, if a person living with HIV is not switched to a fully suppressive antiretroviral regimen, could lead to emergent treatment-resistant HIV-1 strains. Additionally, the long elimination half-life adds challenges to the conduct of clinical studies aiming at addressing pharmacological gaps such as, for instance, the impact of obesity or pregnancy-related physiological changes on the pharmacokinetics of injectable lenacapavir. Furthermore, it is unknown whether the DDI with moderate or strong inducers could be managed by shortening the lenacapavir dosing interval or adding oral lenacapavir to subcutaneous lenacapavir, this question is particularly relevant in settings with a high prevalence of tuberculosis for which the strong inducer rifampicin is one of the first-line treatments. Other knowledge gaps relate to the blood-brain barrier transfer, the placental transfer, as well as the secretion of lenacapavir into the breastmilk or the pharmacokinetics of lenacapavir in neonates, considering the maternal exposure to lenacapavir and the developmental pharmacokinetic changes.

Some of these research gaps can be addressed with physiologically based pharmacokinetic (PBPK) modeling. This approach, recognized by the regulatory authorities, predicts drug pharmacokinetics in virtual individuals by combining *in vitro* data and clinically observed data [36]. PBPK modeling allows the simulation of relevant yet unstudied clinical scenarios. Of interest, PBPK modeling was applied to determine the pharmacokinetics of the first long-acting antiretroviral therapy administered intramuscularly (i.e. cabotegravir and rilpivirine) in virtual obese individuals and pregnant women [37,38]. These studies demonstrated that long-acting cabotegravir and rilpivirine exposures are decreased in obese virtual individuals and during the third trimester of pregnancy. Model predictions suggest that the monthly administration of long-acting cabotegravir/rilpivirine (rather than the recommended bimonthly administration in the general HIV population) could maintain concentrations above the minimal concentrations targets particularly in morbidly obese individuals [37]. Simulations in pregnancy indicate that monthly long-acting cabotegravir could maintain antiviral efficacy throughout pregnancy unlike rilpivirine [38]. PBPK modeling demonstrated also that DDIs between long-acting cabotegravir/rilpivirine and strong inducers are not manageable by reducing the dosing interval whereas DDIs can be managed with moderate inducers [39]. It is unclear whether the findings for intramuscular cabotegravir and rilpivirine apply to lenacapavir given that both the route of administration and the metabolic pathway are different. PBPK modeling could address some of the pharmacological gaps that will be encountered in clinical practice with the scale-up of lenacapavir. Finally, the role of therapeutic drug monitoring (TDM) of lenacapavir needs to be evaluated.

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