MTN-020 and IPM 027 and the MTN-020 DSMB

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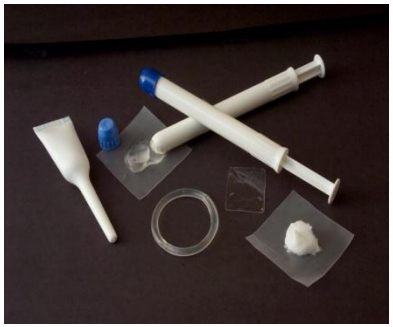
ASPIRE Protocol Team Meeting
22 February 2012

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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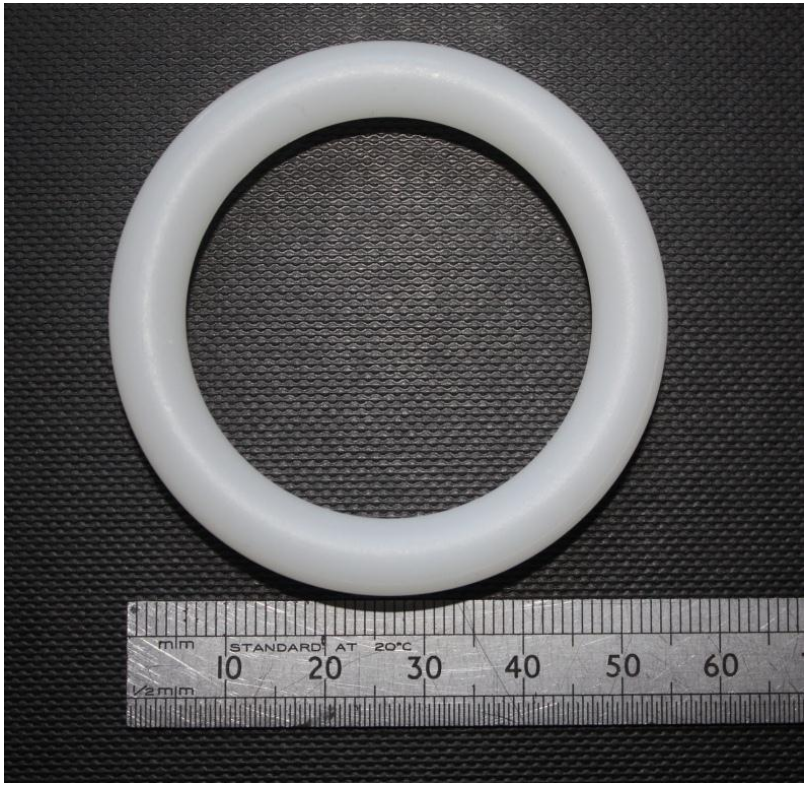
Dapivirine ring

- 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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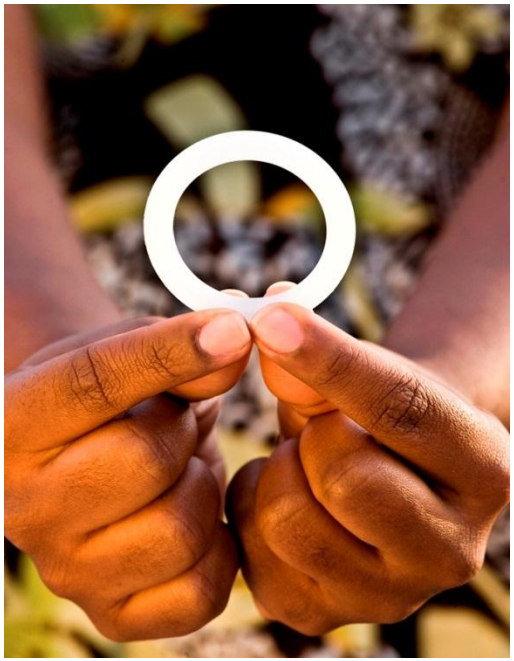
Dapivirine ring for HIV prevention

- 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 and IPM 027, in concert with the entire dapivirine package, will provide strength of evidence to support potential licensure



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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IPM 027 / The Ring Study

A MULTI-CENTRE, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED *SAFETY AND EFFICACY* TRIAL OF A DAPIVIRINE VAGINAL MATRIX RING IN HEALTHY HIV-NEGATIVE WOMEN

MTN-020 and IPM 027

	MTN-020	IPM 027
Design	endpoint driven	fixed time
No. of participants	3,476	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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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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Trial Population

- Women
- HIV-negative
- Sexually active
- 18 - *45* years of age
- Last participant 24 months of follow-up

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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Primary Objective

To assess and compare the **safety and efficacy of dapivirine administered in a silicone elastomer vaginal matrix ring to the placebo vaginal ring,** when inserted once every 4 weeks over a period of approximately 24 months (104 weeks)

Primary Endpoints

- HIV-1 seroconversion
- Grade 2 adverse events (AEs) judged to be related to the investigational product
- Grade 3 and 4 AEs

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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Secondary Objectives

- Adherence
- Acceptability
- Resistance
  - THUS – SIMILAR
- Incident STIs and vaginal flora
- Pregnancy incidence

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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Exploratory Objectives

- HSV-2 and HIV-1 interactions
- Contraception, pregnancy, and HIV seroconversion
- Relationship between drug concentrations and trial outcomes (HIV-1 seroconversion and viral resistance)
- Correlation of drug concentrations and self-reported adherence measures

MTN-020 visit schedule

- Screening
- Enrollment
- Monthly
- Quarterly
- Semi-annual
- PUEV
- Exit (4 weeks after PUEV)

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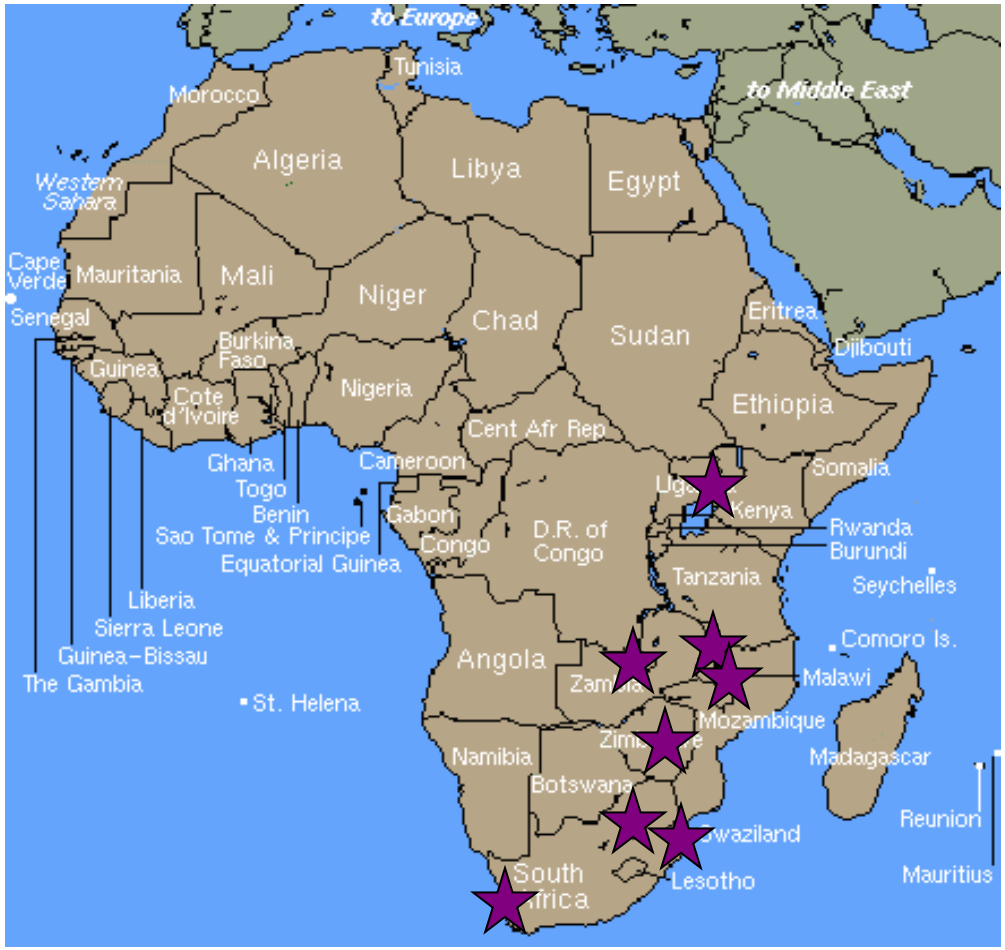
Study Visits and Procedures

- Screening 1/2
- Enrollment
- 4-weekly
- 12-weekly
- 24-weekly
- Annual
- Last Product Use (LPUV)
- Exit Visit (6 weeks after LPUV)

Proposed sites – MTN-020



Blantyre
Lilongwe
Malawi

Cape Town
Durban (8 sites)
Klerksdorp
Johannesburg
South Africa

Kampala
Uganda

Lusaka
Zambia

Harare (3 sites)
Zimbabwe

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Study sites

Blantyre
Malawi

Kigali
Rwanda

Brits
Edendale
Ladysmith
Pinetown
South Africa

Similarities

- Very similar primary, secondary, and exploratory objectives and endpoints

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Similarities

- Very similar primary, secondary, and exploratory objectives and endpoints
- Key goals are identical: efficient enrollment, high retention, promotion of product use/adherence, definitively testing whether this product is safe and effective

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Differences

- Sample size (3476 vs. 1650)
- Follow-up (open-ended vs. fixed 24 months)
- Randomization (1:1 vs. 1:2)
- Sample collection (somewhat different repositories), laboratory testing (027 has more tests), pregnancy (027 will terminate at pregnancy)

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Coordination

- MTN-020 and IPM 027 teams have worked tirelessly to ensure that data collection, counseling/clinical management, oversight are moving in parallel
- MTN-020 and IPM 027 are coordinated within single regulatory/investigational new drug applications (FDA, EMA)

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MTN-020 DSMB

DSMB

- MTN-020 will use the DAIDS Multinational DSMB
- First review of the protocol 26 January 2012
- Anticipate 6 monthly reviews (May/November) of safety and study conduct during the course of the study
- Goal is that all efficacy reviews will coincide with scheduled safety reviews

It takes a team

MTN microbicide trials network

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National Institutes of Health

Statistical Center for HIV/AIDS Research & Prevention
SCHARP

fhi360

Malawi College of Medicine – JHU Research Project

WRHI

MRC SOUTH AFRICA

CIDRZ

UNC Project - Malawi

International Partnership for Microbicides

DESMOND TUTU HIV FOUNDATION

THE AURUM INSTITUTE

University of Zimbabwe, School of Medicine

CAPRISA
CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA