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# The Promise and Pitfalls of Long Acting Injectable Agents for HIV Prevention

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## Abstract

**Purpose of review—**Pre-exposure prophyalxis (PrEP) for HIV prevention is highly effective when taken as prescribed. Adherence to required dosing regimens for protection may pose challenges. Long Acting agents for HIV prevention may have the potential to improve adherence via favorable pharmacokinetics supportive of infrequent dosing. This review focuses on the potential benefits and considerations for the study and use of two long acting injectable agents, cabotegravir (GSK1265744 LA, CAB LA) and rilpivirine (TMC278 LA, RPV LA), for use as chemoprophylaxis for HIV prevention.

**Recent findings—**Oral RPV is FDA approved for HIV treatment (in combination with other antiretrovirals). Both CAB LA and RPV LA are currently in Phase 2a safety/tolerability/ pharmacokinetic studies in anticipation and support of future efficacy evaluation. Both agents have favorable pharmacokinetics, and use is complicated by injection site reactions.

**Summary—**Long acting injectable formulations, if safe and well tolerated, may improve pharmacokinetic coverage of exposures to HIV infection. Complexities around safety, tolerability, and starting/stopping protocols require careful consideration.

### Keywords

cabotegravir; rilpivirine; long-acting injectable antiretroviral; HIV-1; Preexposure Prophylaxis

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## Introduction

Chemoprophylaxis for the prevention of HIV infection has been revolutionized by recent studies showing high-levels of protection against rectal exposures by daily oral tenofovir/emtricitabine (TDF/FTC) [1–4] and by vaginal exposure in a study of HIV discordant couples [5]. Robust efficacy data led to the approval of daily oral TDF/FTC by the US Food and Drug Administration in 2012, for men and women who are at high risk of becoming HIV infected. The registrational studies also indicate a clear dose-response relationship of protection and adherence [6,7]. Although the protection afforded by daily oral use of TDF/FTC has been modeled to be 99% when taken 7 days per week as prescribed, modeled data and clinical cohorts suggest some forgiveness of missed doses for protection against rectal exposures – as few as 4 doses per week appears to preserve high levels of protective efficacy [2,8]. Protection against vaginal exposures has been less rigorously described, but is modeled to be much less forgiving of missed doses than are rectal exposures [9]. This is believed to be attributable to differential tissue pharmacokinetics of the components of TDF/FTC in rectal and cervicovaginal matrices [10]. The challenges of daily or near-daily oral dosing strategies, and the long-term maintenance of such dosing have driven interest in PrEP agents that have more convenient dosing schedules.

The field of long acting (LA) injectable agents has substantial precedent among antipsychotics (e.g., paliperidone palmitate) and contraception (e.g., medroxyprogesterone acetate). Removable depots of contraceptive agents (Norplant), and transdermal patches for sustained drug delivery are attractive, but are limited by molecular size and chemical properties including hydrophobicity and charge. Technologies are evolving rapidly, and a recent presentation of an implantable system appears capable of delivering tenofovir alafenamide (TAF) in sustained fashion in a dog model [11].

For HIV, LA agents have the potential advantage of requiring less-than-daily dosing intervals, some dosed as infrequently as every 2 to 3 months. All LA HIV antiviral agents currently in development require parenteral injections – via subcutaneous, intramuscular (IM), or intravenous routes of administration. Once administered, a LA injectable agent for prevention of HIV would anticipate provision of “coverage” for HIV exposures during the period at which protective levels of the agent remained in the individual. While the exact tissue and/or or plasma correlates of protection remain undefined, LA Injectable agents are intended to provide sustained drug levels in serum, plasma, and relevant mucosal tissues. They additionally have the potential for reduced gastrointestinal toxicity, as well as avoiding some drug-drug interactions. Although LA agents would obviate the need for daily pill taking, they raise novel challenges regarding adherence, safety, and optimizing starting and stopping mechanisms. Two chemical entities are in advanced stages of clinical development for LA prophylactic use (Table 1).

It will be important to evaluate whether cultural or social norms will make the use of injections for HIV prevention differentially acceptable in diverse populations globally. For this reason, evaluation of such perceptions and acceptability are important to capture as part of early phase development programs.

## Cabotegravir

Cabotegravir (CAB, formerly GSK 1265744, ViiV Healthcare) is a novel investigational strand-transfer integrase inhibitor. CAB is a chemical congener of dolutegravir (DTG), with nanomolar in vitro activity against HIV-1 clinical isolates. It is available as both a short acting oral formulation with a half-life of 40 hours, and a LA injectable formulation comprised solely of active drug nanocrystals and not encased in a polymer, micelle, or lipid matrix. The LA formulation has a plasma half-life of 21–50 days. Macaque rectal and vaginal challenge models demonstrate high levels of protection against SHIV acquisition at supraphysiologic challenge doses at drug levels above 3-fold the PA-IC90 for rectal exposures and 4-fold PA-IC90 for vaginal exposures (PA-IC90 is 0.166 ug/mL) [12,13]. Oral CAB 10 mg QD approximates such levels at steady state. CAB LA at a dose of 800 mg administered every 8–12 weeks provides trough levels approximately 6-fold PA-IC90. The 800 mg dose is administered as two simultaneous gluteal IM injections of 2mL each, after which plasma levels are detectable up to 52 weeks after an injection. Because there is no way to remove the drug once injected, a 4-week “lead-in” strategy using oral CAB has been utilized to establish safety parameters. A 30 mg QD dose has been chosen for the oral lead-in to provide sufficient margin of excess above the 3–4 fold PA-IC90 prophylactic target level while being a sensitive probe for drug-related adverse events. Ideally, a LA injectable agent aimed at those challenged by daily oral pill-taking would not require an oral lead-in period; however, this requirement is likely to persist absent extensive safety experience with such agents.

CAB, in combination with other anti-HIV antiretroviral agents, has been investigated for treatment of HIV infection in Phase 2a and ongoing 2b studies. In the LATTE trial, oral CAB at doses of 10, 30, and 60 mg daily, in addition to two nucleoside-analog reverse transcriptase inhibitors, were virologically non-inferior to a dual-nucleoside plus efavirenz regimen; and virologic non-inferiority was maintained after virologically suppressed CAB-treated participants “simplified” their regimens to CAB plus oral rilpivirine (RPV) at both 48 and 96 weeks of total treatment [14,15]. The ongoing LATTE-2 trial is evaluating oral CAB 30 mg QD with dual nucleosides as a lead-in to virologic suppression prior to transition to IM CAB LA plus IM RPV LA (dosed 400 mg (1 × 2 mL) every 4 or 600 mg (1 × 3 mL) every 8 weeks – each with an 800 mg (2 × 2 mL) loading dose, and the every 8 week regimen with an initial one-time week 4 600 mg supplement); again, efavirenz with dual nucleosides is the control comparator.

Evaluation of CAB as a potential PrEP agent is currently in Phase 2a evaluation: The ÉCLAIR study enrolled 127 US-based HIV-uninfected low-risk men in a safety, tolerability, and PK evaluation that employed a 4-week oral lead-in followed by three quarterly IM injection doses, with a 52-week follow-up period after the final injection. ÉCLAIR is randomized 5:1 active CAB: placebo, with data expected in mid-2015. The ongoing HPTN 077 is enrolling 176 low-risk men and women globally to further evaluate safety, tolerability, and PK in broader populations. A 3:1 active CAB: placebo randomization is being used, with data expected in late 2016. It is anticipated that these Phase 2a studies will be followed by efficacy studies in populations of men, transgender women, and women at high risk of acquiring HIV infection. Considerations for the design of phase 3 efficacy

studies for prevention are complex and nuanced now that daily oral TDF/FTC has a robust supportive body of evidence for HIV prevention; the results of upcoming dapivirine ring studies, if positive, may additionally complicate these issue for women. A detailed discussion of the ethics of phase 3 efficacy study designs for HIV prevention is provided in an additional article in this issue [28].

### Rilpivirine

Rilpivirine (RPV, Edurant, Janssen Scientific) was approved by the FDA in May 2011 for the treatment of HIV-1 infection at an oral dose of 25 mg daily. It is a small-molecule non-nucleoside reverse transcriptase inhibitor with picomolar activity against HIV-1 primary clinical isolates [16]. Oral RPV is indicated for HIV-1-infected individuals with viral loads <100,000 c/mL, and is being developed as a LA injectable preparation (also referred to as TMC278LA or RPV LA) [17]. The RPV LA has undergone a series of formulation revisions in order to optimize pharmacokinetics: The particle size and suspension fluid have evolved, with the current formulation (G001) having a particle size of approximately 200 nm in a poloxamer 338 suspension of 300 mg/mL of RPV. Like cabotegravir, rilpivirine is comprised of the pure parent compound and not encased in a nanoparticle or micelle. The dose being brought into prevention trials is 1200 mg, requiring 2 × 2 mL IM gluteal injections. For treatment, RPV LA is being evaluated at doses of 600 mg (1 × 2 mL) every 4 weeks, and 900 mg (1 × 3 mL) every 8 weeks.

Humanized bone marrow/liver/thymus mouse studies suggest that RPV LA level remain above the IC90 level for 4 weeks after a single IM dose, as well as providing protection against vaginal viral challenges for 3–4 weeks post dosing [18]. Phase I studies after single doses suggest pharmacokinetics supporting every 8-week dosing for prevention as well as approximately 2-fold excess concentration in rectal tissue over cervico-vaginal tissues [19]. Explant challenge models suggest rectal tissue protection as delayed as 4-months post dosing, but absence of such protection in a comparable cervicovaginal model [20]. One female participant, followed after a single dose of 300 mg IM of RPV LA in a compartment PK study reporting an exposure approximately 40 days post injection seroconverted approximately 120 days post-dosing (80 days post-exposure) with K101E virus, conferring resistance to the NNRTI class [21].

RPV LA is now being evaluated in HPTN 076, a Phase 2a safety and acceptability study enrolling 132 HIV-uninfected low-risk women in the US and sub-Saharan Africa in a 2:1 active RPV: placebo randomization. The study also employs a 4-week oral lead-in (uniquely employing direct observed therapy to assure oral drug exposure prior to LA dosing), followed by a series of 6 injections of 1200 mg each at 8-week intervals, followed by a 32-week observational period during drug “washout.” Results are expected in early 2017.

## Adherence

Although LA agents obviate the need for a daily or peri-coital pill-taking activity, adherence to injections still requires consumers to comply with even infrequent injections. During clinical trials, injections are administered in a clinic-based setting as a gluteal intramuscular injection – essentially a directly observed therapy (DOT) strategy if the individual presents

to the clinical appointment. If a LA agent becomes approved for prevention by regulatory agencies, issues regarding administration will require thoughtful consideration, either employing family members/friends to give the injections or potentially allowing self-administration. While potentially offering the advantage of not requiring clinic visits for administration, home dosing becomes challenging to characterize and track. Decay pharmacokinetics will need to be sufficiently well defined as to allow clear guidance to users how “late” after the next injection is due protection would be expected to be maintained, and careful guidance developed for late or missed doses. The injectable contraception literature suggests a high rate of non-adherence after initial injectable hormonal contraception use [22,23], and for this reason, even a LA injectable PrEP formulation would not be expected to solve adherence challenges for all patients.

## Safety and Tolerability

As both cabotegravir and rilpivirine’s LA preparations contain nanocrystals of the pure parent compound, there is hope that the LA preparation will not have a substantially different safety profile from the short-acting version of each respective agent – save for complications from the injection itself, injection site reactions (ISRs). The potentially serious safety concern is the non-removability of the preparation if an idiosyncratic or known AE occurs after the injectable is delivered.

### Cabotegravir – Clinical Experience To Date

Approximately 1000 individuals have received the non-FDA approved cabotegravir, divided approximately equally between HIV-infected and HIV-uninfected individuals, and with half receiving the short-acting oral tablet formulation only, and half receiving the LA preparation or both the oral tablet and the LA preparation. In the LATTE study, doses of 10, 30 and 60 mg daily were administered to HIV-infected treatment naïve participants in combination with two nucleoside reverse transcriptase inhibitors (NRTIs), and compared to two NRTI’s with efavirenz. Treatment emergent adverse events included headache, nausea, and diarrhea for cabotegravir-treated participants. Insomnia appeared to be the only adverse event for cabotegravir with a dose-response association [24]. Treatment emergent elevations in alanine aminotransferase (ALT) were more common in cabotegravir groups, and were correlated with dose level. Three participants (two with evidence of steatohepatitis at baseline and one HIV/HCV co-infected) developed serious ALT elevations. All were clinically asymptomatic and ALT abnormalities resolved with withdrawal of the study medication. For the LA preparation, no ALT abnormalities have been reported requiring discontinuation of study product.

In completed studies, ISRs occurred in the majority of participants following IM (74% with any ISR) dosing; however, the reactions were generally mild to moderate (overall ISR Grade 2: 14% in IM without any Grade 3 or 4 ISRs [25]. The most frequent ISRs for IM dosing were pain (71%), erythema (9%) and nodules (7%). Median IM ISR durations were approximately 5 days for pain and erythema, and approximately 22 days for nodules [26].

Data from the ongoing ÉCLAIR and LATTE-2 studies is preliminary, but has generally been consistent with prior data with few withdrawals due to injection-related tolerability (3

discontinuations in ongoing studies). The majority of ISRs have been mild or moderate, with a small percentage of participants reporting more significant (Grade 3) pain/discomfort.

Concern has been raised about the volume of injections and their acceptability. The current preparation of LA cabotegravir is 200 mg/mL; doses under evaluation for treatment and prevention therefore would be 3–4 mL. A 3mL injection could potentially be delivered as a single injection; a 4mL total injection volume would have to be administered as two simultaneous 2mL injections; one in each buttock. The acceptability of such injections at 4–12 week intervals is currently under evaluation in ongoing Phase 2 trials..

### Rilpivirine – Clinical Experience To Date

Over 2000 study participants were exposed to oral rilpivirine (TMC278) during its clinical development, and it was approved by the FDA for the treatment of HIV-1 infection in combination with other antiretroviral agents in 2011. In the Phase 3 registrational studies, the most commonly reported AEs in the TMC278 group were headache, nausea, diarrhea, nasopharyngitis, insomnia, and dizziness, all with similar incidences in the control group, except for dizziness [27]. The majority of AEs were mild to moderate in severity. Treatment emergent laboratory abnormalities include increases in serum creatinine (usually 0.1 mg/dL), reductions in serum cortisol (and ACTH-stimulated cortisol), and increases in ALT, AST and total bilirubin. Post-marketing experience has found instances of nephrotic syndrome and severe cutaneous reactions including DRESS.

To date, more than 200 individuals have been exposed to TMC278 LA in completed and ongoing studies. Overall, the injections have been well tolerated and safe. ISRs have been the most common adverse events. There have been no safety or tolerability observations that preclude multiple dosing.

## Starting Strategies: The Oral Lead-in

As mentioned above, both cabotegravir and rilpirivine's developmental programs are employing an oral lead-in period prior to the administration of the LA preparation. Although it is somewhat antithetical to the purpose of developing a LA preparation to obligate a daily oral run-in, at minimum until the safety profile of the LA preparation is informed by a larger number of exposures, an oral phase will likely be part of both product's initial labeling if approved for HIV prevention.

Clearly, a given person's tolerance of an oral lead-in does not obviate concern for an idiosyncratic or late-onset toxicity at a later time-point after injection – however, the intent is to prevent prolonged exposure in individuals who have a fulminant early reaction or issues with tolerability. Adherence to the oral lead-in period may also compromise sensitivity; counseling around the reason for the lead-in will need to be carefully crafted in order to maximize comprehension of the rationale, whereas the lead-in may otherwise be viewed negatively or as expendable, awaiting the desired injectable preparation. As mentioned, a DOT strategy in the rilipivirine phase 2a studies attempts to maximize pre-injection exposure, however this strategy is unlikely to be tenable in clinical practice.

## Stopping Strategies: The Prolonged pharmacologic “tail”

In considering discontinuation of LA injectable products, the timeline for loss of protective effect will be a critical parameter to determine: How long after the final injection does protection wane? An additional concern then becomes whether as drug levels decline during such a “wash out,” would exposure to HIV resulting in seroconversion select for resistant virus? As noted above, a single case of seroconversion with NNRTI-resistant virus has been documented in a seroconversion event during the pharmacokinetic “wash out” period of a single dose of rilpivirine LA 300 mg during a Phase I tissue PK study [21]. This single case suggests that particularly in high-risk populations in whom LA injectables are being used for HIV-prevention, it may be advisable to “cover” the pharmacologic tail of the injectable agent with daily oral TDF/FTC. The strength of such a recommendation would likely be governed by the reason for discontinuation and ongoing risk profile of the individual.

## Other long-acting chemoprophylactic agents

Other pharmacologic preparations are in pre-clinical and various stages of clinical development to provide prolonged drug exposures either as a result of nanosuspensions, novel vehicles or delivery systems, or immunomodulatory effects. These include vaginal rings delivering single or multiple ART agents, vaginal and rectal gels, fibers, and pessaries, implantable drug delivery systems, and infused monoclonal antibody preparations (broadly neutralizing antibodies and anti-CD4/anti-gp120 preparations). Of course, a prophylactic HIV vaccine, particularly one providing high levels of broad protection with finite dosing and good tolerability, is the “gold standard” from a public health perspective.

## Conclusions

Until such time as a highly effective preventive vaccine against HIV infection is available, novel HIV prevention strategies are desperately needed to stem an ongoing HIV pandemic. Imperfections in the ability to universalize treatment and suppression of HIV infected individuals worldwide with ART to minimize their infectivity, as well as the complicated and fluid nature of sexual dyads, leave a prevention need for those who are at risk of acquiring HIV infection. Chemoprophylaxis with HIV antiretroviral agents has been demonstrated with TDF-containing compounds; however, required levels of adherence to daily or near-daily oral tablets has proven challenging for some populations. LA preparations promise to offer greater choice for achieving prevention, should their safety, tolerability and efficacy be confirmed. Such preparations will not solve the need for careful follow-up for repeat dose administration, safety evaluation, and testing for HIV and other sexually transmitted infections, and in fact pose new complications related to safety at initiation, and vulnerability upon withdrawal. Similar to contraception, HIV prevention is unlikely to be a “one-size fits all” field, and greater variety of options will hopefully provide additional alternatives to at-risk individuals, and ultimately greater numbers of individuals protected against HIV acquisition.

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**Key Points**

- PrEP effectiveness is compromised by challenges around need for regular adherence
- Long Acting injectable agents offer pharmacokinetic advantages, but do not entirely solve adherence challenges
- Use of a long acting agent that cannot be removed after administration obligates a short-acting lead-in to establish safety and tolerability
- Prolonged pharmacologic tail makes discontinuation challenging, particularly if exposures/risk are ongoing – with concern for seroconversion with resistant viral quasispecies
- Injections may be differentially acceptable in diverse populations.

## TABLE 1

Comparison of agents in advanced clinical development.

| | **Cabotegravir** | **Rilpivirine** |
|---|---|---|
| **Class of agent** | Strand-transfer integrase inhibitor | Non-nucleoside reverse transcriptase inhibitor |
| **Oral half-life (plasma)** | 40 hours | 50 hours |
| **Injectable half-life (plasma)** | ≈21 – 50 days | ≈35 days in women<br>≈33 days in men |
| **Stage of development** | Treatment: Phase 2b (oral/LA)<br>Prevention: Phase 2a (oral/LA) | Treatment: Approved for treatment of HIV-1 infection, May 2011 (oral); Phase 2b (LA)<br>Prevention: Phase 2 (oral/LA) |
| **Toxicity** | • Headache<br>• Nausea<br>• Diarrhea<br>• Insomnia<br>• Increased LFTs | • Headache<br>• Nausea<br>• Diarrhea<br>• Nasopharyngitis<br>• Insomnia<br>• Dizziness<br>• Increased serum creatinine<br>• Increased LFTs<br>• Decreased serum cortisol |
| **To date exposure to LA** | ≈500 | >150 |
| **Percent ISR (IM)** | 74% | 95% |