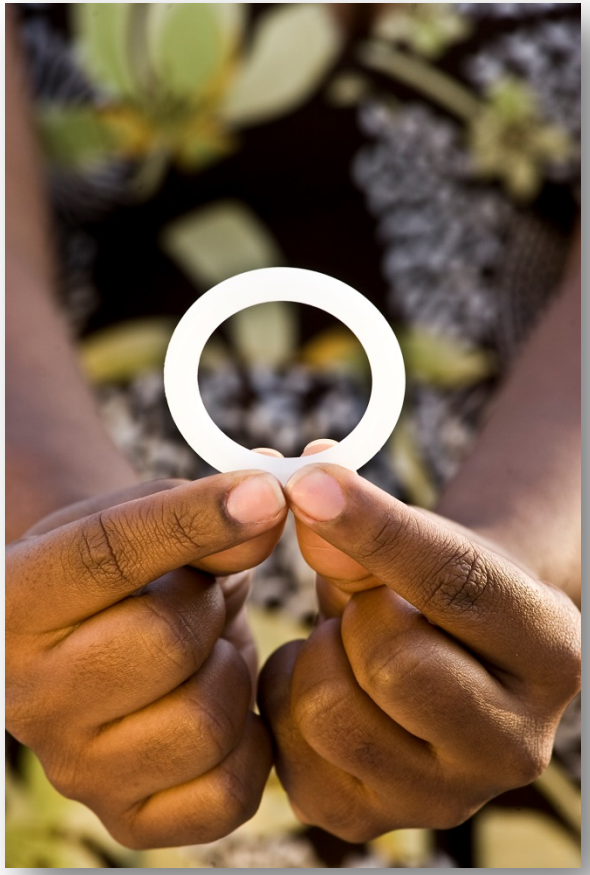
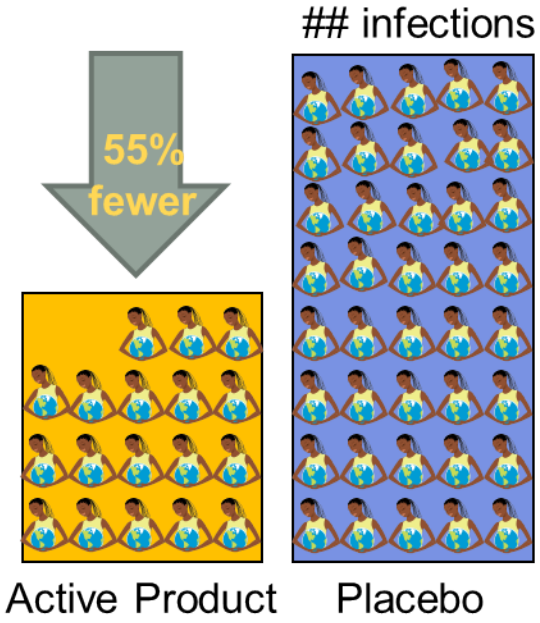
Looking Ahead to Results



First efficacy results to be reported by early 2016

How do prevention trials determine effectiveness?



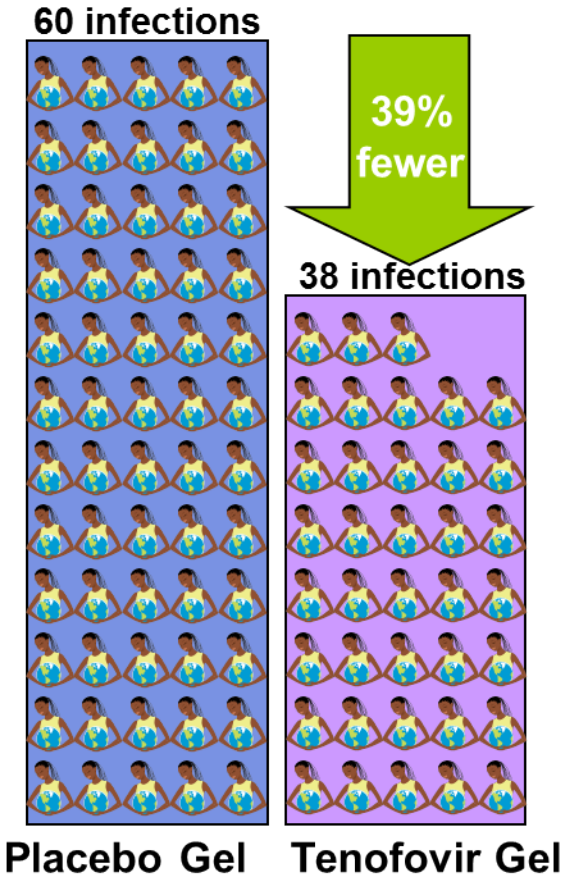
- The number of HIV infections that occurred among women who received an active product is compared with the number of HIV infections that occurred among women in the matched placebo group
- We hope there are fewer HIV infections in the active drug group than in the placebo group and the difference is statistically significant
- In this example, there are 55% fewer women who acquired HIV in the active product group
- Can also say:
  - Active product reduced HIV risk by 55%
  - Active product 55% more effective than placebo
  - Active product 55% effective

The confidence interval matters

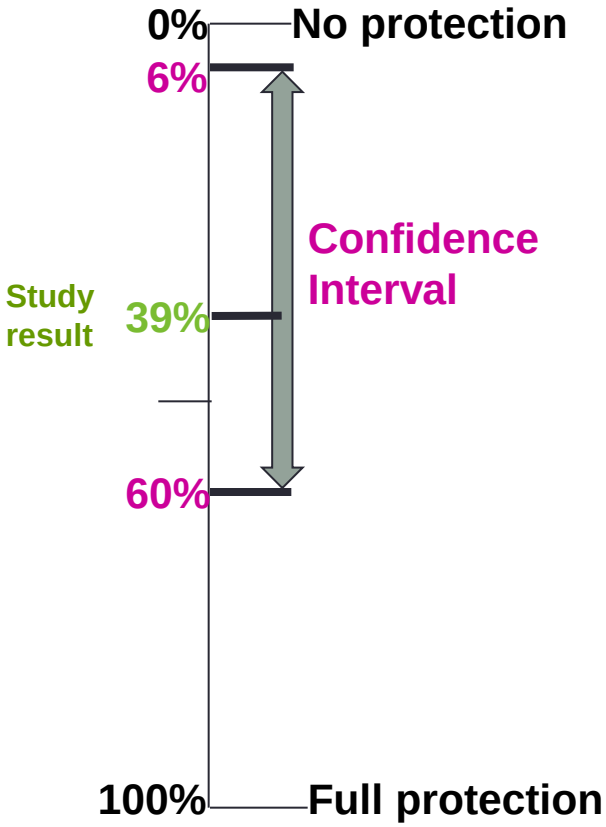
- A study result (level of effectiveness) is only an estimate
- It must be considered in the context of a **confidence interval**, a calculation used to show how precise your result is
- It is expressed as a range, with an upper and lower bound
  - If the result is 55% and the confidence interval is 33 and 74, the product's true effectiveness could be anywhere between 33% and 74%
  - The result can never be statistically significant when the lower number is 0 or less

Example: CAPRISA 004

Tenofovir gel was 39% more effective than placebo gel for protecting against HIV when used before and after sex



According to the confidence interval, the true level of risk reduction could be as low as 6% or as high as 60%



One Trial is Not Enough

At least two Phase III trials are needed to get the full picture of a product

- Consider tenofovir gel
  - CAPRISA 004 (used before and after sex)
    - 39% effective, confidence interval 6% to 60%
  - VOICE (used daily)
    - 15% effective, confidence interval -21% to 40%
  - FACTS 001 (used before and after sex)
    - 0% effective, confidence interval estimated to be -40% to 30%

CAPRISA
CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA

VOICE
VAGINAL + ORAL INTERVENTIONS TO CONTROL THE EPIDEMIC

FACTS
Follow-on African Consortium for Tenofovir Studies

What is good enough?

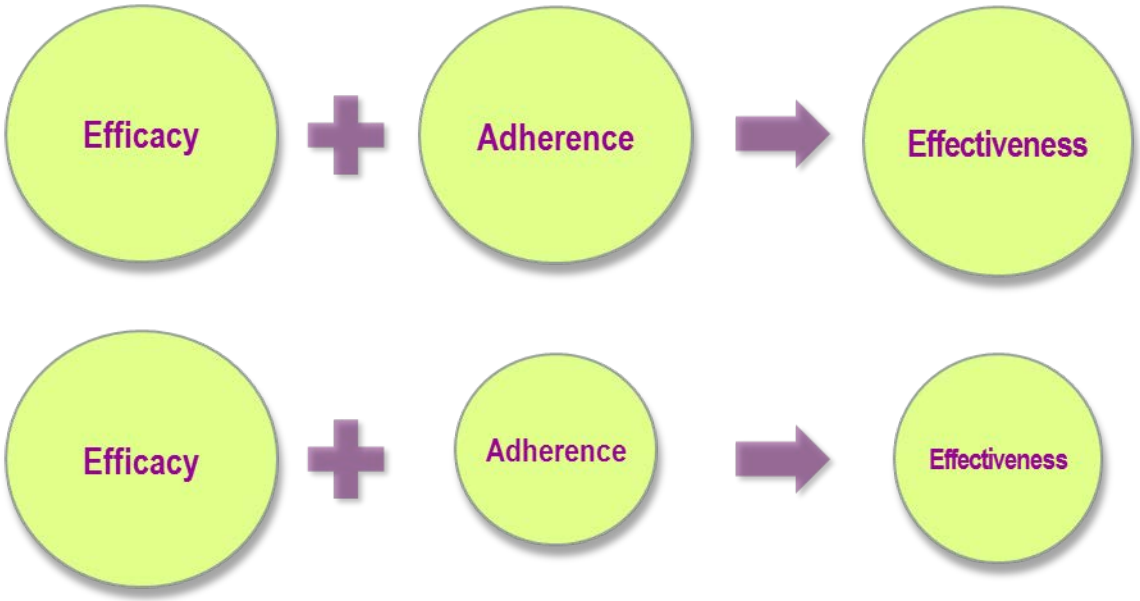
Despite very different results, iPrEx and Partners PrEP were each considered effective according to their respective protocols:

- iPrEx – Truvada **44% effective**
  - Below study's 60% aim, but was statistically significant
  - Confidence interval 15% to 63%
  - Contributed to FDA approval of Truvada for HIV prevention
- Partners PrEP–Truvada **75% effective**; tenofovir **67% effective**
  - Exceeded goal of 60%
  - Confidence intervals: Truvada - 56% to 87%; tenofovir - 44% to 81%
  - Was second pivotal study supporting FDA approval

Learning From Other Trials

No adherence = No HIV protection

Virtually every ARV-based prevention trial has illustrated how participants' product adherence (or lack thereof) can influence outcome



Reporting results of the ring

- ASPIRE and The Ring Study have matched statistical plans so that each study will produce the same kind of data
- Results of each study will include the following:
  - **Standard** (modified) **intent-to-treat** analysis
    - Includes all enrolled participants except participants who were HIV+ at enrollment
  - **Site-restricted intent-to-treat analysis**
    - Excludes pre-specified sites with low adherence
    - Same as standard (modified) intent-to-treat analysis but considers only those participants enrolled at 13 of 15 ASPIRE sites and 6 of 7 Ring Study sites
    - This approach was deemed acceptable by regulators and approved by each study's DSMB 2 years ago

THE RING STUDY
Developing HIV Prevention for Women

ASPIRE

Reporting results of the ring (2)

- Results will also include:
  - **As-treated analysis:** excludes time when participants did not receive product (e.g., missed visits, pregnancy)
  - **PK data (detection of drug in blood) and residual drug in returned rings**
    - Will help provide a picture of women's use of the ring
    - Is higher use associated with higher levels of HIV protection?
      - iPrEX - Truvada was 44% effective overall, but among those whose blood levels suggested regular use, HIV risk was reduced by more than 90%
      - VOICE - Tenofovir gel was 15% effective overall, but among regular users, there was 47% reduction in HIV risk compared to placebo

THE RING STUDY
Developing HIV Prevention for Women

ASPIRE

MTN
microbicide
trials network

ASPIRE

A Study to Prevent Infection
with a Ring for Extended Use

Planning for different outcomes

- Cannot plan for all possible outcomes - focusing on a few general scenarios
- Must consider context: Assumes the Ring Study is ongoing (completion is end of 2016)
- Must consider results implications for open-label extension study (MTN-025/HOPE) for ASPIRE participants
  - Depending on the results, a decision may or may not be straightforward

ASPIRE Results Scenarios

EFFICACY IS CLEAR	EFFICACY WITH QUESTIONS	RESULTS UNCLEAR	INSUFFICIENT EFFICACY
Great news! Results clearly show dapivirine ring is safe and effective Move to implement HOPE HOPE *Out of ASPIRE, there is HOPE*	Good news (?) Results show dapivirine ring is safe and effective Decision about HOPE not straightforward HOPE *Out of ASPIRE, there is HOPE*	Results don't provide clear answers - additional analysis needed?	Results answer the questions - dapivirine ring is safe but not effective *Ring Study probably stops*

Results of Ring Study likely a year away (early 2017)

MTN microbicide trials network

EFFICACY IS CLEAR

Out of ASPIRE … HOPE

ASPIRE **results**

HOPE
Out of ASPIRE, there is HOPE
opens

Participants informed

Former Participants contacted

enrollment → **Approximately 1-year open-label use of dapivirine ring**

IRB/EC informed

→ **HOPE approval**

National and community **Stakeholders** informed

Results of The Ring Study scheduled for early 2017

ASPIRE MTN microbicide trials network

EFFICACY WITH QUESTIONS

- Results show dapivirine ring is safe and effective
- Not able to make definitive statement about intention to implement HOPE at time of release because results require further discussion
- Results may require further discussion
  - Efficacy may be lower than hoped
  - Level of effectiveness across all sites (via the standard modified intent-to- treat analysis) may not be significant but the site-restricted analysis is
- Meanwhile, The Ring Study will be ongoing with results scheduled early 2017
  - Important that The Ring Study collect the data to support potential regulatory approval
  - Unlike ASPIRE, all participants use product for 2 years

ASPIRE MTN microbicide trials network

RESULTS ARE UNCLEAR

- Results may not support moving forward with HOPE
- Further analysis may be needed to understand an unexpected or unusual result
- Meanwhile, The Ring Study will be ongoing with results scheduled early 2017
  - Important that The Ring Study collect the data to better understand ASPIRE results and possibly support regulatory submission
  - Unlike ASPIRE, all participants use product for 2 years

ASPIRE MTN microbicide trials network

INSUFFICIENT EFFICACY

- Study result is not statistically significant
- The study answered the intended question
- The Ring Study would likely stop

ASPIRE MTN microbicide trials network

INTERNATIONAL PARTNERSHIP FOR MICROBICIDES

The Ring Study

Microbicides
Giving Women New Hope and Choice in HIV Prevention

The Ring Study: DSMB Scenarios

CONTINUE AS PLANNED	SAFETY + INSUFFICIENT EFFICACY	SAFETY + EFFICACY
DSMB recommends study continue as planned	Stop Ring Study based on DSMB recommendation, and terminate dapivirine ring program, pending ASPIRE results	Based on DSMB recommendation, amend The Ring Study to open label and initiate open-label follow-on study; submit dossier for regulatory approval, pending ASPIRE results

Scenario Overview

Key Takeaway

Ring Study DSMB recommends study continue as planned to ensure robust results and provide comprehensive data on the ring's efficacy and long-term safety

Immediate Next Step

- Continue The Ring Study

Scenario Overview

Key Takeaway

Results show the dapivirine ring is safe but not efficacious or has limited efficacy

Immediate Next Step

- Stop The Ring Study
- IPM informs and consults with regulators and stakeholders on next steps for the ring
- IPM determines approach to pipeline development once ASPIRE results known

Scenario Overview

Key Takeaway

Great news!

Results show that the dapivirine ring is safe and efficacious

Immediate Next Steps

- Initiate plans for The Ring Study to go open label and/or initiate open-label follow-on study (DREAM/IPM 032)
- IPM prepares dossier for Dec. 2016 regulatory submission, pending ASPIRE results

Efficacy: Two Possibilities

1. Both Phase III studies find the dapivirine ring effective, pivotal moment for the ring and the field
   - ✓ Both open-label extension (OLE) studies begin
   - ✓ IPM pursues regulatory approval
2. ASPIRE shows efficacy and The Ring Study continues; good news but need Ring Study results in 2017 for full picture about the ring
   - ✓ Move to implement HOPE (OLE) for ASPIRE participants, pending results
   - ✓ IPM continues preparing for possible regulatory submission

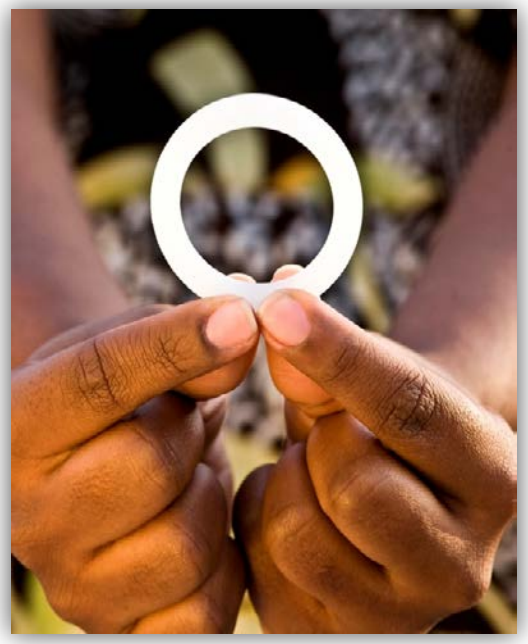
THE RING STUDY
Developing HIV Prevention for Women

ASPIRE

Next Steps: Announcement Considerations

- ASPIRE will report results early 2016
- Results of The Ring Study are scheduled early 2017
  - Available sooner if DSMB recommends unblinding the study in November
- If both Phase III studies find the dapivirine ring safe and effective, it would be a pivotal moment for the future of microbicides
- Critical that results announcement(s):
  - Clearly communicates next steps for the dapivirine ring, including realistic timelines for potential licensure and access
  - Underscores continued need for new HIV prevention options for women, no matter the outcome

Thank you



Questions?