A Phase III Trial of the Dapivirine Vaginal Ring for HIV-1 Prevention in Women

The MTN-020/ASPIRE Study Team

CROI 2016, Boston, USA
Conflict of Interest

• I have received research funding for PrEP, ART for HIV prevention, and microbicides from the Bill & Melinda Gates Foundation, the US NIH, and USAID.

• For some research studies, medication has been donated by Gilead Sciences and the International Partnership for Microbicides.

• I have no other conflicts of interest.
MTN-020/ASPIRE Study Team

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- **Study sites:**
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  - South Africa: Cape Town site (University of Cape Town): Linda-Gail Bekker
  - South Africa: Durban eThekwini site (Centre for AIDS Programme of Research in South Africa): Gonasagrie Nair
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  - Uganda: Kampala site (Makerere University-Johns Hopkins University Research Collaboration): Flavia Matovu Kiweewa, Clemensia Nakabitol
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- **US National Institutes of Health:** Nahida Chakhtoura, Donna Germuga, Cynthia I. Grossman, Lydia E. Soto-Torres

- **International Partnership for Microbicides:** Zeda Rosenberg, Annalene Nel

- **MTN-020/ASPIRE participants and their communities; MTN-020 Community Working Group; MTN-020 Study Monitoring Committee; DAIDS MNDSMB**

- The Microbicide Trials Network is funded by the National Institute of Allergy and Infectious Diseases (UM1AI068633, UM1AI068615, UM1AI067097), with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Institute of Mental Health, all components of the U.S. National Institutes of Health. We are grateful to Dr. Roberta Black at NIAID for her oversight.
Background

• Antiretroviral medications used as prophylaxis can prevent HIV-1 acquisition.

• Some clinical trials of tenofovir-based prophylaxis among African women reported no reduction in HIV-1 because of low adherence to daily- or coitally-prescribed antiretroviral-containing pills and vaginal gels.

• Longer-acting drug delivery methods, such as antiretroviral-containing vaginal rings, may simplify use and provide protection against HIV-1.
MTN-020/ASPIRE was a multi-center, randomized, double-blind, placebo-controlled phase III trial of a vaginal matrix ring containing the non-nucleoside reverse transcriptase inhibitor dapivirine.
MTN-020/ASPIRE

- MTN-020/ASPIRE was a multi-center, randomized, double-blind, placebo-controlled phase III trial of a vaginal matrix ring containing the non-nucleoside reverse transcriptase inhibitor dapivirine.
- The primary objectives were to determine the **effectiveness** and **safety** of dapivirine (25 mg) administered in a silicone elastomer vaginal matrix ring, when inserted once every 4 weeks, in preventing HIV-1 infection among healthy sexually active HIV-1 uninfected women.
Trial Design

• At enrollment, women were randomized 1:1 to dapivirine:placebo.
• Women were counseled to wear the ring continuously, and a new ring was provided at scheduled monthly visits.
• Follow-up was for a minimum of 1 year.
• All received a comprehensive package of HIV-1 prevention services.
Participants

• Between August 2012 and June 2015, a total of 2629 women were enrolled and followed across 15 sites in 4 countries: Malawi (10%), South Africa (54%), Uganda (10%), & Zimbabwe (26%)
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- Participant characteristics were balanced between the arms and defined a population at risk for HIV-1:
  - Median age was 26 years (IQR 22-31)
  - Less than half (41%) were married
  - Nearly all (>99%) reported a primary sex partner & 17% reported more than one partner in the prior 3 months
  - Nearly half did not use a condom with their last sex act
Retention and Follow-up

- 2614 (99.4%) women completed at least one follow-up visit
- Overall, participants attended 91% of expected follow-up visits (97% after accounting for early withdrawals from the study).
- A total of 4280 person-years of follow-up were accrued
  - Median follow-up = 1.6 years, maximum = 2.6 years
Objective Adherence Assessment

- Two objective measures, testing dapivirine, were used to assess adherence:
  - **Plasma.** Measured in quarterly-collected plasma samples: levels >95 pg/mL, indicating at least 8 hours of continuous use, defined adherence.
  - **Ring.** After the first year of the study, residual drug in returned, used rings was also measured: levels <23.5 mg (= 1.5 mg released, indicating at least some use during the month) defined adherence.
  - While the study was ongoing, adherence measures, overall & each site, were reviewed by the study leadership, in a fashion that preserved study blinding.
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  - **Plasma.** Measured in quarterly-collected plasma samples: levels >95 pg/mL, indicating at least 8 hours of continuous use, defined adherence.
  - **Ring.** After the first year of the study, residual drug in returned, used rings was also measured: levels <23.5 mg (≈ 1.5 mg released, indicating at least some use during the month) defined adherence.
  - While the study was ongoing, adherence measures, overall & each site, were reviewed by the study leadership, in a fashion that preserved study blinding.

Importantly, both adherence measures could exclude those who were non-adherent but would overestimate adherence for women who used the ring only for a few hours/days prior to a clinic visit.
Adherence

• Dapivirine was detected in 82% of plasma samples at concentrations >95 pg/mL.
  • Detection increased during the first year of use and stabilized thereafter.
  • Two study sites were identified early in the study as having lower detection of dapivirine compared to other sites, as well as lower retention.
Adherence

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  - Detection increased during the first year of use and stabilized thereafter.
  - Two study sites were identified early in the study as having lower detection of dapivirine compared to other sites, as well as lower retention.

- In the subset of visits where returned rings were available, 84% contained <23.5 mg of dapivirine, and dapivirine levels in plasma and in returned rings were generally correlated.
  - However, high residual dapivirine levels were observed for some visits with plasma dapivirine concentrations >95 pg/mL
HIV-1 Protection

Overall, women in the dapivirine vaginal ring arm had a 27% reduction in the rate of HIV-1 acquisition, compared to placebo.

<table>
<thead>
<tr>
<th>Primary HIV-1 effectiveness intention-to-treat analysis (15 sites)</th>
<th>Dapivirine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td># HIV-1 infections</td>
<td>71</td>
<td>97</td>
</tr>
<tr>
<td>HIV-1 incidence, per 100 person-years</td>
<td>3.3</td>
<td>4.5</td>
</tr>
<tr>
<td>HIV-1 protection effectiveness</td>
<td>27% (1, 46) p=0.046</td>
<td></td>
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</tbody>
</table>
HIV-1 Protection

After excluding data from two sites with lower adherence, the dapivirine ring reduced HIV-1 acquisition by 37%.

Primary HIV-1 effectiveness intention-to-treat analysis (13 sites)

<table>
<thead>
<tr>
<th></th>
<th>Dapivirine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td># HIV-1 infections</td>
<td>54</td>
<td>85</td>
</tr>
<tr>
<td>HIV-1 incidence, per 100 person-years</td>
<td>2.8</td>
<td>4.4</td>
</tr>
<tr>
<td>HIV-1 protection effectiveness</td>
<td>37% (12, 56)</td>
<td>p=0.007</td>
</tr>
</tbody>
</table>

95% CI, p-value

No. at risk 2395 2352 2275 2218 2020 1739 1459 1235 1108 748 428 223

Months since randomization

Placebo

Dapivirine
Subgroups

• In subgroup analyses – by country, education, marital status, STIs at baseline, number of sexual partners, and partner knowledge of study participation – HIV-1 protection was similar to the overall findings.
Subgroups

- In subgroup analyses – by country, education, marital status, STIs at baseline, number of sexual partners, and partner knowledge of study participation – HIV-1 protection was similar to the overall findings.

- However, HIV-1 protection differed significantly by age, with women ≥25 years demonstrating substantial HIV-1 protection while those <25 years of age no statistically significant reduction in HIV-1 incidence:

<table>
<thead>
<tr>
<th>HIV-1 protection effectiveness (95% CI)</th>
<th>Age &lt;25</th>
<th>Age ≥25</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10% (51,43)</td>
<td>61% (32,77)</td>
</tr>
<tr>
<td>Interaction p-value</td>
<td>p=0.02</td>
<td></td>
</tr>
</tbody>
</table>
Age and HIV-1 Protection

- HIV-1 protection effectiveness was explored in additional age-stratified categories, and lack of HIV-1 protection was limited to those ≤21 years of age:

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Effectiveness</th>
<th>Placebo Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 18-21</td>
<td>-27% (-133,31)</td>
<td>5.4%/yr</td>
</tr>
<tr>
<td>Age 22-26</td>
<td>56% (19,76)</td>
<td>6.1%/yr</td>
</tr>
<tr>
<td>Age 27-45</td>
<td>51% (8,74)</td>
<td>3.0%/yr</td>
</tr>
</tbody>
</table>

### Diagrams

**Left Diagram**: Comparison of incidence rates between the intervention and placebo groups for different age ranges.

**Middle Diagram**: Graph showing the progression of intervention and placebo groups over time.

**Right Diagram**: Graph illustrating the incidence rates across different age groups.
Age and HIV-1 Protection

- HIV-1 protection effectiveness was explored in additional age-stratified categories, and lack of HIV-1 protection was limited to those ≤21 years of age:

  - Age 18-21: -27% (-133, 31) placebo incidence 5.4%/yr
  - Age 22-26: 56% (19, 76) placebo incidence 6.1%/yr
  - Age 27-45: 51% (8, 74) placebo incidence 3.0%/yr

- Among women >21 years of age, HIV-1 protection effectiveness was 56% (95% CI 31-71%, p<0.001)
Age and Adherence

- Adherence measures were statistically significantly lower among women 18-21 years compared to women >21 years.

% of visits with plasma dapivirine >95 pg/mL *and* residual ring dapivirine <23.5 mg

- Age 27-45
- Age 22-26
- Age 18-21
Safety

• No statistically significant differences in the frequency of safety endpoints between arms

• Pregnancy incidence was similar between the arms: 3.9 and 4.0 per 100 person-years (p=0.82)

• Among those acquiring HIV-1, detection of non-nucleoside reverse transcriptase inhibitor mutations did not differ by study arm (8/68 assigned to dapivirine and 10/96 assigned to placebo, p=0.80)

<table>
<thead>
<tr>
<th></th>
<th>Dapivirine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAE</td>
<td>48 (4%)</td>
<td>52 (4%)</td>
</tr>
<tr>
<td>Death</td>
<td>3 (&lt;1%)</td>
<td>4 (&lt;1%)</td>
</tr>
<tr>
<td>Grade 4 event</td>
<td>23 (2%)</td>
<td>22 (2%)</td>
</tr>
<tr>
<td>Grade 3 event</td>
<td>162 (12%)</td>
<td>151 (12%)</td>
</tr>
<tr>
<td>Grade 2 event, related</td>
<td>9 (1%)</td>
<td>7 (1%)</td>
</tr>
</tbody>
</table>
MTN-020/ASPIRE Summary

• A monthly vaginal ring containing dapivirine safely reduced incident HIV in African women.
  – Risk was reduced by ~1/3 overall and by >1/2 among those aged ≥22

• These are the first results to demonstrate HIV-1 protection by a sustained-release approach for delivery of an antiretroviral for HIV-1 prevention.

• HIV-1 protection was greater in subgroups with evidence of better adherence to ring use.
Discussion - Adherence

• Strong relationships between adherence and HIV-1 protection are expected in studies of HIV-1 prophylaxis.

• Further pharmacokinetic analyses may help define whether there is a threshold use of dapivirine for protection against HIV-1, analogous to investigations that have followed the initial clinical trials of tenofovir-based prophylaxis.

• Notably, in tenofovir studies, adherence was greater in open-label evaluations following placebo-controlled trials.
Discussion - Age

• HIV-1 protection was not observed for women aged 18-21 and objective markers of adherence were lower in this subgroup compared to women older than 21.

• Both behavioral and biologic effects may have contributed to a lack of HIV-1 protection in women aged 18-21 in this study, and further research is needed to understand the unique prevention needs of this youngest group of women.
Conclusions

• In the placebo arm of this study, HIV-1 incidence was >4% per year (>6% in those aged 22-26). Effective, safe prevention options are needed for women at risk of HIV-1.

• Our results, with those of The Ring Study, provide confirmatory evidence that an antiretroviral vaginal ring can protect against HIV-1.
Phase III Trial Results of the Dapivirine Ring

Dr. Zeda Rosenberg, CEO
International Partnership for Microbicides (IPM)

AVAC Webinar
01 March 2016
ASPIRE and The Ring Study

**ASPIRE**
- Conducted by the Microbicide Trials Network (MTN)
- Funded by the US National Institutes of Health (NIH)
- Led by Dr. Jared Baeten (University of Washington, USA) and Dr. Thesla Palanee-Phillips (Wits RHI, South Africa)

**The Ring Study**
- Conducted by the International Partnership for Microbicides (IPM)
- Supported by governments, multilateral organizations and foundations
- Led by Dr. Annalene Nel (IPM, South Africa) and Dr. Saidi Kapiga (Mwanza Intervention Trials Unit, Tanzania)
# Study designs and timelines

<table>
<thead>
<tr>
<th>The Ring Study</th>
<th>ASPIRE</th>
</tr>
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<tbody>
<tr>
<td><strong>Objectives</strong></td>
<td>Long-term safety and efficacy</td>
</tr>
<tr>
<td><strong>Enrolment</strong></td>
<td>Total: 1959 women ages 18-45 years</td>
</tr>
<tr>
<td></td>
<td>Active arm: 1307</td>
</tr>
<tr>
<td></td>
<td>Placebo arm: 652</td>
</tr>
<tr>
<td></td>
<td>All participants receive a comprehensive HIV-1 prevention package</td>
</tr>
<tr>
<td><strong>Timeline</strong></td>
<td>Started April 2012</td>
</tr>
<tr>
<td><strong>Timeline for Results</strong></td>
<td>Reporting early</td>
</tr>
</tbody>
</table>
4,588 women in four countries

The Ring Study: 7 Research Centres (n = 1959)
- South Africa
  - Kwa-Zulu Natal (3 sites)
  - North-West
  - Western Cape
  - Limpopo
- Uganda
  - Masaka

ASPIRE: 15 NIH Clinical Research Sites (n = 2629)
- South Africa
  - Western Cape
  - Kwa-Zulu Natal (7 sites)
  - Gauteng
- Uganda
  - Kampala
- Zimbabwe
  - Harare (3 sites)
- Malawi
  - Blantyre
  - Lilongwe

The Ring Study

<table>
<thead>
<tr>
<th>Enrolment</th>
<th>Total Number Enrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Africa: Kwa-Zulu Natal</td>
<td>1064</td>
</tr>
<tr>
<td>South Africa: North West</td>
<td>482</td>
</tr>
<tr>
<td>South Africa: Western Cape</td>
<td>97</td>
</tr>
<tr>
<td>South Africa: Limpopo</td>
<td>119</td>
</tr>
<tr>
<td>Uganda: Masaka</td>
<td>197</td>
</tr>
</tbody>
</table>

ASPIRE

<table>
<thead>
<tr>
<th>Enrolment</th>
<th>Total Number Enrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malawi: Blantyre</td>
<td>130</td>
</tr>
<tr>
<td>Malawi: Lilongwe</td>
<td>142</td>
</tr>
<tr>
<td>South Africa: Western Cape</td>
<td>166</td>
</tr>
<tr>
<td>South Africa: Kwa-Zulu Natal</td>
<td>1047</td>
</tr>
<tr>
<td>South Africa: Gauteng</td>
<td>213</td>
</tr>
<tr>
<td>Uganda: Kampala</td>
<td>253</td>
</tr>
<tr>
<td>Zimbabwe: Chitungwiza</td>
<td>448</td>
</tr>
<tr>
<td>Zimbabwe: Harare – Spilhaus</td>
<td>230</td>
</tr>
</tbody>
</table>
Study questions

- Will the ring prevent HIV?
- Is the ring safe?
- Is the ring acceptable?
- Will women use the ring (adherence)?
What did these trials find?

- The dapivirine ring can help protect against HIV
- Age and adherence to ring use was associated with protection
- Monthly use was safe, and no HIV drug resistance was associated with use of the dapivirine ring
### HIV-1 Prevention

#### The Ring Study

- 31% (95% CI 1 to 52, \( p=0.040 \)) relative reduction in HIV-1 incidence overall

- 37% (95% CI 3.5 to 59, \( p \)-value for treatment by age interaction: 0.427) reduction in an as-randomized analysis among women older than 21 years of age

#### ASPIRE

- 27% (95% CI 1 to 46, \( p=0.046 \)) relative reduction in HIV-1 incidence overall

- 56% (95% CI 31 to 71, \( p=0.0003 \)) statistical significant reduction in an as-randomized analysis among women older than 21 years of age
Adherence and HIV-1 protection

Adherence was measured by testing the amount of dapivirine in:

**Blood samples** collected every month

**Used rings** collected every month

Trends indicate that higher levels of product adherence resulted in higher levels of protection against HIV-1 infection (as high as 65% reduction)
Adherence appears linked to efficacy

How was adherence measured?
• By drug levels remaining in used rings and in blood plasma

Results?
• Higher efficacy seen with more consistent use
  • In ASPIRE, adherence and, in turn, HIV protection improved over time
  • Ring Study post-hoc analysis showed strong trend toward higher efficacy in women with less drug remaining in the ring

Summary: Data strongly suggest consistent ring use needed to achieve protection – and greater protection can be achieved with more consistent use
What do the overall results mean?

Combined, the dapivirine ring prevented about $\frac{1}{3}$ of HIV infections – about 1 in 3 women who would have acquired HIV did not.
Protection by age

HIV risk was reduced by more than half (56 percent) among women older than 21 in ASPIRE
Dapivirine Ring Safety

1. Dapivirine vaginal ring was shown to be very safe

2. No difference between the dapivirine and placebo groups in:
   – The Number of adverse events (side effects / health problems) experienced
   – The Number of pregnancies
   – The Number of sexually transmitted infections

3. No significant HIV-1 drug resistance
Summary

- Two trials have shown that the monthly dapivirine ring safely and effectively protected nearly 1/3 of women.

- Higher protection seen in women older than 21 – up to 56%.

- Higher efficacy seen with more consistent use.

- We must work to overcome the barriers to HIV prevention for women under 21.
What’s next?

• Ring Study in South Africa will now provide all women with the dapivirine ring for remainder of their participation
  • Seeking similar approval in Uganda

• IPM is planning an Open-Label Extension (OLE) study (DREAM) to provide former Ring Study participants access to ring and understand how women may use it when they are aware it can safely help offer protection

• NIAID (primary NIH institute that funds MTN) convening consultation March 9 to determine next steps for research, including OLE (HOPE) for ASPIRE participants and study in women ages 16-21 of ring and PrEP
Key Messages
The need

- Women in Africa are at especially high risk of HIV infection, primarily due to unprotected heterosexual sex

- Women have limited options
  - Abstinence, monogamy and use of male condoms are not realistic or practical for many women
  - Daily oral ARV pills, known as PrEP, is a new method, but may not be easy for some women to use – one size does not fit all
Why the dapivirine ring for HIV prevention?

- The ring is the first long-acting and discreet self-initiated HIV prevention method designed for women that has been shown to safely offer protection.
- Product use among women over 21 support the ring as a method that could fit into many women’s lives.
- We hope knowledge of the ring’s safety and efficacy would help encourage its use beyond the clinical trial setting, as seen with oral PrEP, a daily ARV pill.
### Why a vaginal ring for HIV prevention?

<table>
<thead>
<tr>
<th><strong>Longer Acting:</strong></th>
<th><strong>Ease of Use:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Used monthly or longer - sustained release of drug</td>
<td></td>
</tr>
<tr>
<td>May help with consistent use</td>
<td></td>
</tr>
<tr>
<td>Higher adherence → increased effectiveness</td>
<td></td>
</tr>
<tr>
<td>Flexible ring – women insert and remove the ring themselves</td>
<td></td>
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<tr>
<td>Little or no impact on sexual activity</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Safety:</strong></th>
<th><strong>Privacy:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies have shown the ring is safe to use and has very few side effects</td>
<td></td>
</tr>
<tr>
<td>Vaginal rings can be inserted and removed in private</td>
<td></td>
</tr>
<tr>
<td>Rarely felt by women or male partners</td>
<td></td>
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</tbody>
</table>

Vaginal rings are used in the US and Europe to deliver contraception.
Women need options

- Ending the epidemic will require multiple prevention options that meet women’s needs, which can change throughout their lives.

- We hope the ring will join oral PrEP to give women a new way to protect themselves.

- Although we must work to overcome barriers to prevention among the youngest women in Africa, both products could be important options for many women at high risk.
Women need options

- A product that best suits one’s lifestyle and needs is more likely to be used
- Even the most effective product cannot protect against HIV if it is not used
- But women’s preferences are not all the same - just as women have choices in contraception, they need choices for HIV prevention, too