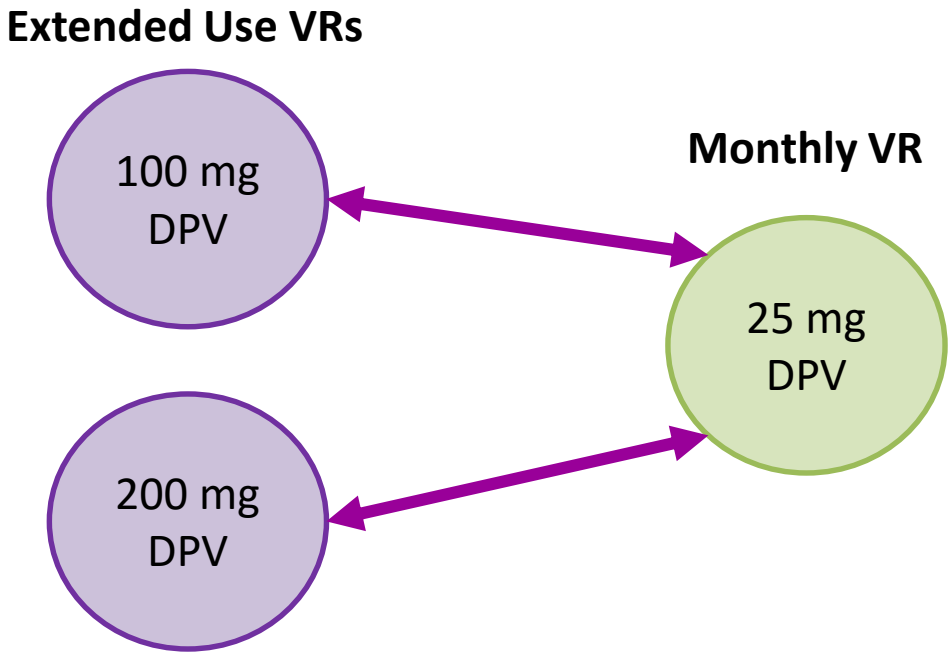
MTN-036/IPM 047
Protocol Overview

Site Specific Training | 11 Sept 2017

MTN-036: Extended Duration Dapivirine Vaginal Rings

The study will compare the safety and PK of two extended use dapivirine (DPV) vaginal rings (VRs) (100mg and 200 mg) to the current monthly 25mg DPV VR.



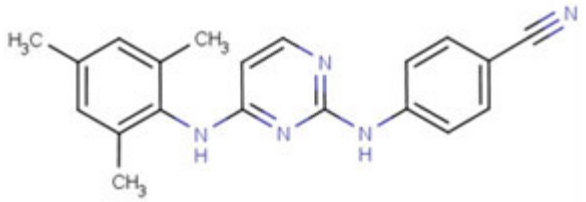
Study Rationale

- Safety and efficacy of the monthly DPV 25 mg 25 mg VR demonstrated in two phase 3 trials
- VRs with higher DPV loading dose may:
  - Allow less frequent replacement of ring (e.g. quarterly)
  - Reduce pt/provider burden, streamline follow-up, improve adherence
  - Achieve higher vaginal fluid/tissues levels
- MTN-036 is the first MTN study to evaluate two extended duration DPV VRs
  - Potential use for multipurpose technology (e.g. HIV and pregnancy prevention)

ASPIRE
A Study to Prevent Infection with a Ring for Extended Use

THE RING STUDY
Developing HIV Prevention for Women

Dapivirine



- Highly potent ARV (NNRTI): binds to and disables the HIV RT enzyme required for viral replication
- Excellent safety profile (25mg rings designed for 28-day use in Phase III trials)
- Delivers high concentrations of active drug to vaginal tissue with low amounts absorbed systemically

Study Summary

Study Design	**Phase 1, three-arm, multi-site, randomized (1:1:1 ratio)**
Study Accrual	**6-9 months**
Participant Follow Up	**94 days**
Study Population	**48 healthy, HIV-uninfected women or those assigned female birth, age 18-45**
Study Sites:	**SF Bridge HIV and Alabama**

Study Summary

Product Use Period: 13 weeks

Study Products: 3 IPM DPV Intravaginal Rings

Monthly Use VR

- DPV 25mg (Ring-004): N=16

Replaced every 4 weeks in the first 8 weeks; then worn for an additional 5 weeks

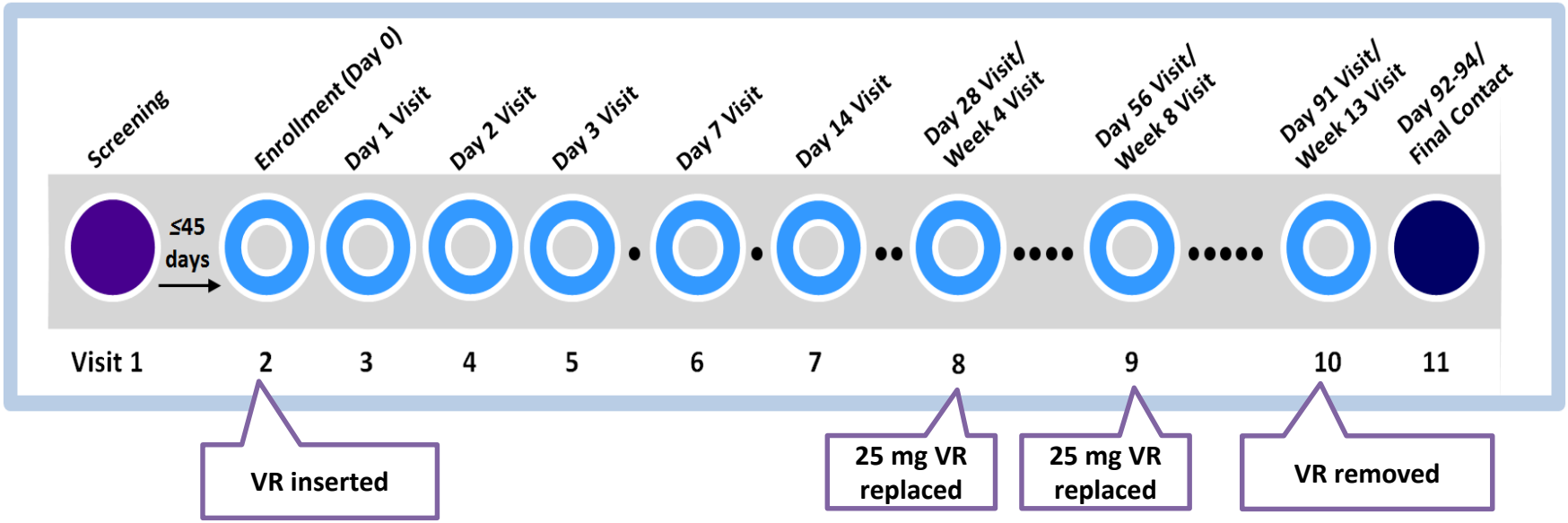
Extended Use VR

- DPV 100mg (Ring-008): N=16
- DPV 200mg (Ring-006): N=16

Worn continuously for 13 weeks

**Participants randomized to extended use rings will not be told their group assignment*

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.

Primary Study Objectives

Pharmacokinetics (PK)

- Compare the local and systemic PK of two extended duration DPV VRs (100 mg and 200 mg) to the current 25 mg DPV VR
- Endpoints: DPV concentrations in plasma, cervicovaginal fluid, and cervical tissue

Safety

- Compare the safety of the two extended duration DPV VRs (100 mg and 200 mg) to the current 25 mg DPV VR when used for 13 weeks.
- Endpoints: Grade 2 or higher genitourinary AEs, and Grade 3 or higher AEs

Secondary Study Objectives

Adherence

- Evaluate participant adherence to the three DPV VRs when used for 13 weeks
- Endpoint: Frequency of study VR removal/expulsions (voluntary and involuntary) and duration without VR in vagina (by self-report); VR use initiation and persistence

Acceptability

- Compare overall acceptability of the two extended duration DPV VRs (100mg and 200 mg) to the current 25 mg DPV VR
- Endpoint: Degree to which study participants liked or disliked using the three DPV VRs (by self-report)

Exploratory Study Objectives

Vaginal Microenvironment

- Describe the genital microenvironment in HIV-uninfected women and those assigned female sex at birth using a DPV VR for 13 weeks
- Endpoints: Changes in microbiota and biomarkers during DPV VR use

Pharmacokinetics (PK)

- Compare the rectal compartment PK of the two extended duration DPV VRs (100mg and 200 mg) when used continuously for 13 weeks to the current 25 mg DPV VR
- Endpoint: DPV concentrations in rectal fluid

Exploratory Study Objectives (Con't)

Adherence

- Evaluate markers of ring use for the three DPV VRs
- Endpoints: Plasma DPV levels and residual DPV levels in returned VRs

Acceptability

- Evaluate components of acceptability of ring use for the three DPV VRs
- Endpoints: Self-reported attitudes about VR attributes; interest/preference in a single vs. dual-purpose indication; proportion of participants who find the study VRs 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 starting 24 hours preceding the Enrollment Visit.
- 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

Key Exclusion Criteria

- Diagnosed with a **UTI or reproductive tract infection (RTI) or an acute STI** requiring treatment at Screening or Enrollment
- 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

Study Accrual Target

Study-wide Accrual Target	• N=48
Site-specific Accrual Target	• 24 participants per site • 3-4 participants/month
Study-wide Accrual Period	• 6-9 months