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A Study to Prevent Infection with a Ring for Extended Use

MTN-020

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On behalf of the ASPIRE team

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MTN microbicide trials network

MTN-020 / ASPIRE

- **A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Phase III Safety and Effectiveness Trial of a Vaginal Matrix Ring Containing Dapivirine for the Prevention of HIV-1 Infection in Women**

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A **S**tudy to **P**revent **I**nfection with a **R**ing for **E**xtended Use

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Overview

- Background and rationale
- Design and objectives
- Protocol overview
- Sites and timelines
- Considerations for optimization of implementation

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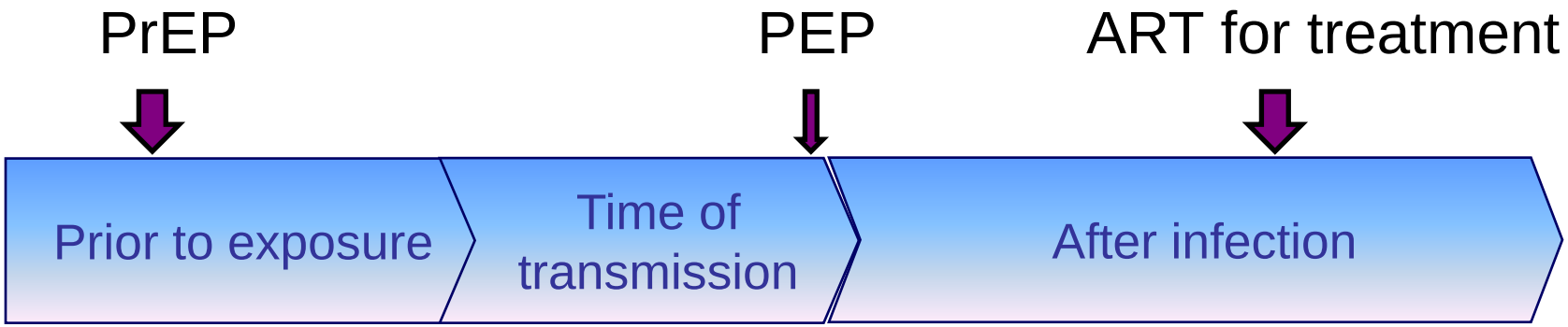
Background and Rationale

Using antiretroviral medications for HIV prevention



Advantages:
Evidence for efficacy in some trials

Challenges:
- Adherence
- Delivery
- Cost-effectiveness
- Resistance

Advantages:
Shorter course than PrEP

Challenges:
- Limited data
- Recognition of risk
- PEP initiation <48 hrs
- Adherence
- Public health impact

Advantages:
Clinical benefits & reduced infectiousness

Challenges:
- Scale up; resources
- Long term adherence
- Long term toxicity
- Resistance

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PrEP for HIV prevention

- Right drug

(safe, effective, ideally not overlapping treatment)

- Right place

(sufficient concentrations at site of exposure)

- Right time

(present when exposed, user-independent adherence)

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Tenofovir-based PrEP for HIV prevention: success and challenges

- During the past two years, large studies of oral and topical tenofovir-based PrEP have demonstrated efficacy for HIV protection:

Trial	PrEP regimen	Population	Reduction in HIV risk
CAPRISA 004	Peri-coital tenofovir gel	Women	39%
iPrEx	Daily oral FTC/TDF	Men who have sex with men	44%
TDF2	Daily oral FTC/TDF	Young heterosexuals	62%
Partners PrEP	Daily oral TDF and FTC/TDF	HIV serodiscordant couples	67% (TDF) 75% (FTC/TDF)

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Tenofovir-based PrEP for HIV prevention: success and challenges

- However, not all trials of tenofovir-based PrEP have found HIV protection:
  - No efficacy for daily oral FTC/TDF in FEM-PrEP trial and for daily tenofovir gel and daily TDF in VOICE study, both studies of women with high HIV incidence

- Across PrEP studies, adherence is likely an important driver of HIV protection

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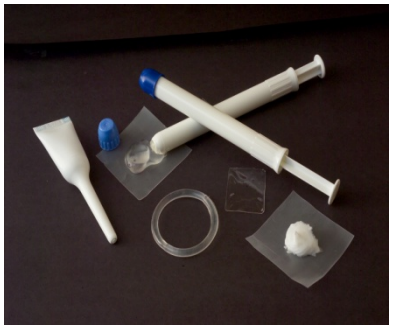
Developing a range of options for antiretroviral-based HIV prevention

Pill



Gel

Vaginal film

Vaginal ring

Injectable

- ✓ Landmark health research is a process of continued development. Tenofovir PrEP is critical first proof on a future pathway.
- ✓ Goals: long acting, safe, effective, low cost and user-friendly
- ✓ Maximize choice & optimize effectiveness

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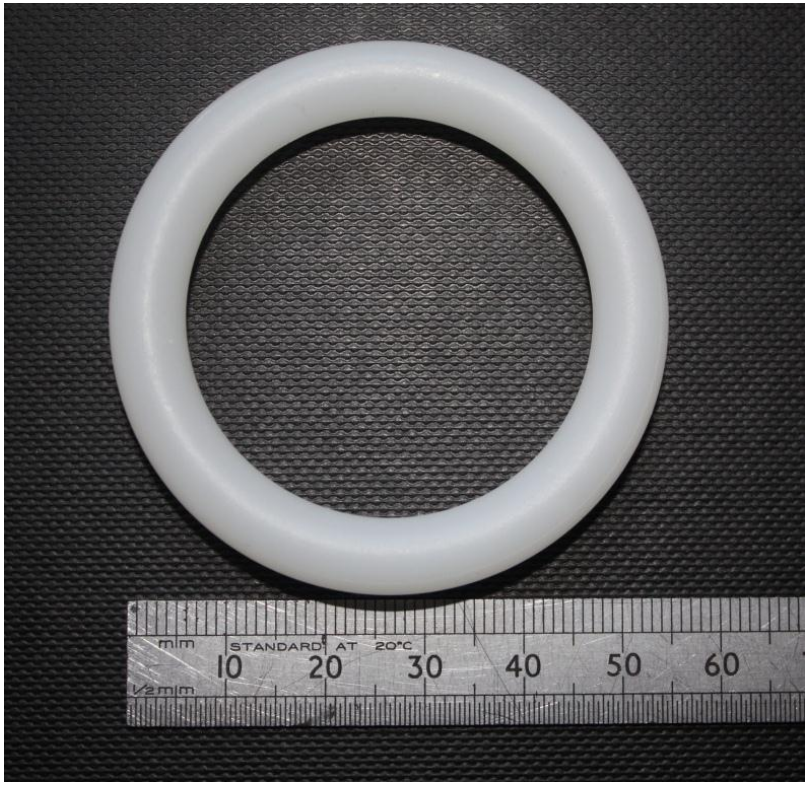
Dapivirine ring

- Dapivirine is a non-nucleoside reverse transcriptase inhibitor
- Flexible ring made of an elastic silicone material
- Measures 56 mm (about 2 ½”) in diameter and 7.7 mm (3/4”) thick
- Designed for 28-day use
- International Partnership for Microbicides (IPM) providing both the placebo ring and the dapivirine ring for the study



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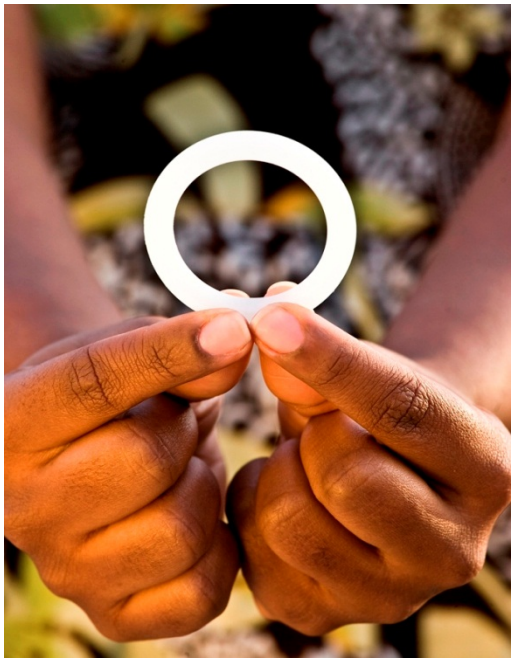
Dapivirine ring for HIV prevention

- Dapivirine ring has shown safety and acceptability in phase I and phase II trials *but its large-scale safety and its effectiveness for HIV protection are unknown*

- MTN-020, in concert with the entire dapivirine package, will provide strength of evidence to support potential licensure
  - First effectiveness study of a *long-acting* product



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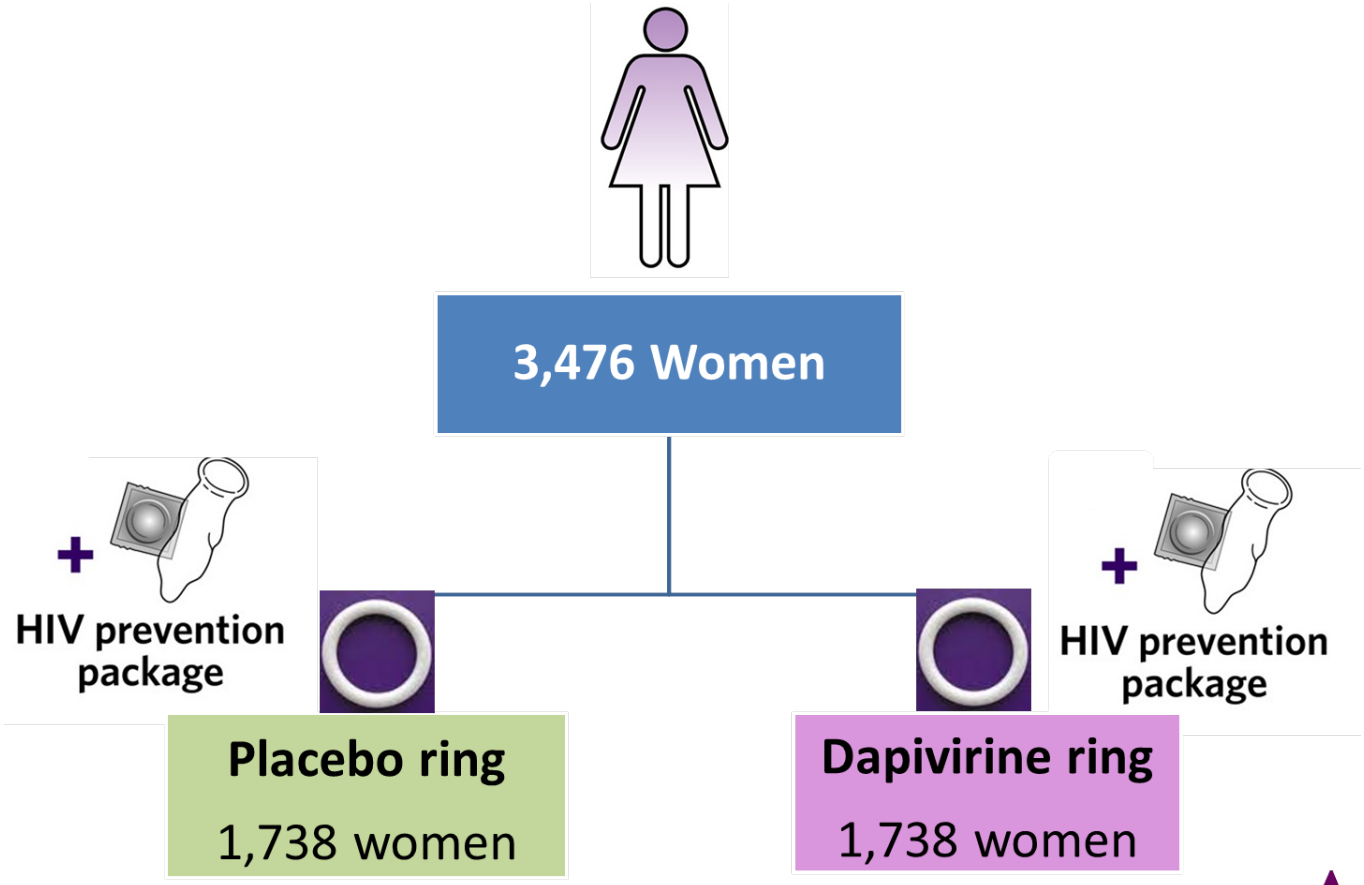
Study Design and Objectives

ASPIRE Study Design



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Primary Objectives

EFFECTIVENESS

- To determine the ***effectiveness*** of dapivirine (25 mg) administered in a silicone elastomer vaginal matrix ring, when inserted once every 4 weeks, in preventing HIV infection among healthy sexually active HIV-uninfected women
  - Primary Effectiveness Outcome: HIV seroconversion

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Primary Objectives

SAFETY

- To assess the ***safety*** of dapivirine (25 mg) administered in a silicone elastomer vaginal matrix ring, when inserted once every 4 weeks over the investigational product use period
  - Primary Safety Outcomes:
    - Grade 2 adverse events (AEs) judged to be related to study product
    - Grade 3 and 4 AEs
    - All serious adverse events

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Secondary Objectives

- Acceptability
  - Self-report
- Adherence
  - Including ring expulsions & removals
- Drug resistance
  - In HIV-1 seroconverters
- Relationship between drug concentrations and HIV-1 seroconversion
  - Concentrations of dapivirine in blood and self-collected vaginal swabs

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Exploratory Objectives

- Describe changes in the genital microenvironment
  - Changes in candidate biomarkers of safety and efficacy
- Assess correlation of steady-state drug concentrations and adherence measures
- Assess delayed seroconversion
  - 4 week post-product completion visit

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Protocol Overview

Participants

- 3476 sexually active HIV-uninfected women who are non-pregnant, contracepting, and 18-45 years of age
- Accrual will require approximately 12 months, with total study duration approximately 24 months
  - Designed so that all participants will achieve 12 months on study product

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Follow-up

- Monthly follow-up, including:
  - HIV serologic testing
  - Contraceptive counseling and provision
  - Clinical safety assessment
  - Study produce provision and adherence counseling
  - Physical and pelvic examination, laboratory safety assessment (every 3-6 months)

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Pregnancy

- Women who become pregnant while in the study will need to stop using the ring but can remain in the study to continue with follow-up visits
- Women will be referred for appropriate care and invited to join MTN-016, an observational registry study that aims to understand if product use has an effect on pregnancy outcomes
- She may be able to rejoin ASPIRE after her pregnancy

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HIV acquisition

- Sites are required to have procedures for care and support for participants who acquire HIV and referral agreements with HIV primary care and ART providers
- The study product will be discontinued immediately
- Antiretroviral resistance testing will be done
- Seroconverters will be invited to join MTN-015
  - MTN-015 is a long-term observational study / registry of seroconverters from MTN studies

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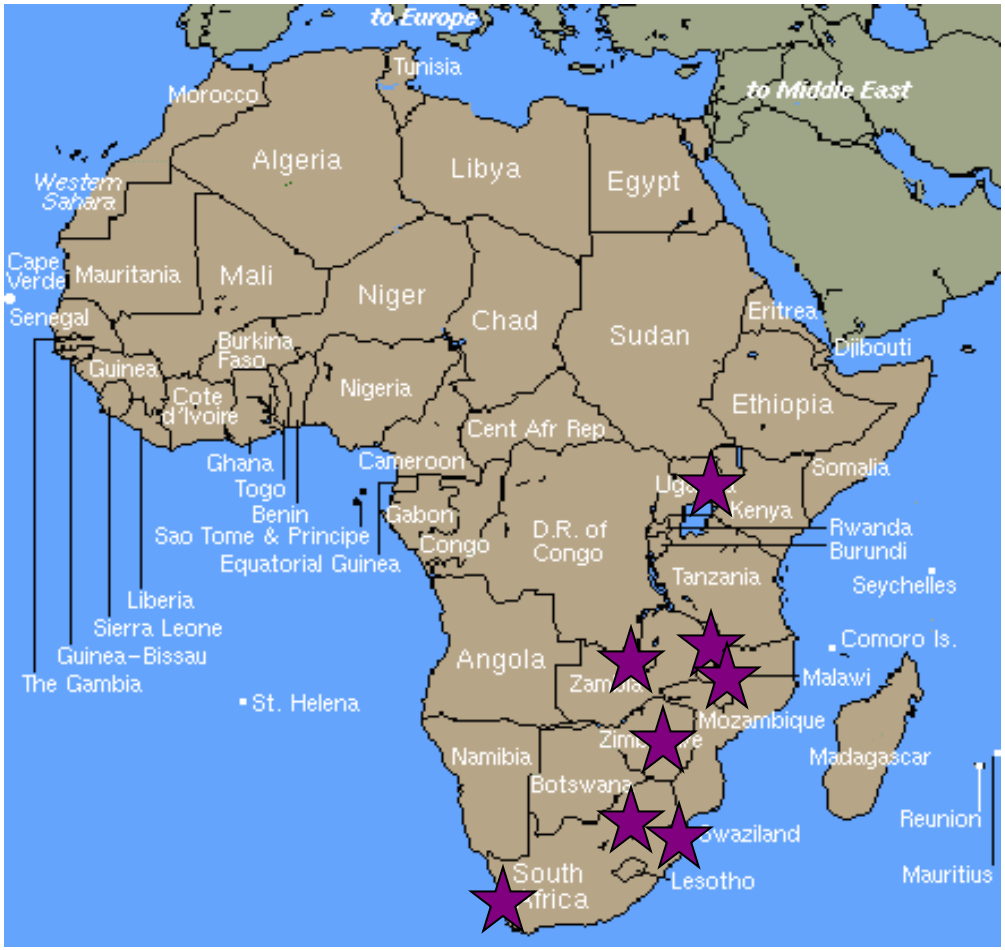
Sites and Timelines

Proposed sites



Blantyre
Lilongwe
Malawi

Cape Town
Durban (8 sites)
Klerksdorp
Johannesburg
South Africa

Kampala
Uganda

Lusaka
Zambia

Harare (3 sites)
Zimbabwe

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ASPIRE to date

- January - March 2011
  - Concept approved by MTN Executive Committee
  - Protocol Consultation Meeting with Site Investigators
- May – July 2011
  - NIAID Strategic Working Group
  - Prevention Science Review Committee
- September 2011
  - v1.0 to sites for IRB submission
- October 2011
  - Community Consultation, Operational Walk-Through
- January 2012
  - DSMB protocol review

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Timeline

2011	• Initiate site IRB and regulatory approval process
2012	• IRB/regulatory approvals, trainings, enrollments begin Q3
2013	• Enrollments and follow-up continue
2014	• End of participant follow-up
2015	• Results

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Clinical development program for dapivirine for HIV prevention

- To date, 25 phase I/II trials of dapivirine (in oral, gel, and ring form) have been conducted
- Trials have demonstrated high safety for topical dapivirine
- Agency reviews (FDA/EMA) have permitted move to efficacy evaluation
- In parallel to MTN-020, IPM will conduct IPM 027 – focus on extended safety plus efficacy

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MTN-020 and IPM 027

	MTN-020	IPM 027
Design	endpoint driven	fixed time
No. of participants	3,475	1,650
Randomization	1:1	2:1
Age	18-45 yrs	18-45 yrs
Product use period	Until end of study (12-24 months)	24 months fixed
Person-years follow-up (all / Dapivirine Vaginal Ring)	4,396 / 2,198	3,150 / 2,100
HIV-1 seroconversions	120	80
Power for 50% effect	97%	83%

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Key Considerations for Optimization of Implementation

Design efficiencies

- Accrual
  - Large number of sites, modest sample size = achievable number of recruitments
  - Focus will be on protocol adherence during screening and enrollment – i.e., really trying to enroll only those who will return as scheduled for follow-up

- Follow-up
  - Streamlined data collection and study procedures = reduced time spent in clinic
  - Allowances for efficiencies for individual women – protocol provisions for extra ring dispensing and off-site visits

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Design efficiencies (2)

- Retention
  - Focus from day one from participant one : resource and attention allocation will be critical
  - *No retention = no adherence*

- Provision of services on-site
  - Contraception : expanding method mix and convenience
  - Partner HIV testing, STI evaluation/referral

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The Big Five

Accrual

Adherence

Retention

Clinical and Laboratory Participant Safety

Data Quality and Timeliness

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ASPIRE TEAM

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National Institutes of Health

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SCHARP

fhi360

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WRHI

MRC SOUTH AFRICA

CIDRZ

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