HPTN 076: TMC278 LA Safe, Tolerable and Acceptable for HIV Pre-Exposure Prophylaxis

Linda-Gail Bekker[1], Sue Li[2], Elizabeth Tolley[3], Mark Marzinke[4], Nyaradzo Mgodi[5], Jessica Justman[6], Shobha Swaminathan[7], Adeola Adeyeye[8], Jennifer Farrior[3], Nirupama Sista[3]

[1]University of Cape Town, SA; [2]Statistical Center for HIV/AIDS Research and Prevention, Fred Hutchinson Cancer Research Center, Seattle, WA, US; [3]FHI 360, Durham, NC, US; [4]Johns Hopkins University, Baltimore, MD, US; [5]University of Zimbabwe, Harare, Zimbabwe; [6]ICAP at Columbia University, New York, NY, US; [7]Rutgers, New Jersey Medical School, Newark, NJ, US; [8]DAIDS/NIAID/NIH, Rockville, MD, US

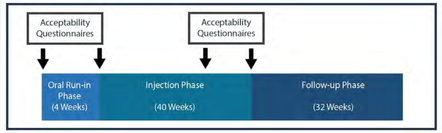
BACKGROUND

- Adherence to daily pre-exposure prophylaxis (PrEP), in either oral or topical gel formulation, is a difficult goal for many and underscores the need for alternative strategies.
- Long-acting injectable PrEP is one such alternative strategy. Given the popularity of long-acting contraceptives among women, the combination of effective, long-acting injectable PrEP with an effective injectable contraceptive is a promising way to prevent both pregnancy and HIV infection.
- HPTN 076 evaluated safety and acceptability of the long-acting injectable form of rilpivirine (TMC278 LA) from Janssen Pharmaceutica, Belgium.

METHODS

- HPTN 076, a phase 2, double-blind, 2:1 randomized trial, compared the safety of 1200mg TMC278 LA to placebo for PrEP in low-risk, sexually active HIV-uninfected women.
- Four sites participated in HPTN 076: Emavundleni 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.
- Injectable product, either TMC278 LA or placebo, was administered on six occasions, eight weeks apart at study Weeks 4, 12, 20, 28, 36, and 44 during the Injection Phase. Product was administered at each time point in two, 2mL gluteal, intramuscular (IM) injections. One injection was given in each buttock. All study participants are followed to Week 76, 32 weeks after the last injection visit.
- Prior to injections, participants were given 28 doses of daily oral product, either placebo or 25mg rilpivirine (RPV). Participants were observed taking the oral product up to six times in clinic. The remaining doses were self-administered during study Weeks 0 – 4 (Oral Run-in Phase).
- Participants presenting with Grade (Gr) 2 or greater RELATED Adverse Events (AEs) during the Oral Run-in phase did not progress to the Injection Phase. On a case-by-case basis, participants with Grade 3 or 4 UNRELATED AEs were permitted to move into the Injection Phase.
  - In general, study product was paused during the Injection Phase using the same criteria. Product was re-started in specific instances after review and consensus by study clinicians.

FIGURE 1. Three Phases of HPTN 076.



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METHODS, CONTINUED

- RPV drug concentrations were determined via a validated liquid chromatographic-tandem mass spectrometric (LC-MS/MS) method with a lower limit of quantification of 1 ng/mL.
- Participants identified one or more attributes of injectable prevention they liked and disliked at baseline. Participants' interest in future injectable PrEP use was measured at Week 44 by level of agreement with six items. Comparisons by arm were made between participants who "agreed a lot" to each statement.

RESULTS

PARTICIPANT DISPOSITION

- A total of 136 (100 African, 36 US) women were enrolled.
- During the Oral Run-in Phase, ten women withdrew (8 active arm, 2 placebo arm) and four had product discontinued (3 active arm, 1 placebo arm).
- During the Injection Phase, one woman withdrew (placebo arm) and 16 product discontinuations occurred (10 active arm, 6 placebo arm).

TABLE 1. Participant Characteristics.

	Overall (N=136)	African Sites (N= 100)	US Sites (N=36)
Median Age	31 years (IQR: 25,38)	31 years (IQR: 22,37)	32 years (IQR: 28,40)
Median Weight	75 kg (IQR: 64,89)	72 kg (IQR: 63,87)	83 kg (IQR: 72,100)
Marital Status	46% married	56% married	19% married
Race	94% Black	100% Black	78% Black
Employment Status	60% unemployed	65% unemployed	47% unemployed

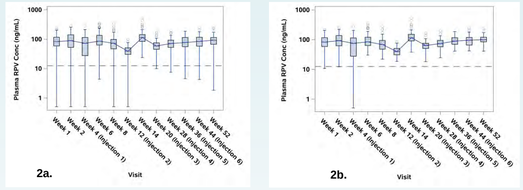
INJECTION PHASE: SAFETY DATA

- A total of 122 (80 active arm, 42 placebo arm) women received ≥ one injection; 64 active arm and 34 placebo arm participants received all six injections.
- Of the 16 product discontinuations during Injection Phase, six (8%) active arm and two (5%) placebo arm were due to AEs including one placebo arm participant with prolonged QTc interval.
- Transient Gr ≥2 liver abnormalities occurred in nine (11%) of active arm participants compared with four (10%) in the placebo arm.
- Three active arm participants developed Gr ≥3 injection site reactions compared with none in the placebo arm.
- **The differences in AEs observed between the two arms were not statistically significant.**

INJECTION PHASE: DRUG CONCENTRATION

- In participants receiving at least one injection:
  - The median plasma trough concentration (C_{Trough}) of RPV during the injection phase was 68.2 ng/mL.
  - The concentration two weeks (C_{2Wk}) after the first and second injections (at Weeks 6 and 14) was 85.5 ng/mL and 113 ng/mL, respectively.
  - At Week 52 (eight weeks after last injection), the C_{Trough} was 91.9 ng/mL.
- In participants receiving all six injections, less than 2% had RPV concentrations below the protein-adjusted 90% inhibitory concentration (PA-IC_{90}) at any given time point after Week 4 when injections began.

FIGURE 2. Rilpivirine Concentration in Active Arm Participants (a) Receiving at Least One Injection (N=80) and (b) Receiving all Six Injections (N=64).*



The solid line connects the median concentration over time.
The dashed line is the PA-IC_{90} for RPV (=12.5 ng/mL).

* For categorical variables, # (%) was reported and for continuous variables, median was reported. The Fisher's exact test was used to compare the number of AEs between the two arms. Boxplots summarize the distribution of plasma RPV concentration at each visit, where the mid-line of the box denotes the median and the ends of the box denote the 25th and 75th percentiles, with whiskers extended to the extreme data points that are no more than 1.5 times the interquartile range (IQR), and the diamond denotes for the mean.
# The variability seen in Figure 2a is reflective of participants receiving between one and six injections.

ACCEPTABILITY DATA

- The majority of participants liked that the injectable was:
  - Easier to use (>80%)
  - Potential to provide longer-term protection (>73%)
- Some participants disliked that the injectable was:
  - Painful (~30%)
  - Had side effects (31-37%)
- Acceptability did not differ by arm. At the last injection visit 68% of women strongly agreed that they would definitely use and 80% 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.
- Participants reported strongest interest in future use of an injectable that prevented both HIV and pregnancy.

RESULTS, CONTINUED

ACCEPTABILITY DATA, CONTINUED

FIGURE 3. Potential Attributes of Injectable PrEP (a) Liked and (b) Disliked by Participants.

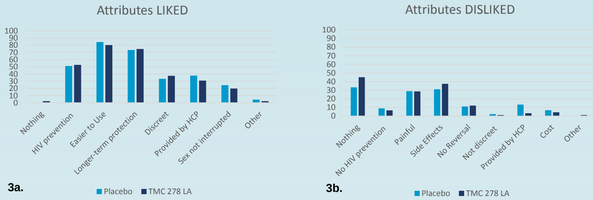
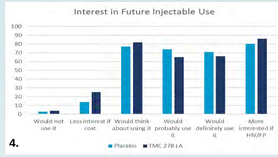


FIGURE 4. Percentage of Participants Interested in Future Injectable PrEP Use.



CONCLUSIONS

- The lower quartile RPV concentrations were consistently above the PA-IC_{90} at all times through eight weeks post injection.
- TMC278 LA IM injections administered every eight weeks in this clinical trial cohort of African and US women were safe, overall well tolerated and acceptable.
- Data from this study support further development of injectable agents for PrEP.

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