

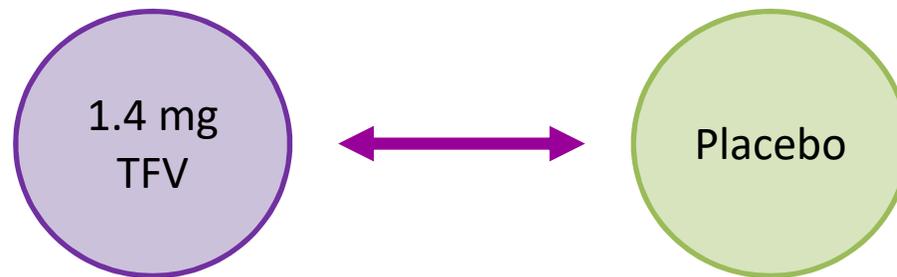
MTN-038

Protocol Overview



MTN-038: Extended Duration Tenofovir Vaginal Ring

The study will compare the safety and PK of the Tenofovir (TFV) extended duration intravaginal ring (IVR) to a placebo IVR.



Study Design	Phase 1, two-arm, multi-site, randomized (2:1 ratio), placebo-controlled
Participant Follow Up	92 days (91 days of continuous IVR use)
Study Population	48 healthy, HIV-uninfected women or those assigned female birth, age 18-45 (inclusive)
Study Sites	Pittsburgh, San Francisco, and Alabama

Study Rationale



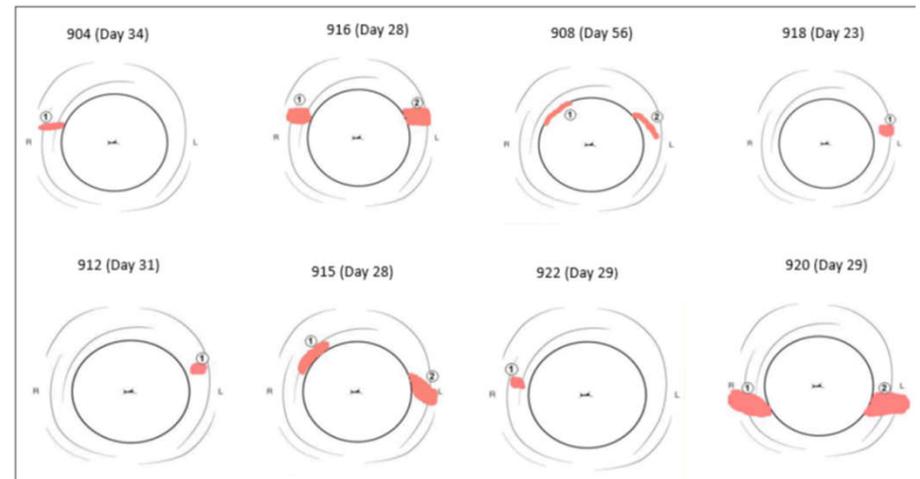
- Safety/tolerability of TFV in vaginal gel and oral tablet formulations demonstrated
- Daily/pericoital TFV vaginal gel not consistently effective for HIV prevention, likely due to low adherence
- While daily oral PrEP found to be protective in some studies, high adherence (6-7 doses/week) needed to protect against vaginal exposures
- Extended duration TFV IVR could overcome adherence/efficacy issues with vaginal gel and daily oral formulations, reduce patient and provider burden
- TFV delivered intravaginally may help prevent HSV-2
- MTN-038 is the first MTN study to evaluate the TFV VR in humans for the intended 90 days of use
 - Potential use for multipurpose technology (e.g. HIV, HSV and pregnancy prevention)

Tenofovir (TFV)/TFV IVR

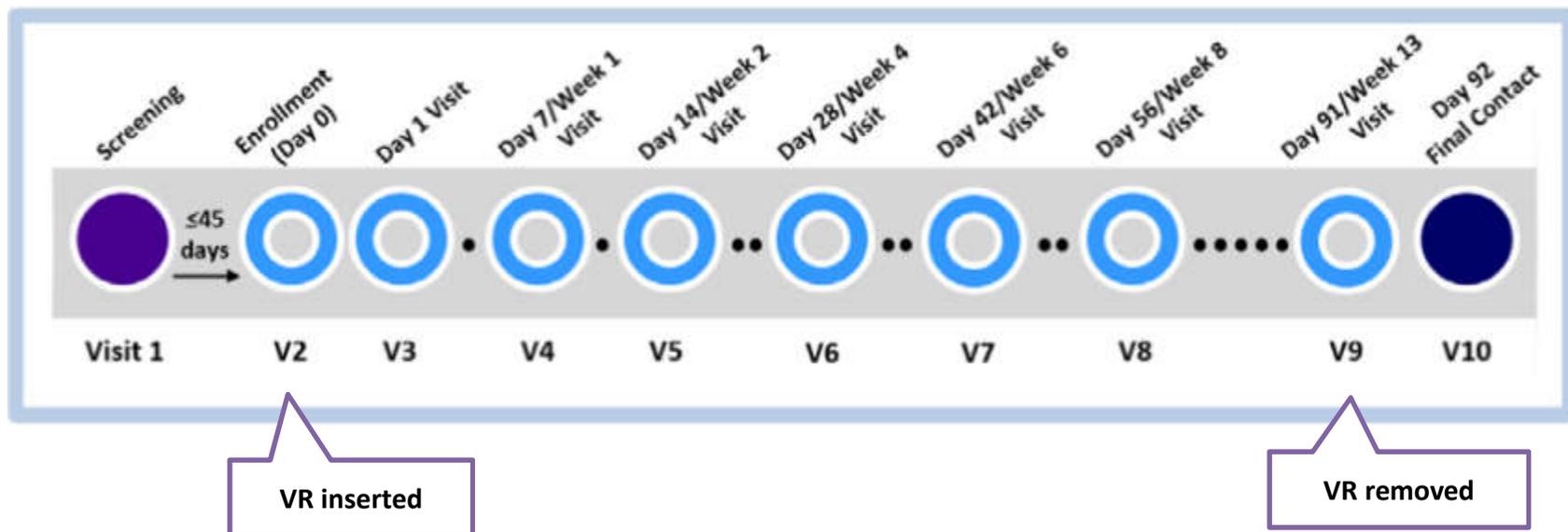
- Highly potent ARV (NtRTI): inhibits HIV RT enzyme via chain termination, preventing viral replication
- TFV 1% vaginal gel demonstrated to be well tolerated
- Polyurethane reservoir ring containing 1.4 g of TFV, designed to release ~10 mg/day over 90 days
- Target based on trying to achieve sustained PK in the vaginal compartment that matched or exceeded peak PK from TFV 1% gel

Safety of Tenofovir IVR

- Tenofovir IVR found to be safe and well-tolerated in 2 CONRAD studies (128, 130)
- TDF IVR was evaluated in 3 month study of sexually active women
 - 17 ppts enrolled prior to termination (12 TDF, 5 placebo)
 - Among 12 ppts in TDF arm:
 - 2 completed study without complications, 2 had ring removed preemptively
 - 8 ppts in TDF arm developed G1 vaginal/cervical ulceration
 - Occurred average 32 days after ring use (range 23-56 days)
 - 4 were symptomatic, 3 had bilateral ulcers
 - All ulcers resolved after ring removal
 - No ulcerations in placebo arm
- Modifications to MTN-038
 - Added safety visit at day 42
 - Added vaginal and cervical ulceration to ICF Risk section
 - Collection of CVF for biomarkers



Study Visit Schedule



The participant's menstrual cycle must be considered when scheduling Visit 2- Enrollment (Day 0).
Ideally no bleeding occurs during the first 7 days of product use.

Study Accrual Target

Study-wide Accrual Target

48 participants

Site Accrual Period

6-9 months from site's first enrollment

Site-specific Accrual Target

Pittsburgh	Bridge HIV	UAB
n=24	n=12	n=12
3-4 participants/month	2-3 participants/month	2-3 participants/month

Primary Study Objectives

Pharmacokinetics (PK)

- Characterize the local and systemic pharmacokinetics of one TFV IVR used continuously for 91 days
- Endpoints: TFV levels in plasma, cervicovaginal fluid, rectal fluid, and cervical tissue; TFV-DP levels in cervical tissue

Safety

- Evaluation the safety of one TVF IVR used continuously for 91 days.
- Endpoints: Grade 2 or higher genitourinary AEs, and Grade 3 or higher AEs

Secondary Study Objectives

Adherence

- Evaluate participant adherence to one TFV IVR used continuously for 91 days
- Endpoint: Frequency of study IVR removal/expulsions (voluntary and involuntary) and duration without IVR in vagina (by self-report); IVR use initiation and persistence (whether IVR in place at study visits)

Acceptability

- Evaluate the overall acceptability of one TFV IVR used continuously for 91 days
- Endpoint: Degree to which study participants liked or disliked using the IVR (by self-report)

Exploratory Study Objectives

Vaginal Microenvironment

- Describe the genital microenvironment in HIV-uninfected participants during 91 days of continuous IVR use
- Endpoints: Changes in microbiota and biomarkers; impact of microbiota on TFV levels in tissue and plasma

Pharmacodynamics (PD)

- Determine the anti-HIV activity in CVF and cervical tissue, and anti-HSV-2 activity in CVF
- Endpoint: Measures of HIV inhibition in CVF and cervical tissue; measures of HSV-2 inhibition in CVF

Exploratory Study Objectives (Cont'd)

Adherence

- Evaluate markers of ring use for the TFV IVR
- Endpoints: Plasma and CVF TFV levels; residual drug levels in returned IVRs; biomarkers of IVR use

Acceptability

- Evaluate components of acceptability of ring use for the TFV IVR
- Endpoints: Self-reported attitudes about IVR attributes; interest/preference in a single vs. dual-purpose indication; proportion of participants who find the study IVR to be at least as acceptable as other HIV prevention methods

Key Inclusion Criteria

- Assigned female sex at birth
- Available for all visits and able and willing to comply with all study procedural requirements.
- For the duration of study participation, willing to **refrain from inserting any non-study vaginal products or objects** into the vagina or rectum starting 24 hours preceding the Enrollment Visit.
- Willing to **abstain from receptive vaginal or anal sexual activities** for 72 hours prior to each clinical visit and for 72 hours after biopsy collection
- Willing to **use male condoms** for penile-vaginal intercourse (PVI) and penile-rectal intercourse for the duration of study participation
- Per participant report, using an **effective, method of contraception 30 days prior to Enrollment** and intending to continue the use of an effective method for the duration of study participation
- **Regular menstrual cycles** of at least 21 days
- **HIV-uninfected**

Key Exclusion Criteria

- Diagnosed with a **symptomatic UTI or reproductive tract infection (RTI) or an acute STI** requiring treatment at Screening or Enrollment
- Clinically apparent **Grade 2 or higher pelvic exam finding**
- Report or evidence of a **gynecologic or genital procedure** 45 days or less prior to Enrollment.
- Use of **Post-exposure prophylaxis (PEP) for HIV exposure and/or Pre-exposure prophylaxis (PrEP)** for HIV prevention within the 3 months prior to Enrollment
- Currently **breastfeeding or pregnant** or planning to become pregnant or breastfeed during the study period
- **Abnormal laboratory results** for ALT, AST, hemoglobin, creatinine clearance, or a positive Hepatitis B surface antigen result