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Research Paper

Safety and tolerability of injectable Rilpivirine LA in HPTN 076: A phase 2 HIV pre-exposure prophylaxis study in women

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ABSTRACT

Background: Daily oral TDF/FTC is protective against HIV infection when used for pre-exposure prophylaxis (PrEP). However, daily adherence to oral PrEP is difficult for many; therefore, finding alternative PrEP strategies remains a priority. HPTN 076 evaluated the long-acting injectable form of rilpivirine (RPV), known as RPV LA for safety, pharmacokinetics and acceptability.

Methods: HPTN 076 (NTC 02165202) was a phase 2, double-blind, 2:1 randomized trial comparing the safety of 1200mg RPV LA (LA) to placebo (P). The study included a 28-day oral run-in phase of daily, self- administered oral RPV (25 mg), with directly observed oral dosing about six times. Of 136 enrolled sexually active, HIV-uninfected, low HIV-risk African (100) and US (36) adult women, injectable product was administered in two gluteal, intramuscular (IM) injections once every eight weeks to 122 participants following the oral run-in phase. A maximum of six injection time points occurred over a 48-week period. Acceptability, safety, tolerability and pharmacokinetic (PK) data were collected throughout the study. This paper includes primary endpoint data collected up to the week 52 post enrollment.

Findings: The median age of the enrolled population was 31 years (IQR: 25,38), median weight 75 kg (IQR: 64, 89), median body mass index (BMI) 30 (IQR: 27, 35), 46% married, 94% Black and 60% unemployed. A total of 122 (80 LA, 42 P) women received at least one injection and 98 (64 LA, 34 P) received all six injections. During the injection phase, three women withdrew from the study (2 LA, 1 P) and 16 women discontinued study product (10 LA, 6 P). Fourteen women (11 LA and 3 P) discontinued oral study product and did not enter the injection phase. Study product discontinuations were not significantly different between the two arms throughout. Of the product discontinuations in the injection phase, 8% in LA and 5% in P arm were due to adverse events (AEs), including one randomized to the P arm with prolonged QTc interval on EKG. The proportion of women who experienced Grade 2 or higher AEs during the injection phase as the primary outcome was not significantly different between the two arms [73.8%, 95% CI: (63.2%, 82.1%) for LA and 73.8%, 95% CI: (58.9%, 84.7%), $p>0.99$]. Transient Grade ≥ 2 liver abnormalities occurred in 14% of women in the LA arm compared with 12% in P arm. Three LA women (4%) developed Grade 3 injection site reactions compared with none in P arm. In participants who received at least 1 injection, the geometric mean of overall RPV trough concentrations (C_{trough}) was 62.2 ng/mL. In participants who received all six injections, the geometric mean of C_{Trough} through the injection phase and after the last injection were 72.8 ng/mL and 100.9 ng/mL, respectively. At week 52 (eight weeks after last injection), the geometric mean of RPV C_{trough} was 75.0 ng/mL. At the last injection visit (Week 44), 80 % of women who answered acceptability questions strongly agreed that they would think about using- and 68% that they would definitely use a PrEP injectable in the future.

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Interpretation: RPV LA IM injections every eight weeks in African and US women were safe and acceptable. Overall, despite more injection site reactions and pain in the participants receiving RPV LA the injections were well tolerated. Data from this study support the further development of injectable PrEP agents.

1. Introduction

Despite an extraordinary effort in scale up of HIV treatment to more than 21 million individuals worldwide in 2018, it is estimated that almost 2 million new HIV infections are occurring worldwide each year, with a great proportion occurring among young women in sub-Saharan Africa [1]. This has resulted in a renewed focus on HIV prevention efforts, which includes the administration of antiretroviral-based pre-exposure prophylaxis (PrEP) to HIV negative individuals at risk of acquiring infection. The last six years have seen the licensure and scale up of PrEP in a combined oral formulation containing tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) [2]. Numerous randomised controlled trials and implementation reports indicate that oral PrEP efficacy is closely linked to sufficient dosing [3]. Oral PrEP is recommended once daily during periods of potential HIV exposure [4], especially in women where it is thought that daily dosing may be needed to ensure sufficient concentration in the female genital tissue [5]. However, consistent daily dosing of PrEP is a difficult goal for many, particularly younger populations, and underscores the urgent need for alternative, longer-acting strategies [6,7]. Long-acting injectable antiretrovirals for PrEP is one such alternative strategy. By providing an injectable depot form of an antiretroviral agent, regimens for HIV prevention can be administered less frequently. Given the popularity of long-acting contraceptives among some women, the co-administration of effective, long-acting injectable antiretrovirals for PrEP with effective injectable contraceptive is a promising way to prevent both pregnancy and HIV infection in sexually active young women [8].

Rilpivirine (RPV) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) approved by the US Food and Drug Administration for once-daily oral administration as 25 mg EDURANT® tablets. The drug is effective as part of therapeutic regimens for the treatment for ARV-naïve HIV-infected patients and is not currently approved for prevention. Long-acting RPV (RPV LA) is a novel poloxamer-containing the long-acting suspension of TMC278, well-suited for delivery via intramuscular (IM) injection. It is currently being developed as a therapy for HIV [9]. Prior studies have shown safety of RPV LA in HIV-uninfected populations [10]. Extensive modeling work and prior clinical studies of RPV LA indicate that an 8-week dosing interval of 1200 mg per dose would provide sustained antiviral concentrations in vaginal tissue throughout the 8-week time period [10]. This dosing interval may be ideal for young women accessing both hormonal contraception and injectable PrEP and facilitate more consistent drug delivery.

The study known as HPTN 076 set out to evaluate the safety, acceptability and pharmacokinetics (PK) of RPV LA in sexually active women from the US and Africa who were at relatively low risk for HIV acquisition. It was conducted under the ClinicalTrials.gov identifier: NTC 02165202.

Research in context

Evidence before this study

Oral PrEP in a combined oral formulation containing tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) was first licensed for prevention in 2012. Consistent daily dosing of PrEP is a difficult goal for many, particularly younger populations and alternative, longer-acting PrEP strategies are needed which will require less frequent dosing. RPV LA and Cabotegravir LA are two such products under development and currently in late phase treatment trials. This study was one of two phase 2 studies (HPTN 076 and HPTN 077) conducted in a variety of populations globally to investigate the safety and acceptability of the LA products as pre-exposure prophylaxis.

Added value of this study

This study was conducted in women who have sex with men in USA and SSA since in many settings women have an elevated risk of acquiring HIV, and current understanding is that women in particular need daily dosing of oral PrEP to ensure acceptable tissue levels for HIV prevention. Given young women's use of injectable contraception, particularly in SSA, an efficacious, safe, injectable PrEP agent is desirable. HPTN 076 demonstrated that RPV LA was both safe and acceptable to this cohort of US and SSA women.

Implications of all the available evidence

Long acting injectable PrEP should be further developed for use among men and women at risk of HIV worldwide. Intramuscular injections of LA antiretrovirals every 8 weeks was found to be safe and acceptable in this study and in the study of cabotegravir LA. The preferred product profile of cabotegravir LA, especially the need for cold chain storage of RPV LA has meant that cabotegravir LA has moved forward to efficacy trials which are currently underway in both MSM and African women.

2. Methods

2.1. Study design

The HPTN 076 study was a multi-site, Phase II, double-blind, two-arm, randomized (2:1, active: placebo) trial designed to compare the safety, tolerability and acceptability of IM administered 1200 mg RPV LA to placebo, in this case normal saline (P; 0.9% NaCl) in lower-risk, sexually active HIV-uninfected women in Africa and US. The study was also designed to assess RPV PK after RPV LA administration, including concentrations at week 76, 32 weeks after the last injection at week 44. The primary analysis presented here includes data up to, and including week 52 after enrollment.

In order to screen for initial safety and tolerability of the active product, the study included a 28-day oral run-in phase of self-administered daily oral RPV (25 mg), prior to the injection phase RPV LA. Participants randomized to the placebo arm received oral placebo tablets prior to injection phase of saline solution. Following the oral run-in phase, injectable products were administered IM at 8-week intervals and follow up continued to week 76 to assess long-term drug concentrations after the final (6^{th}) injection at week 44. (Fig. 1).

2.2. Setting

Four sites participated in HPTN 076; the Emavundleni Clinical Research Site (CRS) in Cape Town, South Africa; Spilhaus CRS in Harare, Zimbabwe; Bronx Prevention Center CRS in Bronx, NY; and Rutgers New Jersey Medical School CRS in Newark, NJ.

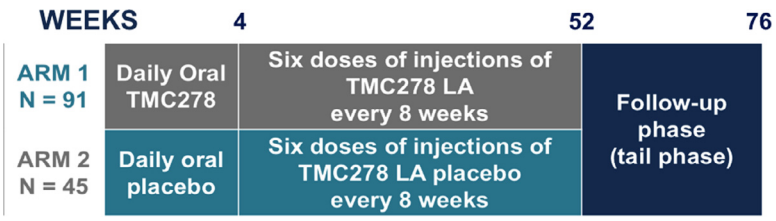

Fig. 1. Schema of the HPTN 076 study.

2.3. Study participants

Inclusion criteria required women to be between the ages of 18 and 45 years (inclusive); female at birth and to have no history in the last six months nor evidence at screening of an active sexually transmitted infection. Women were excluded if they were pregnant, breastfeeding, or HIV-infected. Participants agreed to use effective contraceptive methods throughout the study and injectable, implantable, and oral hormonal contraceptive options, as well as condoms, were provided by the sites. Study product was withheld if women became pregnant on study. All potential participants were evaluated by medical practitioners or study coordinators for symptoms of acute HIV infection, any evidence of heart disease, including electrocardiographic abnormalities, or other chronic illnesses prior to enrollment.

2.4. Randomization and masking

Eligible participants were randomized to either RPV LA or placebo at a ratio of 2:1. Randomization was stratified by site. Site pharmacists were unblinded to treatment assignments in order to provide appropriate study product. The HPTN Laboratory Center staff were also unblinded to facilitate targeted PK analysis of those participants on active product; all other site and study personnel and the participants remained blinded to assignment from study entry until the end of study.

2.5. Study procedures

The double-blind study included an oral run-in phase. After enrollment and randomization, participants were dispensed 28 doses of daily oral product, either 25 mg RPV tablets or placebo for once daily administration. Participants were observed while taking the study product by site staff on approximately six occasions during the first two weeks of the oral run-in at week 0 (enrollment), at week 2 (oral run-in safety visit), and on four separate visits under direct observation (DOT) between weeks 0 and 4. The remaining doses were self-administered during study weeks 0–4 (oral run-in phase).

In the injection phase, the injectable product, either RPV LA or placebo, was administered eight weeks apart at study weeks 4, 12, 20, 28, 36, and 44. Product was administered at each time point via two, 2 ml gluteal IM injections. One injection was given in each buttock by site staff who were specifically approved to do these procedures. These staff, who were also blinded to treatment assignment, did not participate in any other trial related activities. All study participants were followed to week 76, which was 32 weeks after the last injection visit. Post-injection study visits were conducted two weeks after the first and second injections. Participants were given post-injection memory aids after each injection visit to assist with tolerability assessments and reporting. These were reviewed at each subsequent visit.

All participants provided cervicovaginal and rectal fluid samples on one occasion at week 36 (preferred) or week 44 when subjects were expected to reach steady state concentrations. A subset of women from the US sites were invited to participate in vaginal tissue biopsy sampling during week 36 (preferred) or week 44 (same visit as their corresponding fluid collections) in order to obtain localized tissue drug concentrations. Secondary outcomes, including results of tissue and genital fluid analyses, cervicovaginal and rectal drug concentrations are not included in this paper.

2.6. Product discontinuation

Study product was withheld in any woman with a reactive HIV test, a positive pregnancy test or anyone who expressed a desire to become pregnant. All clinical adverse events (AEs) were solicited and recorded at each site visit. AEs were graded using the DAIDS toxicity table version 1.0 and assessed to be product related or not by site staff according to version 2.0. Any related AE assessed as Grade (Gr) $\geq$ 2 or unrelated Gr $\geq$ 3 was reported to the Clinical Management Committee (CMC) for evaluation and assessment of product continuation. Participants who presented with a Gr $\geq$ 2 AE related to study product or Gr $\geq$ 3 unrelated AE also had product withheld. Permanent product discontinuations were discussed with the CMC to reach that decision. On a case-by-case basis, participants with Gr 3 or 4 unrelated AEs were permitted to move into the injection phase after consultation with the clinical management team and some participants with Gr 3 or 4 unrelated AEs could resume study product after approval from the CMC.

2.7. Outcomes

The primary endpoint of the study was the proportion of women in each treatment arm who experienced any Gr $\geq$ 2 clinical or laboratory AE from the time of the first injection to eight weeks after the last injection (week 52) amongst participants receiving at least one injection. Injection Site Reactions (ISRs) were evaluated in two ways: participant self-report and site clinician evaluation. The participant's self-report occurred after each injection, starting on the evening of the injection day, and then daily for the next seven days. ISRs were assessed as none, mild, moderate, or severe by the participant on the post-injection symptom log, which served as a memory aid. Women were free to provide this information or not, partially or for the entire assessment period. At each post-injection clinic visit, the site clinician entered all ISRs reported by the participant in an AE log. An ISR based on symptoms and signs which were visible or still ongoing at the clinic visit was documented according to the clinician's judgment. These observations were graded for pain upon and without touch, itching, and measurable assessments for redness, swelling, induration, and bruising. All gradable objective assessments made by the clinician were reported in the AE log, in a similar way to the self-assessed gradable symptoms.

2.8. Electrocardiogram (EKG) assessment

Women with abnormal resting EKGs and a history of risk factors for Torsade de Pointes were excluded at screening. This was based on preclinical data which had suggested possible QT prolongation in animal studies. EKGs were repeated at every study visit. Participants with a prolonged QT interval or QTcF > 500 ms and/or an increase in QTcF from baseline of >60 ms underwent a confirmatory measurement within 48 h. If the QTcF >500 ms and/or the increase in QTcF from baseline of >60 ms persisted, then study product was stopped and participants continued in follow up.

2.9. Acceptability

Questionnaires, including baseline and follow-up preferences about HIV prevention product use and acceptability of eight injection attributes, were administered to all study participants during four study visits (weeks 0, 4, 28 and 44). Participants identified one or more aspects of injectable prevention they liked and disliked at baseline and provided recommendations for changes at week 28. Participants' interest in future injectable PrEP use was measured at weeks 28 and 44 by level of agreement with six items.

2.10. Laboratory testing

There were 19 scheduled visits throughout the course of the HPTN 076 study, including screening, enrollment and four DOT visits during the oral run-in phase of the study. HIV, hepatitis B virus (HBV), hepatitis C antibody (HCAb), bacterial sexually transmitted infections (Neisseria Gonorrhoea, Chlamydia Trachomatis and syphilis) testing, safety (complete blood count, creatinine, phosphate, aspartate aminotransferase [AST], alanine aminotransferase [ALT], creatinine phosphokinase [CPK], total bilirubin, total protein, glucose, calcium, alkaline phosphatase, urine dipstick for protein and glucose, potassium, magnesium) testing and pregnancy testing were performed at screening. Safety testing was repeated at every scheduled visit with the exception of DOT visits 1, 2 and 4. HIV rapid testing using an FDA-cleared HIV rapid test (differed by site), an instrumented 4th generation antigen-antibody testing, and pregnancy testing were also performed at every scheduled visit or as needed, with the exception of DOT visits 1, 2 and 4. Additionally, a negative HIV RNA test was required within 28 days prior to study enrollment; if the rapid HIV test or instrumented 4th generation antigen-antibody test was reactive, confirmatory testing was performed per local guidelines using a second sample collected on a different date to confirm infection. Site laboratories prepared and stored plasma, cervicovaginal and rectal fluid, and for those sites that participated in biopsy sampling, vaginal biopsy tissue for systemic and compartmental PK analysis of RPV.

Additional testing was performed at the HPTN Laboratory Center (Johns Hopkins University, Baltimore, MD). This included confirmation of all seroconversion events; HIV RNA testing was performed, when needed, using samples from the visit prior to seroconversion to detect acute HIV infection. Samples from the final study visit were tested using the Architect HIV $^{1}/_{2}$ Combo (Abbott) to confirm that participants who were not identified as HIV positive during the study were indeed uninfected.

2.11. Drug concentrations

Blood samples for RPV PK plasma analysis were collected at study visit week 0, the third DOT visit and weeks 2 and 4 during the oral run in and then at weeks 6, 8, 12, 14, 20, 28, 36, 44, 52, 64 and 76. Sampling for drug concentrations was chosen to coincide with pre-injection times (Weeks 4, 12, 20, 28, 36 and 44), to estimate the lowest concentrations (trough) during each dosing period. Week 52 sampling provided the same pre-dose concentration prior to a theoretical seventh injection (not included in this study). Samples collected at Weeks 64 and 76 provided terminal elimination data for RPV at the end of dosing and are not presented in this report. RPV drug concentrations were determined via a validated liquid chromatographic-tandem mass spectrometric (LC-MS/MS) assay with a lower limit of quantification for plasma of 1 ng/mL [11]. The assay was validated in accordance with FDA, Guidance for Industry: Bioanalytical Method Validation recommendations and was peer-reviewed by the DAIDS-funded Clinical Pharmacology Quality Assurance (CPQA) program [12].

2.12. Statistical analysis

The baseline demographics were tabulated for all enrolled participants and by treatment arm. For the primary endpoints, we conducted a modified intention-to-treat (mITT) analysis that included all participants who received at least one injection. The proportion of participants who experienced Gr $\geq$ 2 clinical AEs or laboratory abnormalities after the first injection at week 4 to the primary visit at week 52 (eight weeks after the last injection) were compared between RPV LA and placebo arms using Fisher exact test. We included the participants in the RPV LA treatment arm who received at least one injection for the plasma RPV concentration analysis. The geometric means of RPV concentrations and their 95% confidence intervals at visits between week 4 and week 52 were calculated among the participants who received at least one injection and a sub-group who received all six injections. For acceptability questionnaires, we used Fisher's exact test to compare participants' responses about preferences at the baseline and week 28 and interest in future use of an injectable method for HIV prevention between RPV LA and placebo arm. The study had over 80% power to detect $\geq$13−29% difference in the proportion of Grade 2 or higher clinical AEs or laboratory abnormalities between the RPV LA (n = 80) and P (n = 42) treatment arms when the smaller proportion in two arms ranged from 0 to 50%. The ability of the study to detect serious AEs (SAEs) was expressed by the true event rate above which at least one SAE would likely be observed and the true event rate below which no events would likely be observed. Specifically, for the RPV LA arm (n = 80), there was a 90% chance of observing at least one event if the true rate of such an event was 2.9% or more, and there was a 90% chance of observing no events if the true rate was 0.1%.

2.13. Management of the study

The Ethics Committees and/or Institutional Review Boards of each of the participating clinical sites, the US FDA, the Medicines Control Council of South Africa and Medicines Control Authority of Zimbabwe approved the protocol. The CMC was made up of the protocol chair, study site investigators and other key protocol team members. The study conduct and safety of the participants was reviewed by an independent Safety Management Committee of the HPTN every six months with feedback reported to the protocol team.

Janssen Pharmaceutica (Beerse, Belgium) supplied the oral RPV and placebo tablets as well as the RPV LA and injectable placebo. The study was designed and managed by PATH and the HIV Prevention Trials Network with funding from the National Institutes of Health, (USA) and Bill & Melinda Gates Foundation. The corresponding author had full access to all the data in the study and final responsibility for the decision to submit for publication. All co-authors approved the final manuscript.

3. Results

3.1. Participants' baseline characteristics

Baseline characteristics of the study population are shown in Table 1. A total of 136 (100 African, 36 US) women at relatively low risk of HIV infection were enrolled with a median age of 31 years (IQR: 25,38), median weight of 75 kg (IQR: 64, 89), and median Body Mass Index (BMI) 30 (IQR: 27, 35). Almost half (46%) were married, 94% were Black and 60% unemployed.

3.2. Retention

HPTN 076 was conducted from 13 April 2015 until 27 February 2017. Of the 295 women who were screened, 237 were in the sub-Sharan African (SSA) sites and 58 in the US sites. Based on a pre-specified 2:1 randomization ratio, 136 women were enrolled and randomized into the LA (n = 91) and placebo (n = 45) arms.

Table 1
Baseline characteristics and pregnancy and HIV through the study.

	Overall (*n* = 136)	Placebo (*n* = 45)	TMC278 LA (*n* = 91)
Site			
US	36/136 (26%)	12/45 (27%)	24/91 (26%)
Africa	100/136 (74%)	33/45 (73%)	67/91 (74%)
Age			
Median (IQR)	31 (25,38)	30 (25,39)	31 (26,36)
Weight			
Median (IQR)	75 (64,89)	73 (63,88)	76 (67,89)
BMI			
Median (IQR)	30 (27,35)	29 (27,35)	31 (26,35)
Marital Status			
Married/civil union/legal partnership	63/136 (46%)	18/45 (40%)	45/91 (49%)
Living with primary or main partner	7/136 (5%)	2/45 (4%)	5/91 (5%)
Have primary or main partner, not living	21/136 (15%)	6/45 (13%)	15/91 (16%)
Single/divorced/widowed	45/136 (33%)	19/45 (42%)	26/91 (29%)
Employment Status			
Full-time employment	23/136 (17%)	9/45 (20%)	14/91 (15%)
Part-time employment	31/136 (23%)	14/45 (31%)	17/91 (19%)
Not employed	82/136 (60%)	22/45 (49%)	60/91 (66%)
Became Pregnant during study	2/136 (1.5%)	1/45 (2.2%)	1/91 (1.1%)
HIV Acquired during study	1/136 (0.7%)	1/45 (2.2%)	0/91 (0.0%)

A total of 122 (90%) women (80 (88%) in LA arm, 42 (93%) in placebo arm) received at least one injection. Among these women, there were 16 (13%) in whom product discontinuation occurred (10 (13%) in LA arm, 6 (14%) in placebo arm). Ninety-eight (80%) women (64 (80%) in the LA arm and 34 (81%) in the P arm) received all six injections. Fourteen women (11 (12%) in LA and 3 (9%) in placebo) did not enter the injection phase (Figure 2). Retention differences between LA and placebo arms were not significant ($p > 0.3$).

3.3. Tolerability and adverse events

There were no statistically significant differences in proportion of Gr 2 or higher (Gr $\geq$ 2) AEs between the LA and the placebo arm (Table 2). Fifty-nine (73.8 %) women in the LA arm and 31 (73.8 %) in the placebo arm reported Gr $\geq$ 2 AE during the injection phase. The most common AEs during the injection phase, particularly so in LA arm participants, were injection site reactions (LA 19% vs P 10%, $p = 0.39$), including injection site pain (LA 13% vs P 2%, $p = 0.10$), and procedural pain (LA 9% vs P 5%, $p = 0.72$). Three LA arm participants developed Gr 3 ISRs compared with none in the placebo arm. No participant withdrew from study participation due to ISRs. Weight loss >5% was considered to be Gr $\geq$ 2. A similar proportion of women experienced Gr $\geq$ 2 weight loss in RPV LA and the placebo arm (14% in both). The most common laboratory AEs included transaminase increases, decreased blood glucose concentrations, and proteinuria (Table 2). Among the sixteen (10 in LA and 6 in P) participants in whom product discontinuation occurred during the injection phase, 6 (8%) in the LA arm and 2 (5%) in the placebo arm were due to AEs, including one participant in the placebo arm with prolonged QTc interval. Transient Gr $\geq$ 2 liver abnormalities occurred (all self-limiting) in eleven (14%) of LA arm participants compared with five (12%) in the placebo arm. The difference in the proportion of product discontinuation due to AEs was not significant difference between LA and placebo ($p = 0.71$)

SAEs were rare during the injection phase and all were unrelated. Two cases of acute pancreatitis (Gr 3 and Gr 4) occurred in the placebo arm and one case of acute renal stones occurred in the LA arm (Gr 3). One death due to hemorrhagic stroke deemed unrelated to the study product occurred in an LA arm participant after week 52.

3.4. Plasma RPV concentrations

Similar concentrations were measured in those participants who received all six injections as in those who received at least one injection. As shown in Tables 3 and 4 as well as Fig. 3, the geometric mean of plasma trough concentration (C_{Trough}) of RPV rose slowly with successive injections before falling slowly after the sixth injection. In participants in the LA arm who received all six injections, all had C_{Trough} values above the protein-adjusted 90% inhibitory concentration (PA-IC90) and $\geq$89% and >38% of samples collected after the fourth to sixth injections had C_{Trough} values above 4xPA-IC90 and 8xPA-IC90, respectively (Table 4, Fig. 3).

3.5. Seroconversions and pregnancies on study

One African participant in the placebo arm acquired HIV infection during the injection phase. Two participants, one from each arm, became pregnant; one pregnancy went to term with a normal outcome and one was terminated as per participant choice. This participant recommenced study product post termination (Table 1). Both had study product withheld in the first trimester.

3.6. Acceptability

In general, the injections were acceptable to the majority of participants. At baseline, participants liked that the injectable was easier to use (82%) and had the potential to provide longer-term protection (74%) (Fig. 4a). At week 28, just after the fourth injection, the majority of participants (55% in LA and 57% in P) recommended no changes to the injectable PrEP regimen. Among those who recommended changes, providing a single injection −even with increased (16%) or reduced volume of drug (11%), was most common. Seventeen percent of participants in the placebo arm, but 8% of those in the LA arm, recommended that the injection be given in the arm instead of the gluteal region (Fig. 4b). When asked for HIV prevention preferences at baseline, 74% of women preferred injections every other month, 15% preferred daily oral pills, 4% vaginal rings and 7% other methods (Table 5). When they were asked for preferences at week 28, 89% of women preferred 8 weekly injectable PrEP, 10% daily oral pills, and 1% vaginal gel.

There was no significant difference in responses between two arms at both time points. Almost three-quarters of participants expressed a baseline preference for an injectable over other HIV prevention options, prior to having received any injections. At week 28, almost 90% of participants expressed this preference. At the last injection visit (week 44), 68% of women strongly agreed that they would definitely use and 88% indicated that they would think about using a PrEP injectable in the future. At the last injection visit, only 4% of participants “strongly agreed” that they would NOT use an injectable PrEP agent if it were available. Eighty-four percent of women reported strongest interest in future use of an injectable that prevented both HIV and pregnancy as compared to other modalities (Table 5).

4. Discussion

RPV LA IM injections administered in two injections every eight weeks on six occasions in this clinical trial cohort of African and US women were safe and well-tolerated. RPV LA is one of two products under consideration for development as an injectable depot PrEP agent requiring less frequent dosing. RPV LA is a NNRTI, and despite global use of NNRTIs for HIV treatment, it has been considered suitable for prevention because it has antiviral activity on

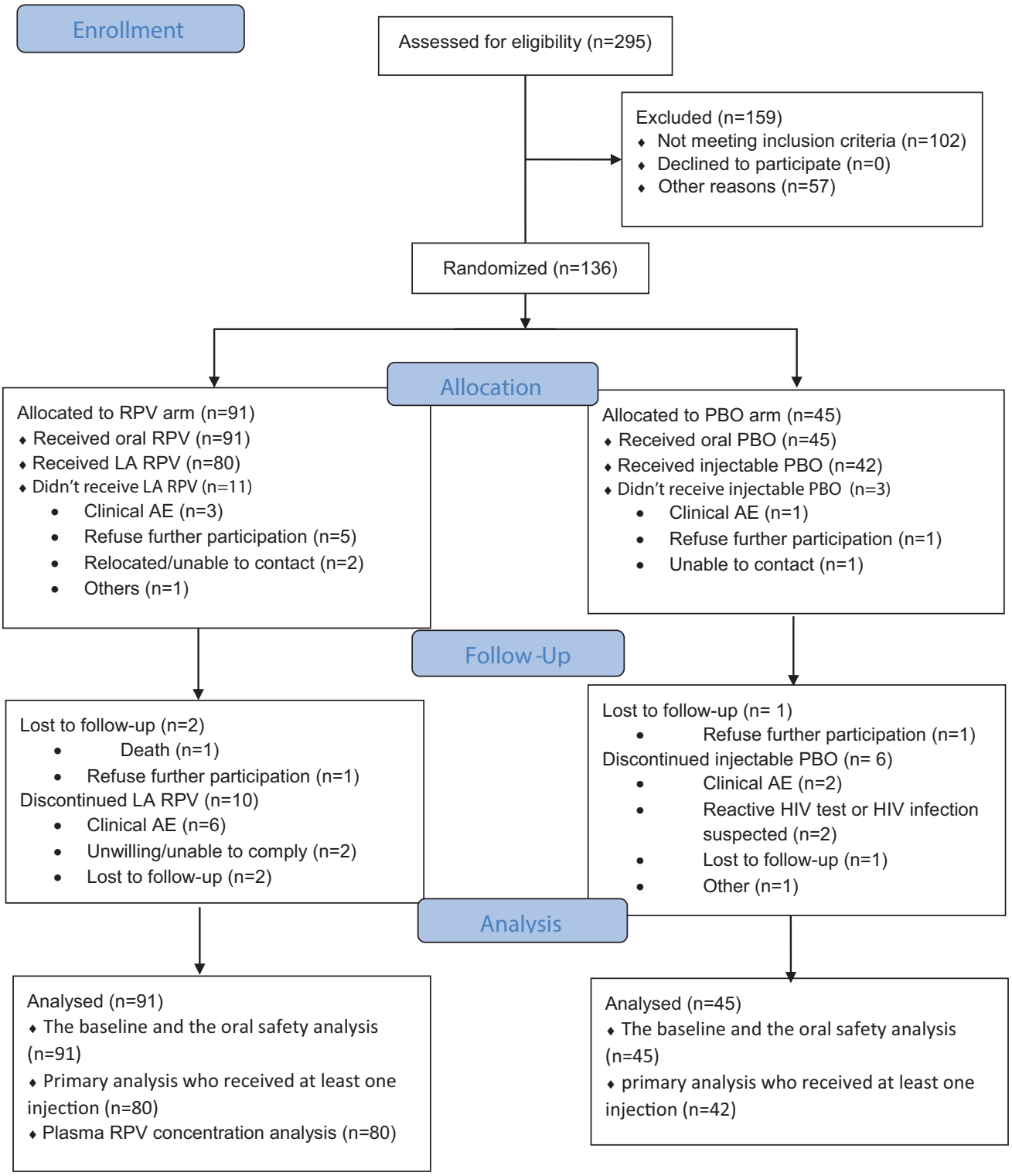

Fig. 2. Consort diagram for HPTN 076.

some clinical isolates resistant to first generation NNRTIs [13,14]. An alternative agent, now in further efficacy evaluation, comes from the integrase inhibitor family and is known as Cabotegravir LA [15]. This long-acting injectable has recently been shown to be safe and tolerable in healthy volunteers [16]. Both these agents are currently under development as combination treatment for HIV infection [9,17].

A relatively common event in this study was injection site discomfort, which may have been due to ISRs. In this study, there was more injection site pain reported by the RPV LA participants than placebo. In repeated dose studies with RPV LA, local effects including erythema and induration were noted by study participants. The local effects in terms of clinical symptoms and of histopathological lesions are considered to be a reaction to the deposited material rather than due to an irritating potential of RPV LA [13,14]. In HPTN 076 there were no severe reactions resulting in longer term sequelae and generally, despite the volume and the fact that both gluteal muscles had injections administered every 8 weeks, the injections were well tolerated.

Table 2
Proportion of women who experienced Grade 2 or higher adverse events (AEs) during the injection phase (Week 4-Week 52) among the women who received at least one injection (reported events experienced by 5 or more women).

	TMC278 LA (n = 80)		Placebo (n = 42)		
	n (%)	95% CI	n (%)	95% CI	*P*-value
Any AE[a]	**59 (73.8)**	**(63.2, 82.1)**	**31 (73.8)**	**(58.9, 84.7)**	**>0.99**
Any ISR[b]	**15 (18.8)**	**(11.7, 28.7)**	**4 (9.5)**	**(3.8, 22.1)**	**0.39**
Injection site pain	10 (12.5)	(6.9, 21.5)	1 (2.4)	(0.4, 12.3)	0.10
Procedural pain	7 (8.8)	(4.3, 17.0)	2 (4.8)	(1.3, 15.8)	0.72
Weight loss	11 (13.8)	(7.9, 23.0)	6 (14.3)	(6.7, 27.8)	>0.99
Haematuria	7 (8.8)	(4.3, 17.0)	3 (7.1)	(2.5, 19.0)	>0.99
Alanine aminotransferase increased	7 (8.8)	(4.3, 17.0)	2 (4.8)	(1.3, 15.8)	0.72
Blood glucose decreased	5 (6.3)	(2.7, 13.8)	3 (7.1)	(2.5, 19.0)	>0.99
Aspartate aminotransferase increased	5 (6.3)	(2.7, 13.8)	2 (4.8)	(1.3, 15.8)	>0.99
Blood creatinine increased	3 (3.8)	(1.3, 10.5)	3 (7.1)	(2.5, 19.0)	0.41
Blood phosphorus decreased	3 (3.8)	(1.3, 10.5)	3 (7.1)	(2.5, 19.0)	0.41
Headache	3 (3.8)	(1.3, 10.5)	3 (7.1)	(2.5, 19.0)	0.41
Respiratory tract infection	5 (6.3)	(2.7, 13.8)	1 (2.4)	(0.4, 12.3)	0.66
Injection site pruritus	4 (5.0)	(2.0, 12.2)	1 (2.4)	(0.4, 12.3)	0.66
Upper respiratory tract infection	2 (2.5)	(0.7, 8.7)	3 (7.1)	(2.5, 19.0)	0.34
Urinary tract infection	4 (5.0)	(2.0, 12.2)	1 (2.4)	(0.4, 12.3)	0.66

[a] AE: adverse event.
[b] ISR: injection site reaction.

It is notable that both clinical and laboratory toxicity were not shown to be a significant concern in this study. Previous studies in humans concluded that QT interval prolongation was not observed in individuals exposed to a 25 mg daily dose of RPV [18] which gives plasma RPV concentrations very similar to those measured in this study. This observation was recapitulated in our study, where the only evidence of QT interval prolongation was in a participant in the placebo arm. Some transaminase elevation was seen leading to temporary study drug discontinuation, but this laboratory AE was not significantly more frequent in the LA arm and was not considered clinically relevant.

The oral lead-in phase with some doses under direct observation was included in this healthy volunteer safety study as a check for any AEs which could have precluded IM dosing with RPV LA. Although part of the design of this safety study, it was not envisaged that an oral run in would be needed in future development of the long acting PrEP agent and indeed phase 1 clinical studies have been successfully completed without this provision [19,20].

In addition, this sample of US and African women found the injections acceptable. In particular, it is important to note that these women, who share geographic and demographic similarities to the kind of women who would benefit from an injectable PrEP agent in the future (although lower risk in keeping with a phase 2 study) found the less frequent dosing attractive and acceptable, apparently offsetting the discomfort of relatively large double site IM injections. Injectable contraception is the preferred option among many SSA women [8] and is currently administered as an 8- or 12-weekly dose. An 8-week injectable PrEP dosing interval, which would allow women to combine their PrEP visit with a simultaneous contraceptive clinic visit, will require that plasma levels are maintained throughout the dosing period. In HPTN 076, among women who received all six injections, the RPV trough concentrations were consistently above the PA-IC90 (12.5

Table 3
Geometric mean and 95% CI of plasma RPV concentration by visit among the participants who received at least one injection and among the participants who received all six injections.

visit	Participants who received at least one injection (n = 80)		Participants who received all six injections (n = 64)	
	GMean	95% CI	GMean	95% CI
Week 4 (Injection 1)	38.0	(26.0, 55.5)	42.1	(28.7, 61.9)
Week 6	94.4	(82.7, 107.8)	90.3	(78.5, 103.9)
Week 8	73.3	(64.8, 82.9)	70.7	(62.3, 80.3)
Week 12 (Injection 2)	40.2	(37.1, 43.6)	40.1	(36.7, 43.8)
Week 14	116.3	(103.0, 131.4)	128.7	(114.8, 144.2)
Week 20 (Injection 3)	57.4	(51.2, 64.2)	62.7	(56.8, 69.2)
Week 28 (Injection 4)	64.9	(56.8, 74.1)	74.4	(68.0, 81.4)
Week 36 (Injection 5)	71.4	(61.3, 83.2)	87.9	(79.9, 96.6)
Week 44 (Injection 6)	72.5	(61.2,85.9)	91.0	(82.2, 100.6)
Week 52	75.0	(61.6, 91.4)	100.9	(92.7, 109.8)

Table 4
Proportion of RPV trough concentration (C_{trough})>1xPA-IC90, >4xPA-IC90, and >8xPA-IC90 after each injection among the participants who received at least one injection of TMC278 LA and the participants who received all six injections of TMC278 LA.

	Received at least one injection (n = 80)			Received all six injections (n = 64)		
	>1xPA-IC90	>4xPA-IC90	>8xPA-IC90	>1xPA-IC90	>4xPA-IC90	>8xPA-IC90
Injection #1	78/78 (100%)	24/78 (30.8%)	0/78 (0%)	64/64 (100%)	19/64 (29.7%)	0/64 (0 %)
Injection #2	78/79 (98.7%)	54/79 (68.3%)	7/79 (8.9%)	64/64 (100%)	49/64 (76.5%)	6/64 (9.3%)
Injection #3	78/80 (97.5%)	63/80 (78.8%)	17/80 (21.2%)	64/64 (100%)	57/64 (89.0%)	14/64 (21.9%)
Injection #4	75/78 (96.1%)	60/78 (76.9%)	25/78 (32.05%)	63/63 (100%)	56/63 (88.9%)	24/63 (38.1%)
Injection #5	74/79 (93.7%)	65/79 (82.3%)	31/79 (39.2%)	64/64 (100%)	60/64 (93.8%)	30/64 (46.9%)
Injection #6	72/77 (93.5%)	66/77 (85.7%)	29/77 (37.7%)	62/62 (100%)	61/62 (98.4%)	28/62 (45.2%)

Note: protein-adjusted 90% inhibitory (PA-IC90) is 12 ng/mL.

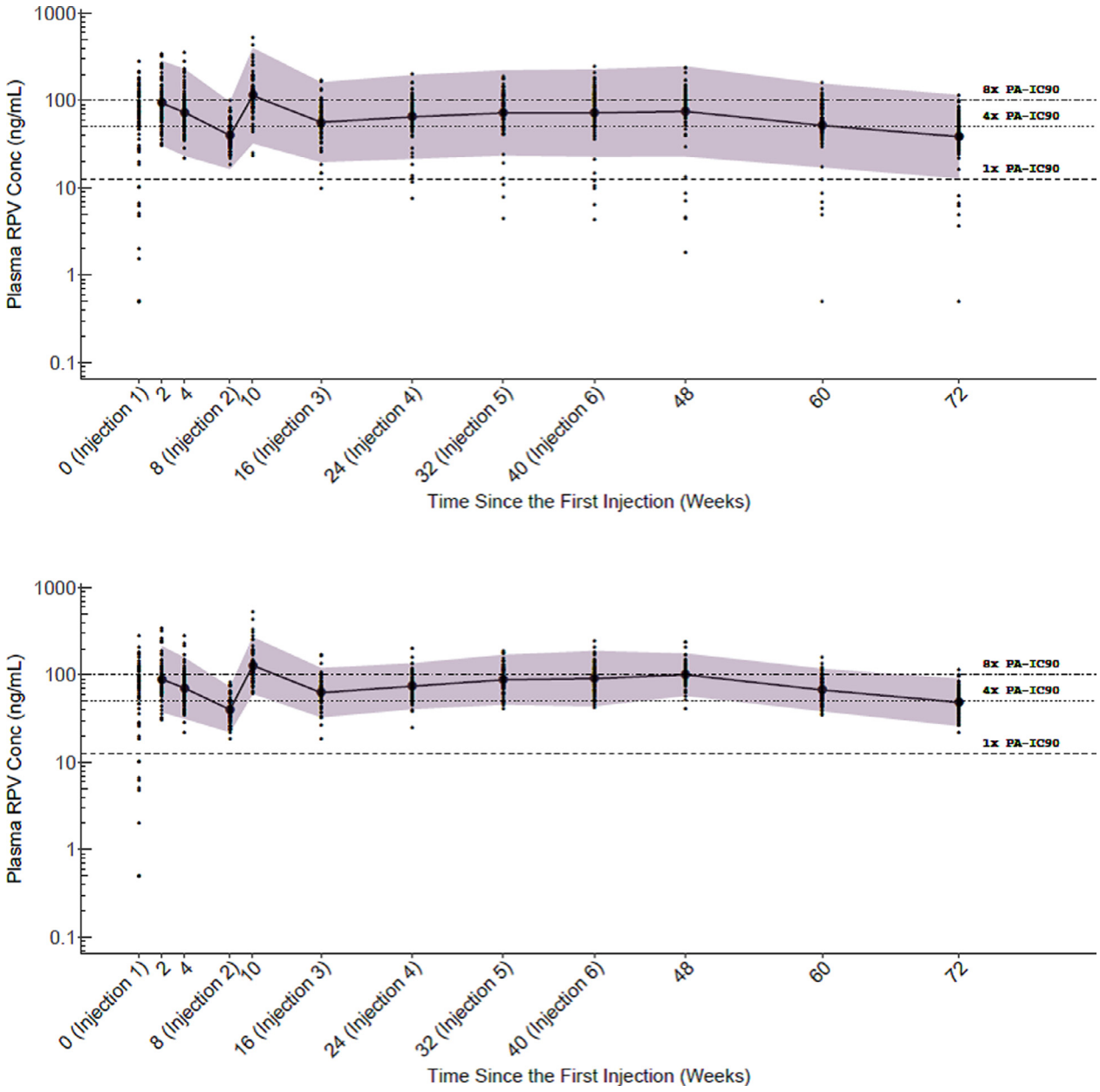

Fig. 3. Plasma RPV concentration by visit among the participants who received at least one injection (top panel) and among the participants who received all six injections (bottom panel). Small dots represent individual participants' RPV concentrations, big dots represent the geometric means connected by solid lines between visits, and shaded area represent the 90% prediction intervals. PA-IC90 (12.5ng/mL) is protein-adjusted concentration required for 90% viral inhibition.

ng/mL) which is an arbitrary value in the absence of any known relationship between PrEP efficacy and plasma concentration.

In a prior clinical dose finding study known as SSAT040, a breakthrough infection occurred in one female participant [20]. This volunteer had received a low single dose (300 mg RPV LA) 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 was found to be newly HIV-seropositive [21]. HPTN 076 demonstrated that the higher dose (1200mg 8-weekly) maintained much higher RPV concentrations but was also well tolerated.

Whilst the safety, tolerability and acceptability of RPV LA has been well demonstrated in the HPTN 076 study, RPV LA must be kept in the clinic or pharmacy between 2-8^{0}C and must not be frozen. Widespread PrEP administration is likely to need non-clinical administration in a variety of field settings and the need for controlled refrigeration adds a complexity that is likely to limit its administration in the field. As an alternative, therefore, the integrase inhibitor Cabotegravir LA has been advanced to downstream prevention efficacy trials. HPTN 077 was a sister phase 2 study that tested this agent [16] at the time that HPTN 076 was underway, and has been followed by two studies, HPTN 083 and HPTN 084, that are currently evaluating the efficacy and safety of Cabotegravir LA in men who have sex with men and African women respectively [22,23]. In conclusion, HPTN 076 demonstrated the safety of RPV LA and adds additional support for the acceptability and further development of a long-acting injectable PrEP agent.

Declaration of Competing Interest

Linda-Gail Bekker serves on advisory boards and has received honoraria from Merck, GSK and Gilead. She has also been recipient of donated antivirals for clinical trials from Gilead. Craig W. Hendrix reports grants from NIH during the conduct of the study. He also reports grants from Gilead, ViiV/GSK, the Gates Foundation, and

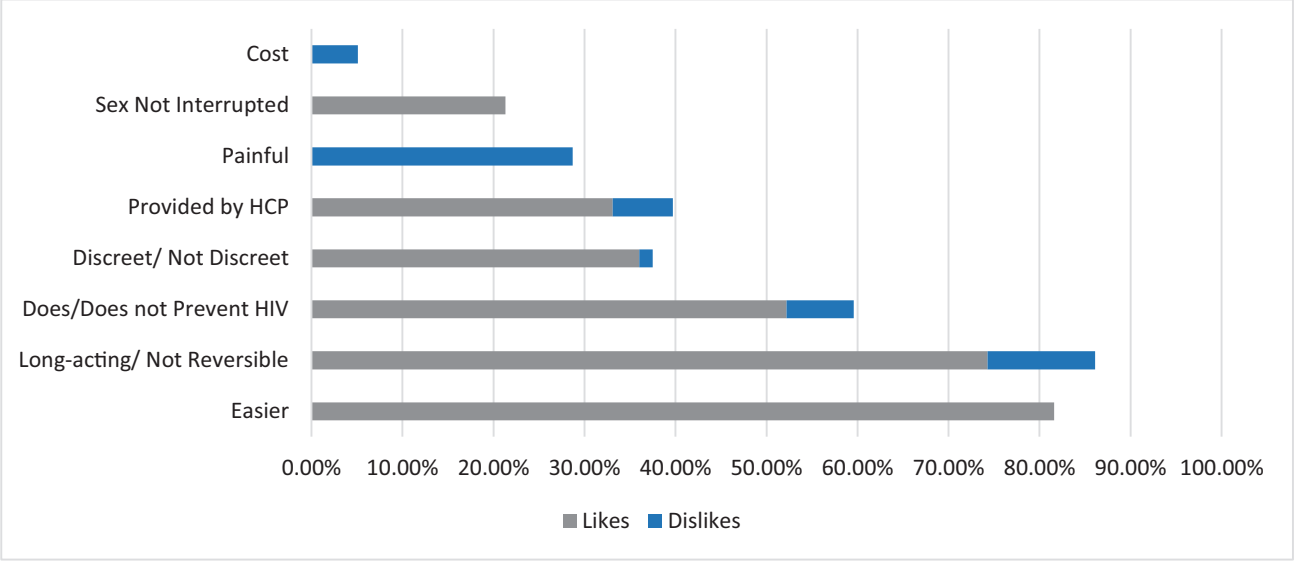

Fig. 4a. Participants' likes and dislikes of an injectable PrEP product at baseline.

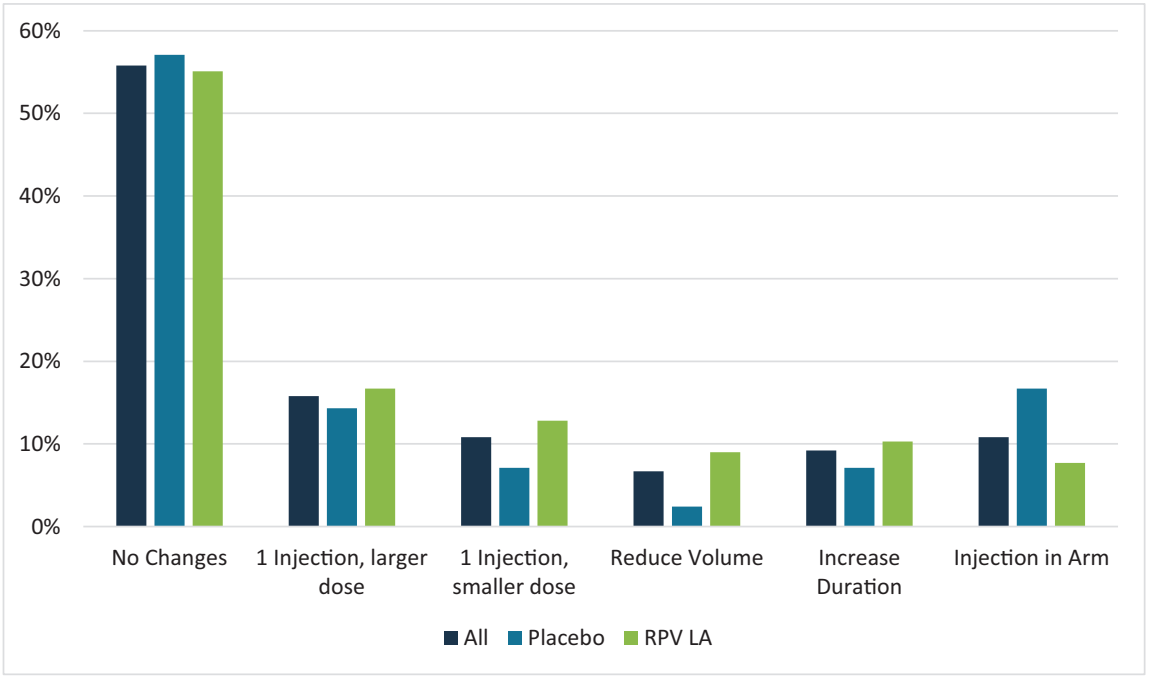

Fig. 4b. Recommendations for injectable changes, by arm, at week 28.

Merck, as well as personal fees and non-financial support from Merck, non-financial support from Gilead outside the submitted work. In addition, he has a patent US 10, 092, 509 B2 issued to Johns Hopkins University. Mark Marzinke reports grants from NIH during the conduct of the study and grants from NIH and ViiV/GSK outside the submitted work. Peter Williams reports other support from Johnson & Johnson, outside the submitted work.

Contributors

Linda-Gail Bekker, Jessica Justman, Shobha Swaminathan, Nyaradzo Mgodi were involved in the management of the participants, data collection and execution of the study. LG Bekker, Nirupama Sista, Jennifer Farrior, Sue Li, Jessica Justman, Shobha Swaminathan, Nyaradzo Mgodi, Z. Mike Chirenje, Estelle Piwowar Manning, Paul Richardson, Betsy Tolley were involved in the design, writing of the protocol and execution of the study. Mark A. Marzinke, Craig W. Hendrix, Estelle Piwowar-Manning, Susan H. Eshleman, Paul Richardson, were all involved in data collection, laboratory investigations, safety management and analysis. LG Bekker, Nirupama Sista, Jennifer Farrior, Sue Li, Estelle Piwowar-Manning, Susan H. Eshleman, Betsy Tolley were all involved in data management, analysis and interpretation of the study. LG Bekker wrote the first draft of the manuscript. All the authors were involved in editing and finalizing the manuscript as well as giving final approvals.

Table 5
Acceptability of injectable PrEP as compared to other PrEP modalities by arm.

	Overall *n* = 136 (%)	Placebo *n* = 45 (%)	TMC278 LA *n* = 91 (%)
Baseline prevention preference			
No preference	0/136 (0%)	0/45 (0%)	0/91 (0%)
Bi-monthly injection	101/136 (74%)	35/45 (78%)	66/91 (73%)
Daily oral pill	20/136 (15%)	6/45 (13%)	14/91 (15%)
Vaginal ring	5/136 (4%)	1/45 (2%)	4/91 (4%)
Vaginal gel	0/136 (0%)	0/45 (0%)	0/91 (0%)
Other	10/136 (7%)	3/45 (7%)	7/91 (8%)
Follow-up prevention preference (Week 28)			
No preference	0/113 (0%)	0/40 (0%)	0/73 (0%)
Bi-monthly injection	101/113 (89%)	36/40 (90%)	65/73 (89%)
Daily oral pill	11/113 (10%)	3/40 (8%)	8/73 (11%)
Vaginal ring	0/113 (0%)	0/40 (0%)	0/73 (0%)
Vaginal gel	1/113 (1%)	1/40 (3%)	0/73 (0%)
Other	0/113 (0%)	0/40 (0%)	0/73 (0%)
Week 44			
Would definitely use injection			
a lot (disagree)	6/112 (5%)	2/35 (6%)	4/77 (5%)
somewhat (disagree)	3/112 (3%)	1/35 (3%)	2/77 (3%)
a little (disagree)	3/112 (3%)	1/35 (3%)	2/77 (3%)
a little (agree)	10/112 (9%)	3/35 (9%)	7/77 (9%)
somewhat (agree)	14/112 (13%)	3/35 (9%)	11/77 (14%)
a lot (agree)	76/112 (68%)	25/35 (71%)	51/77 (66%)
Would be more interested in using injection if it was for both HIV and pregnancy			
a lot (disagree)	2/112 (2%)	1/35 (3%)	1/77 (1%)
somewhat (disagree)	4/112 (4%)	2/35 (6%)	2/77 (3%)
a little (disagree)	0/112 (0%)	0/35 (0%)	0/77 (0%)
a little (agree)	7/112 (6%)	2/35 (6%)	5/77 (6%)
somewhat (agree)	5/112 (4%)	2/35 (6%)	3/77 (4%)
a lot (agree)	94/112 (84%)	28/35 (80%)	66/77 (86%)

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