# How Can a Significant Outcome of One Trial Impact Ongoing or Future Trials?

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

**Joint Civil Society and MTN Community Working Group Meeting**
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# Overview

- Placebo-controlled trials
- After the placebo: What then?
- Determining Standards of Prevention
- How can one trial impact another?
- DSMB reviews
- What happened in VOICE?
- Tenofovir gel: What do we need to be prepared for?

# What is a placebo-controlled trial?

- A type of study that aims to determine how effective a treatment or intervention is compared to “no treatment at all.”
- One group of participants uses the active treatment and another group uses a placebo
  - Placebos look the same but do not contain an active product.

# Why a placebo-controlled trial?

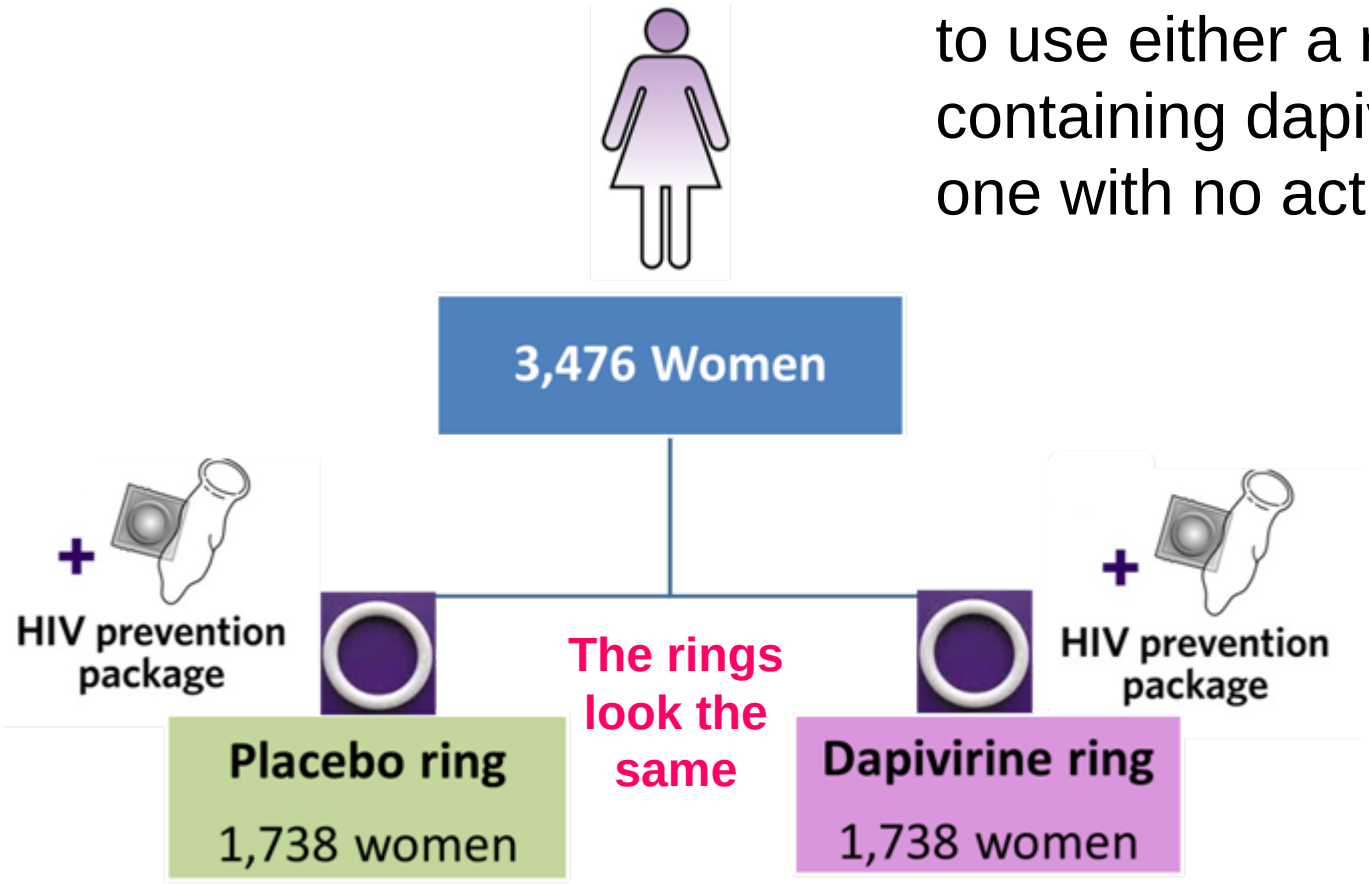
- Considered the gold standard
  - Best way to determine if a new drug or product is safe and effective
- Important for licensure
  - Regulators usually want to see data from a placebo-controlled trial
- Conducted when there is not already an approved product widely available and/or no clear evidence supporting a new indication
  - All HIV prevention trials currently use a placebo

# How does it work?

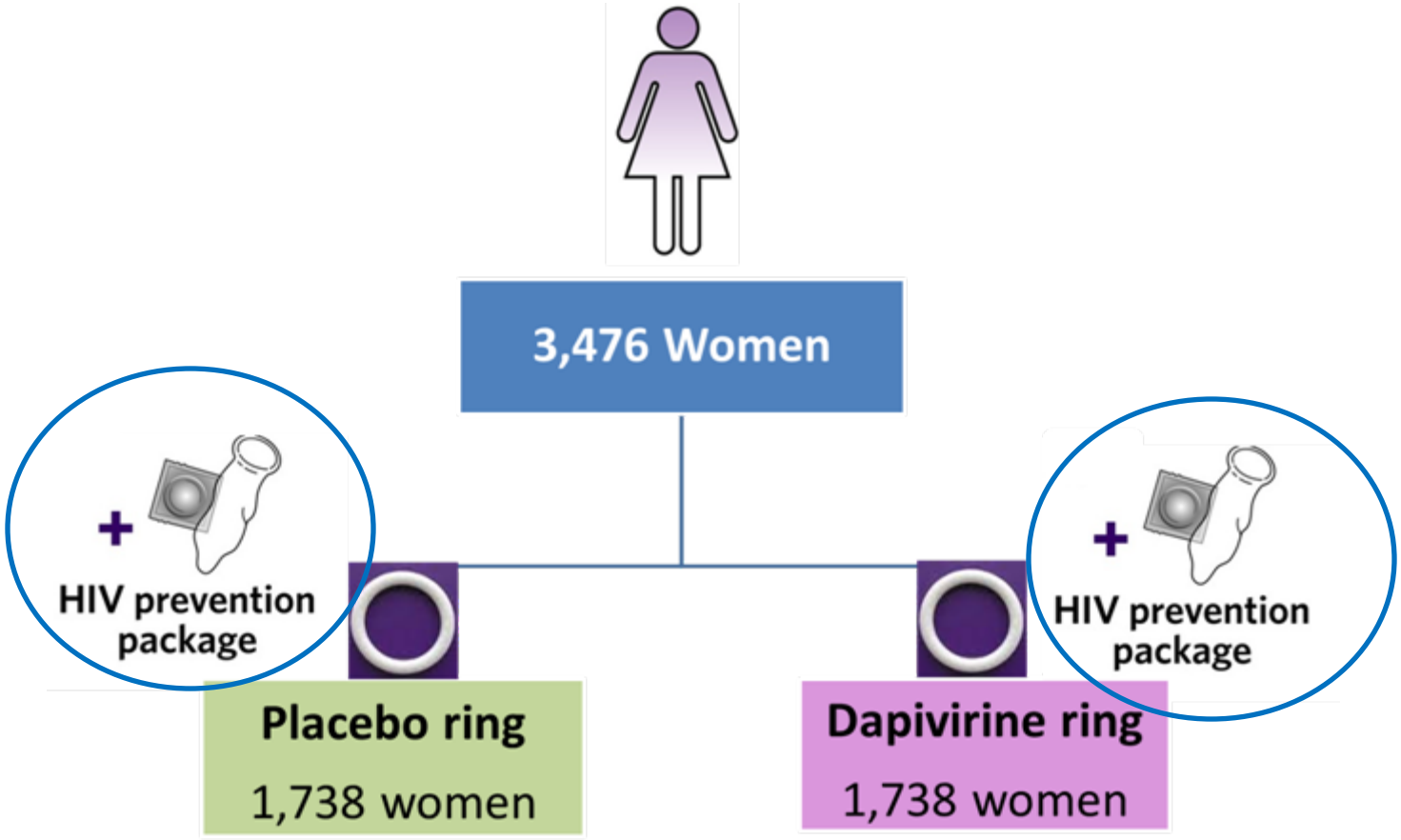
- Participants in a trial are similar in age, risk, etc.
- They are randomly assigned to a study group like a roll of a dice
- Neither the researchers nor the participants knows the group they are in

# Example: ASPIRE Study Design

Women will be randomized to use either a ring containing dapivirine or one with no active drug



# What's an HIV prevention package?



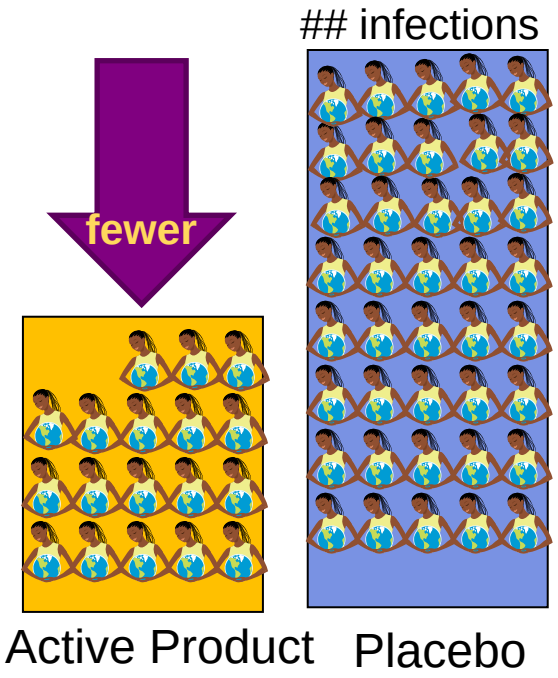
# What's an HIV prevention package?

- Researchers want to make sure that participants have access to prevention methods that we know can work to reduce the risk of HIV
  - Called "standards of prevention"
- All women receive HIV counseling, condoms, risk reduction counseling, and treatment for STIs at each clinic visit.
- Participants are still at risk of HIV infection, because none of these methods are perfect, and the trials are conducted in areas with high HIV rates

# How do we determine efficacy?

- At the end of a study, we compare the number of HIV infections that occurred among women who received an active product with the number of HIV infections that occurred among women in the placebo group

- If there are significantly fewer HIV infections in the group using the active product compared to the placebo, this means it is more effective for reducing the risk of HIV than a placebo



# What if we had an effective product?

- Would we still use a placebo?
- Would the standards of prevention change?

# Alternative study designs

- Say we had an effective product, we might design future studies to compare the known active product to a new, unproven product, instead of a placebo
- In the HIV treatment world, placebo-controlled trials are no longer conducted

# Redefining the standard of prevention

- In the future, it could also be possible to add an active product to the standard prevention package used in a trial
- What is considered “standard” in one country may not be the same in another country, especially if that intervention is not available

# New Questions for HIV Prevention

- When is it no longer ethical to have a placebo group in an HIV prevention study?
  - Is it when a trial has found a product effective?
  - One trial or two trials?
  - How effective?
  - Or when that product has been approved and is available?
- Should the drug or intervention be part of the prevention package?
  - Should HIV prevention study participants receive this new effective prevention product if is not available in the community?
  - Who decides?

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# What if there is an ongoing trial?

If one trial has a significant outcome – either a positive *or* a negative finding, what happens to other trials in the field?

- Should the trial stop testing the product?
- Is there still valuable information to be gained by continuing?
- What decisions need to be made with future trials?

# Responding to External Information

- Several years ago, three research groups started clinical trials to find out whether circumcising adult men could prevent some of them from becoming infected with HIV
- The trials were done in South Africa (in an area known as Orange Farm), Kenya, and Uganda

# Responding to External Information

- The Orange Farm trial stopped early because results were very favorable to circumcision
- Could the other two trials (in Kenya and Uganda) continue ethically?
- The DSMB recommended **continuing** because:
  - Studies were nearly finished and could either agree with or disagree with the Orange Farm result
- Both studies confirmed the result in this case

# Why does a study or an arm of a study stop early?

- Study teams define **stopping rules** before the study starts
- DSMBs reviewing blinded data use these as a guide to determine whether a study should continue, be modified or stop before its scheduled end.
- A Data Safety Monitoring Board (DSMB) is a group of independent experts that conducts routine reviews of blinded data while a trial is ongoing
  - 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

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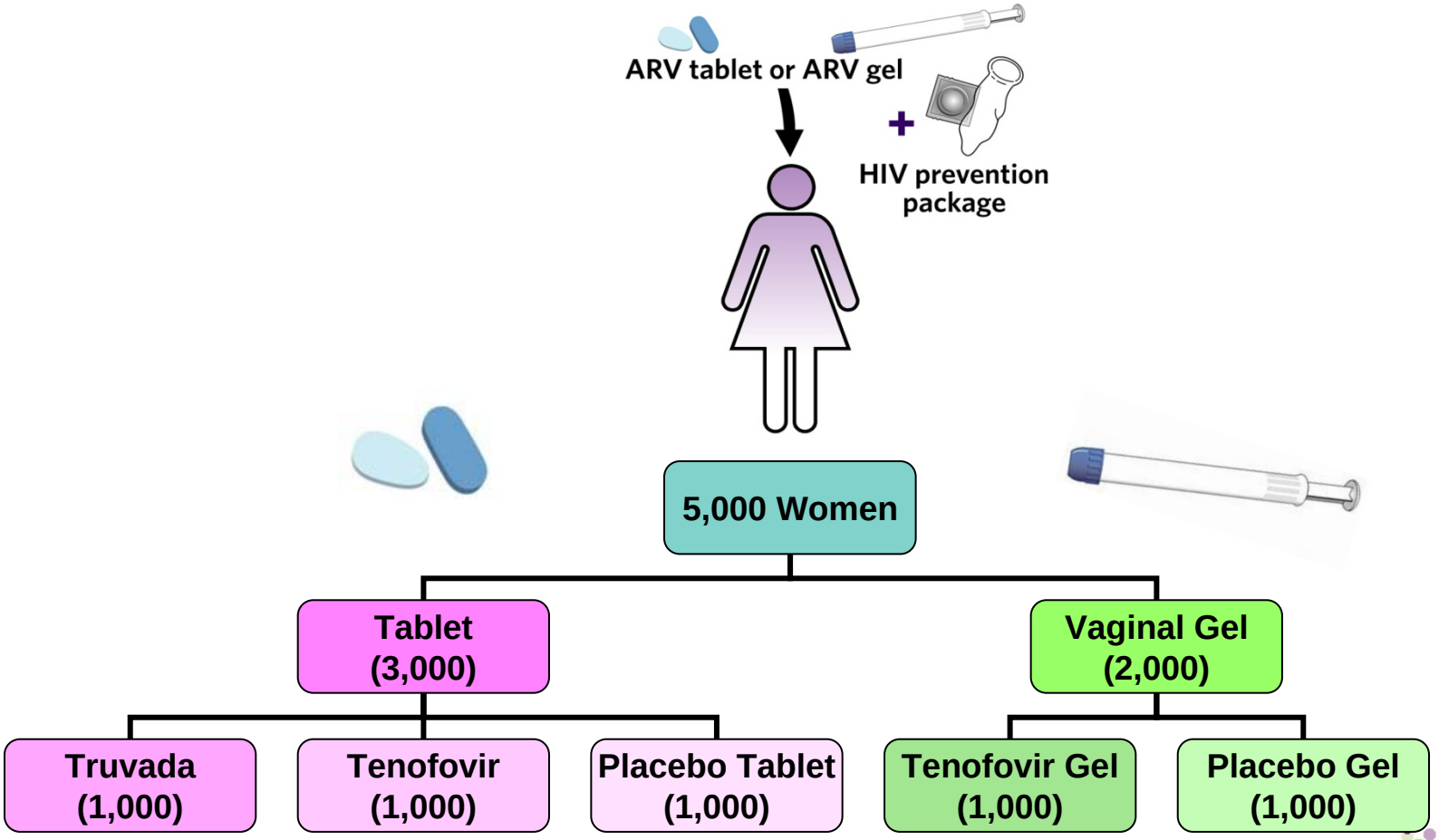
# VOICE
# A Randomized Placebo Controlled Trial




## Five study groups

# DSMB Reviews of VOICE

- There have been 5 face-to-face reviews to date:
  - Dec. 2009; June 2010; Dec. 2010; May 2011; Sept. 2011
  - May and Sept 2011 were reviews of efficacy
  - Until Sept. 16 review, recommended to continue with no changes each time
- Met by conference call soon after results released of Partners PrEP and TDF2 studies (July 2011)
  - Recommended VOICE continue with no changes
  - Decided to hold next full review earlier than planned

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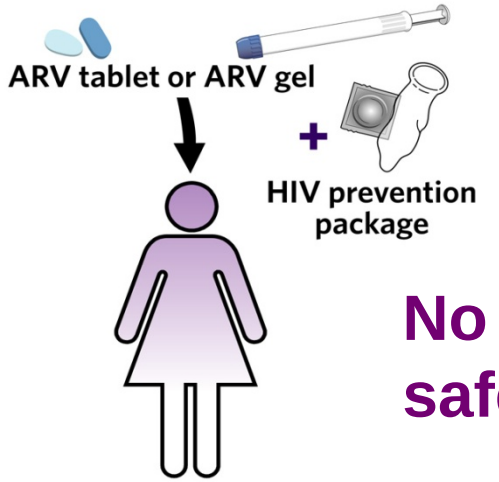
# DSMB Review Sept 16 2011

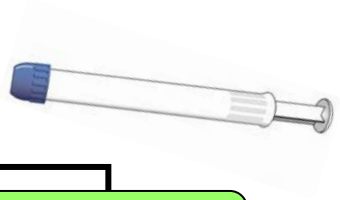
- No safety concerns with any of the products
- Stop testing oral tenofovir tablet because it will not be possible to demonstrate it is effective for reducing HIV in the women in the trial
  - Oral tenofovir no better than a placebo
- The other arms of the study should continue
  - To determine whether oral Truvada tablet or tenofovir gel are effective

# VOICE Study Post DSMB

Sept. 16 DSMB – closed the oral tenofovir arm because not possible to show it is effective in VOICE




**No concerns about safety of any product**



- **5,000 Women**
  - **Tablet (3,000)**
    - **Truvada (1,000)**
    - ~~**Tenofovir (1,000)**~~
    - **Placebo Tablet (1,000)**
  - **Vaginal Gel (2,000)**
    - **Tenofovir Gel (1,000)**
    - **Placebo Gel (1,000)**

**Five study groups**

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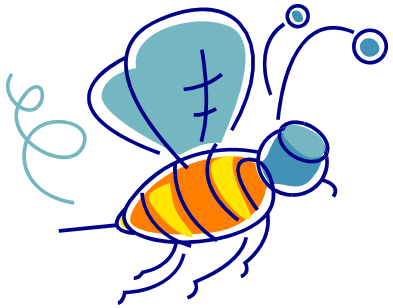
# The DSMB for VOICE

- National Institute of Allergy and Infectious Diseases (NIAID) Prevention Trials DSMB reviews VOICE
  - 10 members, including 3 from Africa (1 of whom is a bioethicist)
- 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).
- **Next review is Nov. 15**

# The buzz about tenofovir gel……

- A lot of talk about what if tenofovir gel is found effective in VOICE or FACTS 001
  - How will this impact ongoing or planned trials?
  - Will this mean no more placebo?
  - Will this mean changing the standard of prevention?
  - When will the gel be available?



- But what if tenofovir gel is <u>not</u> effective?
  - DSMB review or final study results could find this

# But……

- But what if tenofovir gel is not effective?
  - A VOICE DSMB review or the final study results could find this

# VOICE may not find gel effective

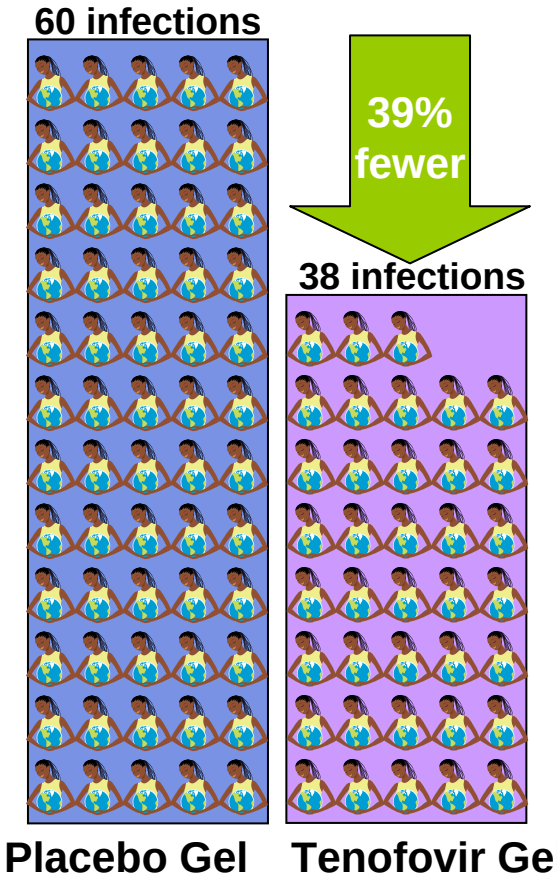
- Remember HPTN 035 and MDP 301?
  - HPTN 035 found PRO 2000 30 % effective but this was not statistically significant
    - Confidence interval 7 to 54 %
  - MDP 301 was a larger Phase III trial that did not find it effective at all
- More than one trial is needed to confirm a result or to help get closer to the truth

# What were the results of CAPRISA 004?

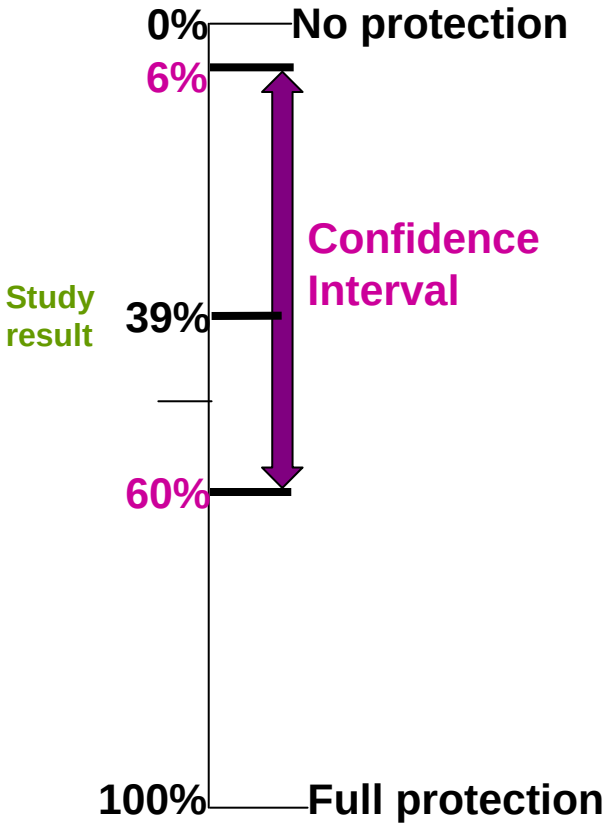
- VOICE and FACTS 001 are hoping to confirm the results of CAPRISA 004
- Tenofovir gel was found to be 39% more effective than placebo gel for protecting against HIV when used before and after sex
- But the true effectiveness may be low as 6% and as high as 60% (confidence interval)

# CAPRISA 004

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

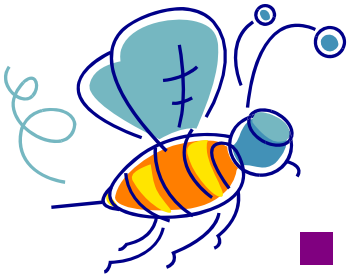



**According to the confidence interval, the true level of risk reduction might be as low as 6% or as high as 60%**



# Managing expectations

- VOICE or FACTS may confirm the results of CAPRISA 004, but that could also mean that these studies find tenofovir gel reduces the risk of HIV by only 6%, 15% or 20%
- Would tenofovir gel still be considered for approval?
- We need to be sure that in all the buzz about tenofovir gel we include this as a possibility
- Important to manage expectations



# Questions about tenofovir gel

**What if it is effective?**

- Will placebo-controlled trials still be ethical?
- Should it be introduced into the standard HIV prevention package?
- What if available in one country and not another?
- How will all this affect ASPIRE?

**What if it's not effective?**

# Acknowledgements

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