Acceptability of and Adherence to the Dapivirine Vaginal Ring for HIV-1 Prevention

Adherence 2019, June 17-19, 2019, Miami, FL

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Disclosures

• Discussion of drug that is investigational and not FDA approved
• No conflicts of interest to declare
Objective

- MTN-020/ASPIRE was a phase III trial in healthy HIV-negative sexually-active women to evaluate safety and effectiveness of monthly 25 mg dapivirine vaginal ring (DVR).
- Assessed the relationship between acceptability and adherence to inform future ring introduction.
- 2,629 women aged 18-45
- 15 sites in South Africa, Zimbabwe, Malawi and Uganda
- Randomized 1:1 to 25 mg DVR or placebo ring
- DVR was well tolerated and reduced risk of HIV-1 infection by 30% overall and ≥50% among those with greater adherence

Baeten J et al., NEJM 2016
ASPIRE Study Design

• Monthly follow-up for 1-3 years
• Acceptability measures captured using audio computer-assisted self-interview (ACASI) at Month-3 and Product Use End visit (PUEV)
• Analysis sample: randomized to 25 mg DVR
Conceptual Model

**Influencing factors**
- Social and structural context
  - Organizations
  - Partner
    - Individual characteristics

**Product acceptability**
- Product-associated norms
- Partner’s attitude
- Effects of product use on sex
- Use attributes
  - Product characteristics
    - Delivery mechanism
    - Efficacy (if known)
    - Dosing regimen

**Preference & Choice**

**Adherence**
- Initiation
- Execution
- Discontinuation

Non-Adherence

• Plasma dapivirine concentrations (quarterly)
  – Liquid chromatography-tandem mass spectrometry assay
  – ≤95 pg/ml indicates no evidence of use past 8 hours

• Residual dapivirine in returned ring (monthly)
  – Started one year after trial initiation
  – Acetone extraction and high-pressure liquid chromatography
  – ≥23.5 mg indicates no evidence of use in past month
Non-Adherence

• Non-adherence
  – Cross sectional: Month-3 plasma dapivirine concentrations ≤95 pg/ml
  – Cumulative: ≥ 20% of used rings post Month-3 had no evidence of use (≥23.5 mg residual drug)
## Acceptability Measures

<table>
<thead>
<tr>
<th>Component</th>
<th>Measure</th>
<th>Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosing regimen</strong></td>
<td>• Difficulty keeping the ring inserted as instructed</td>
<td>M-3</td>
</tr>
<tr>
<td></td>
<td>• Uncomfortable to have the ring inside you every day</td>
<td>M-3</td>
</tr>
<tr>
<td><strong>Use attributes</strong></td>
<td>• Aware of ring during normal daily activities</td>
<td>M-3</td>
</tr>
<tr>
<td></td>
<td>• Difficulty inserting</td>
<td>M-3</td>
</tr>
<tr>
<td></td>
<td>• Mind wearing the ring during menses</td>
<td>PUEV</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>• Felt ring during sex</td>
<td>M-3</td>
</tr>
<tr>
<td></td>
<td>• Mind wearing during sex</td>
<td>PUEV</td>
</tr>
<tr>
<td><strong>Partner</strong></td>
<td>• Partner felt ring during sex</td>
<td>M-3</td>
</tr>
<tr>
<td></td>
<td>• Ring unacceptable to partner</td>
<td>PUEV</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>• Less than ‘very likely’ to use in the future</td>
<td>PUEV</td>
</tr>
</tbody>
</table>
Methods

• Poisson regression models with robust standard errors to estimate relative risk of non-adherence, adjusted for country, enrollment post adherence support activities, and months in study.
## Results

**Total N=1,267 (96%)**

- 99% had Month-3 plasma results
- 97% had residual drug results post Month-3
- 75% had ≥ 12 DVRs

### Demographics

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median years (IQR)</td>
<td>26 (22-31)</td>
</tr>
<tr>
<td>Has primary partner</td>
<td>99%</td>
</tr>
<tr>
<td>Follow-up, median mos. (IQR)</td>
<td>23 (15-29)</td>
</tr>
<tr>
<td>Country</td>
<td></td>
</tr>
<tr>
<td>South Africa</td>
<td>54%</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>26%</td>
</tr>
<tr>
<td>Malawi</td>
<td>10%</td>
</tr>
<tr>
<td>Uganda</td>
<td>10%</td>
</tr>
<tr>
<td>Month-3 ACASI</td>
<td>98%</td>
</tr>
<tr>
<td>PUEV ACASI</td>
<td>89%</td>
</tr>
<tr>
<td>Number rings post month-3 with residual drug, median (IQR)</td>
<td>18 (12-21)</td>
</tr>
</tbody>
</table>
Acceptability

• Ring was acceptable to most participants
  – 96% were likely to use DVR in the future at PUEV
  – Differed by country

![Acceptability Chart]

- Zimbabwe: 75% very likely, 25% likely, 0% unlikely, 0% very unlikely
- Uganda: 76% very likely, 24% likely, 0% unlikely, 0% very unlikely
- South Africa: 58% very likely, 42% likely, 0% unlikely, 0% very unlikely
- Malawi: 52% very likely, 48% likely, 0% unlikely, 0% very unlikely
Acceptability

• Few women reported DVR as unacceptable across all components.

Month-3

Unable to wear as instructed: 44%
Felt ring during sex: 26%
Aware during normal activities: 21%
Partner felt ring during sex: 19%
Difficulty inserting: 15%
Uncomfortable wear every day: 13%

Product Use End Visit

Ring unacceptable to partner: 12%
Minded wearing during menses: 17%
Minded wearing during sex: 18%
Cross Sectional Non-Adherence: Month-3

- 22% had no evidence of use in past 8 hours before Month-3 visit
Cumulative Non-Adherence: Post Month-3

- Minded during sex
- Aware during normal activities
- Felt ring during sex
- < Very likely to use in future
- Partner felt ring during sex
- Minded during menses
- Unable to wear as instructed
- Unacceptable to partner
- Uncomfortable to wear every day
- Difficulty inserting

- 25% had no evidence of use in ≥ 20% of used rings post Month-3 (N=1,092)
Conclusions

• The DVR was highly acceptable to participants and partners, and the majority expressed future likelihood of use, although with country variation.

• Almost every component of acceptability was associated with non-use, especially, interference with sex.

• Discomfort associated with early non-use, but not long-term use.

• The negative impact of ring awareness during sex and ring discomfort should be addressed through counseling and skill building in future ring interventions.
Acknowledgements

The Microbicide Trials Network is funded by the National Institute of Allergy and Infectious Diseases (UM1AI068633, UM1AI068615, UM1AI106707), 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.

The International Partnership for Microbicides developed the dapivirine ring and supplied rings for this trial.
MTN-020/ASPIRE Study Team

MTN-020/ASPIRE leadership: Jared M. Baeten (protocol chair), Thesla Palanee-Phillips (protocol co-chair), Elizabeth R. Brown (protocol statistician), Katie Schwartz (FHI 360 senior clinical research manager), Lydia E. Soto-Torres (DAIDS medical officer)

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Malawi: Lilongwe site (University of North Carolina Project): Francis Martinson

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

South Africa: Durban – Botha's Hill, Chatsworth, Isipingo, Tongaat, Umkomaas, Verulam sites (South African Medical Research Council): Vaneshree Govender, Samantha Siva, Nitesha Jeenarain, Zakir Gaffoor, Arendevi Pather, Logashvari Naidoo, Gita Ramjee

South Africa: Johannesburg site (Wits Reproductive Health and HIV Institute): Thesla Palanee-Phillips

Uganda: Kampala site (Makerere University-Johns Hopkins University Research Collaboration): Flavia Matovu Kiweewa, Clemensia Nakabiito

Zimbabwe: Chitungwiza-Seke South, Chitungwiza-Zengeza, Harare-Spihlaus sites (University of Zimbabwe-University of California San Francisco Collaborative Research Program): Nyaradzo M. Mgodzi, Felix Mhlanga, Zvavahera M. Chirenje


Microbicides Trials Network Laboratory Center (Magee-Womens Research Institute, University of Pittsburgh, Johns Hopkins University): Craig W. Hendrix, Edward Livant, Mark A. Marzinke, John W. Mellors, Urvi M. Parikh

Microbicides Trials Network Statistical and Data Management Center (Fred Hutchinson Cancer Research Center): Elizabeth R. Brown, Jennifer Berthiaume, Marla Husnik, Karen Patterson, Barbra A. Richardson, Daniel W. Szydlo


International Partnership for Microbicides: Zeda Rosenberg, Annelene Nel

MTN-020/ASPIRE participants and their communities and the MTN-020 Community Working Group
Extra Slides (as needed)
ASPIRE Adherence Engagement Activities

- Group-level support implemented March 2013
- Activity types included milestone events, social events, group discussions, male involvement events, couples workshops, and annual/holiday events
- Promoted trial ownership/involvement, understanding of research and how adherence affects trial outcomes
- Increased staff/participant morale, rapport and built participant/peer relationships

Schwartz K, et. al. HIV R4P 2014
## Cumulative Adherence

<table>
<thead>
<tr>
<th>Proportion of rings with evidence of non-use (≥23.5 mg)</th>
<th>Median # rings (IQR)</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>17 (12-21)</td>
<td>552</td>
<td>51</td>
</tr>
<tr>
<td>&gt;0% and &lt;20%</td>
<td>20 (15-21)</td>
<td>271</td>
<td>25</td>
</tr>
<tr>
<td>≥20% and &lt;70%</td>
<td>18 (12-21)</td>
<td>183</td>
<td>17</td>
</tr>
<tr>
<td>≥70%</td>
<td>15 (9-21)</td>
<td>86</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>18 (12-21)</td>
<td>1,092</td>
<td>100</td>
</tr>
</tbody>
</table>