Implementation Update
ASPIRE Protocol Team Meeting
October 2013
Outline

- Meeting overview

ASPIRE

- Where we’ve been
- Where we are
- Where we are going
Meeting overview

A packed day:

- MORNING: focus on adherence – what we are doing, learning, and changing at the community, in-clinic, and individual levels
- AFTERNOON: lively discussion of clinical safety, retention, and data quality
- THROUGHOUT: remembering our Big 5 metrics, working together as a team
- END OF THE DAY: Awards!
Where we have been
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
The Big Five

Accrual

Data Quality and Timeliness

Clinical and Laboratory Safety

Retention

Adherence
ASPIRE calendar

- January 2011 and ongoing
  - Multilevel consultations on the science and implementation, leading to protocol version 1.0 in September 2011

- August 2012 - present
  - Start and go! Enrollments, follow-up, highest-quality execution of all protocol aspects
October 2012  (<100 enrolments)
ASPIRE calendar

- January 2011 and ongoing
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- August 2012 - present
  - Start and go! Enrollments, follow-up, highest-quality execution of all protocol aspects
- November 2012, May 2013
  - DSMB
- May 2013
  - Malawi sites activated
- April, August & October 2013
  - SMC reviews
## March 2013: learning from PrEP trials

<table>
<thead>
<tr>
<th></th>
<th>HIV protection for FTC/TDF versus placebo</th>
<th>% of blood samples with tenofovir detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partners PrEP</td>
<td>75%</td>
<td>81%</td>
</tr>
<tr>
<td>TDF2</td>
<td>62%</td>
<td>79%</td>
</tr>
<tr>
<td>iPrEx</td>
<td>44%</td>
<td>51%</td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td>No HIV protection</td>
<td>~30%</td>
</tr>
<tr>
<td>VOICE</td>
<td>No HIV protection</td>
<td>~30%</td>
</tr>
</tbody>
</table>

No adherence = no HIV protection
Efficacy and effectiveness

Efficacy + Adherence → Effectiveness

Efficacy + Adherence → Effectiveness
Adherence is Everything

Jared Baeten MD PhD
Thesla Palanee PhD

ASPIRE Adherence Meeting
Durban, South Africa
14 March 2013
Adherence Action!

- Products don’t work if they aren’t used
- Since March 2013:
  - Recognition of priority: scale-up across sites
  - Participant and staff engagement activities
  - IoR and SCs involved with difficult participants counselling
  - Fun waiting room discussions and social events
  - HIV ribbon and ring activities
  - Male partner engagement efforts
  - Visual inspection of the rings
  - PK data reviewed, shared, and acted upon
  - Learning from qualitative component of ASPIRE
Where we are
15 Sites across 4 countries

- Blantyre
- Lilongwe
- Malawi
- Cape Town
- Durban (7 sites)
- Johannesburg
- South Africa
- Kampala
- Uganda
- Harare/Chitungwiza (3 sites)
- Zimbabwe
# Accrual (23 Oct 2013)

<table>
<thead>
<tr>
<th>Site</th>
<th>First enr</th>
<th># enr</th>
<th>scr:enr ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>MA – Blantyre</td>
<td>13 JUN 13</td>
<td>36</td>
<td>1.6</td>
</tr>
<tr>
<td>MA – Lilongwe</td>
<td>17 JUN 13</td>
<td>43</td>
<td>1.5</td>
</tr>
<tr>
<td>SA – Cape Town</td>
<td>19 SEP 2012</td>
<td>150</td>
<td>1.3</td>
</tr>
<tr>
<td>SA – CAPRISA eThekwini</td>
<td>10 OCT 2012</td>
<td>150</td>
<td>3.2</td>
</tr>
<tr>
<td>SA – MRC/Botha’s Hill</td>
<td>10 SEP 2012</td>
<td>120</td>
<td>2.5</td>
</tr>
<tr>
<td>SA – MRC/Chatsworth</td>
<td>11 SEP 2012</td>
<td>115</td>
<td>2.7</td>
</tr>
<tr>
<td>SA – MRC/Isipingo</td>
<td>19 SEP 2012</td>
<td>117</td>
<td>2.6</td>
</tr>
<tr>
<td>SA – MRC/Tongaat</td>
<td>17 SEP 2012</td>
<td>103</td>
<td>3.3</td>
</tr>
<tr>
<td>SA – MRC/Verulam</td>
<td>13 SEP 2012</td>
<td>114</td>
<td>2.4</td>
</tr>
<tr>
<td>SA – MRC/Umkomaas</td>
<td>14 SEP 2012</td>
<td>87</td>
<td>2.5</td>
</tr>
<tr>
<td>SA – WHRI/Hillbrow</td>
<td>30 OCT 2012</td>
<td>141</td>
<td>1.8</td>
</tr>
<tr>
<td>UG – Kampala</td>
<td>21 AUG 2012</td>
<td>205</td>
<td>1.6</td>
</tr>
<tr>
<td>ZI – Seke South</td>
<td>01 NOV 12</td>
<td>155</td>
<td>1.9</td>
</tr>
<tr>
<td>ZI – Spilhaus</td>
<td>30 OCT 12</td>
<td>150</td>
<td>1.8</td>
</tr>
<tr>
<td>ZI – Zengeza</td>
<td>13 NOV 12</td>
<td>146</td>
<td>1.8</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>1832</strong></td>
<td></td>
<td><strong>2.1</strong></td>
</tr>
</tbody>
</table>
Screen outs

- As of 24 October 2013:
  - 3940 screened, 1840 enrolled (2.1 ratio)
  - 242 did not complete screening
  - 27 declined enrollment
  - 2100 ineligible
    - 718 (34.1%) HIV+
    - 71 (8.1%) pregnant, planning, or breastfeeding
    - 408 (19.4 %) clinical/laboratory exclusion
    - 507 (24.1%) “other” including investigator decision
Who is enrolling?

- Mean age: 27.1 years, Median: 26 years
  - 41% <25 years, 15% ≥35 years
- Unmarried: MA (33%), SA (92%), UG (37%), ZI (13%)
- Secondary schooling: MA (56%), SA (96%), UG (50%), ZI (85%)
- 100% had a primary partner in past 3 months
  - 19% had ≥1 other partner in past 3 months
Retention: As at 17 Oct 13

- 1667/1701 Month 1 visits (98%)
- 1562/1622 Month 2 visits (96%)
- 1485/1549 Month 3 visits (96%)
- 1392/1467 Month 4 visits (95%)
- 1273/1355 Month 5 visits (94%)
- 1183/1272 Month 6 visits (93%)
- 1096/1172 Month 7 visits (94%)
- 961/1038 Month 8 visits (93%)
- 813/870 Month 9 visits (93%)
- 704/768 Month 10 visits (92%)
- 576/626 Month 11 visits (92%)
- 324/351 Month 12 visits (92%)
- 111/119 Month 13 visits (93%)
- 23/23 Month 14 visits (100%)
Retention: few missed visits!

AND, RINGS ARE OFTEN DISPENSED AHEAD OF PLANNED MISSED VISITS!
Adherence Measurements and Monitoring

- We have learned much (and reacted to much) about non-use, non-interest?
  - Who returns without rings in place? Rings coming out?
  - Qualitative interviews, staff observations
  - Blood and swab samples
Data Quality = unmatched!

<table>
<thead>
<tr>
<th>Site</th>
<th>Total Records</th>
<th>Total QCs</th>
<th>QC Rate Per 100 Records</th>
<th>% QCs Resolved</th>
<th>% CRF Pages Received Within 7 Days</th>
<th>Mean Days to Fax in AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spilhaus/Zimbabwe</td>
<td>10294</td>
<td>103</td>
<td>1.0</td>
<td>98%</td>
<td>98%</td>
<td>3.5</td>
</tr>
<tr>
<td>Seke South/Zimbabwe</td>
<td>9883</td>
<td>163</td>
<td>1.6</td>
<td>99%</td>
<td>99%</td>
<td>11</td>
</tr>
<tr>
<td>Blantyre/Malawi</td>
<td>812</td>
<td>25</td>
<td>3.1</td>
<td>96%</td>
<td>89%</td>
<td>7.0</td>
</tr>
<tr>
<td>Lilongwe/Malawi</td>
<td>894</td>
<td>21</td>
<td>2.3</td>
<td>100%</td>
<td>98%</td>
<td>3.1</td>
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<tr>
<td>MRC - Chatsworth</td>
<td>11509</td>
<td>632</td>
<td>5.5</td>
<td>98%</td>
<td>93%</td>
<td>11.3</td>
</tr>
<tr>
<td>MRC - Botha’s Hill</td>
<td>12038</td>
<td>897</td>
<td>5.8</td>
<td>100%</td>
<td>97%</td>
<td>7.8</td>
</tr>
<tr>
<td>MRC - Umkomaas</td>
<td>8691</td>
<td>400</td>
<td>4.6</td>
<td>100%</td>
<td>95%</td>
<td>3.6</td>
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<tr>
<td>MU-JHU/Kampala, Uganda</td>
<td>15239</td>
<td>390</td>
<td>2.6</td>
<td>97%</td>
<td>97%</td>
<td>11.1</td>
</tr>
<tr>
<td>Zengeza/Zimbabwe</td>
<td>9345</td>
<td>127</td>
<td>1.4</td>
<td>100%</td>
<td>99%</td>
<td>7.8</td>
</tr>
<tr>
<td>MRC - Isipingo</td>
<td>10616</td>
<td>271</td>
<td>2.6</td>
<td>94%</td>
<td>95%</td>
<td>3.6</td>
</tr>
<tr>
<td>MRC - Tongaat</td>
<td>10002</td>
<td>380</td>
<td>3.8</td>
<td>99%</td>
<td>99%</td>
<td>2.6</td>
</tr>
<tr>
<td>MRC - Verulam</td>
<td>11285</td>
<td>266</td>
<td>2.6</td>
<td>100%</td>
<td>98%</td>
<td>4.0</td>
</tr>
<tr>
<td>CAPRISA eThekwini</td>
<td>12089</td>
<td>422</td>
<td>3.5</td>
<td>98%</td>
<td>98%</td>
<td>2.3</td>
</tr>
<tr>
<td>WRHI/Johannesburg</td>
<td>9179</td>
<td>509</td>
<td>5.5</td>
<td>98%</td>
<td>96%</td>
<td>4.8</td>
</tr>
<tr>
<td>Emavundleni/Cape Town</td>
<td>11226</td>
<td>418</td>
<td>3.7</td>
<td>100%</td>
<td>99%</td>
<td>2.1</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>143082</strong></td>
<td><strong>4854</strong></td>
<td><strong>3.4</strong></td>
<td><strong>99%</strong></td>
<td><strong>97%</strong></td>
<td><strong>5.8</strong></td>
</tr>
</tbody>
</table>
Safety

Safety is the co-primary endpoint of the study

- Evaluating whether the product is safe is just as important as whether the product is effective for HIV prevention
- Regulatory authorities will scrutinize safety data and careful attention to safety documentation is critical
Laboratory

- Laboratory results and archived samples are central to this study
- THANK YOU TO ALL THE WORK!
Contraceptive Action Team

- Incredibly motivated and innovative approaches to broaden contraceptive mix, counsel on highly-effective and safe methods, and provide methods on site

- Mix is diverse: 20% IUDs, ~15% implants currently!
Team communications

- Monthly team calls
  - Tremendously valuable, site-driven, sharing experiences

- Weekly priority emails from FHI360 to sites
  - Collating protocol team priorities

- Listservs
  - Cross-site communications/sharing
Where we are going
ASPIRE protocol planned to enroll approximately 3476 women, anticipating a background HIV incidence of 3.9% per year

- With at least 120 HIV seroconversions required to assess HIV protection with confidence
- Goal to have 12 months of safety data per participant to assess safety, with early participants contributing longer

Recent data (VOICE, FEM-PrEP) have demonstrated that HIV incidence is, unfortunately, higher than 3.9% per year in several settings

- Fewer than 3476 enrollees may be necessary.
- Considerations ongoing. End enrollment = Q1/Q2 2014.
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- May 2013
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- August & October 2013
  - SMC reviews
- 19 November 2013
  - DSMB review
Timeline

2011
• Initiate site IRB and regulatory approval process

2012
• IRB/regulatory approvals, trainings, start

2013
• Enrollments, follow-up

2014
• End of enrollment, continue follow-up

2015
• Completion of follow-up, results
Retention from day 1 to day X

- Every enrolment should be considered
  - ASPIRE is a many-month, multi-hour commitment
  - Trust your instincts, trust team instincts, keep your enthusiasm

- How can we continue to create cultures that make sites places where participants want to spend several hours each month? (and staff each day of each month)
Adherence Success (?)!

- Creative ideas from all members of the team are leading to adherence success in ASPIRE
  - Counseling
  - Engagement
  - Analysis

- We truly have the opportunity to demonstrate a potentially revolutionary HIV prevention intervention
Accural → Retention → Adherence → Safety → Quality

- Smart accrual
- High retention
- Motivated adherence (engagement)
- 100% attention to data quality & participant safety

Everything else flows from these.
We are all in this together

- We all work together – all parts of the study are all our business

  Recruitment | QC/QA  
  Retention   | Regulatory 
  Adherence   | Safety Monitoring 
  Sample collection | Space/facilities 
  Staff morale | Study drug/pharmacy 
  Community/outreach | Contraception 
  Communications | Lab-clinic interface 
  Lab quality | Monitoring follow-up
ASPIRE …

OPPORTUNITY
IT TAKES A TEAM

Malawi College of Medicine – JHU Research Project

UNC Project - Malawi