

Profile of cabotegravir and its potential in the treatment and prevention of HIV-1 infection: evidence to date

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Abstract: Modern antiretroviral therapy has demonstrated effectiveness in preexposure prophylaxis (PrEP) and treatment of HIV infection. There is a demand for prevention and treatment regimens that could overcome challenges of improving adherence, toxicity, and dosing convenience. Cabotegravir is an integrase strand transfer inhibitor and an analog of dolutegravir. Unlike dolutegravir, cabotegravir has a long half-life and can be formulated into a long-acting nanosuspension for parenteral administration. Initial pharmacokinetic studies in humans have demonstrated adequate drug levels with intramuscular (IM) administration at 4 weekly and 8 weekly intervals, with few interactions with commonly used concomitant medications. Preliminary animal PrEP studies have shown that IM cabotegravir can prevent simian/HIV acquisition from rectal, vaginal, and intravenous challenge. Currently, there are two ongoing Phase II studies assessing cabotegravir as a PrEP agent in humans: ÉCLAIR and HPTN077. Cabotegravir has been studied in combination with rilpivirine as long-acting IM maintenance therapy. The Long-Acting Antiretroviral Treatment Enabling study demonstrated that those switching to oral cabotegravir/rilpivirine once virologically suppressed were more likely to maintain suppression than those continuing standard efavirenz-based therapy (82% vs 71% at 24 weeks). Initial results of the Long-Acting Antiretroviral Treatment Enabling-2 study of parenteral regimens found that 12 weeks after randomization to parenteral or oral regimens, there was no difference in proportions virologically suppressed on cabotegravir/rilpivirine daily orally vs IM every 4 weeks or 8 weeks (91% vs 94% vs 95%). The injections were well tolerated as, although they caused injection site pain in most recipients, most participants reported satisfaction with parenteral therapy. Cabotegravir offers a new member of the integrase strand transfer inhibitor class with potential for alternative mode of delivery. We await Phase III studies to define its efficacy and real-world experience to learn which patient groups stand to benefit most from the novel mode of delivery of treatment and PrEP.

Keywords: integrase inhibitor, long-acting antiretroviral therapy, preexposure prophylaxis

Introduction

Modern combined antiretroviral therapy (ART) controls HIV infection and has reduced morbidity and mortality, with dramatic improvements in survival and quality of life for people living with HIV.^{1,2} With an increasing range of antiretroviral agents available, more individuals can be successfully treated with minimal toxicity and inconvenience. In addition, antiretroviral agents have been shown to prevent acquisition of HIV infection among high-risk individuals, used as either event-driven or ongoing preexposure prophylaxis (PrEP) as part of combination HIV prevention.³⁻⁸

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There are ongoing challenges in HIV treatment and prevention, including maximizing adherence, tolerability, and patient convenience while minimizing toxicity and cost. The simplest to administer single-tablet regimens can improve adherence and may reduce viremia and hospitalizations.^{9,10} Single-tablet regimens have also been used successfully in PrEP but are not suitable for every individual.^{5–8} Toxicity, resistance, and possible increased cardiovascular risk with the commonly used nucleos(t)ide reverse transcriptase inhibitor (NRTI) backbones have led to studies on NRTI-sparing treatment regimens with some success.^{11–14} The problems of NRTI toxicity, particularly the renal and bone toxicity,^{15,16} seen in prolonged treatment with tenofovir disoproxil fumarate and largely ameliorated by the use of tenofovir alafenamide¹⁷ are also relevant for PrEP regimens.^{3,4} Longer acting (LA) regimens could reduce the need for adherence to daily tablet regimens for treatment or prevention. Although parenterally administered drugs have operational challenges such as how and where an injection is delivered, a successful precedent is demonstrated in contraception and antipsychotic treatment.¹⁸ However, as demonstrated with LA contraceptive injection regimens, depot injection does not guarantee complete adherence.^{19,20} Additional concerns regarding LA antiretrovirals include the difficulty in withdrawing therapy for adverse effects once administered, potential for development of drug resistance during washout periods, and tolerability of regular injections, and these have led to questions on how to start and stop the regimens.²¹ Here, evidence to date on cabotegravir, its pharmacokinetics, and use as PrEP and treatment is reviewed and discussed.

Pharmacokinetics

Cabotegravir is an integrase strand transfer inhibitor (INSTI), from the carbamoyl pyridone class, and is an analog of dolutegravir.²² The INSTI class has moved quickly into routine use for HIV treatment since the licensing of the first-in-class raltegravir in late 2007²³ and now features as a preferred option in treatment guidelines globally.^{24–28} Unlike dolutegravir, cabotegravir has the unique feature of a long half-life and can be formulated as a nanoparticle injection that can be given at prolonged intervals. Therefore, cabotegravir has the potential to act as part of parenterally delivered LA treatment for or prevention of HIV infection. It can be used as single-agent PrEP or delivered with rilpivirine as LA injection maintenance therapy, which could potentially avoid NRTI-associated toxicity and increase therapeutic options. It is hoped that removing the need for daily adherence to oral medication may improve treatment success in individuals

who struggle with adherence, reducing HIV acquisition^{3,4} and the risk of progression to AIDS²⁹ or death.³⁰

Cabotegravir has properties in common with its analog dolutegravir, including a higher barrier to resistance than the earlier INSTIs raltegravir and elvitegravir²² and, while it has reduced efficacy in the presence of common INSTI mutations (G140S and Q148H, E92Q and N155H), it still demonstrates activity.^{31,32} Cabotegravir also has activity against all common clades of HIV-1 *in vitro*³¹ and good potency at low concentrations, with 5–30 mg daily oral dosing shown to reduce HIV-1 RNA by 2.2–2.3 log₁₀ in a 10-day monotherapy trial³³ and has a protein binding-adjusted 90% inhibitory concentration (IC₉₀) of 166 ng/mL.³⁴

Cabotegravir has an elimination half-life of ~40 days after oral administration,³⁵ compared with 13–14 hours for dolutegravir.³⁶ It also has low water solubility and high potency and can be formulated as a nanosuspension for LA injection at a concentration of 200 mg/mL.³³ Simulation using physiologically-based pharmacokinetic modeling has demonstrated that children would likely achieve sufficient cabotegravir concentrations with monthly weight-based dosing, suggesting feasibility of use in the pediatric population.³⁷

Cabotegravir is primarily metabolized by uridine 5'-diphosphoglucuronosyltransferase 1A1 (UGT1A1) with a contribution from UGT1A9 and is predominantly excreted in feces.³⁷ Cabotegravir is also a substrate of the drug efflux transporters p-glycoprotein and breast cancer resistance protein, both of which can be inhibited by protease inhibitors, though the impact of these transporters on the intestinal absorption of cabotegravir is thought to be minimal due to its high intrinsic membrane permeability.³⁷ It does not induce or inhibit cytochrome P450 (CYP) or UGT enzymes *in vitro* and is anticipated to have few drug–drug interactions.³⁷ In contrast to dolutegravir, *in vivo* concomitant dosing with midazolam (a CYP substrate) found no effect on the levels of either drug.³⁷ The induction of CYP3A by etravirine suggested that coadministration may decrease levels of cabotegravir, though this was not seen in studies of coadministration to healthy volunteers.³⁸ Cabotegravir also differs from dolutegravir in that it inhibits organic anion transporter (OAT) 1 and OAT3, whereas dolutegravir inhibits OAT2.³⁷ Therefore, cabotegravir has the potential to increase exposure to OAT1/3 substrates, the most commonly used being methotrexate and tenofovir. While concerns remain about coadministration raising methotrexate plasma concentrations, there is less concern regarding tenofovir as it appears to be adequately secreted via efflux through multidrug resistance-associated pump 4, which is not inhibited by cabotegravir.³⁷ Importantly,

a small study in healthy volunteers of coadministration with rifampicin showed that cabotegravir exposure was reduced by 59% by coadministration with rifampicin, and the 30 mg dose will therefore not be recommended for those taking rifampicin.³⁹ This is key for widespread use and feasibility in difficult-to-reach populations, since individuals starting rifampicin may need additional oral cabotegravir to supplement LA dosing. Recommended dose adjustments are yet to be defined.

The nonnucleoside reverse transcriptase inhibitor (NNRTI) rilpivirine also has a long elimination half-life⁴⁰ (~45 hours) and is being investigated for use with cabotegravir as LA maintenance ART. Cabotegravir and rilpivirine have been coadministered with no significant effect on plasma concentrations of either drug.⁴¹ Studies have also demonstrated safe coadministration when both drugs are given intramuscularly (IM). Regimens in which rilpivirine 1,200 mg loading dose was given followed by 900 mg monthly injections coupled with IM 800 mg cabotegravir loading dose and either 200 mg IM or 400 mg IM 4 weekly produced steady-state rilpivirine levels equivalent to regular oral dosing and cabotegravir concentrations above the target of $>IC_{90}$ four times consistently through therapy, persisting for 2 months after the last IM administration.³⁴

Initial macaque models led to the postulated target plasma cabotegravir concentration of $>4\times IC_{90}$ as potentially effective PrEP for human trials.⁴² To evaluate pharmacokinetics in humans, IM doses of 100 mg, 200 mg, 400 mg, and 800 mg as well as 100 mg, 200 mg, and 400 mg subcutaneously were administered to healthy subjects. All six individuals given one 800 mg IM injection maintained blood concentrations of over four times IC_{90} for 16 weeks.³³ This result was repeated when 800 mg IM dosing was given at 12-week intervals to ten subjects who then maintained cabotegravir concentrations in the target range for the full 24 weeks.³⁴ However, in the larger ÉCLAIR study (Evaluate the Safety, Tolerability and Acceptability of Long Acting Infections of the HIV Integrase Inhibitor GSK1265744 in HIV-Uninfected Men), pharmacokinetic measurements in 91 participants given 800 mg IM every 12 weeks for a total of three injections found that mean plasma cabotegravir concentrations were below the target $>4\times IC_{90}$, and investigators planned to proceed with a dose of 600 mg IM at 8-week intervals.⁴³ Adequate drug exposure ($>4\times IC_{90}$) was also seen in monthly dosing regimens given at 400 mg IM once or as two separate 200 mg IM injections.³³ Target concentrations were also met using subcutaneous regimens, which have the advantage of being patient-administered.³³ Of interest, though with uncertain

relevance to PrEP, cabotegravir concentrations were lower in genital compartments, with female genital tract concentrations 16%–28% of median plasma concentrations and rectal tissue $<8\%$ of plasma concentrations.³³ Similar lower cabotegravir levels were also found in the vaginal, cervical, and rectal tissue in macaque studies, which still found cabotegravir effective as PrEP.^{42,44}

Preexposure prophylaxis

The potential for cabotegravir as PrEP is still under evaluation with macaque models demonstrating good efficacy and human studies now at Phase IIa, with a Phase IIb/III comparative study recruiting soon.⁴⁵ Macaque studies have evaluated cabotegravir as PrEP against simian/human immunodeficiency virus SF162P3 (SHIV_{SF162P3}), an R5-tropic enveloped virus close to commonly transmitted HIV strains.⁴⁶ The same models have previously accurately predicted the efficacy of tenofovir and tenofovir/emtricitabine as PrEP in humans.^{6,47} It is possible for macaques to achieve equivalent plasma concentrations of cabotegravir to those targeted in humans,^{32,44} though simians, in common with most smaller mammals, are known to metabolize drugs at a faster rate than humans,⁴⁸ and for this reason, an increased frequency of dosing of cabotegravir is used in macaque trials to achieve the same target of $>4\times IC_{90}$.^{42,44}

Macaque models have been used to assess the efficacy of cabotegravir as a PrEP agent against common routes of human infection: intravaginal, rectal, and intravenous. Studies of intravaginal drug administration have found good efficacy: in one study, six pigtail macaques given IM cabotegravir and then subjected to repeat vaginal SHIV inoculum at low concentration over 12 weeks did not acquire SHIV, while all six macaques in the placebo arm were rapidly infected.⁴² In a previous study,⁴⁴ two of eight rhesus macaques dosed with IM depot medroxyprogesterone acetate to make their vaginal tissue more closely mimic that of humans developed SHIV after cabotegravir administration, compared with all four controls. In the two infected macaques, measured cabotegravir concentrations were the same as the uninfected macaques and above target concentrations throughout, meaning the acquisitions could not be linked to plasma cabotegravir concentrations. In the two infected animals, no INSTI resistance and no specific variation in the sequence of the infecting virus from the initial inoculum and virus isolated from the infected controls was found. Authors postulated that SHIV acquisition resulted from initial local infection of vaginal tissue, with subsequent viral dissemination out of that tissue compartment as plasma drug levels fell. There was concern

in this rhesus macaque model about the lower concentrations of cabotegravir in the genital tract, the concomitant use of depot medroxyprogesterone acetate causing excessive thinning of the vaginal epithelium,⁴⁴ and a higher dose of SHIV inoculum than would occur in human semen, suggesting that this model is less reflective of human physiology than the pigtail macaque model.⁴⁹

Cabotegravir also has demonstrated efficacy against rectal SHIV challenge in macaques. In a repeat challenge study, the eight macaques treated with cabotegravir did not acquire SHIV during periods of target plasma concentrations and during washout, while those given placebo acquired SHIV rapidly. A follow-up experiment within the same study was conducted to determine minimal drug concentrations that afford protection. In this experiment, a single dose of cabotegravir was given to 12 macaques followed by repeat weekly rectal challenge until acquisition occurred. Infection occurred at a median of 10 weeks (range 6–17 weeks), leading to estimations that IM cabotegravir has a 28-fold protective effect compared with placebo and that concentrations of $>3\times$ IC₉₀ had a 100% protective effect, while concentrations $>1\times$ IC₉₀ had 97% protective effect against perrectal infection.⁴⁴

An intravenous SHIV challenge study in macaques, designed to use cabotegravir doses to replicate drug concentrations shown to be protective in genital challenge experiments, found that 21/24 macaques treated with cabotegravir remained uninfected compared with none of the controls. Drug concentration at the time of challenge was closely associated with virus acquisition, with mean drug concentration being higher in uninfected macaques (2.58 µg/mL [range 1.00–5.56 µg/mL; n=21]) than in the infected (1.17 µg/mL [range 0.67–1.93 µg/mL; n=3]).⁵⁰ These results suggest a role for cabotegravir as PrEP in people who inject drugs.

Currently, there are two ongoing studies of cabotegravir as PrEP: ÉCLAIR and HPTN (HIV Prevention Trials Network) 077.^{51,52} As with early pharmacokinetic studies of injectable cabotegravir LA, both include a 4-week lead-in of oral drug and a 1-week washout period prior to injection to establish toxicity and tolerability.^{33,51,52} ÉCLAIR is a Phase IIa study randomizing 127 men at low risk of acquiring HIV to receive cabotegravir IM or placebo at a 5:1 ratio. As mentioned earlier, it has led to a newer proposed regimen of 600 mg IM every 8 weeks due to lower than expected mean plasma concentrations.⁵⁰ HPTN077 aims to recruit 194 males and females to be randomized 3:1 to receive cabotegravir 800 mg IM (as two 400 mg injections) every

12 weeks after oral lead-in or placebo; 12-week results are expected in 2017.⁵²

HIV-1 treatment studies

The major cabotegravir treatment studies to date are the Phase II Long-Acting Antiretroviral Treatment Enabling (LATTE-1)⁵³ (oral cabotegravir/rilpivirine dual therapy) and LATTE-2⁵³ (parenteral dual therapy), which have reported results to 96 weeks and 32 weeks, respectively.

In the dose-ranging LATTE-1, in the USA and Canada, 243 ART-naïve HIV-positive individuals with viral load $>1,000$ copies/mL, CD4⁺ T-cell count >200 cells/µL, and no major drug resistance-associated mutations were randomized 1:1:1:1, stratified by viral load and chosen NRTI backbone, to receive oral cabotegravir once daily (od) at 10 mg, 30 mg, or 60 mg or efavirenz 600 mg od, all with a dual NRTI backbone (investigator-selected tenofovir/emtricitabine or abacavir/lamivudine). The median viral load was 4.31 log copies/mL and median CD4 count 416 cells/µL. Study participants were 96% male (with women more likely to be excluded at screening because of restrictions on pregnancy and hormonal contraception), 62% White, and 31% African or African-American. At week 24, those in the cabotegravir arms who were virologically suppressed switched to a two-drug maintenance regimen of oral cabotegravir at the randomized dose plus rilpivirine 25 mg. The primary end point was virological suppression at <50 copies/mL at week 48 (24 weeks of maintenance therapy). Virological suppression and continuation to maintenance at 24 weeks was achieved in 207 participants, with more discontinuations due to adverse events in the efavirenz than cabotegravir arms (9/62 [15%] vs 6/181 [3%]) and a shorter time to suppression in the cabotegravir groups, as would be expected for an INSTI-containing regimen. At 48 weeks, proportions with virological suppression were 82% in the combined cabotegravir vs 71% in the efavirenz groups, and at 96 weeks (72 weeks of maintenance therapy), suppression was achieved in 76% of individuals in the combined cabotegravir groups and 84% in the efavirenz group (Table 1). Among those with baseline viral loads $>100,000$ copies/mL, no differences were seen, although numbers were small. One participant developed INSTI resistance mutations by week 48 but that individual had evidence of cabotegravir and rilpivirine exposure $<50\%$ of study average during induction and maintenance phases. No patients were inadvertently enrolled into LATTE-1 with preexisting NNRTI resistance.

These results are consistent with the dolutegravir vs efavirenz studies,^{54,55} and a 30 mg dose of cabotegravir was

Table 1 Summary of LATTE-1 study results – treatment efficacy

Study group (dose of cabotegravir)	Number starting regimen at 24 weeks	Number with VL <50 at week 48 (24 weeks of investigational combination) for ITT-E population	Number with VL <50 at week 96 (72 weeks of investigational combination) for per-protocol population	No virological data or discontinuation for reason other than nonresponse
10 mg	52/60	48/60 (80%)	41/52 (79%)	6
30 mg	53/60	48/60 (80%)	45/53 (85%)	5
60 mg	55/61	53/61 (87%)	51/55 (93%)	3
EFV + 2 NRTI	–/62 ^a	44/62 (71%)	39/47 (83%)	14

Notes: In LATTE-1 to 48 weeks and 96 weeks (as all-oral od regimen with rilpivirine 25 mg).⁵² ^aAll those in the EFV group who completed the week 24 visit were eligible to continue into the continuation phase on the same regimen, regardless of virological suppression.

Abbreviations: EFV, efavirenz; ITT-E, intention-to-treat, exposed; LATTE, Long-Acting Antiretroviral Treatment Enabling; NRTI, nucleos(t)ide reverse transcriptase inhibitor; od, once daily; VL, viral load.

Table 2 Summary of LATTE-2 study results – treatment efficacy

Regimen from 20 weeks as maintenance	Number with VL <50 at 32 weeks (12 weeks maintenance) in ITT-maintenance exposed analysis	Virological nonresponse at 32 weeks
CAB 400 mg, RPV 600 mg q 4 weeks IM	108/115 (94%)	1 (<1%)
CAB 600 mg, RPV 900 mg q 8 weeks IM	109/115 (95%)	5 (4%)
CAB 30 mg, ABC/3TC od oral	51/56 (91%)	2 (4%)

Note: In LATTE-2 to 32 weeks (oral induction followed by parenteral maintenance therapy).⁵⁶

Abbreviations: ABC, abacavir; CAB, cabotegravir; IM, intramuscular; ITT, intention-to-treat; LATTE, Long-Acting Antiretroviral Treatment Enabling; od, once daily; RPV, rilpivirine; 3TC, lamivudine; VL, viral load.

chosen to proceed based on close review of reasons for discontinuation in each group. Adverse events reported for cabotegravir included the headache and insomnia common with dolutegravir use. There were two individuals with known steatohepatitis receiving 60 mg of cabotegravir who developed raised transaminase levels over eight times the upper limit of normal with no other explanation that resolved on drug discontinuation. These adverse events will need to be further investigated in Phase III trials and caution against parenteral, long-acting therapy without oral lead-in for the ART naive.⁵³

In the subsequent Phase IIb LATTE-2 study, not yet published but with 32-week data presented as a late-breaking abstract at CROI 2016, investigation moved on to the parenteral formulations, evaluating not only the INSTI–NNRTI dual therapy combination but also long-acting parenteral therapy as treatment for HIV-1. This study again enrolled ART-naive individuals, in Europe and North America, and started a regimen of abacavir, lamivudine, and cabotegravir 30 mg od for a 20-week induction period. In the final 4 weeks of the induction phase, rilpivirine 25 mg od was added to the induction regimen as a lead-in to assess drug safety and tolerability. Those with a measured undetectable HIV RNA during weeks 16–20 were randomized 2:2:1 to IM cabotegravir 400 mg/rilpivirine 600 mg every four weeks; cabotegravir 600 mg/rilpivirine 900 mg every 8 weeks or continuation of the induction oral regimen as maintenance therapy. The primary end point was virological failure and safety at 32 weeks of maintenance therapy using the Food

and Drug Administration snapshot analysis. Both parenteral therapy groups had a cabotegravir loading dose at day 1, and the 8 weekly dosing group also had an additional loading dose at week 4.

At 20 weeks, 91% of 309 individuals starting the study had undetectable viral loads and were randomized. At 32 weeks of maintenance therapy, proportions with undetectable viral loads were 94% (4 weekly parenteral therapy); 95% (8 weekly parenteral therapy), and 91% (oral therapy), where most of those considered failure were not due to virological failure and the two who did have virological failure did not have detectable resistance (Table 2). Most in the parenteral therapy groups (92%) reported injection site reactions (ISRs), lasting a median 3 days, but most (82%) of these were grade 1 or minor and proportions reporting ISRs reduced over time to 33% at week 32.⁵⁶

Pharmacokinetic substudies of the parenteral drugs showed cabotegravir concentrations within the same range as for oral dosing in the earlier LATTE-1 study. For rilpivirine, drug concentrations were lower in the initial weeks of parenteral therapy, and it may be that other delivery strategies are required for the accompanying NNRTI. It is planned that the 48-week data will contribute to selection of a dose for future Phase III trials of this regimen,⁵⁶ which are in preparation for naive and experienced populations.

Tolerability of long-acting injections

One of the key questions in the long-term feasibility of LA cabotegravir treatment regimens is whether patients will find

improved or at least equivalent tolerability compared with oral regimens. The most common systemic side effect in all those administered cabotegravir was headache (7%), and the only dose-dependent side effect was insomnia. Other side effects included nausea and diarrhea.⁵³ The most common adverse effect of LA cabotegravir was ISR including pain (71%–92%), erythema (9%), and nodule formation (7%).^{34,56} ISRs occurred twice as frequently in participants receiving cabotegravir than in the placebo arm but were not dose dependent. Nodule formation was associated with subcutaneous administration and not with an IM route.³⁴ Notably, those in the 4 weekly parenteral therapy arm suffered slightly more adverse events and discontinuations than those in the 8 weekly therapy arm, and 1% reported less satisfaction than with oral induction therapy, compared with no reports of lower satisfaction in the 8 weekly arm.⁵⁴ Initial results from Phase IIa study found that although a majority had anxiety and experienced pain following injections,²¹ 93.8% of participants using cabotegravir as PrEP in the ÉCLAIR study expressed an interest in continuing if it was effective,²¹ and 74% of participants on a 12 weekly regimen said they were happy to continue, with 62.5% expressing preference for IM over oral cabotegravir.⁵⁷ However, this will need to be repeated in a real-world setting, including individuals who have struggled with adherence outside of clinical trial settings, or those without an enteral route of drug administration, to get a more representative view of likely treatment satisfaction postmarketing.

Conclusion and future outlook

Cabotegravir as a long-acting preparation has to date shown great potential both as PrEP and treatment for HIV-1. Macaque studies demonstrate good efficacy and proof of principle for PrEP for the major human transmission routes of intravaginal, intra-anal, and intravenous. The intravenous inoculum protection route may have particular significance in populations in which the HIV epidemic is driven by injecting drug use. At present, there is still uncertainty around the ideal dosing and its penetration into vaginal and rectal tissues, and no direct comparison with other PrEP regimens to fully assess efficacy, although at the time of writing, work has begun on a randomized, placebo-controlled trial comparing cabotegravir with tenofovir/emtricitabine as PrEP, which plans to report in 2020.⁴⁵ Studies are also limited by being animal models in a laboratory environment where the inoculum is delivered in a controlled manner not accounting for real-world factors such as variable sexual practices or the presence of other sexually transmitted infections.

Demonstration of efficacy in humans in real-world settings is needed, and trials are underway.

Results are also very promising for rilpivirine and cabotegravir as a dual combination in a provisional success for NRTI-sparing, protease inhibitor-sparing dual therapy.^{53,56} The IM regimen is unlikely to be a panacea for those with adherence difficulties, as those starting ART with a plan for long-acting parenteral therapy are likely always to require oral lead in, which necessitates high adherence at least in the short term. In addition, parenteral therapy is, for now, limited to those without resistance to rilpivirine, which may be an issue for many highly experienced individuals who struggle with adherence, due to multiple previous regimens and may limit the reach of this therapy with its promise to solve adherence-related virological failure.

This novel drug, which has so far demonstrated good efficacy in trials, has great promise as a future therapy. Despite some pain and anxiety being reported by trial participants, it is well tolerated and often a more popular option than oral equivalents.

Cabotegravir now needs to be studied in larger, Phase III studies of more diverse patient groups, since most LATTE participants were Caucasian men and all in developed country settings. Looking further into the future, these regimens could be most useful in difficult-to-reach populations, where health care delivery is most challenging. As well as work on further pharmacokinetic studies and use in those with hepatic and renal impairment, we look forward to results of comparative trials of PrEP⁴⁵ and upcoming Phase III treatment trials in both naive and experienced populations that hope to bring this drug into the clinical setting.

Disclosure

The authors report no conflicts of interest in this work.

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