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

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Developing a range of options for antiretroviral-based HIV prevention

- 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
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
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
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

<table>
<thead>
<tr>
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<th>MTN-020</th>
<th>IPM 027</th>
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<tbody>
<tr>
<td><strong>Design</strong></td>
<td>endpoint driven</td>
<td>fixed time</td>
</tr>
<tr>
<td><strong>No. of participants</strong></td>
<td>3,476</td>
<td>1,650</td>
</tr>
<tr>
<td><strong>Randomization</strong></td>
<td>1:1</td>
<td>2:1</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>18-45 yrs</td>
<td>18-45 yrs</td>
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<tr>
<td><strong>Product use period</strong></td>
<td>Until end of study (12-24 months)</td>
<td>24 months fixed</td>
</tr>
<tr>
<td><strong>Person-years follow-up (all / Dapivirine Vaginal Ring)</strong></td>
<td>4,396 / 2,198</td>
<td>3,150 / 2,100</td>
</tr>
<tr>
<td><strong>HIV-1 seroconversions</strong></td>
<td>120</td>
<td>80</td>
</tr>
<tr>
<td><strong>Power for 50% effect</strong></td>
<td>97%</td>
<td>83%</td>
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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
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
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
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
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
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)
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
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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- 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
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)
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).
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