

ASPIRE

A Study to Prevent Infection
with a Ring for Extended Use

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**Next Steps for HIV Prevention in Women:
Tenofovir Gel and Beyond**

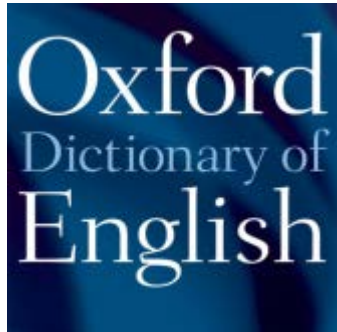
**Joint Civil Society and MTN Community Working Group Meeting
8 October, 2011, Cape Town**



Overview

- Design and rationale
- Study objectives
- Participants and enrollment
- Study procedures
- Safety monitoring
- Timelines
- Questions and discussion

What does ASPIRE mean?



aspire(as·pire)

Pronunciation: /ə'spī(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*



m-w.com

as·pire

verb \ə-'spī(-ə)r\
intransitive verb

1 : **to seek to attain or accomplish a particular goal** <*aspired to a career in medicine*>



What does ASPIRE mean?

ASPIRE

\ə-'spī(-ə)r\
noun:

1. A Phase III study that seeks to determine whether a woman's use of a vaginal ring containing the antiretroviral (ARV) drug 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*



ASPIRE: At a glance

- First Phase III trial of a vaginal ring for HIV prevention
 - First study to evaluate effectiveness of a long-acting product intended for extended use
- First effectiveness study of an ARV-based HIV prevention product using a drug other than tenofovir
- Designed to provide the strength of evidence to support potential licensure
- Will involve about 3,476 women at several sites in Africa
- Will begin mid 2012; results late 2014 or early 2015




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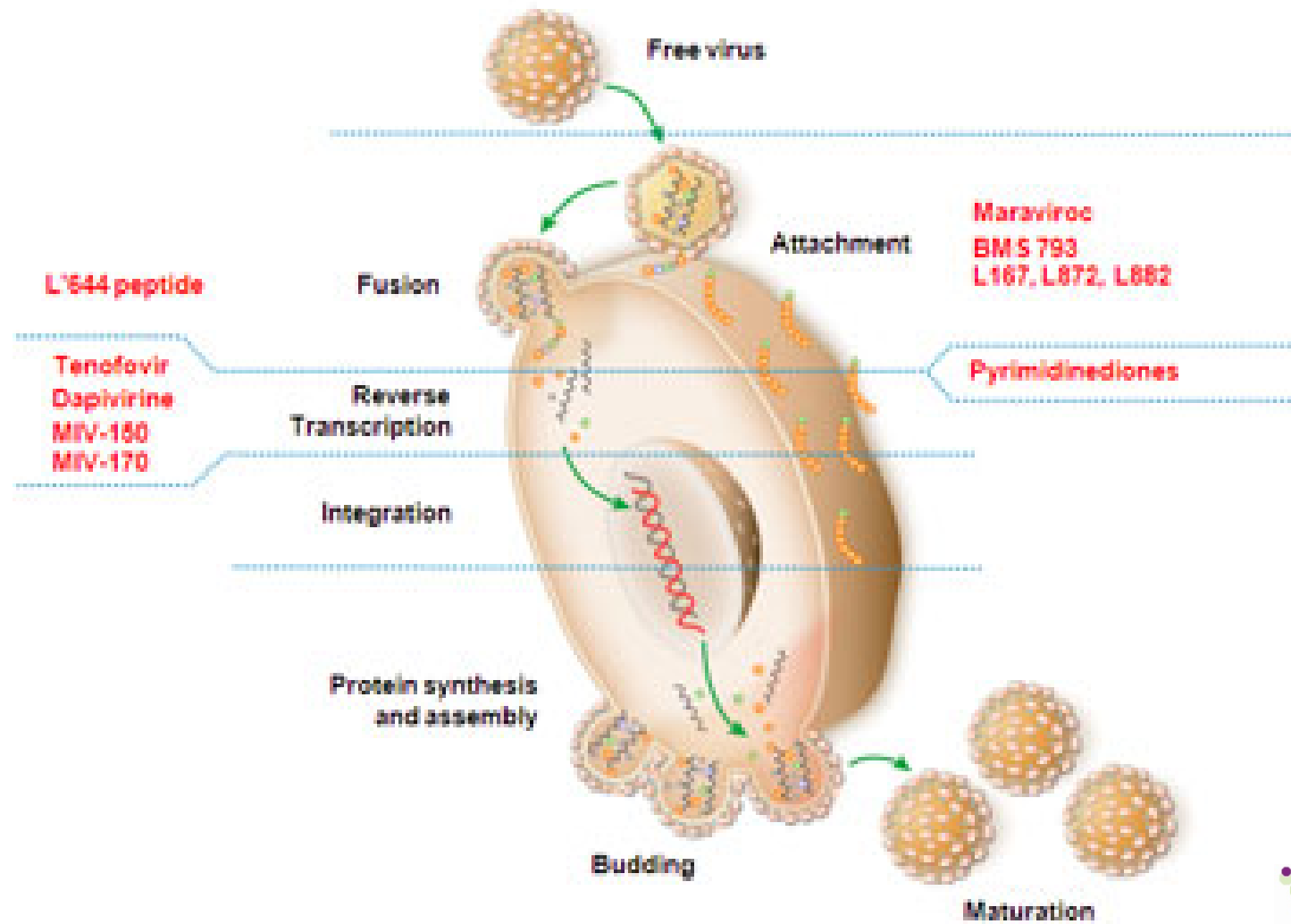
Rationale and Design

Rationale: Key Points

- Dapivirine ring is a new product that has shown promise in Phase I and Phase II trials
- A placebo-controlled trial can provide the most clear information about whether a new product is safe and effective
- Regulators need clear answers about the safety and effectiveness of a product in order to consider approving it for widespread use



How Dapivirine Works

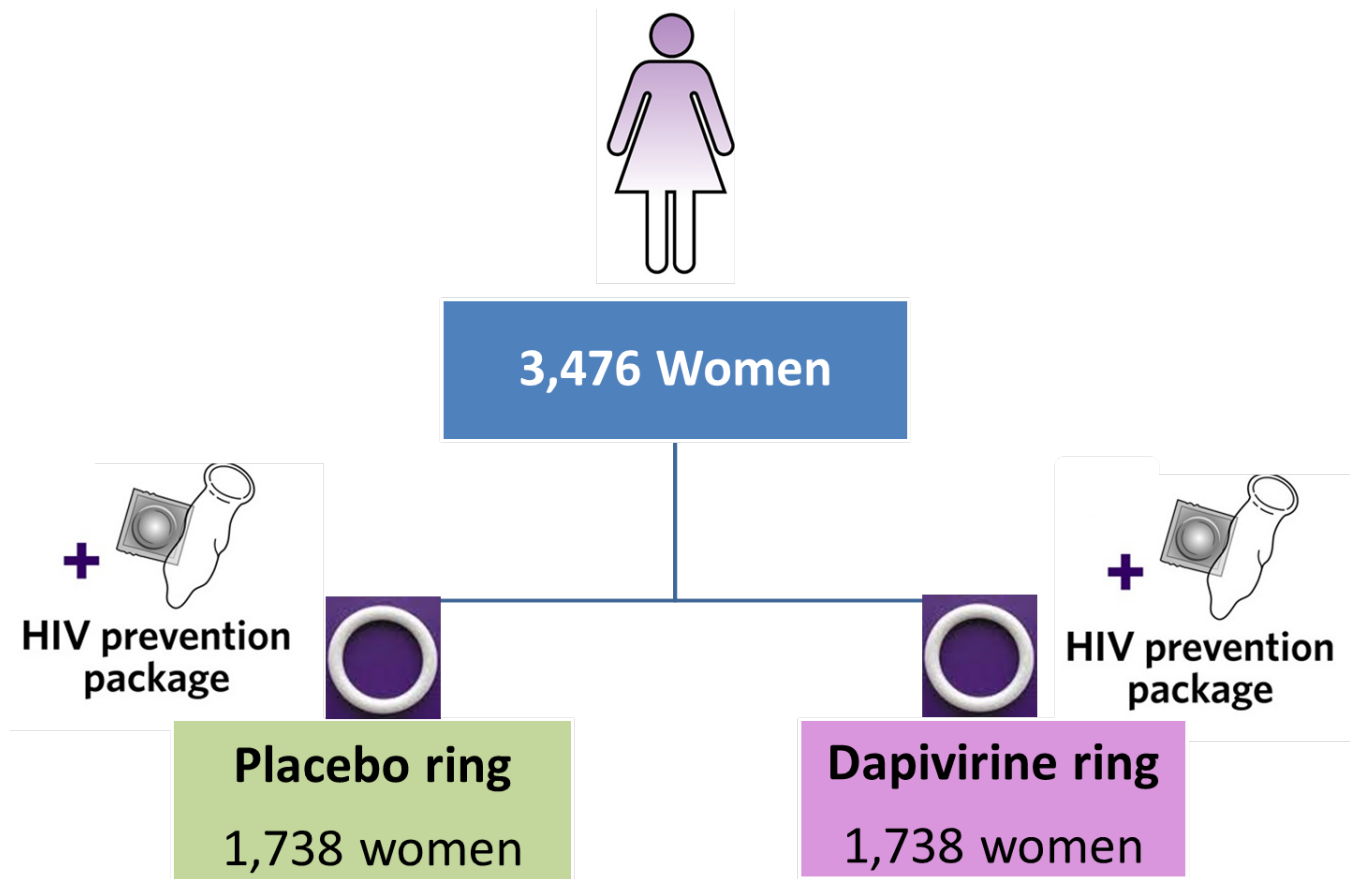


How the study is designed

- Phase III trial evaluating safety and effectiveness
- Women who enroll will be randomly assigned to one of two study groups:
 - One group will use a vaginal ring containing dapivirine
 - One group will use a vaginal ring containing a placebo
 - Both rings look the same, and no one knows which ring a woman has been assigned to use
- Women will replace the ring every 4 weeks while in the study - over the course of at least 1 year
- All women will receive standard HIV prevention package

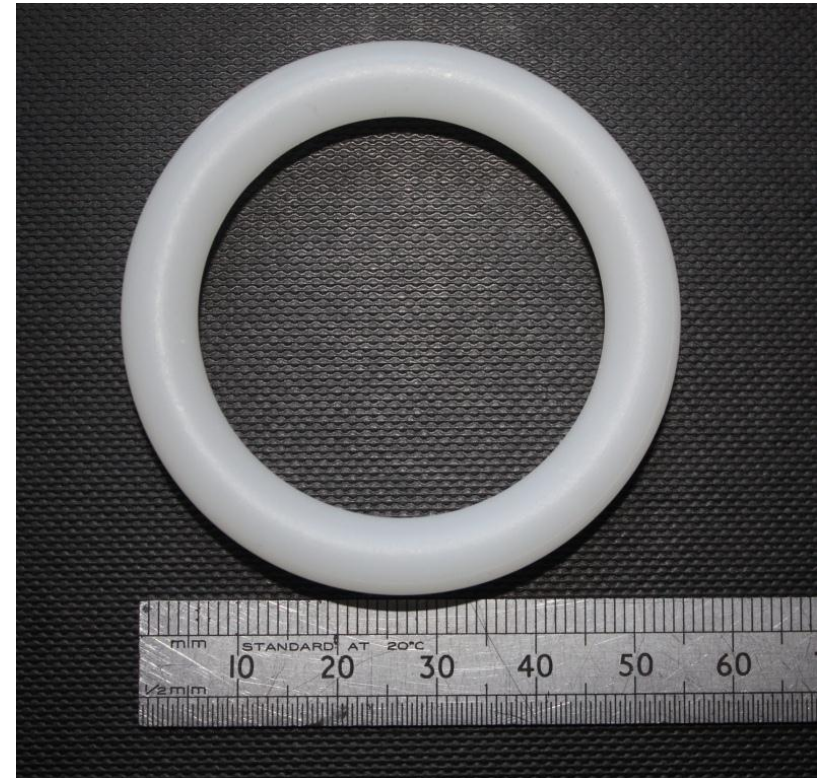


ASPIRE Study Design



About the dapivirine ring

- Flexible ring made of an elastic silicone material
- Measures 56 mm (about 2 ½”) in diameter and 7.7 mm (¾”) thick
- When inside the vagina, the ring releases the drug (active or placebo) slowly over time
- Designed for 28-day use
- IPM providing both the placebo ring and the dapivirine ring for the study





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Study Objectives

Study Objectives

- Are the questions we want to answer in a study
- Grouped by how important they are to the study:
 - Primary objectives
 - Secondary objectives
 - Exploratory objectives
- Each objective looks to answer the question in specific way
 - e.g., results of certain medical or laboratory tests, responses to behavioral questionnaires

Primary Objective #1

□ *Is the ring effective in preventing HIV?*

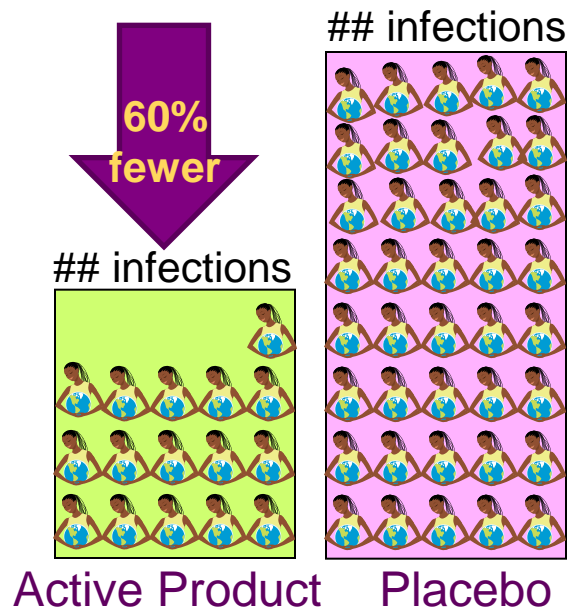
In protocol speak:

- “To determine the effectiveness of dapivirine (25 mg) administered in a silicone elastomer vaginal matrix ring, when inserted once every 4 weeks, in preventing HIV-1 infection among healthy sexually active HIV-uninfected women”

Measuring Primary Objective #1

□ *How will we determine whether the ring is effective in preventing HIV?*

- At the end of the study we will compare the number of HIV infections that occurred among women in the group using the dapivirine ring with the number of HIV infections in the group using a placebo ring
- We hope to see a minimum of 60% fewer infections compared to the placebo



Primary Objective #2

□ *Is the ring safe to use?*

In protocol speak:

- “To assess the safety of dapivirine (25 mg) administered in a silicone elastomer vaginal matrix ring to the placebo VR, when inserted once every 4 weeks over the investigational product use period”

Measuring Primary Objective #2

- ***How will we determine whether the ring is safe to use?***
 - Participants' health assessed at each study visit
 - Physical exam
 - Blood and urine tests of immune, liver and kidney function
 - Check for STIs, vaginal infections, other problems
 - Monthly visits will include a pelvic exam
 - We will compare the number, frequency and type of side effects/problems between the two groups
 - Were they related to use of the product or not?

Secondary Objective #1

- *Will women find it acceptable to use?*

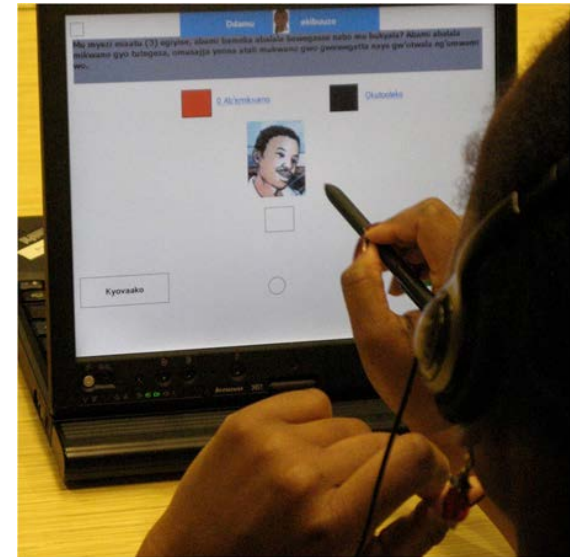
In protocol speak:

- “To evaluate the acceptability of the study VR (dapivirine or placebo) in HIV-uninfected women, when inserted once every 4 weeks over the investigational product use period”

Measuring Secondary Objective #1

□ *How will we determine whether women will find the ring acceptable to use?*

- Participants will be asked questions in staff interviews or using ACASI – Audio Computer-Assisted Self-Interview
- Will be conducted at quarterly visits and final product use visit
- Looking to know:
 - Does she have discomfort?
 - Is the ring noticeable during daily activity or sex?
 - Is her partner aware of the ring during sex?
 - How easy is it to insert and remove?
 - What do she and her partner think about the ring?



Secondary Objective #2

- ***Will women use the ring, and use it properly?***

In protocol speak:

- “To evaluate the *adherence* to the study VR (dapivirine or placebo) in HIV-uninfected women, when inserted once every 4 weeks over the investigational product use period”

Measuring Secondary Objective #2

- ***How will we know if women use the ring as instructed?***
 - Adherence will be measured at all monthly visits and final product using questionnaires and ACASI
 - Looking to know:
 - Since the last visit, did she take the ring out or did it come out on its own?
 - Why did she take it out or did it come out?
 - How long was it out?

Secondary Objective #3

□ *Will drug resistance be a problem?*

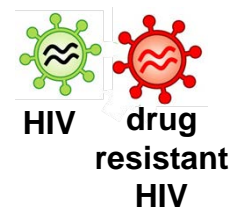
In protocol speak:

- “To assess the frequency of HIV-1 *drug resistance* in women who acquire HIV-1 infection while using the investigational product”

Measuring Secondary Objective #3

□ *How will we determine whether women develop drug resistance?*

- If a woman becomes infected, special tests will be done that detect mutations (errors) in the genetic makeup of HIV
- We know that HIV can use certain mutations as a disguise – we know some of the disguises to look for
- Different mutations are associated with resistance to a specific ARV or ARV class



Special tests can identify resistance

Secondary Objective #4

- ***How much drug needs to be in the tissue to protect against infection?***

In protocol speak:

- “To evaluate the *relationship between drug concentration and HIV seroconversion*”

Measuring Secondary Objective #4

- ***How will we determine how much drug needs to be in tissue to protect against HIV?***
 - Each month, research staff will take samples of blood and vaginal fluid; women will also be tested for HIV
 - If a woman tests positive for HIV, further testing will be done of her blood and vaginal fluid samples
 - At the end of the study will look at blood and vaginal fluid samples from all women in the dapivirine ring group
- ➔ Is there less drug in tissue of women who became infected?

Exploratory Objectives

- Other questions we want to answer:
 - Does use of the ring alter the normal balance of “good” bacteria inside the vagina?
 - Are there “biomarkers” that we can use to signify safety and efficacy?
 - Changes in the types of cells, proteins or biochemicals that could be used as a simple test?
 - Is adherence related to drug concentration levels?
 - Are women becoming infected during the 2-month follow-up period, after they stopped using product?

At the end of the day...(study)

- ❑ Can the ring protect against HIV?
- ❑ Is it safe to use?
- ❑ Will women like using it?
- ❑ Will women actually use it?



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Participants and Enrollment

Who can participate?

- HIV-uninfected, sexually active women between ages of 18 to 45
- Women must also meet other inclusion and exclusion criteria

Additional Inclusion Criteria

- Able and willing to provide **written informed consent** and adequate locator information
- Agree **not to participate in other research studies** involving drug, vaccines, medical devices or vaginal products during the study
- Be using an effective method of **contraception** at enrollment and intending to do so while in the study
 - hormonal methods (except contraceptive ring); IUD; tubal ligation

Exclusion Criteria



- Women must **NOT** be:
 - Pregnant or currently breastfeeding, or planning to become pregnant during the study
 - Planning to relocate away from the study site to be away for more than 8 consecutive weeks
 - Diagnosed with urinary tract infection, pelvic inflammatory disease, an STI or reproductive tract infection requiring treatment
 - *Treatment will be offered and women may join the study if resolved*

Exclusion Criteria II

- *Women must **NOT** have*
 - Known adverse reaction to the study product or latex
 - Used PEP for HIV exposure within last 6 months
 - Had a pregnancy outcome (birth, miscarriage, abortion) or gynecologic/genital procedure in last 90 days
 - Certain medical conditions; abnormal blood, urine tests
 - Been in a study of a drug, device, vaccine or vaginal product in last 60 days
 - Participated in VOICE or any other trial of PrEP or a vaginal microbicide in the last year

Women will provide informed consent

- To be screened for the study
- To enroll in the study
- Translated into local languages to help ensure understanding and inclusiveness
- Is a continuous process throughout the study



Goals of Informed consent

To help women understand:

- risks and benefits of being in the study
- potential social harms of being in the study
- safety and efficacy of the study product is not known
- What happens at study visits; different tests and procedures
- How randomization works and why both study groups are important to the study's success
- Why adhering to study visits and procedures is important
- She can withdraw from the study at any time



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While in the Study: Study Visits and Procedures

Learning how to use the ring



- ❑ Women will learn how to insert and remove the ring on the day they are enrolled
- ❑ Staff will explain that the ring should remain in place until the next monthly visit, when she will remove the ring and insert a new one
- ❑ Staff will remind women at each visit how the ring is inserted and removed
- ❑ A woman can ask to have for help at anytime

Vaginal Ring Do's and Don'ts

- Do:**
- Wear the ring all day and everyday between study visits
 - Wash the ring with the bottled water provided before reinserting it, if the ring had to be removed or came out on its own
 - Come to the study clinic if help is needed
 - Use tampons during menstruation if preferred

- Don't:**
- Use any other vaginal product or device, such as a lubricant, spermicide, diaphragm, contraceptive vaginal ring or vaginally applied medication
 - Don't engage in practices such as douching

Study Visits and Procedures

- At each monthly visit
 - Safety checks
 - HIV testing
 - HIV/STD risk reduction counseling
 - Condoms and condoms counseling
 - STI testing as clinically indicated
 - Adherence interviews and counseling
 - Questions about sexual behaviors, condom use
 - Informed consent as needed
 - Locator information
 - Receive and insert a new ring
- Pelvic and clinical exams at quarterly visits or as needed



Can't come to the clinic?

- Women may opt to have study visits at the clinic, in her home, or at other community-based location, depending on site capacity and site/participant preferences
- If genital symptoms are reported during an off-site visit, the participant is instructed to report to the study clinic as soon as possible for a pelvic exam.



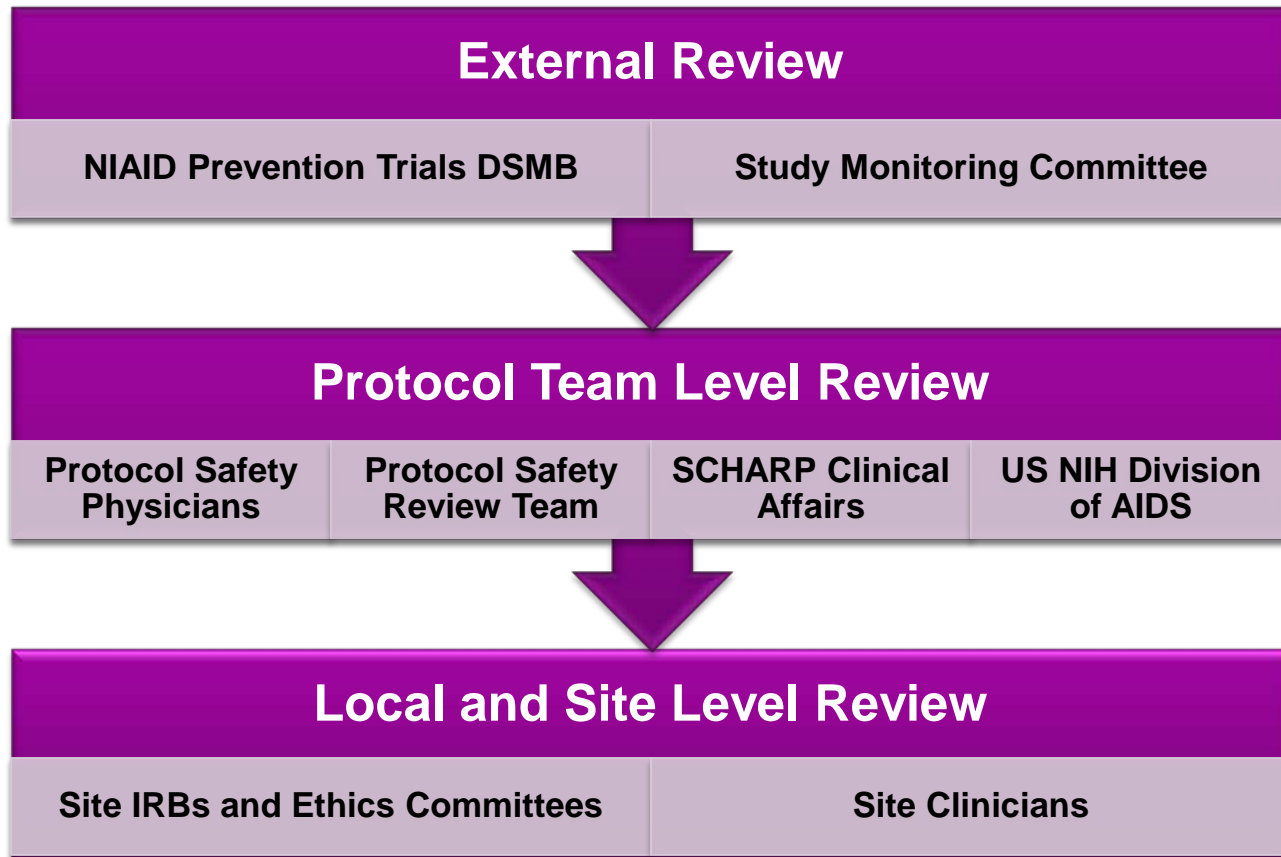
The logo for the ASPIRE study. It features the word "ASPIRE" in a purple, serif font. A green ring is positioned around the letter "A".

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Safety Monitoring

Many Layers of Safety Monitoring



At the local and site level

- IRBs and ECs must review and approve protocol
 - provide oversight throughout the study
- Site clinicians monitor safety and wellbeing of participants at each monthly visit
 - Tests and questions about key symptoms
 - HIV testing
 - Pregnancy testing
 - Counseling on safe use of the product and practices
 - Rings can only be dispensed to the enrolled study participant or clinic staff on her behalf
- If there is any question about safety, staff will stop a participant's use of the ring

What if a women becomes pregnant?



- Women who become pregnant while in the study will need to stop using the ring but can remain in the study to continue with follow-up visits
- Women will be referred for appropriate care and invited to join MTN-016, an observational registry study that aims to understand if product use has an effect on pregnancy outcomes
- She may be able to rejoin ASPIRE after her pregnancy

What if a woman acquires HIV?

- All sites are required to have procedures for care and support for participants who acquire HIV and referral agreements with HIV primary care and ART providers
- Resistance testing is done
 - If identified, this can help those treating her infection better manage her care
- She will be invited to join MTN-015
 - MTN-015 is a long-term observational study
 - Frequent lab testing in MTN-015 can help in the management of her care

What if a woman acquires HIV?

- We will stop product immediately
- Retrieve the ring
- She will be provided with HIV-related information and counseling by site staff
- Counseling and testing for her partner will be offered
- She will be referred to local care and support services
 - Medical care, including ART
 - Psychosocial services
 - Other programs, e.g., offered by CBOs
- She can remain in study and continue with monthly visits

Safety monitoring by the team

- Protocol safety physicians
- Protocol safety review team
- Statistical data and monitoring center
- DAIDS medical officer

External Safety Monitoring: DSMBs

- A Data Safety Monitoring Board (DSMB) is a group of independent experts that conducts routine reviews of data while a trial is ongoing
- A DSMB looks at blinded data at several time points during a trial – about two times a year
 - Are there safety concerns?
 - Will the trial be able to answer the study questions?
 - Do any of the study questions already have clear answers?
 - Should the trial keep going, stop early or be modified?
- Also may evaluate emergent data from other trials

The DSMB for ASPIRE

- National Institute of Allergy and Infectious Diseases (NIAID) Prevention Trials DSMB will review ASPIRE
 - 10 members, including 3 from Africa

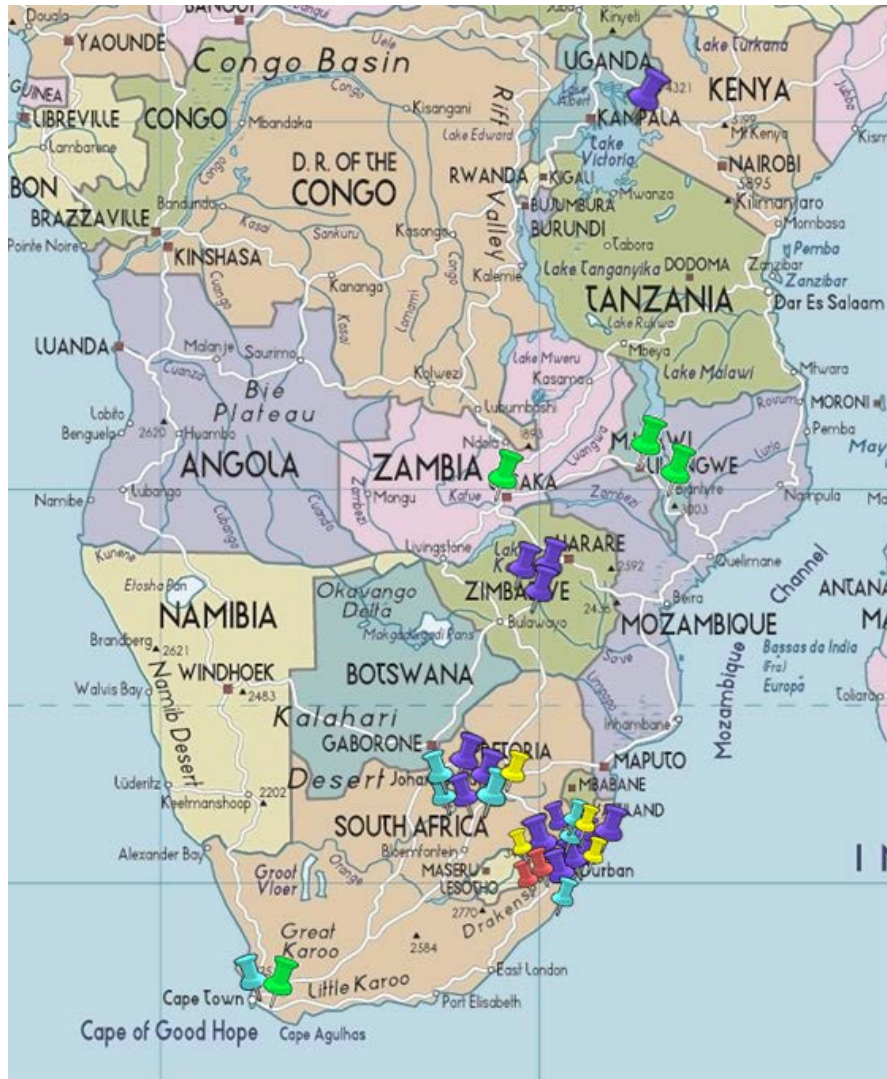


- At any time, the DSMB could recommend the study be modified or stopped due to product effectiveness, product safety or futility (the study cannot answer the questions it was designed to).
- Decisions are based on:
 - Pre-determined statistical parameters and stopping rules set by the study team and the DSMB
 - Ethical principles

Challenges and Variables

- Final or interim results of ongoing trials
 - VOICE?
 - FACTS-001?
 - CAPRISA-008?
- Interim data reviews of IPM's Phase II Safety Study?
- Other trials on the horizon?
- Approval or availability of tenofovir gel or oral PrEP?
 - In some countries but not others?

When ASPIRE begins mid 2012



- ❑ **VOICE** – Ongoing at 15 sites in South Africa, Zimbabwe and Uganda; 11 in South Africa
- ❑ **FACTS 001** – Enrolling at 7 sites in South Africa
- ❑ **CAPRISA 008** – Enrolling at 2 sites in KwaZulu-Natal, South Africa
- ❑ **The Ring Study (IPM 027)** - Beginning to enroll in South Africa?
- ❑ **ASPIRE** – Beginning to enroll in Cape Town, Malawi and Zambia



Adapting to Change

- All women receive HIV counseling, condoms, risk reduction counseling, and treatment for STIs at each clinic visit.



- What if tenofovir gel is approved or if either the gel or oral PrEP is introduced?



- Depending on timing, changes to ASPIRE may be required.
- ASPIRE will closely monitor relevant national policies and the global HIV prevention landscape
- Engage with policy makers, governments and other stakeholders about these important issues throughout the study.



Standards of prevention

- What if new prevention strategies are incorporated into national HIV prevention policies?
 - Women will be counseled about the new intervention
 - The site will either offer the intervention or women will be referred to local centers with appropriate expertise, in accordance with WHO/UNAIDS guidelines and local practice and standards.



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Timelines

Running on Time

- January 2011
 - Concept approved by MTN Executive Committee
- 30 March 2011
 - Protocol Consultation Meeting with Site Investigators
- 11 May 2011
 - NIAID Strategic Working Group gave approval
- 19 July 2011
 - Prevention Science Review Committee
- 29 September 2011
 - Regulatory and Medical Officer approval
- 9 October 2011
 - Protocol Team Operational Walk-Through

Next steps

- Sites will submit protocol to IRBs/ECs and in-country regulatory authorities for review and approval
- Expect first sites to enroll participants mid 2012
 - Non-VOICE sites
 - Cape Town, Zambia, Malawi (Blantyre and Lilongwe)
- Modifications and amendments are possible at any time throughout the trial

What's our timeline?

2011

Sites begin seeking approval of IRBs/ECs and in-country regulatory authorities

2012

Sites begin enrolling
VOICE sites begin after VOICE follow-up is complete
(approximately Sept)

2013

Continue enrolling and following participants

2014

Complete study and follow-up

2015

Report results early 2015

Acknowledgements

MTN is funded by NIAID (5U01AI068633), NICHD and NIMH, all of the U.S. National Institutes of Health

