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REVIEW ARTICLE

Pharmacokinetics and Pharmacodynamics of Cabotegravir, a Long-Acting HIV Integrase Strand Transfer Inhibitor

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Abstract

Available antiretroviral drugs have demonstrated effectiveness in both pre-exposure prophylaxis and treatment of HIV infection. However, some concerns still persist regarding these therapies, mainly related to patient adherence, drug toxicity and dosing convenience. Cabotegravir is a potent integrase strand transfer inhibitor with a chemical structure similar to dolutegravir that is under clinical evaluation both as oral and long-acting injectable (LAI) formulations for both the prevention or treatment of HIV infection. Indeed, preclinical and clinical studies have consistently shown that LAI cabotegravir is readily absorbed following intramuscular and subcutaneous administration, with an elimination half-life of approximately 40 days, permitting infrequent dosing, possibly once every 1 or 2 months (eventually combined with rilpivirine). Here, we reviewed the existing literature on the preclinical and clinical pharmacokinetics and pharmacodynamics of LAI cabotegravir, with emphasis on the actual pharmacokinetic challenges of this novel formulation, as well as its potential to act as a victim or perpetrator of drug–drug interactions.

Key Points

Cabotegravir is a potent integrase strand transfer inhibitor with a chemical structure similar to dolutegravir that is under clinical evaluation both as oral and long-acting injectable formulations.

Radioactivity studies showed that cabotegravir circulates mainly in the plasma (with a protein binding > 99%) and with limited partitioning in blood cells. Regarding tissues, cabotegravir is distributed mainly in the lung, liver, renal and adrenal medulla, and skin, with limited penetration in the brain. Cabotegravir is mainly eliminated in feces (primarily as unchanged drug) and in urine (as glucuronide metabolite).

At clinically relevant concentrations, cabotegravir did not inhibit or induce any phase I or phase II metabolic enzymes, as well as main drug protein transporters (with the exception of OAT1 and OAT3 whose activity is significantly inhibited by cabotegravir). Cabotegravir has low propensity to cause clinically significant drug–drug interactions.

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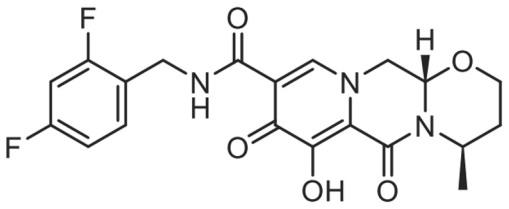
1 Introduction

The advent of highly active antiretroviral therapy has significantly reduced AIDS-related mortality and morbidity and improved the quality of life of HIV-infected patients [1, 2]. However, HIV infection continues to be a major global health threat. Indeed, according to the UNAIDS 2017 report, nearly 38 million people are living with HIV, and nearly 1.8 million of new HIV infections were recorded last year [3]. Taken together, these data underline the need to identify approaches able to guarantee optimal adherence of patients to their maintenance antiretroviral therapies, as well as the importance of preventing HIV transmission eventually through the adoption of pre-exposure prophylaxis (PrEP)-based strategies. From a pharmacological viewpoint both requirements could eventually be accomplished by the availability of long-acting injectable (LAI) formulations of antiretroviral drugs. LAI antiretroviral agents, being administered on a monthly or less-frequent basis, may indeed provide key advantages compared with traditional once-daily formulations in both adherence and convenience for HIV treatment and prevention [4–6].

Cabotegravir (also known as GSK1265744 or GSK744) is a potent integrase strand transfer inhibitor (INSTI) with a chemical structure similar to dolutegravir (Fig. 1) that is under clinical evaluation both as oral and LAI formulations [7–9]. As shown in Table 1, cabotegravir is characterized by low aqueous solubility, slow metabolism and high melting point, all conditions that permitted its formulation as a 200 mg/mL LAI product. In this review, we aimed to summarize the pre-clinical and clinical pharmacokinetics as well as the pharmacodynamics of LAI cabotegravir.

Dolutegravir



Cabotegravir

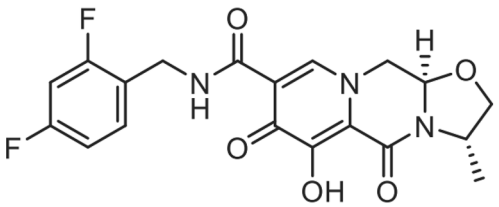


Fig. 1 Chemical structures of dolutegravir and cabotegravir

2 Literature Search Strategy

A MEDLINE PubMed search for articles published from January 2006 to July 2018 was completed matching the terms cabotegravir or GSK1265744 or GSK744 with pharmacology, pharmacokinetics, pharmacodynamics, drug–drug interactions (DDIs), or LAI. Additional studies were also identified from the reference list of retrieved articles or extracted from proceedings of international conferences dealing with HIV drugs.

Table 1 Physicochemical and pharmacokinetic properties of cabotegravir

Properties	Data
Molecular weight, g/mol	405 (427 for sodium salt)
Water solubility	0.015 mg/mL at pH 6.8
Partition coefficient	1.04
Melting point	248–251 °C
Acid dissociation constant	10.04
Protein binding	>99%
Blood-to-plasma ratio	44%
Transport/distribution	P-Glycoprotein, breast cancer resistance protein
Metabolism	Uridine diphosphate-glucuronosyltransferase (UGT) 1A1 and UGT1A9
Elimination	Nearly 60 and 27% of the administered dose recovered in feces (primarily as unchanged drug) and in urine (as a glucuronide metabolite), respectively
Metabolic enzymes induction	None
Metabolic enzymes inhibition	None
Transport proteins induction	None
Transport proteins inhibition	Organic anion transporter (OAT) 1 and OAT3

3 Preclinical Pharmacokinetics

The disposition, biotransformation and excretion of cabotegravir between different animal species was thoroughly investigated by Bowers et al. using [^{14}C]cabotegravir as a probe [10]. Total recovery of radioactivity in mice, rats and monkeys was > 90%, with feces representing the predominant route of elimination, accounting for 79–95% of the administered dose in intact animals, with no major differences between species. Conversely, the percentage of the administered dose excreted in the urine of monkeys (11%) was nearly ten-fold higher compared with mice and rats (< 1% of the administered dose). In the same experiment, the authors investigated in detail the drug distribution in the tissues of rats given a single oral suspension of [^{14}C]cabotegravir. They found that radioactivity was distributed to tissues, with peak concentrations observed in most cases on day 1 post dose. Overall, elimination of [^{14}C]cabotegravir was slow, with > 50% of tissues containing measurable radioactivity at day 28 post dose. The highest tissue-to-blood ratios were measured in the lung (89%), liver (50%), renal and adrenal medulla (56%), bulbourethral gland (64%) and skin (46%). Levels of radioactivity in the brain were low (< 5%), but still quantifiable up to day 7 post dose. Tissues relevant to HIV infection (acting as potential virus reservoirs), such as lymph nodes, spleen, thymus and bone marrow had quantifiable levels or radioactivity (ranging from 7 to 20%) up to day 7, then gradually declining below the lower limit of quantification by day 28. As far as metabolite profiling, the glucuronic acid metabolite (M1) was the principal component presenting 34, 43 and 80% of the radioactivity extract in the urine of mice, rats and monkeys, respectively. Minor metabolites identified in urine included a glucose conjugate (M2), cysteine conjugate (M3) and an oxidation product (M5). All these metabolites represented < 5% of the radioactivity for all the animal species investigated. M1 was also the predominant component in the bile of mice, rats and monkeys representing 46, 88 and 68% of the biliary radioactivity, respectively. A glutathione derivative (M4) was found solely (25% of radioactivity) in mice bile. Metabolites M2 and M3 were found exclusively in monkey bile.

More recently, a multi-modal molecular imaging approach (based on magnetic resonance imaging coupled with matrix-assisted laser desorption ionization imaging mass spectrometry) has been employed to investigate temporal cabotegravir LAI distribution in rats following either intramuscular (IM) or subcutaneous (SC) administration [11]. This methodology demonstrated that the cabotegravir LAI depot volume increased rapidly in IM-injected rats compared with those treated with the SC formulation; this was associated with the presence of macrophages in the depot region (gastronecmius). Co-registration of the cabotegravir ion images with immunohistochemical images established that the drug was taken up by macrophages associated with the depot. Interestingly, the subsequent depot expansion observed in animals treated with both cabotegravir formulations was associated with an increase in macrophage infiltration and edema in and around the depot region, which in turn was correlated to plasma drug concentration at early time points.

Tissue pharmacokinetics of LAI cabotegravir were mainly investigated in nonhuman primates (available studies were extensively reviewed in Ref. [8]). The levels of cabotegravir were first assessed in plasma and rectal biopsy tissues of macaques given a single dose of 10 or 30 mg/kg [12]. A linear correlation between plasma and tissue concentration was observed, with a mean rectal-to-plasma ratio of 21% (ranging from 8 to 54%). Subsequently, the animals treated with the 30 mg/kg dose were necropsied 3 weeks after the second LAI cabotegravir dose to thoroughly assess the distribution of cabotegravir in other tissues. The drug was identified in the colon, ileum, jejunum, duodenum, tonsil, spleen, liver and muscle with tissue-to-plasma ratios of 28, 31, 21, 25, 30, 16, 41 and 8%, respectively. The distribution of LAI cabotegravir in lymph nodes (cervical, inguinal, mesenteric and axially) was also explored, with ratios ranging from 15 to 23%. Other investigators have assessed the vaginal and cervical tissue distribution of LAI cabotegravir given at 50 mg/kg in female rhesus macaques undergoing repeat high-dose intravaginal simian/HIV challenge [13, 14]. Low tissue-to-plasma ratios were found (from 6 to 23% and from 8 to 30% for the vagina and cervix, respectively). However, despite the observed low cabotegravir concentrations in mucosal tissues, levels remained above the protein-adjusted 90% inhibitory concentrations (PA-IC_{90}) in vaginal secretions from pigtail macaques during dosing cycles with the 50 mg/kg regimen [14].

4 Clinical Pharmacokinetics

The first-time-in-human study dealing with the pharmacokinetics, safety and tolerability of cabotegravir (given orally) was published by Spreen et al. [15]. This double-blind, placebo-controlled study consisted of a dose escalation of single (part A) and multiple (part B) oral doses in 48 healthy subjects. In part A, the subjects received cabotegravir doses ranging from 5 to 50 mg whereas in part B, subjects were given cabotegravir oral doses ranging from 5 to 25 mg daily for 14 days. Dose-proportional increases in drug exposure and low pharmacokinetic variability were observed, with a mean plasma half-life of 31.5 h. Such results were confirmed by a human mass balance study involving six healthy

subjects who received either a single oral dose of 28.2 mg of [^{14}C]cabotegravir or LA formulations of unlabeled cabotegravir (200–800 mg) designed with the intention of investigating the metabolism and excretion of this drug [10]. This study documented that concentrations of radioactivity were approximately double in plasma compared to those in blood, indicating limited partitioning of cabotegravir into blood cells. Moreover, it was found that after oral administration, 58.5% and 26.8% of the dose was recovered in feces (mainly as cabotegravir) and urine (almost exclusively as cabotegravir glucuronide and, to a lesser extent, as glucose conjugate), respectively; most of the radioactivity was recovered in the first 216 h post dose (82.7%), confirming the results from animal studies.

Subsequently, the same investigators published studies dealing, respectively, with the pharmacokinetics of LA cabotegravir administered as a single dose or as a multiple dose by SC or IM injections in healthy volunteers [16, 17]. The results of these studies are summarized in Table 2. The first investigation showed that moving from 100 mg to 800 mg single doses, the plasma cabotegravir pharmacokinetics increased less than proportionally; however, the pharmacokinetic parameters seemed to increase proportionally to dose after split injections (i.e., from 400 mg to 2 × 200 mg). The single-dose study also documented that (a) both routes of LAI cabotegravir administration provide detectable plasma concentrations for up to 52 weeks and (b) LA cabotegravir administered as 2 separate injections achieved mean drug concentrations at 4 weeks, largely above the PA-IC$_{90}$. Taken together, these results suggest that a dosing frequency of once monthly or longer is possible for enabling the treatment or prevention of HIV infection. The study also provided preliminary evidence that patient gender might significantly impact on LAI cabotegravir bioavailability; a trend for higher plasma exposure in female subjects after SC administration was observed. The multiple-dose study showed that, after loading doses of 800 mg required to shorten the time to steady state, monthly injections of 200 or 400 mg of LAI cabotegravir (combined with LAI rilpivirine) provided plasma concentrations at the end of the dosing interval that exceeded the PA-IC$_{90}$ by at least four-fold. No major differences were found in the pharmacokinetics of cabotegravir when comparing the two routes of parenteral drug administration. However, the fact that adverse events were reported more frequently with the SC dosing, and the lack of SC formulations for the companion drug LAI rilpivirine, provide two strong rationales for the use of IM dosing, as investigated in the LATTE-2 study, a randomized, open-label, phase 2b, non-inferiority trial investigating the efficacy and safety of LA IM cabotegravir and rilpivirine in adults with HIV infection [18].

To date, no studies have specifically dealt with the pharmacokinetics of LAI cabotegravir in pediatric patients. However, whole-body physiologically-based pharmacokinetic models have been recently developed for the in silico prediction of the optimal LAI cabotegravir dosing administration to children and adolescents [19]. With this modeling approach, the authors identified IM loading and maintenance doses of cabotegravir ranging from 200 to 600 mg and from 100 to 250 mg, respectively, across various body weight groups of children ranging from 15 to 70 kg.

5 Pharmacodynamics

Similar to other INSTIs (raltegravir, elvitegravir, dolutegravir and the most recent bictegravir), the antiviral effect of cabotegravir is exerted through the inhibition of HIV

Table 2 Summary of the pharmacokinetic studies of LAI cabotegravir in healthy subjects

Study	Design	Cabotegravir, Dose/route	Plasma $AUC_{0-\infty}$, g × h/mL	$T_{1/2}$, days	T_{max}, days	C_{trough}, g/mL	Median tissue/plasma ratios (%)
Spreen et al. 2014 [16]	Phase I, open-label single-dose, dose escalation parallel design 9 cohorts	100 mg IM	920	33.3	9.0		400 mg IM unsplit
		200 mg IM	1234	53.9	44.5		Cervical: 20%
		400 mg IM	2652	38.3	69.0		Vaginal: 28%
		800 mg IM	5872	25.4	7.6		Rectal: 0%
		100 mg SC	689	50.4	16.5		400 mg IM split
		200 mg SC	1706	42.7	6.0		Cervical: 16%
		400 mg SC	2734	42.8	27.0		Vaginal: 19%
							Rectal: 8%
Spreen et al. 2014 [17]	Phase I, open-label repeat-dose parallel design 4 cohorts	30 mg oral	147	n.a.	2.0	4.9	
		200 mg SC	1244	n.a.	6.0	1.7	
		200 mg IM	1242	n.a.	6.0	1.6	
		400 mg IM	2473	n.a.	6.0	3.3	
		800 mg IM	4467	n.a.	15.0	1.1	

SC subcutaneous, *IM* intramuscular, $T_{1/2}$ half-life, T_{max} time of maximum drug concentration, *AUC* area under the concentration–time curve from time zero to infinity, *n.a* not available

integrase, a virally encoded enzyme that (a) catalyzes the removal of the terminal two nucleotides on the respective 3′ ends of the viral DNA (3′ processing) and (b) facilitates the nicking of host chromosomal DNA by the newly exposed 3′ hydroxyl moieties, resulting in strand transfer of the viral dsDNA [20, 21]. In particular, cabotegravir and dolutegravir contain a two-metal binding pharmacophore consisting of a carbamoyl pyridone moiety (Fig. 1) and were optimized to deliver the attributes that would differentiate them as new INSTIs [7–9]. In vitro studies showed that cabotegravir maintained activity against single and several multiple integrase mutants but has decreased efficacy against a small subset of multimutated viruses resistant to other INSTIs [22]. As expected, cabotegravir retained its activity against HIV mutant viruses resistant to other antiretroviral drug classes and had no antagonistic effect with NRTIs, NNRTIs or PIs.

A recently published study found that cabotegravir (together with dolutegravir and bictegravir) had higher antiretroviral potency not only in HIV-1B but also in non-B subtypes compared with the first two approved INSTIs, raltegravir and elvitegravir [23]. In particular, cabotegravir is a subnanomolar inhibitor of HIV-1 integrase-catalyzed viral cDNA strand transfer, with an in vitro half maximal inhibitory concentration of 0.22 nmol/L against HIV-1 BAL in peripheral blood mononuclear cells, and a PA-IC_{90} of 166 ng/mL [5].

6 Pharmacokinetic/Pharmacodynamic Relationships

The pharmacokinetics and pharmacodynamics of cabotegravir in HIV-infected patients ($n = 11$) were characterized by Spreen et al. in two separate proof-of-concept studies [15]. In particular, this double-blind, placebo-controlled study consisted of a dose escalation of single (part A) and multiple (part B) oral doses in 48 healthy subjects and an oral dose (part C) in 11 HIV-1-infected subjects. In part A, two cohorts of 9 subjects received either 5 and 25 mg or 10 and 50 mg. In part B, three cohorts of 10 subjects received 5, 10, or 25 mg once daily for 14 days. In part C and the phase IIa study, HIV-infected patients received 5 or 30 mg once daily for 10 days. Dose-proportional increases in drug exposure were observed in healthy and HIV-1-infected subjects. In HIV patients, cabotegravir monotherapy significantly reduced plasma HIV-RNA from baseline to day 11 with a mean decrease of 2.2 to 2.3 log10 copies/mL, respectively. E_{max} model fit analyses failed to identify minimum cut-off values for cabotegravir plasma trough concentrations associated with HIV-RNA changes from baseline to day 11 post treatment. As a matter of fact, once-daily doses of 5 or 30 mg of cabotegravir were always associated with measured drug concentrations (ranging roughly from 1 to 5 μg/mL) above the minimum target therapeutic concentrations ($4 \times$ PA-$IC_{90} = 0.66$ μg/mL), and produced a significant reduction in plasma HIV-RNA viral load with no differences between cabotegravir doses or plasma trough concentrations.

In the only study available dealing with pharmacokinetic/toxicodynamic correlations, no relationship was found between cabotegravir plasma concentrations and differences in QT variations from baseline in healthy subjects treated with supratherapeutic cabotegravir oral doses (150 mg) [24].

7 Drug–Drug Interactions

Cabotegravir is primarily metabolized by glucuronidation via UGT1A1 and, to a lesser extent, to UGT1A9 (Table 1). Cytochrome (CYP)-mediated metabolism is expected to be minimal [10, 25]. Cabotegravir is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) but, due to its high permeability, these transporters are not expected to affect cabotegravir intestinal absorption [25]. Results from in vitro studies showed that, at clinically relevant concentrations, cabotegravir did not inhibit or induce phase I (cytochromial) or phase II metabolic enzymes. Similarly, no relevant inhibitory effect on hepatic, intestinal, or renal drug transporters [Pgp, BCRP, multidrug resistance protein (MRP) 2/4, organic anion transporting polypeptide (OATP) 1B1/3, organic cation transporter (OCT) 1/2, bile salt export pump (BSEP)] was found. Conversely, it was found that cabotegravir inhibits the renal multidrug and toxin extrusion transporters (MATE) 1/2-K (IC_{50}: 14–18 μM) and OAT1 and 3 (IC_{50}: 0.4–0.8 μM). Based on these results, DDIs may therefore take place between cabotegravir and OAT1 or OAT3 substrates, becoming potentially clinically relevant when cabotegravir is co-administered with narrow therapeutic index drugs, such as methotrexate (an OAT3 substrate). There is less concern regarding tenofovir, another OAT1/3 substrate, as it appears to be adequately secreted via efflux through multidrug resistance-associated pump 4, which is not inhibited by cabotegravir [25].

Human studies dealing with potential DDIs involving cabotegravir are summarized in Table 3. Ford and coworkers conducted three independent, open-label, crossover studies aimed at assessing the effects of potential DDI perpetrators, namely etravirine, rilpivirine, or rifampin, on the pharmacokinetics of oral cabotegravir given at 30 mg to adult healthy volunteers [26–28]. As shown in Table 3, cabotegravir AUC and C_{max} were not significantly affected by concomitant NNRTI administration. Conversely, coadministration of rifampin reduced cabotegravir AUC by nearly 60%, whereas oral clearance was increased 2.4-fold [28]. The authors concluded (a) that the 30 mg dose of cabotegravir is not recommended in patients concomitantly given rifampin and (b) that rifampin is also expected to increase

Table 3 Summary of drug–drug interaction studies dealing with oral cabotegravir

Study	Design	Population	Regimen	PK results
Ford et al. 2013 [26]	Two-period, single-sequence, crossover study	12 healthy subjects (23–48 years old)	Period 1: 30 mg of cabotegravir for 10 days Period 2: 30 mg of cabotegravir with 200 mg etravirine for 14 days	Cabotegravir GMR (90% CI): AUC = 1.01 (0.96–1.06) C_{max} = 1.04 (0.99–1.09) C_{trough} = 1.00 (0.94–1.06)
Ford et al. 2013 [27]	Two-cohort, three period single-sequence, crossover study	28 healthy subjects (20–48 years old)	Period 1: 30 mg of cabotegravir for 12 days Period 2: 25 mg of rilpivirine for 12 days Period 3: 30 mg of cabotegravir with 25 mg rilpivirine for 12 days	Cabotegravir GMR (90% CI): AUC = 1.12 (1.05–1.19) C_{max} = 1.05 (0.96–1.15) C_{trough} = 1.14 (1.04–1.24)
Ford et al. 2017 [28]	Single-dose, fixed-sequence, crossover study	15 healthy subjects (21–65 years old)	1 dose of cabotegravir 30 mg on day 1 600 mg of rifampin from day 8 to day 28 1 dose of cabotegravir 30 mg on day 21	Cabotegravir GMR (90% CI): AUC = 0.41 (0.36–0.46) C_{max} = 0.94 (0.87–1.02) CL/F = 2.4 (2.2–2.8)
Ford et al. 2018 [29]	Fixed-sequence, crossover study	15 healthy subjects (33–55 years old)	Period 1: 30 mg of cabotegravir for 14 days Period 2: 30 mg of cabotegravir with 300 mg rifabutin for 14 days	Cabotegravir GMR (90% CI): AUC = 0.79 (0.74–0.83) C_{max} = 0.83 (0.76–0.90) C_{trough} = 0.74 (0.70–0.78) CL/F = 1.27 (1.20–1.38)
Reese et al. 2016 [25]	Single dose, crossover study	12 healthy subjects (23–48 years old)	Period 1: 3 mg of midazolam for 10 days Period 2: 3 mg of midazolam with 30 mg of cabotegravir for 14 days	Midazolam GMR (90% CI): AUC = 1.08 (0.96–1.22) C_{max} = 1.09 (0.94–1.26)
Trezza et al. 2017 [30]	Fixed-sequence, crossover study	20 healthy women (18–45 years old)	Period 1: LNG 0.15 mg/EE 0.03 mg for 10 days Period 2: LNG 0.15 mg/EE 0.03 mg with 30 mg cabotegravir for additional 10 days	LNG GMR (90% CI): AUC = 1.12 (1.07–1.18) C_{max} = 1.05 (0.96–1.15) C_{trough} = 1.07 (1.01–1.15) EE GMR (90% CI): AUC = 1.02 (0.97–1.08) C_{max} = 0.92 (0.83–1.03) C_{trough} = 1.00 (0.92–1.10)

GMR geometric mean ratio, *CI* confidence interva, C_{max} maximum drug concentration, C_{trough} drug concentration at the end of dosing interval, *CL/F* apparent clearance; AUC: area under the concentration–time curve, *LNG:* levonorgestrel, *EE* ethinyl estradiol

cabotegravir clearance following LAI administration. Therefore, the coadministration of cabotegravir and rifampin is not recommended irrespective of the route of drug administration. A more recent phase II study documented that rifabutin increased cabotegravir oral clearance by 27% and reduced AUC, C_{max}, and C_{trough} by 21, 17 and 26%, respectively [29]. However, cabotegravir concentrations remained above the PA-IC_{90}, providing indirect evidence that rifabutin and oral cabotegravir can be given together without dose adjustments.

The other two studies dealt with the potential role of cabotegravir not as the victim but as the perpetrator of DDIs. The first one showed that oral cabotegravir does not affect the pharmacokinetics of midazolam taken as CYP3A probe, thus providing evidence that cabotegravir is neither a CYP inhibitor nor inducer [25]. The second study documented that coadministration of oral cabotegravir with an oral contraceptive containing levonorgestrel (LNG) and ethinyl estradiol (EE) did not affect the pharmacokinetics of these hormones, supporting coadministration of cabotegravir in combination with LNG- and EE-containing oral contraceptives in clinical practice [30].

8 LAI Cabotegravir as PrEP

As discussed above, LAI cabotegravir has a pharmacokinetic profile in HIV-1-uninfected individuals that makes it amenable for dosing every 3 months, offering an alternative to tenofovir-based daily PrEP regimens [8]. The efficacy of LAI cabotegravir as PrEP was evaluated first in macaques to establish proof-of-concept [12]. In this study, LAI cabotegravir was administered at 50 mg/kg doses at two time points

4 weeks apart beginning 1 week before virus administration, and the macaques were challenged weekly for 8 weeks. At this dose the drug protected all the animals against repeated low-dose challenges. In a second experiment, the macaques were untreated or were given LAI cabotegravir 50 mg/kg 1 week before virus administration and challenged repeatedly until infection occurred. All untreated macaques became infected quickly after 1 or 2 challenges, whereas the LA cabotegravir-treated animals remained aviremic throughout the initial phase of simian/HIV challenges, but as the plasma drug concentrations declined they became infected, gradually and successively. Overall, the treated animals were infected after 6–17 virus challenges compared with 1–7 challenges for the untreated controls. In particular, all infections occurred when the plasma cabotegravir concentrations were < 0.5 µg/mL, corresponding approximately to 3x PA-IC_{90} values.

Subsequently, two other concomitant studies investigated whether monthly injections of LAI cabotegravir prevented simian/human immunodeficiency virus (SHIV) infection by vaginal challenge in macaques [13, 14]. In the first study, the authors examined the efficacy of LAI cabotegravir (50 mg/kg monthly) in female rhesus macaques treated with depot medroxyprogesterone acetate, which promotes viral transmission vaginally [13]. No infection was detected in the cabotegravir-treated rhesus macaques, whereas viremia was detected 1–2 weeks after SHIV challenge in all the control animals. The cabotegravir-treated rhesus macaques were given a second drug administration at week 4 and further challenged at weeks 5 and 7. LAI cabotegravir treatment protected six of eight female rhesus macaques against three high-dose SHIV challenges, whereas all the control animals became infected after the first challenge. In the second study, female pigtail macaques were exposed to intravaginal inoculations of SHIV twice a week for up to 11 weeks [14]. Half of the animals received LAI cabotegravir every 4 weeks, and half received placebo. Cabotegravir protected all the macaques from infection whereas the controls were all infected after a median of 4 (range 2–20) vaginal challenges with SHIV. Interestingly, efficacy was related to high and sustained vaginal and plasma drug concentrations that remained above the protein-adjusted 90% inhibitory concentration during the dosing cycles.

More recently Andrews et al. determined the relative effective concentrations of LAI cabotegravir against a panel of recombinant viruses containing integrase coding regions derived from various clades of HIV-1 with the goal of assessing the preventive effect of cabotegravir against intravenous SIV challenge [31]. The animals were injected with LA cabotegravir IM at different time points (group 1: 50 mg/kg at week 0 and 4; group 2: 50 mg/kg at week 0; group 3: 25 mg/kg at week 0 and 50 mg/kg at week 4) and infected with the virus on week 2. LAI cabotegravir was highly effective in all treated groups, with 88% of treated macaques remaining aviremic. The plasma concentrations of cabotegravir at the time of virus challenge (week 2) results were more important for protection than sustaining therapeutic plasma concentrations with the second LA cabotegravir injection. The results of this study suggest a role for LAI cabotegravir in preventing HIV infection in people who inject drugs or who receive contaminated blood transfusion.

The above-mentioned experimental findings provided the rationale for the design of ECLAIR, a multicenter, double-blind, randomized phase 2a trial in which HIV-uninfected men were randomized to receive a 4-week oral lead-in phase with 30 mg of cabotegravir ($n = 106$) or placebo ($n = 21$), followed by three IM injections of LA cabotegravir 800 mg or saline placebo at 12-week intervals as PrEP strategy [32]. Eighteen percent versus five percent of subjects treated with cabotegravir or placebo, respectively, did not complete the study mainly for injection-site pain/injection intolerability. Assessment of cabotegravir plasma trough concentrations, performed for each injection, showed lower than expected drug exposure. The ECLAIR study was designed to evaluate the safety and pharmacokinetics of LAI cabotegravir as PrEP, not its efficacy. However, it is interesting to note that the only patient in the cabotegravir arm acquiring HIV infection had drug plasma trough concentrations well below the PA-IC_{90} value. Based on their findings, the authors concluded that LAI cabotegravir was well tolerated with an acceptable safety profile, supporting its use as an alternative to orally administered PrEP. On the other hand, as the pharmacokinetic data suggest that 800 mg administered every 12 weeks is a suboptimal regimen, alternative dosing strategies are actually being investigated.

9 Discussion and Conclusion

LAI cabotegravir possesses a number of pharmacokinetic and pharmacodynamic features, including optimal and prolonged systemic drug exposure, acceptable penetration in different tissues and a high genetic barrier against resistant viruses, making it a promising candidate both as PrEP and treatment for HIV-1 infection.

Based on the available literature, cabotegravir also has the additional advantage of a low potential to cause DDIs. It should be recognized, however, that available clinical studies designed to characterize the pharmacokinetics of cabotegravir, as well as its potential to act as perpetrator and/or victim of DDIs, used almost exclusively the oral drug formulation. Given that the LAI formulation delivers cabotegravir to systemic circulation as does the oral formulation, and clearance and elimination mechanisms are the same regardless of the route of administration, it can be hypothesized that drug interaction data can apply to both formulations. Notable exceptions

would be any drug interaction at gastrointestinal tract level (e.g., co-dosing with divalent metal cation antacid which can cause chelation and poor absorption). Other yet unaddressed issues relate to the selection of optimal LA cabotegravir dose and/or frequency of drug administration. Indeed, in the ongoing LATTE-2 trial two doses are actually being investigated, i.e., 400 mg at 4-week intervals versus 600 mg at 8-week intervals, both combined with LA rilpivirine [18]. In this regard, the possible role of therapeutic drug monitoring (TDM) as a tool for optimizing the frequency of LAI cabotegravir administration has not yet been duly studied. However, the preclinical PrEP data showed a clear dose–response relationship [12–14]. Such evidence, together with anecdotal clinical reports from the ECLAIR study [32] and from LAI rilpivirine [33], foster the potential concerns related to the long pharmacokinetic tail of LAI antiretroviral formulations, usually associated with subtherapeutic drug concentrations which may facilitate the emergence of viral resistance. In these scenarios, TDM of cabotegravir might eventually be useful for the identification of patients requiring more versus less frequent LAI administrations.

Other potential concerns and challenges for LAI cabotegravir may relate to high-volume dosing and injection site reactions. On this regard, a new myristoylated cabotegravir prodrug with improved antiretroviral profiles has recently been developed with the goal of improving the drug delivery profile of LAI formulations [34]. This novel formulation formed crystals that are formulated into nanoparticles of a stable size and shape, facilitating avid monocyte-macrophage entry, retention and reticuloendothelial system depot formulation. Interestingly, studies in mice and macaques consistently showed that the pharmacokinetics of the myristoilated cabotegravir was four-times greater than that recorded with LAI cabotegravir [34]. Data in humans are, however, presently pending. Therefore, the LAI cabotegravir formulation (eventually combined with LAI rilpivirine for HIV treatment or as monotherapy for HIV PrEP) represents the most promising non-traditional delivery system of antiretrovirals for HIV treatment and prevention at the present time.

Compliance with Ethical Standards

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References

1. Walensky RP, Paltiel AD, Losina E, Mercincavage LM, Schackman BR, Sax PE, et al. The survival benefits of AIDS treatment in the United States. J Infect Dis. 2006;194:11–9.
2. Wada N, Jacobson LP, Cohen M, French A, Phair J, Muñoz A. Cause-specific life expectancies after 35 years of age for human immunodeficiency syndrome-infected and human immunodeficiency syndrome-negative individuals followed simultaneously in long-term cohort studies, 1984–2008. Am J Epidemiol. 2013;177:116–25.
3. Joulaei H, Shooshtarian S, Dianatinasab M. Is UNAIDS 90-90-90 target a dream or a reality for Middle East and North Africa region on ending the AIDS epidemic? A review study. AIDS Rev. 2018;20:83–93.
4. Landovitz RJ, Kofron R, McCauley M. The promise and pitfalls of long-acting injectable agents for HIV prevention. Curr Opin HIV AIDS. 2016;11:122–8.
5. Spreen WR, Margolis DA, Pottage JC Jr. Long-acting injectable antiretrovirals for HIV treatment and prevention. Curr Opin HIV AIDS. 2013;8:565–71.
6. Owen A, Rannard S. Strengths, weaknesses, opportunities and challenges for long acting injectable therapies: insights for applications in HIV therapy. Adv Drug Deliv Rev. 2016;103:144–56.
7. McPherson TD, Sobieszczyk ME, Markowitz M. Cabotegravir in the treatment and prevention of Human Immunodeficiency Virus-1. Expert Opin Investig Drugs. 2018;27:413–20.
8. Andrews CD, Heneine W. Cabotegravir long-acting for HIV-1 prevention. Curr Opin HIV AIDS. 2015;10:258–63.
9. Trezza C, Ford SL, Spreen W, Pan R, Piscitelli S. Formulation and pharmacology of long-acting cabotegravir. Curr Opin HIV AIDS. 2015;10:239–45.
10. Bowers GD, Culp A, Reese MJ, Tabolt G, Moss L, Piscitelli S, Huynh P, et al. Disposition and metabolism of cabotegravir: a comparison of biotransformation and excretion between different species and routes of administration in humans. Xenobiotica. 2016;46:147–62.
11. Jucker BM, Alsaid H, Rambo M, Lenhard SC, Hoang B, Xie F, et al. Multimodal imaging approach to examine biodistribution kinetics of Cabotegravir (GSK1265744) long acting parenteral formulation in rat. J Control Release. 2017;268:102–12.
12. Andrews CD, Spreen WR, Mohri H, Moss L, Ford S, Gettie A, et al. Long-acting integrase inhibitor protects macaques from intrarectal simian/human immunodeficiency virus. Science. 2014;343:1151–4.
13. Andrews CD, Yueh YL, Spreen WR, St Bernard L, Boente-Carrera M, Rodriguez K, Gettie A, et al. A long-acting integrase inhibitor protects female macaques from repeated high-dose intravaginal SHIV challenge. Sci Transl Med. 2015;7:270ra4.
14. Radzio J, Spreen W, Yueh YL, Mitchell J, Jenkins L, García-Lerma JG, et al. The long-acting integrase inhibitor GSK744 protects macaques from repeated intravaginal SHIV challenge. Sci Transl Med. 2015;7:270ra5.
15. Spreen W, Min S, Ford SL, Chen S, Lou Y, Bomar M, et al. Pharmacokinetics, safety, and monotherapy antiviral activity of GSK1265744, an HIV integrase strand transfer inhibitor. HIV Clin Trials. 2013;14:192–203.
16. Spreen W, Ford SL, Chen S, Wilfret D, Margolis D, Gould E, et al. GSK1265744 pharmacokinetics in plasma and tissue after single-dose long-acting injectable administration in healthy subjects. J Acquir Immune Defic Syndr. 2014;67:481–6.
17. Spreen W, Williams P, Margolis D, Ford SL, Crauwels H, Lou Y, et al. Pharmacokinetics, safety, and tolerability with repeat doses of GSK1265744 and rilpivirine (TMC278) long-acting nanosuspensions in healthy adults. J Acquir Immune Defic Syndr. 2014;67:487–92.
18. Margolis DA, Gonzalez-Garcia J, Stellbrink HJ, Eron JJ, Yazdanpanah Y, Podzamczer D, et al. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial. Lancet. 2017;390:1499–510.

19. Rajoli RKR, Back DJ, Rannard S, Meyers CF, Flexner C, Owen A, et al. In silico dose prediction for long-acting rilpivirine and cabotegravir administration to children and adolescents. Clin Pharmacokinet. 2018;57:255–66.
20. Podany AT, Scarsi KK, Fletcher CV. Comparative clinical pharmacokinetics and pharmacodynamics of HIV-1 integrase strand transfer inhibitors. Clin Pharmacokinet. 2017;56:25–40.
21. Park TE, Mohamed A, Kalabalik J, Sharma R. Review of integrase strand transfer inhibitors for the treatment of human immunodeficiency virus infection. Expert Rev Anti Infect Ther. 2015;13:1195–212.
22. Yoshinaga T, Kobayashi M, Seki T, Miki S, Wakasa-Morimoto C, Suyama-Kagitani A, et al. Antiviral characteristics of GSK1265744, an HIV integrase inhibitor dosed orally or by long-acting injection. Antimicrob Agents Chemother. 2015;59:397–406.
23. Neogi U, Singh K, Aralaguppe SG, Rogers LC, Njenda DT, Sarafianos SG, et al. Ex-vivo antiretroviral potency of newer integrase strand transfer inhibitors cabotegravir and bictegravir in HIV type 1 non-B subtypes. AIDS. 2018;32:469–76.
24. Lou Y, Buchanan AM, Chen S, Ford SL, Gould E, Margolis D, et al. Effect of cabotegravir on cardiac repolarization in healthy subjects. Clin Pharmacol Drug Dev. 2016;5:509–16.
25. Reese MJ, Bowers GD, Humphreys JE, Gould EP, Ford SL, Webster LO, et al. Drug interaction profile of the HIV integrase inhibitor cabotegravir: assessment from in vitro studies and a clinical investigation with midazolam. Xenobiotica. 2016;46:445–56.
26. Ford SL, Gould E, Chen S, Lou Y, Dumont E, Spreen W, et al. Effects of etravirine on the pharmacokinetics of the integrase inhibitor S/GSK1265744. Antimicrob Agents Chemother. 2013;57:277–80.
27. Ford SL, Gould E, Chen S, Margolis D, Spreen W, Crauwels H, et al. Lack of pharmacokinetic interaction between rilpivirine and integrase inhibitors dolutegravir and GSK1265744. Antimicrob Agents Chemother. 2013;57:5472–7.
28. Ford SL, Sutton K, Lou Y, Zhang Z, Tenorio A, Trezza C, et al. Effect of rifampin on the single-dose pharmacokinetics of oral cabotegravir in healthy subjects. Antimicrob Agents Chemother. 2017;61:e00487–517.
29. Ford S, Lou Y, Lewis N, D'Amico R, Spreen W, Patel P. Rifabutin (RBT) decreases cabotegravir (CAB) exposure following oral co-administration. In: 19th International Workshop on Clinical Pharmacology. Baltimore. 22–24 May 2018. Oral abstract 12.
30. Trezza C, Ford SL, Gould E, Lou Y, Huang C, Ritter JM, et al. Lack of effect of oral cabotegravir on the pharmacokinetics of a levonorgestrel/ethinyl oestradiol-containing oral contraceptive in healthy adult women. Br J Clin Pharmacol. 2017;83:1499–505.
31. Andrews CD, Bernard LS, Poon AY, Mohri H, Gettie N, Spreen WR, et al. Cabotegravir long acting injection protects macaques against intravenous challenge with SIVmac251. AIDS. 2017;31:461–7.
32. Markowitz M, Frank I, Grant RM, Mayer KH, Elion R, Goldstein D, et al. Safety and tolerability of long-acting cabotegravir injections in HIV-uninfected men (ECLAIR): a multicentre, double-blind, randomised, placebo-controlled, phase 2a trial. Lancet HIV. 2017;4:e331–40.
33. Penrose KJ, Parikh UM, Hamanishi KA, Else L, Back D, Boffito M, et al. Selection of rilpivirine-resistant HIV-1 in a seroconverter from the SSAT 040 trial who received the 300-mg dose of long-acting rilpivirine (TMC278LA). J Infect Dis. 2016;213:1013–7.
34. Zhou T, Su H, Dash P, Lin Z, Dyavar Shetty BL, Kocher T, et al. Creation of a nanoformulated cabotegravir prodrug with improved antiretroviral profiles. Biomaterials. 2018;151:53–65.