What does ASPIRE mean?

aspire\(\text{\textasciitilde}sp\text{\textasciitilde}r\)  
Pronunciation: /əˈspīər/  
verb  
[no object]  
direct one’s hopes or ambitions toward achieving something:  
we never thought that we might aspire to those heights  
[with infinitive]:  
other people will aspire to be like you
What does ASPIRE mean?

aspire (as·pire)

Pronunciation: /əˈspī(ə)r/

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direct one’s hopes or ambitions toward achieving something:
we never thought that we might aspire to those heights
[with infinitive]:
other people will aspire to be like you

ASPIRE
\ə-ˈspī(-ə)r\
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
verb:
1. To seek to end the HIV epidemic < We aspire to prevent HIV
Outline

- Meeting overview
- Past
- Present
- Future
Meeting overview

- A great day:
  - MORNING: focus on ASPIRE, Ring Study, CAT and Lab updates
  - AFTERNOON: Qualitative work, BRWG update and how to prep for Regulatory inspections, 015 and 016
  - THROUGHOUT: strong coffee and remembering our Big 5 metrics, working together as a team
Past
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

Retention

Clinical and Laboratory Safety

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

- November 2012, May 2013
  - DSMB reviews

- August & October 2013
  - SMC reviews

- November 2013
  - DSMB review
Efficacy and effectiveness

Efficacy + Adherence → Effectiveness

Efficacy + Adherence → Effectiveness
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
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
  - Collection of used rings
Present
15 Sites across 4 countries

Blantyre
Lilongwe
**Malawi**

Cape Town
Durban (7 sites)
**Johannesburg**
**South Africa**

Kampala
Uganda

Harare/Chitungwiza (3 sites)
**Zimbabwe**
## Accrual (19 Feb 2014)

<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>85</td>
<td>1.5</td>
</tr>
<tr>
<td>MA – Lilongwe</td>
<td>17 JUN 13</td>
<td>84</td>
<td>1.4</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>176</td>
<td>3.1</td>
</tr>
<tr>
<td>SA – MRC/Botha’s Hill</td>
<td>10 SEP 2012</td>
<td>147</td>
<td>2.3</td>
</tr>
<tr>
<td>SA – MRC/Chatsworth</td>
<td>11 SEP 2012</td>
<td>125</td>
<td>2.8</td>
</tr>
<tr>
<td>SA – MRC/Isipingo</td>
<td>19 SEP 2012</td>
<td>117</td>
<td>2.7</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>118</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>167</td>
<td>1.8</td>
</tr>
<tr>
<td>UG – Kampala</td>
<td>21 AUG 2012</td>
<td>243</td>
<td>1.5</td>
</tr>
<tr>
<td>ZI – Seke South</td>
<td>01 Nov 12</td>
<td>193</td>
<td>1.9</td>
</tr>
<tr>
<td>ZI – Spilhaus</td>
<td>30 OCT 12</td>
<td>195</td>
<td>1.7</td>
</tr>
<tr>
<td>ZI – Zengeza</td>
<td>13 Nov 12</td>
<td>179</td>
<td>1.8</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>2169 (!!!)</strong></td>
<td></td>
<td><strong>2.1</strong></td>
</tr>
</tbody>
</table>
Enrolments

- 2169 – on schedule to achieve current targets in ~May 2014!
Screen outs

- As of 19 February 2014:
  - 4503 screened, 2168 enrolled (2.1 ratio)
  - 261 did not complete screening
  - 28 declined enrollment
  - 2046 ineligible
    - 777 (38%) HIV+
    - 172 (8%) pregnant; 27 (1%) breastfeeding
    - 408 (17.5 %) clinical/laboratory exclusion
    - 572 (28%) “other” including investigator decision
Who is enrolling?

- Mean age: 27.3 years, Median: 26 years
  - 39% <25 years, 14% ≥35 years
- Unmarried: MA (19%), SA (92%), UG (34%), ZI (16%)
- Secondary schooling complete: MA (11%), SA (45%), Zim (5%), and Uganda (50%).
- 100% had a primary partner in past 3 months
  - 18% had ≥1 other partner in past 3 months
Retention: As at 12 Feb 14

- 2001/2044 Month 1 visits (98%)
- 1911/1982 Month 2 visits (96%)
- 1801/1877 Month 3 visits (96%)
- 1713/1810 Month 4 visits (95%)
- 1619/1720 Month 5 visits (94%)
- 1527/1643 Month 6 visits (93%)
- 1467/1568 Month 7 visits (94%)
- 1347/11485 Month 8 visits (93%)
- 1278/1375 Month 9 visits (93%)
- 1182/11288 Month 10 visits (92%)
- 1101/1204 Month 11 visits (91%)
- 981/1083 Month 12 visits (92%)
- 812/912 Month 13 visits (89%)
- 681/779 Month 14 visits (87%)
- 587/669 Month 15 visits (88%)
- 374/420 Month 16 visits (89%)
- 150/172 Month 17 visits (87%)
- 35/37 Month 18 visits (95%)

FEW MISSED VISITS AND RINGS ARE OFTEN DISPENSED AHEAD OF PLANNED MISSED VISITS!

RETENTION SUMMARY:

OVERALL = 93.3%
EXCLUDING TERMS = 96.6%
LAST 3 MONTHS = 96.8%
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?
  - IoR discretion to terminate ppts who are non-adherent to study visits or product
  - Qualitative interviews, staff observations
  - Blood and swab samples
  - Off-site visits to deliver rings
  - Ring drug level assessments
# Data Quality and Timeliness

## Use of iDatafax

### MTN-020 (ASPIRE) DATA MANAGEMENT QUALITY REPORT

**January 2014**

<table>
<thead>
<tr>
<th>Site</th>
<th>Total Records</th>
<th>Total QCs</th>
<th>QC Rate Per 100 Records</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>2135</td>
<td>25</td>
<td>1.2</td>
<td>98%</td>
<td>4.8</td>
</tr>
<tr>
<td>Seke South/Zimbabwe</td>
<td>2024</td>
<td>21</td>
<td>1.0</td>
<td>99%</td>
<td>4.4</td>
</tr>
<tr>
<td>Blantyre/Malawi</td>
<td>704</td>
<td>43</td>
<td>5.6</td>
<td>100%</td>
<td>24.7</td>
</tr>
<tr>
<td>Lilongwe/Malawi</td>
<td>786</td>
<td>13</td>
<td>1.7</td>
<td>30%</td>
<td>19.6</td>
</tr>
<tr>
<td>MRC - Chatsworth</td>
<td>966</td>
<td>29</td>
<td>3.0</td>
<td>97%</td>
<td>4.0</td>
</tr>
<tr>
<td>MRC - Botha's Hill</td>
<td>1247</td>
<td>67</td>
<td>5.4</td>
<td>95%</td>
<td>9.8</td>
</tr>
<tr>
<td>MRC - Umkomaas</td>
<td>685</td>
<td>35</td>
<td>5.1</td>
<td>94%</td>
<td>1.5</td>
</tr>
<tr>
<td>MU-JHU/Kampala, Uganda</td>
<td>2368</td>
<td>73</td>
<td>3.1</td>
<td>98%</td>
<td>4.7</td>
</tr>
<tr>
<td>Zengeza/Zimbabwe</td>
<td>1688</td>
<td>18</td>
<td>1.1</td>
<td>99%</td>
<td>2.7</td>
</tr>
<tr>
<td>MRC - Isipingo</td>
<td>1161</td>
<td>32</td>
<td>2.8</td>
<td>99%</td>
<td>1.2</td>
</tr>
<tr>
<td>MRC - Tongaat</td>
<td>1044</td>
<td>32</td>
<td>3.1</td>
<td>99%</td>
<td>6.4</td>
</tr>
<tr>
<td>MRC - Verulam</td>
<td>1137</td>
<td>20</td>
<td>1.8</td>
<td>100%</td>
<td>0.3</td>
</tr>
<tr>
<td>CAPRISA eThekwini</td>
<td>1794</td>
<td>97</td>
<td>5.4</td>
<td>98%</td>
<td>3.7</td>
</tr>
<tr>
<td>WRH-Johannesburg</td>
<td>1583</td>
<td>69</td>
<td>4.4</td>
<td>96%</td>
<td>3.9</td>
</tr>
<tr>
<td>Emavundeni/Cape Town</td>
<td>1496</td>
<td>51</td>
<td>3.4</td>
<td>100%</td>
<td>17.5</td>
</tr>
</tbody>
</table>

**TOTAL**

| 20878 | 625 | 3.0 | 96% | 7.7 |

*ASPIRE - A Study to Prevent Infection with a Ring for Extended Use*
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
Contraceptive Action Team

- Meeting in Johannesburg : Feb 2014
- Incredibly motivated and innovative approaches to broaden contraceptive mix, counsel on highly-effective and safe methods, and provide methods on site
- Coming soon : Implants in SA
- Real change
Laboratory

- Laboratory results and archived samples are central to this study
- Sample shipments
- Ring Shipments

- THANK YOU FOR ALL THE HARD WORK
Team communications

- Monthly Protocol team calls
  - Tremendously valuable, site-driven, sharing experiences
- IoR calls regards the PK data
- Qualitative calls
- Weekly priority emails from fhi360 to sites
  - Collating protocol team priorities
- Listservs
  - Cross-site communications/sharing
- FHI360 Site assessment visits
- Patrick Ndase, MTN Regional Physicians site visits
Future
We are all in this together

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

  Recruitment
  Retention
  Adherence
  Sample collection
  Staff morale
  Community/outreach
  Communications
  Lab quality

  QC/QA
  Regulatory
  Safety Monitoring
  Space/facilities
  Study drug/pharmacy
  Contraception
  Lab-clinic interface
  Monitoring follow-up

ASPIRE
A Study to Prevent Infection with a Ring for Extended Use
The Big Five

- Accrual
- Retention
- Adherence
- Data Quality and Timeliness
- Clinical and Laboratory Safety
End of enrollment

- 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 of ≥12 months of safety per participant
- Recent data (VOICE, FEM-PrEP) have demonstrated that HIV incidence is, unfortunately, higher than 3.9% per year in several settings; in addition, ASPIRE enrollment has been >1 y
  - Thus, fewer than 3476 enrollees may be necessary. *Note: this does not imply anything (+ or -) about ring effectiveness in the trial.*
  - We anticipate that the current site targets will be sufficient. To confirm with SMC & DSMB in May.
  - End of enrollment = Q2 2014!
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
- November 2012, May 2013
  - DSMB reviews
- August & October 2013
  - SMC reviews
- November 2013
  - DSMB review
- May 2014
  - 5th = SMC, 29/30 = DSMB
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

- ASPIRE is a many-month, multi-hour commitment
  - We have amazing retention now
  - Trust the teams, keep your enthusiasm
  - Team call: Off-site visits to ensure retention and adherence

- 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)
  - Team call: Addressing participant fatigue
Adherence monitoring in MTN-020

- Monthly shipping, testing, and review of plasma dapivirine data, according to a pre-defined plan

- Information is reviewed by-site, rather than by-subject, preserving blinding. MOCK example:

<table>
<thead>
<tr>
<th>SITE</th>
<th>% SAMPLES WITH DAPIVIRINE</th>
<th>ADHERENCE ESTIMATE = middle column x 2 (since ½ expected placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>48</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>80</td>
</tr>
</tbody>
</table>
Adherence monitoring in MTN-020

- Monthly shipping, testing, and review of plasma dapivirine data, according to a pre-defined plan
- Information is reviewed by-site, rather than by-subject, preserving blinding.
- Results? We are optimistic!
Accural → Retention → Adherence → Safety → Quality

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

*Everything else flows from these*
ONE CHANCE
OUR CHANCE
IT TAKES A TEAM

Malawi College of Medicine – JHU Research Project

UNC Project - Malawi