Vaginal Ring Use in a Phase 3 Microbicide Trial: A Comparison of Objective Measures of Adherence in ASPIRE with Self-reports of Product Use

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On behalf of: Barbra A. Richardson, Marla Husnik, Elizabeth R. Brown, Flavia Matovu Kiweewa, Ashley J. Mayo, Jared M. Baeten, Thesla Palanee-Phillips, Ariane van der Straten, for the MTN-020/ASPIRE study team
Background

• Behavioral assessments are potentially useful for understanding trial outcomes

• Yet, accurate measurement of adherence to study products has been challenging in microbicide trials

• Participants are often reluctant to admit that they have not used product as directed; several trials (e.g. Fem-PrEP and VOICE) have shown substantial discrepancies between self-reports and biomarkers of adherence

• This “biological-behavioral adherence gap” appears to vary inversely with the level of adherence as measured by biological data (van der Straten et al. JIAS 2016:19)
MTN 020/ASPIRE

- MTN-020/ASPIRE: multi-center, randomized, double-blind, placebo-controlled phase III trial of a vaginal matrix ring containing the NNRTI dapivirine

- 2629 women enrolled — 1313 in Dapivirine group and 1316 in the placebo group — and followed for 12-33 months

- Median follow-up was 1.6 years and maximum 2.6 years

- Effectiveness was found to be 27% (p=0.046)

- Adherence measured both by self report and via more objective measures: dapivirine levels in plasma samples and residual dapivirine in used rings
Research questions

• Is there an association between self-reports of ring use and more objective measures of adherence in ASPIRE?

• Based on objective measures of ring use, did non-adherent participants in ASPIRE over-report ring use?

• In the ASPIRE trial, might the ring have been less effective in younger women because they were more likely than older women to remove it?
Methods

Sample: active arm participants

Measures of dapivirine ring use:

- Dapivirine plasma concentrations
  - Measured quarterly
  - >95 pg/ml: level typically achieved within 8 hours of continuous use

- Residual dapivirine levels in used rings
  - Measured monthly beginning 12 months after study initiation
  - <23.5mg: amount of drug released consistent with some use during the month
Methods (continued)

– Self-reports of product use

  • Measured monthly via CRF

  • Dichotomous measures based on two questions:

    – How many times in the past month has the participant had the vaginal ring out, in total? [ring ever out vs. ring never out]

    – How many of these times was the vaginal ring out for more than 12 hours continuously? [ring ever out>12 hours vs ring never out >12 hours]
Exclusion criteria

• Any visit reported to be on product hold
• Follow-up visits without self-report, plasma concentration and residual ring data*
• Follow-up visits with no access to ring
• Follow-up visits ≥ 32 days since last visit

* Dapivirine residual ring data were collected only after 12 months and thus exclude the first calendar year of follow-up. All analyses were also done with visits that included self-report and dapivirine plasma concentrations, for which there is a larger sample; several are shown here.
### Characteristics of participants at baseline with self-report, plasma concentration, and residual-ring data N=1211

<table>
<thead>
<tr>
<th>Age group</th>
<th>18-21</th>
<th>≥ 22</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20.3%</td>
<td>79.7%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Married</th>
<th>41.5%</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th># of partners in past 3 months</th>
<th>0</th>
<th>1</th>
<th>2+</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>28.7%</td>
<td>58.4%</td>
<td>12.9%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Country</th>
<th>Malawi</th>
<th>South Africa</th>
<th>Uganda</th>
<th>Zimbabwe</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10.6%</td>
<td>52.6%</td>
<td>10.3%</td>
<td>26.5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Timing of first visit with self-report, plasma, and residual ring data</th>
<th>3 months</th>
<th>6 months</th>
<th>9 months</th>
<th>12 months</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>44.8%</td>
<td>12.8%</td>
<td>14.7%</td>
<td>21.2%</td>
<td>6.5%</td>
</tr>
</tbody>
</table>
## Ring non-adherence by age group aggregated over all visits*

<table>
<thead>
<tr>
<th></th>
<th>18 – 21</th>
<th>≥ 22</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ring ever out</strong></td>
<td>5.5%</td>
<td>3.8%</td>
</tr>
<tr>
<td><strong>Plasma ≤ 95 pg/ml or Residual ring ≥ 23.5 mg</strong></td>
<td>23.8%</td>
<td>17.4%</td>
</tr>
<tr>
<td><strong>(# of visits)</strong></td>
<td>(1208)</td>
<td>(5037)</td>
</tr>
</tbody>
</table>

*Limited to visits with self report data, plasma and residual ring data
Ring non-adherence assessed via self report and biological measure at quarterly visit, by age group

Plasma ≤ 95 pg/ml or RR ≥ 23.5 mg, aged 18-21

Plasma ≤ 95 pg/ml or RR ≥ 23.5 mg, aged ≥ 22

Ring ever out, aged 18-21

Ring ever out, aged ≥ 22
Biological measure of non-adherence among participants who report ring never out, aggregated over all visits

% Plasma ≤ 95 pg/ml or RR ≥ 23.5 mg

- 17.9% for All
- 22.9% for Age 18-21
- 16.7% for Age ≥ 22

Self-report:
- Never out

• Younger women were slightly more likely to underreport nonadherence
Are younger women more likely to report non-adherence?

Generalized Estimating Equations (GEE)* outcome: ring out; predictor: age

Visits with plasma, self-report, and residual ring data

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ring ever out</td>
<td>Age 18-21</td>
<td>1.48 (1.09, 2.02)</td>
</tr>
<tr>
<td>Ring ever out &gt; 12 hours</td>
<td>Age 18-21</td>
<td>1.12 (0.65, 1.93)</td>
</tr>
</tbody>
</table>

Visits with plasma and self-report data

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ring ever out</td>
<td>Age 18-21</td>
<td>1.61 (1.26, 2.07)</td>
</tr>
<tr>
<td>Ring ever out &gt;12 hours</td>
<td>Age 18-21</td>
<td>1.69 (1.20, 2.39)</td>
</tr>
</tbody>
</table>

*GEE models account for within-participant correlation due to repeated outcome measures
## Reasons* for ring being out by age

N=418 visits

<table>
<thead>
<tr>
<th>Reason</th>
<th>18-21 (N=117)</th>
<th>≥22 (N=301)</th>
<th>OR (95%CI)**</th>
<th>P-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical/hygienic</td>
<td>17.1%</td>
<td>22.9%</td>
<td>0.69 (0.39, 1.23)</td>
<td>0.7</td>
</tr>
<tr>
<td>Study related procedures</td>
<td>36.8%</td>
<td>30.9%</td>
<td>1.30 (0.79, 2.13)</td>
<td>0.3</td>
</tr>
<tr>
<td>Social/sexual</td>
<td>13.7%</td>
<td>14.0%</td>
<td>0.98 (0.50, 1.91)</td>
<td>1.0</td>
</tr>
<tr>
<td>Came out on its own</td>
<td>8.5%</td>
<td>8.0%</td>
<td>1.08 (0.50, 2.34)</td>
<td>0.8</td>
</tr>
</tbody>
</table>

* Participants could report more than one reason
**From GEE models; limited to visits with plasma and self-report
Do self-reports of ring adherence predict biological measures?

Multivariable models of ring adherence:

• Outcome = composite biological measure of adherence: plasma $>95$ pg/ml and residual ring $<23.5$ mg

• Predictors = age group and self-report of adherence

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>p-value</th>
<th>aOR (95% CI)*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ring never out</td>
<td>2.54 (1.88, 3.43)</td>
<td>&lt;0.001</td>
<td>2.22 (1.60, 3.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age 18-21</td>
<td>0.68 (0.52, 0.88)</td>
<td>0.004</td>
<td>0.79 (0.60, 1.05)</td>
<td>0.11</td>
</tr>
</tbody>
</table>
Research questions:

• Is there an association between self-reports of ring use and more objective measures of adherence in ASPIRE? Yes

• Based on objective measures of ring use, did non-adherent participants in ASPIRE over-report ring use? Yes

• In the ASPIRE trial, might the ring have been less effective in younger women because they were more likely than older women to remove it? Yes
Summary

• Ring removal underreported in ASPIRE among participants who were not adherent according to biological measures

• At nearly 1/5 of visits where women reported that the ring was never out, plasma or residual ring levels suggested very low or no use at all during the month

• Younger women were significantly more likely to report the ring out but age was not associated with plasma DPV level or residual DPV in ring in models with self-report of ring removal

• That age not significant in multivariable models suggests it was removal of ring that likely accounted, at least in part, for difference in the objective measure of adherence
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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  - 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
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- **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

- **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, 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. We are grateful to Dr. Roberta Black at NIAID for her oversight.**