Getting to MTN-025/HOPE: The **Why**, **How**, and **What** of an Open Label Extension after ASPIRE

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aspire (as·pire)

Pronunciation: /əˈspīr(ə)r/

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

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 >
Imagine…

About 1 year from now
Outline

Thinking about an open-label extension after ASPIRE: the why, how, and what

- Why do an open-label extension
- How have open-label extensions been done to date?
- What do we contribute with MTN-025/HOPE?
WHY

Why do an open-label extension?
Research

The research pathway does not end at phase III:

- Laboratory/Preclinical
- Early clinical safety (Phase I / II)
- Efficacy & safety (Phase III)
Research

The research pathway does not end at phase III:

- Licensure
- Manufacturing and scale-up
- Access, demonstration, roll-out

Laboratory/Preclinical  Early clinical safety (Phase I / II)  Efficacy & safety (Phase III)  STILL A LOT TO DO

STILL A LOT TO DO
Efficacy to Implementation

• The pathway from demonstration of efficacy to large-scale implementation is not instantaneous.

• Open label extensions bridge efficacy to implementation by providing first access to a product
  • The term “post-trial access” refers to making the prevention product tested in the trial available to trial participants (1) should the new product or procedure be scientifically validated and (2) in the form of follow-on, open label, or other such studies before product licensure or approval, should an efficacy or effectiveness trial have a compelling positive finding, with no safety concerns. (UNAIDS/AVAC Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials 2011)
Open-label extensions

- A core principle of ethical conduct of biomedical HIV prevention research is the provision of access to proven products in the immediate post-trial period.

- If the ring is found effective in ASPIRE, there is an obligation for former participants to have the opportunity to access the dapivirine vaginal ring. As the ring will not yet be licensed, access must be provided through a research protocol.

- As a research protocol, it will need to ask important research questions that move the field forward
Open label extension (OLE)

- OLE is not the same as the trial
  - it is not full out delivery = has to incorporate being a regulated piece of research
  - partial step towards understanding what use would be like in a population with full access and knowledge about it’s then-proven effectiveness
Dapivirine Ring Program Timeline

- **2012**: The Ring Study (ASPIRE)
- **2013**: Regulatory consultations for DPV Ring
- **2014**: DDI: miconazole
- **2015**: Male condom functionality, Post-menopausal women safety
- **2016**: Female condom functionality, Adolescent safety
- **2017**: PK: Open label extended use, PK: Menses, Regulatory submissions

**Open-label extension studies**
How have open-label extensions been done?
Open label extensions

- Open-label extensions have as the primary goal to provide first access to the product that was found safe and effective in a clinical trial to the participants who took part in that trial.
  - They are not to be confused with demonstration projects or full-scale product introduction but they should move the field in that direction.

- The approach they take may vary
  - Different factors to consider, taking into account the prevention product, the population needs, community goals, research priorities, regulatory requirements, etc.
Open label extensions

- In the last few years, several randomized trials have found antiretroviral-based prevention approaches to safe and effective for HIV prevention. These trials then provided participants access to those products through open-label extensions. These can give us a roadmap for dapivirine in terms of:
  - Timelines
  - Research goals
  - Approach
Three examples

Trial results
Partners PrEP Study
iPrEx
CAPRISA 004

Open label use
Partners PrEP Study Extension
iPrEx OLE
CAPRISA 008
Example #1: Partners PrEP Study

The study:

- Involved 4,747 HIV serodiscordant couples (in committed relationship with an HIV-infected partner) at 9 sites in Kenya and Uganda
- HIV negative partners randomly assigned to 1 of 3 groups: daily tenofovir, daily Truvada, daily placebo
- Started 2008

The results:

- An interim review in July 2011 found both products definitively protective against HIV (tenofovir 67%, Truvada 75%) and the placebo arm was stopped immediately
Example #1: Partners PrEP Study

- Active arms continued
- Couples in the placebo arm were re-randomized to tenofovir or Truvada for 1 year to collect additional data on safety and efficacy of tenofovir vs. Truvada as PrEP.
**Example #1: Partners PrEP Study**

<table>
<thead>
<tr>
<th>Partners PrEP Study Extension</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary research question</strong></td>
</tr>
<tr>
<td><strong>Additional questions</strong></td>
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</tbody>
</table>
| **Research Approach**          | • Randomized trial of two different PrEP regimens  
                                 | • All participants received an active product; counseled on efficacy and safety  
                                 | • **Monthly follow-up** for 1 year |
| **Enrollment**                 | 89% of those eligible |
| **Timeline**                   | Started 3 months after results known, completed December 2012 |
Example #2: iPrEx

The study:
- Involved 2,499 men who have sex with men and transgender women at 11 sites in Brazil, Ecuador, Peru, South Africa, Thailand, US
- Randomized to either daily use of Truvada or placebo
- Started 2007

The results:
- Went to scheduled completion and results released in November 2010.
- Truvada 44% more effective than placebo for protecting against HIV
## Example #2: iPrEx

<table>
<thead>
<tr>
<th>iPrEx OLE</th>
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<tbody>
<tr>
<td><strong>Primary research question(s)</strong></td>
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<tr>
<td><strong>Research Approach</strong></td>
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<tr>
<td><strong>Enrollment</strong></td>
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<tr>
<td><strong>Timeline and status</strong></td>
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</tbody>
</table>
Example #3: CAPRISA 004

The study:
- Involved 889 women at 2 sites in KwaZulu-Natal, South Africa
- Randomized to either tenofovir gel or placebo gel, to be used before and after sex
- Started 2007

The results:
- Results released in July 2010
- First proof of concept for a microbicide
- Tenofovir gel 39% effective, i.e., there were 39% fewer infections than with placebo
### Example #3: CAPRISA 004

<table>
<thead>
<tr>
<th>CAPRISA 008</th>
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<tbody>
<tr>
<td><strong>Primary research question(s)</strong></td>
</tr>
<tr>
<td>• To develop and assess an implementation model for tenofovir gel provision through family planning services, including measurement of adherence.</td>
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<tr>
<td>• To collect additional safety data needed for possible licensure</td>
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<tr>
<td><strong>Research Approach</strong></td>
</tr>
<tr>
<td>Randomized trial (research clinic vs. family planning clinic), follow-up monthly x 3 then quarterly thereafter for up to 2 years</td>
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<tr>
<td><strong>Enrollment</strong></td>
</tr>
<tr>
<td>85% of those eligible (but high HIV incidence during the gap, only about half of CAP 004 subjects are in CAP 008)</td>
</tr>
<tr>
<td><strong>Timeline and status</strong></td>
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<tr>
<td>Protocol finalized 4 months after results; 2 year gap due to regulatory delays. Study now ongoing; results expected 2015</td>
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Open label extension studies

- **Common themes:**
  - All were implemented to provide access to an effective product.
  - All were conducted as research protocols, with different designs and somewhat different research goals.
  - All included continued evaluation of safety among their primary goals, as well as adherence.
  - All had time-limited follow-up and some gap between release of results and first enrollment (3 months to >2 years).
WHAT

What can we contribute with MTN-025/HOPE?
Having HOPE now

- Although it may be 12-18 months until we know whether or not the ring is effective, we need to plan for possible success now

- If the ring is effective, our goal will be to provide former participants access to the ring as soon as possible
  - Within a research protocol

- MTN-025 / HOPE for ASPIRE participants
Input for HOPE

- Planning for an open-label extension to ASPIRE started last October (or even before). To get this right, many people have been consulted:
  - MTN leadership, DAIDS/NIMH leadership, IPM, ASPIRE investigators and teams, MTN CWG, MTN BRWG, MTN BSWG, DAIDS PSRC, community stakeholders (4 countries), DAIDS SWG
HOPE process

“This is a very good process that the study team has embarked on because post trial access is very critical to the study participants as they await policy regulations and roll out of the product to the rest of the population.”

-Uganda meeting participant
What should HOPE study?

- Two key questions for dapivirine vaginal ring OLE emerged:
  - safety – as much and collected as perfectly as possible for this brand new product (which would be under review for product approval)
  - adherence – especially to a known effective product

- Additional questions informative but these were key. Some questions (e.g., dapivirine in pregnant women) may be better in their own, distinct protocols
What approach?

- Across the consultative process:
  - Generally agreed that **access to effective product and research that would move the field towards implementation** were the priorities
  - Variety of opinions about design approaches: randomized/not randomized, shorter vs. longer time between follow-up visits (1, 3, 6 months), etc.
MTN-025 protocol

Population

- Sexually active HIV-uninfected women who are non-pregnant, contracepting, and 18-45 years of age and who participated in MTN-020 / ASPIRE

Procedures

- A goal to assess a more “real world” frequency for clinic follow-up and distribution of rings
- HIV testing, risk-reduction, contraceptive provision on-site, safety monitoring, product provision and counseling, pregnancy and HIV care
- Follow-up for 1 year
MTN-025 objectives

- **Primary Objectives**
  - To characterize the *safety* profile associated with open label use
  - To characterize *adherence* to open label use

- **Secondary Objectives**
  - To assess the *incidence* of HIV-1 infection
  - To assess the frequency of HIV-1 *drug resistance*

- **Exploratory Objectives**
  - To explore *participant understanding of efficacy, ring acceptability, and delivery feasibility*. Uniquely, to characterize MTN-020 participants who choose not to enroll in MTN-025 (*decliner population*).
MTN-025 design 1.0

- **Randomized**, open-label, phase IIIb trial, comparing a **monthly** vs. **quarterly** visit schedule
Why 1 vs. 3 month follow-up?

Consider the “real world”

- Monthly visits may be too burdensome for both women and health care providers.
- Less frequent visits would be optimal but all the clinical trials are for monthly follow-up and women may not be ready to transition immediately to quarterly follow-up.
- For the quarterly visits, women would receive 3 rings (or have the option for a pharmacy-only pick-up for the intervening months if they did not want 2 extra rings at home).
Randomized design?

In consultations, we received feedback that the randomized design may not be the most forward-moving approach:

- Monthly visits for a year may be tiresome and not move the field forward.
- Moving to quarterly visits could move the field forward more quickly.
  - Thus, taking the kind of aggressive, forward-thinking approach we like.
REMEMBER

- Two key questions for dapivirine vaginal ring OLE emerged:
  - safety when delivered in an open-label fashion
  - adherence when delivered in an open-label fashion
  - NEITHER OF THESE QUESTIONS REQUIRES A RANDOMIZED DESIGN
REMEMBER

- Other OLEs have not used randomized designs:
  - Most recently, iPrEx OLE has provided pivotal data that MSM want and use PrEP, with a nonrandomized follow-up schedule of monthly x 3 months, then quarterly thereafter
MTN-025 design 1.1

- Nonrandomized, open-label, phase IIIB trial, transitioning from a monthly to a quarterly visit schedule
Nonrandomized design?

Advantages

- Keeps a monthly lead-in, to bring women back into ring follow-up, re-counsel on adherence, explain/re-explain efficacy from the clinical trial
- Transitions to quarterly follow-up and thus moves towards real-world faster (but not too fast)
- Keeps all the key aims of the study: safety, adherence, resistance, HIV incidence, acceptability, etc.
- Avoids operational challenges such as trying to explain randomization to a visit schedule, potential differential reimbursement between visit schedules, etc.
Key scientific outcomes

- Important data on safety with open-label use, coincident with regulatory submission of this product.
- Assessment of adherence, transitioning from monthly clinical trial visits to quarterly visits to mimic delivery settings.
- Measurement of the key outcomes of HIV-1 incidence and resistance once efficacy is known.
- Understanding declines of the ring (as one prevention tool is not for everyone).
Discussion considerations

- **Timing.**
  - *Cannot delay implementation, should ASPIRE prove efficacious*

- **Listening to all stakeholders.**
  - *Many people have contributed opinions to this process.*

- **Operations.**
  - *Sites have moved into / towards regulatory submission of the randomized design*
MTN-025 Summary

• In accordance with international ethical principles regarding the conduct of HIV-1 prevention research, former MTN-020/ASPIRE participants will have the opportunity to enroll in MTN-025 and have access to the dapivirine ring, if it is found safe and effective in ASPIRE
  • Those who decline MTN-025 will provide information on reasons for decline.

• MTN-025 / HOPE is designed to provide key scientific information about the safety of and adherence to the ring, information that is a necessary bridge to implementation.
Thank you

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