Jared Baeten MD, PhD
Thesla Palanee-Phillips, PhD

*Implementation Update*
ASPIRE Protocol Team Meeting
March 2015
Meeting overview

- An exciting day!
  - Updates on ASPIRE & The Ring Study and from SCHARP, Laboratory Center, Safety Docs, Communications, CWG and Qualitative Team
  - Site presentations: PUEV updates and participants responses, maintaining participant contact, and plans for results dissemination
  - General focus on preparations for closeout and beyond!
Outline

ASPIRE

- Looking back
- Looking forward
Looking Back
Challenges of the past: learning from tenofovir trials

No adherence = no HIV protection
## Challenges of the past: learning from PrEP trials

<table>
<thead>
<tr>
<th>PrEP Type</th>
<th>HIV protection: PrEP vs. placebo (when PrEP taken)</th>
<th>% of samples with tenofovir detected</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Partners PrEP</strong></td>
<td>75% (90+% when taken)</td>
<td>81%</td>
</tr>
<tr>
<td><strong>TDF2</strong></td>
<td>62%</td>
<td>79%</td>
</tr>
<tr>
<td><strong>BTS</strong></td>
<td>49%</td>
<td>67%</td>
</tr>
<tr>
<td><strong>iPrEx</strong></td>
<td>44% (90-100% when taken)</td>
<td>51%</td>
</tr>
<tr>
<td><strong>FEM-PrEP</strong></td>
<td>No HIV protection</td>
<td>&lt;40%</td>
</tr>
<tr>
<td><strong>VOICE</strong></td>
<td>No HIV protection</td>
<td>&lt;30%</td>
</tr>
<tr>
<td><strong>FACTS 001</strong></td>
<td>No HIV protection</td>
<td>&lt;50%</td>
</tr>
</tbody>
</table>

Women need strategies that make adherence workable.
FACTS 001

- Overall HIV incidence was no different for those randomized to tenofovir gel compared to placebo. There was evidence that HIV rates were lower in women with tenofovir detected in a genital sample.

- Many women seemed to have used the gel at some point in FACTS 001, but not enough women used the gel enough of the time to provide enough HIV protection to see an overall trial effect.

- Better products are needed in order for women to be able to achieve drug levels sufficient for HIV protection.
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
Developing dapivirine ring for HIV prevention

- Dapivirine is a non-nucleoside reverse transcriptase inhibitor of HIV
- Formulated into a flexible silicone ring, it could provide a reliable, long-lasting, woman-initiated method to protect against HIV acquisition
- MTN-020 was designed as a pivotal clinical trial to provide the strength of evidence to support licensure of dapivirine ring for HIV prevention, along with complementary studies:
  - IPM 027 (efficacy & safety)
  - >25 completed phase I/II studies
  - ongoing/planned work in adolescents/post-menopausal women, drug-drug interactions
15 Sites across 4 countries

Blantyre
Lilongwe
Malawi

Cape Town
Durban (7 sites)
Johannesburg
South Africa

Kampala
Uganda

Harare/Chitungwiza (3 sites)
Zimbabwe
The Big Five

Accrual

Retention

Data Quality and Timeliness

Clinical and Laboratory Safety

Adherence
Accrual completed June 2014

<table>
<thead>
<tr>
<th>Site</th>
<th>First enr</th>
<th># enr</th>
</tr>
</thead>
<tbody>
<tr>
<td>MA – Blantyre</td>
<td>13 JUN 13</td>
<td>130</td>
</tr>
<tr>
<td>MA – Lilongwe</td>
<td>17 JUN 13</td>
<td>142</td>
</tr>
<tr>
<td>SA – Cape Town</td>
<td>19 SEP 2012</td>
<td>166</td>
</tr>
<tr>
<td>SA – CAPRISA eThekwini</td>
<td>10 OCT 2012</td>
<td>244</td>
</tr>
<tr>
<td>SA – MRC/Botha’s Hill</td>
<td>10 SEP 2012</td>
<td>180</td>
</tr>
<tr>
<td>SA – MRC/Chatsworth</td>
<td>11 SEP 2012</td>
<td>150</td>
</tr>
<tr>
<td>SA – MRC/Isipingo</td>
<td>19 SEP 2012</td>
<td>117</td>
</tr>
<tr>
<td>SA – MRC/Tongaat</td>
<td>17 SEP 2012</td>
<td>103</td>
</tr>
<tr>
<td>SA – MRC/Verulam</td>
<td>13 SEP 2012</td>
<td>150</td>
</tr>
<tr>
<td>SA – MRC/Umkomaas</td>
<td>14 SEP 2012</td>
<td>103</td>
</tr>
<tr>
<td>SA – WRHI</td>
<td>30 OCT 2012</td>
<td>213</td>
</tr>
<tr>
<td>UG – Kampala</td>
<td>21 AUG 2012</td>
<td>253</td>
</tr>
<tr>
<td>ZI – Seke South</td>
<td>01 NOV 12</td>
<td>224</td>
</tr>
<tr>
<td>ZI – Spilhaus</td>
<td>30 OCT 12</td>
<td>230</td>
</tr>
<tr>
<td>ZI – Zengeza</td>
<td>13 NOV 12</td>
<td>224</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td><strong>2629</strong></td>
</tr>
</tbody>
</table>
Who enrolled?

- Median age: 26 years, with 39% <25 years
- Unmarried: 59% overall, 92% in SA
- 100% had a primary partner in past 3 months
  - 17% had ≥1 other partner in past 3 months
  - 64% had informed their primary partner about the ring at baseline
- STIs were common: 12% CT, 4% GC, 7% TV

A population at risk for HIV and in need of new prevention strategies
Retention

- Current #s:
  - Month 1: 98%
  - Month 3: 96%
  - Month 6: 94%
  - Month 12: 91%
  - Month 18: 89%
  - Month 24: 87%
  - Month 32: 100%

RETENTION SUMMARY:

OVERALL = 91.45% of all expected visits
EXCLUDING TERMINATIONS = 97.14%
LAST 3 MONTHS = 96.68%!
Adherence Action!

What we’ve done together:

- Recognition of adherence a priority across all ASPIRE sites
- Participant and staff engagement activities
- Careful counselling for challenging cases
- Fun waiting room discussions and social events
- Male partner engagement efforts
- Learning from the qualitative component of ASPIRE
- Visual inspection of rings and collection of used rings

Testing of plasma and rings, with real-time action, tailored to each site’s needs
# Data Quality and Timeliness

## MTN-020 A Study to Prevent Infection with a Ring for Extended Use (ASPIRE)

**DATA MANAGEMENT QUALITY REPORT**
Cumulative: Study Start through February 2015

<table>
<thead>
<tr>
<th>Site</th>
<th>Total Records</th>
<th>Total QCs</th>
<th>QC Rate Per 100 Records (Goal &lt; 6)</th>
<th>% QCs Resolved</th>
<th>% CRF Records Faxed within 7 days (Goal ≥ 95%)</th>
<th>Mean Days to Fax in AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Blantyre/Malawi</td>
<td>18324</td>
<td>495</td>
<td>2.7</td>
<td>96%</td>
<td>91%</td>
<td>26.0</td>
</tr>
<tr>
<td>2. Lilongwe/Malawi</td>
<td>20460</td>
<td>646</td>
<td>3.2</td>
<td>96%</td>
<td>90%</td>
<td>10.5</td>
</tr>
<tr>
<td>3. Emavundleni/Cape Town</td>
<td>34986</td>
<td>1111</td>
<td>3.2</td>
<td>97%</td>
<td>99%</td>
<td>7.5</td>
</tr>
<tr>
<td>4. CAPRISA eThekwini</td>
<td>49237</td>
<td>1873</td>
<td>3.8</td>
<td>97%</td>
<td>96%</td>
<td>8.3</td>
</tr>
<tr>
<td>5. MRC - Botha's Hill</td>
<td>36677</td>
<td>1462</td>
<td>4.0</td>
<td>98%</td>
<td>95%</td>
<td>10.7</td>
</tr>
<tr>
<td>6. MRC - Chatsworth</td>
<td>31527</td>
<td>1107</td>
<td>3.5</td>
<td>95%</td>
<td>93%</td>
<td>12.9</td>
</tr>
<tr>
<td>7. MRC - Isipingo</td>
<td>27721</td>
<td>784</td>
<td>2.8</td>
<td>94%</td>
<td>97%</td>
<td>9.6</td>
</tr>
<tr>
<td>8. MRC - Tongaat</td>
<td>24486</td>
<td>885</td>
<td>3.6</td>
<td>98%</td>
<td>98%</td>
<td>5.8</td>
</tr>
<tr>
<td>9. MRC - Verulam</td>
<td>31086</td>
<td>623</td>
<td>2.0</td>
<td>96%</td>
<td>99%</td>
<td>3.0</td>
</tr>
<tr>
<td>10. MRC - Umkomaas</td>
<td>22282</td>
<td>743</td>
<td>3.3</td>
<td>99%</td>
<td>98%</td>
<td>6.0</td>
</tr>
<tr>
<td>11. WRHI/Johannesburg</td>
<td>39943</td>
<td>2039</td>
<td>5.1</td>
<td>97%</td>
<td>94%</td>
<td>12.3</td>
</tr>
<tr>
<td>12. MU-JHU/Kampala, Uganda</td>
<td>53022</td>
<td>1188</td>
<td>2.2</td>
<td>99%</td>
<td>98%</td>
<td>8.5</td>
</tr>
<tr>
<td>13. Seke South/Zimbabwe</td>
<td>41816</td>
<td>395</td>
<td>0.9</td>
<td>99%</td>
<td>98%</td>
<td>5.3</td>
</tr>
<tr>
<td>14. Spilhaus/Zimbabwe</td>
<td>44329</td>
<td>395</td>
<td>0.9</td>
<td>99%</td>
<td>98%</td>
<td>4.5</td>
</tr>
<tr>
<td>15. Zengeza/Zimbabwe</td>
<td>39367</td>
<td>431</td>
<td>1.1</td>
<td>89%</td>
<td>99%</td>
<td>7.6</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>515263</strong></td>
<td><strong>14177</strong></td>
<td><strong>2.3</strong></td>
<td><strong>97%</strong></td>
<td><strong>97%</strong></td>
<td><strong>8.7</strong></td>
</tr>
</tbody>
</table>
Clinical & Laboratory Safety

- **Thank you** for so much work in the safety management & monitoring and laboratory collaboration and oversight:
  - Tremendous efforts on clinical safety documentation and follow-through.
  - Huge efforts to do real-time shipping and testing of plasma and residual drug levels. *This has been a revolution for this study and the results will be a revelation for the field.*
Timeline
2011-2012: Rapid Kick-off

Phase III Trial of Dapivirine Ring Begins in Africa: ASPIRE testing new HIV prevention approach for women

WASHINGTON, D.C., July 24, 2012 – A large clinical trial testing the long-term safety and effectiveness of a new approach for preventing HIV in women – a vaginal ring used once a month – is now underway in Africa, researchers announced today at the XIX International AIDS Conference (AIDS 2012).

- January 2012: SSP Development meeting
- June 2012: First training and first CAT meeting
- July 2012: First Site Activation
- August 2012: First Enrollment
- October 2012: ‘Oh ASPIRE’ song debuted at the MTN Regional Meeting
February 2013: First round of PK specimens shipped; First qualitative interview

March 2013: VOICE results, Durban Adherence Workshop (10 days later!), and first ring appearance data

June 2013: All 15 ASPIRE sites enrolling

July 2013: First IoR review of adherence data and site metrics

August 2013: First ring collected for testing

October 2013: ASPIRE engagement and adherence session at Regional meeting

November 2013: No one contraceptive method with >50% use (all sites combined)
2014: Continuing Strong

New contraceptive implant free to women in SA, says Motsoaledi

ASPIRE Phase III trial of a vaginal ring for HIV prevention completes enrollment of 2,629 women
MTN’s trial testing dapivirine ring on track to finish next year; IPM’s sister Phase III trial ongoing

April 2014: First batch of rings shipped for testing

Health Minister Aaron Motsoaledi briefs the media media after

A SMALL contraceptive device installed under the skin will be made available free of charge to all women from next week, Health Minister Aaron Motsoaledi told MPs on Wednesday.
2015: Looking Ahead

June 2015: Final participant visit for ASPIRE
August 2015: Database lock
September 2015: Final FHI 360 assessment visit conducted
End 2015: Results!
Looking Ahead
What does ASPIRE mean?

aspire\(\text{as} \cdot \text{pire}\)

Pronunciation: /əˈspī(ə)r/  

verb:  

direct one’s hopes or ambitions toward achieving something:  

we never thought that we might aspire to those heights

noun:

1. A Phase III study that seeks to determine whether a woman’s use of a vaginal ring containing dapivirine is a safe and effective method for protecting against HIV infection.  
2. A Study to Prevent Infection with a Ring for Extended Use

dream:

Quote from the qualitative component of ASPIRE:  

If we find something that helps us it will not just help me alone but it will also help future generations. This is something which is good.
Dapivirine Ring Timeline

- **2012**
  - The Ring Study
  - Dapivirine Ring Regulatory Consultations

- **2013**
  - Supporting safety and clinical pharmacology studies

- **2014**
  - MTN-025
  - ASPIRE

- **2015**
  - Efficacy Results?
  - IPM 032

- **2016**
  - Regulatory submissions

- **2017**
  - ASPIRE results
End of follow-up

- We anticipated that the required number of HIV seroconversions for the protocol will be accrued in Q2 2015 - this permitted us to initiate study close-out.

- Close-out was planned as an orderly exit of participants between March and June 2015, followed by rapid data cleaning and database closure (August 2015).

- Results planning is already underway. Tentative plan (with lots of steps to get there) is a results unblinding in November 2015, with public release soon after.
Much to do in the next months

How can we keep retention and adherence as priorities until the last day of data collection?

How can we make data cleaning as efficient as possible?

How can we keep up the enthusiasm and commitment all the way until the last participant exit and beyond?

Countdown has begun!
What we have learned

- Women are interested in a ring for prevention.
- Real-time adherence monitoring can be done in a trial, and women are adherent to a ring.
- Women want prevention options.
- Contraceptive options matter.
- Male involvement, in many different ways, is part of prevention in women.
Much more to learn

- Efficacy and safety of the dapivirine ring for prevention.

- Whether HIV protection is greater when adherence is greater.

- Safety of the ring in women who become pregnant, and then safety in pregnancy and lactation and in other populations.

- Use of the ring in real-world settings....
In real-world settings, PrEP works

- New data – including from CROI 2015 – show us that PrEP really can work in open-label studies that follow clinical trials.
545 enrolled

276 assigned to IMMEDIATE

269 assigned to DEFERRED

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of infections</th>
<th>Incidence (per 100 PY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate</td>
<td>3</td>
<td>1.3</td>
</tr>
<tr>
<td>Deferred</td>
<td>19</td>
<td>8.9</td>
</tr>
</tbody>
</table>

**Efficacy**  = 86% (90% CI: 58 – 96%)

**P value**  = 0.0002

**Rate Difference**  = 7.6 (90% CI: 4.1 – 11.2)

**Number Needed to Treat**  = 13 (90% CI: 9 – 25)
• Only 2 HIV infections observed in 1013 high-risk serodiscordant couples, compared with nearly 40 infections expected.

• The observed incidence is a 96% reduction compared to expected.

<table>
<thead>
<tr>
<th>EXPECTED</th>
<th>OBSERVED</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=39.7 infections</td>
<td>N=2 infections</td>
</tr>
<tr>
<td>incidence = 5.2 (95% CI 3.7-6.9)</td>
<td>incidence = 0.2 (95% CI 0.0-0.9)</td>
</tr>
</tbody>
</table>

IRR observed vs. expected = 0.04 (95% CI 0.01-0.19) or a 96% reduction (95% CI 81-99%) P<0.0001
In real-world settings, PrEP works

- New data – including from CROI 2015 – show us that PrEP really can work in open-label studies that follow clinical trials.

- Because people want prevention tools that work.
Out of ASPIRE … HOPE

- **Participants** informed
- **IRB/EC** informed
- National and community **Stakeholders** informed

**RESULTS**

- Former Participants contacted

**HOPE**

- HOPE approval
- Enrollment
- Approximately 1-year open-label use of dapivirine ring
THE WORLD IS WATCHING ASPIRE
A Study to Prevent Infection with a Ring for Extended Use
Thank you

Malawi College of Medicine – JHU Research Project

Participants and communities
Acknowledgements

MTN is funded by NIAID (UM1AI068633, UM1AI068615, UM1AI06707), NICHD and NIMH, all of the U.S. National Institutes of Health