Long-acting rilpivirine for HIV prevention

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Purpose of review
Long-acting injectable antiretroviral (ARV) formulations are being developed for the treatment and prevention of HIV infection. The purpose of this review is to summarize recent preclinical and clinical data on TMC278 (rilpivirine), a nonnucleoside reverse transcriptase inhibitor (NNRTI), that is being developed for both a treatment and prevention indication.

Recent findings
Long-acting rilpivirine has demonstrated efficacy in preventing HIV acquisition in a humanized mouse model and has been found to be well tolerated and acceptable in several Phase I clinical trials. Pharmacokinetic data from Phase I studies suggest that 1200 mg of long-acting rilpivirine administered every 8 weeks would be associated with plasma and tissue levels of rilpivirine anticipated to be necessary for preventing HIV infection. This regimen is being evaluated in the HPTN-076 Phase II expanded safety study that will enroll women in South Africa, Zimbabwe, and the USA. The HPTN-076 study requires a 4-week run in with oral rilpivirine (25 mg capsules) before receiving 1200 mg of rilpivirine. It is not yet certain whether oral dosing will remain a prerequisite in future trials or post licensure.

Summary
Long-acting rilpivirine shows promise as a candidate agent for HIV prevention. Preclinical efficacy has been demonstrated in a murine model. Phase I studies have shown good safety and efficacy, but breakthrough infection and resistance have been documented with lower doses of long-acting rilpivirine. Phase II development for a prevention indication is ongoing.

Keywords
long-acting injectable antiretroviral, nanoformulation, rilpivirine, TMC278 long-acting

INTRODUCTION
Despite advances in the diagnosis and treatment of HIV infection, new cases continue to occur on a daily basis in both the developed and developing world. In the USA, the licensure of tenofovir/emtricitabine for HIV prevention provides a new option for individuals at risk for HIV infection. However, it is clear that daily oral preexposure prophylaxis (PrEP) is not suited for all at-risk populations. This is perhaps exemplified in the VOICE study in which over 5000 women in sub-Saharan Africa were randomized to receive oral or topical tenofovir as PrEP. The study failed to demonstrate the efficacy of either product. Tenofovir was only detected in the plasma of 30\% or less of the participants suggesting very low levels of product adherence. To make matters worse, the participants least likely to take the study product were young unmarried women who were at the greatest risk for HIV infection [1\textsuperscript{*}]. This same population routinely uses intermittent injectable progestins such as depot-medroxyprogesterone acetate (DMPA) for contraceptive purposes [2] and might be anticipated to favor an injectable form of PrEP. Recent qualitative surveys support this hypothesis and extend the potential interest in injectable PrEP to include other groups such as men who have sex with men (MSM) [3,4\textsuperscript{*}].

An ideal long-acting antiretroviral (ARV) PrEP agent will need to have most, if not all, of the following characteristics to be successful; ideally the product should be given as a single intramuscular injection...
Long acting antiretrovirals for treatment and prevention

KEY POINTS

- Long-acting rilpivirine is an NNRTI drug, which is licensed for the treatment of HIV-1 infection that is also being developed as a potential long-acting ARV PrEP agent.
- Proof of efficacy has been observed in a humanized mouse vaginal infection model and Phase I studies have demonstrated that 1200 mg of long-acting rilpivirine is well tolerated and acceptable.
- Breakthrough HIV infection with the subsequent selection of NNRTI resistance was seen in one participant who received a single dose of 300 mg of long-acting rilpivirine, although the participant did have a good virological response when started on a non-NNRTI ARV regimen.
- An ongoing Phase II study will evaluate the safety and acceptability of 8-weekly injections in United States and African study participants.

PRECLINICAL DEVELOPMENT

Rilpivirine is an nonnucleoside reverse transcriptase inhibitor (NNRTI) that is currently licensed for the treatment of chronic HIV infection [5]. NNRTI act early in the cycle of viral replication, are potent ARV agents, and unlike tenofovir do not require metabolism to be active against HIV. Several NNRTI drugs have been evaluated as PrEP agents. Nevirapine is an important agent for the prevention of mother-to-child transmission of HIV infection [6]. UC781, MIV-150, and dapivirine have all been evaluated in gel or intravaginal ring formulations [7–9]. Initial studies in rats and dogs established an optimal 200 nm nanosuspension formulation with 300 mg of TMC278 per milliliter of the final formulation [10,11]. Currently, the long-acting rilpivirine formulation does require storage between 2 and 8°C, which has implications for PrEP implementation.

In a study conducted using immunodeficient mice reconstituted with human thymus, liver fragments and donor-matched human hematopoietic stem cells [12], Snyder et al. were able to show that mice given long-acting rilpivirine intramuscularly were protected from HIV infection when challenged with HIV-1,[CHO40 [13].

CLINICAL DEVELOPMENT

Four Phase I clinical trials of long-acting rilpivirine have been completed and one trial is ongoing. During this process, several different formulations and injection sites have been used and details of these studies are provided below.

The C146 study

Sixty healthy participants were enrolled in the C146 clinical trial of the F004 formulation (100 mg/ml nanosuspension) of long-acting rilpivirine containing poloxamer 338. The pharmacokinetics (PK) and safety of long-acting rilpivirine were evaluated for at least 12 weeks following a single subcutaneous (SQ) or intramuscular injection of 200, 400, or 600 mg in six panels of healthy volunteers. In healthy participants, similar pharmacokinetic profiles were obtained after SQ (umbilicus region) and intramuscular (gluteal muscles) injections of long-acting rilpivirine. Following a rapid initial absorption, reaching its maximum at Day 4 (median), plasma concentrations of rilpivirine slowly declined, with plasma concentrations sustained above 10 ng/ml for up to 20 weeks after a single 600-mg dose. At this dose level, maximum plasma concentrations were approximately 110 ng/ml (median). The pharmacokinetics were demonstrated to be dose proportional for the range from 200 to 600 mg, both for SQ and intramuscular dosing, except for the Cmax, which increased less than proportional to the dose between 400 and 600 mg injections after intramuscular dosing. The C146 trial showed favorable safety and tolerability and no serious adverse events (SAE), grade 3 or grade 4 adverse events, or rash were reported. Injections were well tolerated, particularly when administered intramuscularly in the gluteus. Placebo injections were better tolerated than injections with long-acting rilpivirine; injections of 600 mg intramuscularly in the gluteus were better tolerated than 600 mg SQ and better than 400 mg intramuscularly in the deltoid. Indurations at the injection site were more frequent after SQ than after intramuscular injections. Injection site reactions (pain, erythema, edema, and site induration) were also more pronounced and long-lasting after SQ than after intramuscular administration. Administration of 400 mg intramuscularly in the deltoid muscle was also well tolerated with injection site pain noted predominantly during the first week post dosing.
**C150 study**

A single-dose intramuscular Phase I study of the F006 formulation (300 mg/ml nanosuspension) of long-acting rilpivirine, containing polysorbate 80 as excipient, was completed. The formulation was associated with poor PK exposure and is no longer in development.

**C158 study**

This study in healthy volunteers examined the safety, tolerability and PK of the G001 formulation (300 mg/mL nanosuspension) of long-acting rilpivirine, which contains poloxamer 338. The C158 study had an adaptive design; participants in the open-label Part 1 received either a single intramuscular dose of 300 mg (Panel 1, n = 6) or 600 mg (Panel 2, n = 5) in the gluteus. After data review of interim pharmacokinetic and local safety/tolerability data of all participants in both panels, it was decided to continue in Part 2 with monthly intramuscular injections in the gluteus of respectively 1200 mg (loading dose), 600 mg, and 600 mg in Panel 3 (six participants on long-acting rilpivirine, two participants on vehicle). The Cmax following a single intramuscular dose of long-acting rilpivirine 1200 mg was 139.5 ng/ml. The plasma concentrations of rilpivirine, after single 300, 600, 1200 mg intramuscular doses of long-acting rilpivirine (G001 formulation) were well below the concentrations associated with QTc prolongation in humans. During this study, no SAEs were noted. Adverse events were generally mild and transient. Overall, laboratory findings were normal and besides some mild, transient, and expected increases in few inflammatory parameters (i.e., fibrinogen and C-reactive protein levels), there was no evidence of systemic adverse reaction to treatment. There were no effects on vital signs, on body temperature, or on electrocardiograph profile including the absence of any effect on QTc.

The SSAT040 study

This study was an exploratory dose-ranging study, conducted at a single center in UK, which aimed to determine the initial feasibility of long-acting rilpivirine for PrEP use by measuring plasma exposure over 84 days after a single intramuscular dose given to 60 female HIV-negative volunteers [14**]. This allowed comparison with paired samples of collected vaginal fluid, as a proxy for tissue drug exposure, and a more limited number (2 per participant) of vaginal tissue biopsies, at assorted intervals spanning 7–56 days post dose. At the time the study was performed, in the absence of any data to guide the target drug concentrations required to inhibit HIV-1 infection from tissue models, a plasma rilpivirine concentration of 50 ng/ml was used for comparison; this being the upper limit of the lowest quartile of plasma concentrations found to be effective in the oral rilpivirine Phase 3 treatment studies. The protocol used a phased adaptive design, from starting doses of 300 and 600 mg, the plasma concentrations over 28 days were compared with this target and a decision made to use a higher dose of 1200 mg in subsequent phases, rather than using the option to reduce the administered dose to 150 mg. Additionally, a small sub-study of six male volunteers all received a 600-mg dose and followed a similar protocol with rectal fluid and tissue sampling.

All doses administered were well tolerated and resulted in a rapid onset of detectable drug in plasma and tissue within the first 24 h, reaching maximum concentrations from 6–8 days and showing prolonged persistence with detectable rilpivirine in all samples through to day 84 (Fig. 1). The ratio of drug detectable in vaginal fluid to that in plasma remained at or above 0.8 throughout the study with higher maximum concentrations at peak (days 5–8); this was consistent with vaginal tissue concentrations measured at days 7, 14, 28, and 56. This gave a good indication that plasma concentrations could be measured as a proxy for tissue exposure in any later efficacy studies. Dose proportionality was confirmed between stratified doses and by day 28, volunteers in the 600-mg dose had dropped plasma concentrations from 82 ng/ml at maximum to just below the 50 ng/ml target, whereas those receiving 1200 mg peaked at 160 ng/ml, declining to 83 and 45 ng/ml at days 28 and 56, respectively.

![FIGURE 1. PK profile of TMC278 based on the SSAT040 data.](image-url)
An indication of an effect on viral inhibition was demonstrated using an ex-vivo assay [15], with cervicovaginal lavage fluid from volunteers receiving 1200 mg, but not 300 mg, when compared with fluid collected before the dose.

Male volunteers appeared to experience higher peak plasma concentrations compared with females receiving 600 mg, though this effect was limited to the early postdose period and was no longer observed in concentrations after day 28. Rilpivirine concentrations in collected rectal fluid appeared to be significantly lower than in plasma; however, tissue concentrations were more closely matched. This is likely because of technical issues when measuring rectal fluid concentrations with assay interference and sample contamination. There were no adverse events of a serious nature, nor of moderate severity or greater and serial electrocardiographs showed no prolongation of QT interval over the course of the study.

A significant consideration with the use of an antiretroviral drug with prolonged action for PrEP is that persistence of drug at levels lower than that required to prevent infection may form a selective pressure for new resistance mutations in cases where infection has occurred. Just such a breakthrough infection occurred in one female participant in SSAT040 illustrating the reality of this concern [16]. This volunteer had received the 300-mg dose and became infected during a single episode of vaginal intercourse with a new male sexual partner, without protocol-specified use of barrier contraception. The partner had previously tested negative within 8 weeks prior to the infectious exposure and on subsequent testing was found to be newly HIV-seropositive. The infection event occurred at day 40 postdose and retrospective viral load testing confirmed no detectable plasma HIV RNA until first detectable on day 56 at 370 copies/ml, and subsequently on day 84 where the viral load peaked at 644 925 copies/ml. Importantly, in this participant, rilpivirine remained detectable above assay limits up to 9 months after the single 300-mg dose. Taken together, these results indicate that the 300-mg dose would not provide protection against infection and where infection occurred could readily select for NNRTI resistance. In the case of the infection event not being recognized, this selection pressure would be exerted for a considerable time, potentially allowing the accumulation of further resistance.

The MWRI-01 study
Healthy HIV-1 seronegative participants were enrolled into three cohorts. Twelve women and six men received an intramuscular dose of either 1200 (Cohort 1; N = 18) or 600 mg (Cohort 2: N = 18) of long-acting rilpivirine. A third cohort will enroll 12 participants (8 women and 4 men) who will receive 1200 mg of long-acting rilpivirine every 8 weeks for 16 weeks. Plasma and tissue (rectal, cervical, and vaginal) are collected before and after exposure to long-acting rilpivirine. Participants are followed for up to 4 months after receiving long-acting rilpivirine. Safety, acceptability, compartmental PK, and pharmacodynamics (colo-rectal and genital ex-vivo explant challenge with HIV-1BaL) are characterized throughout the study. Enrollment and follow-up are completed for the first two single-dose cohorts and enrollment is ongoing for the multiple dose cohort.

The HPTN-076 study
This Phase II expanded safety study of long-acting rilpivirine is currently enrolling HIV-negative women in the USA, South Africa, and Zimbabwe. Following enrollment, approximately 132 participants will be randomized (2 : 1) to receive either daily oral rilpivirine (25 mg) or placebo for 4 weeks. In the absence of any safety signals, they will then progress to receive 1200 mg of long-acting rilpivirine or placebo every 8 weeks for a total of six injections. The primary objective of the study is to characterize the safety of multiple injections of long-acting rilpivirine. However, 96/132 of the participants will be enrolled in Africa and so the study may generate some preliminary efficacy data. As with the SSAT040 and MWRI-01 studies, the 1200 mg dose of long-acting rilpivirine is administered as a 2 ml intramuscular injection in both gluteal muscles.

Another long-acting nanoparticle suspension, the integrase strand-transfer inhibitor GSK1265744 (Cabotegravir), has been studied with long-acting rilpivirine for potential use in treatment [17]. In a human volunteer study, intramuscular injections 3-monthly maintained plasma concentrations well above the IC90 and trough concentrations achieved with effective oral administration [18]. Nonhuman primate studies have suggested that this agent provides effective protection at vaginal and rectal
mucosa against viral challenge [19,20]. Thus, combination of two agents for HIV prevention may be considered in the future, potentially providing synergistic efficacy and protection against the development of resistance.

CONCLUSION

Long-acting rilpivirine given intramuscularly is tolerated well at single and multiple doses and favorable pharmacokinetics allied to evidence of protection at tissues vulnerable to HIV infection supports its further development for PrEP. This strategy may also circumvent the negative impact of nonadherence to daily oral PrEP. Concerns remain about the potential for breakthrough HIV infection and the development of NNRTI resistance. In addition, the use of a long-acting injectable PrEP agent brings a number of implementation challenges, which differ significantly from those associated with the use of oral PrEP.

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Conflicts of interest

A.J. is an employee of Gilead Sciences Inc.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as: ■ of special interest  ■■ of outstanding interest


This is an extremely important article that demonstrated the challenges of adherence to daily oral and topical PrEP regimens. These findings have driven the need to develop sustained delivery PrEP interventions such as an injectable ARV agent such as long-acting rilpivirine


Important evidence that MSM, who account for the majority of new HIV infections in the USA, are interested in the concept of long-acting injectable PrEP and that such studies should be conducted in this at-risk population.


This is a critical study that characterized the safety, acceptability, and pharmacokinetic profile of long-acting rilpivirine. The study also provided preliminary ex-vivo/in-vitro evidence of antiviral activity against HIV. Most importantly, the study also describes a case of breakthrough HIV infection that occurred in a woman receiving a 300-mg dose of long-acting rilpivirine.


