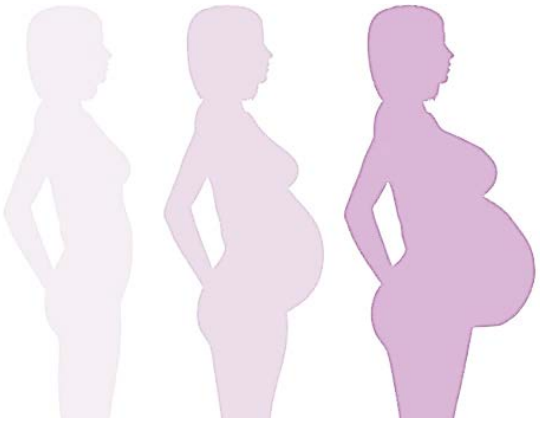
MTN-042:Key Questions



Stakeholders Consultation
5-6 April 2018
Johannesburg, South Africa

MTN
microbicide trials network

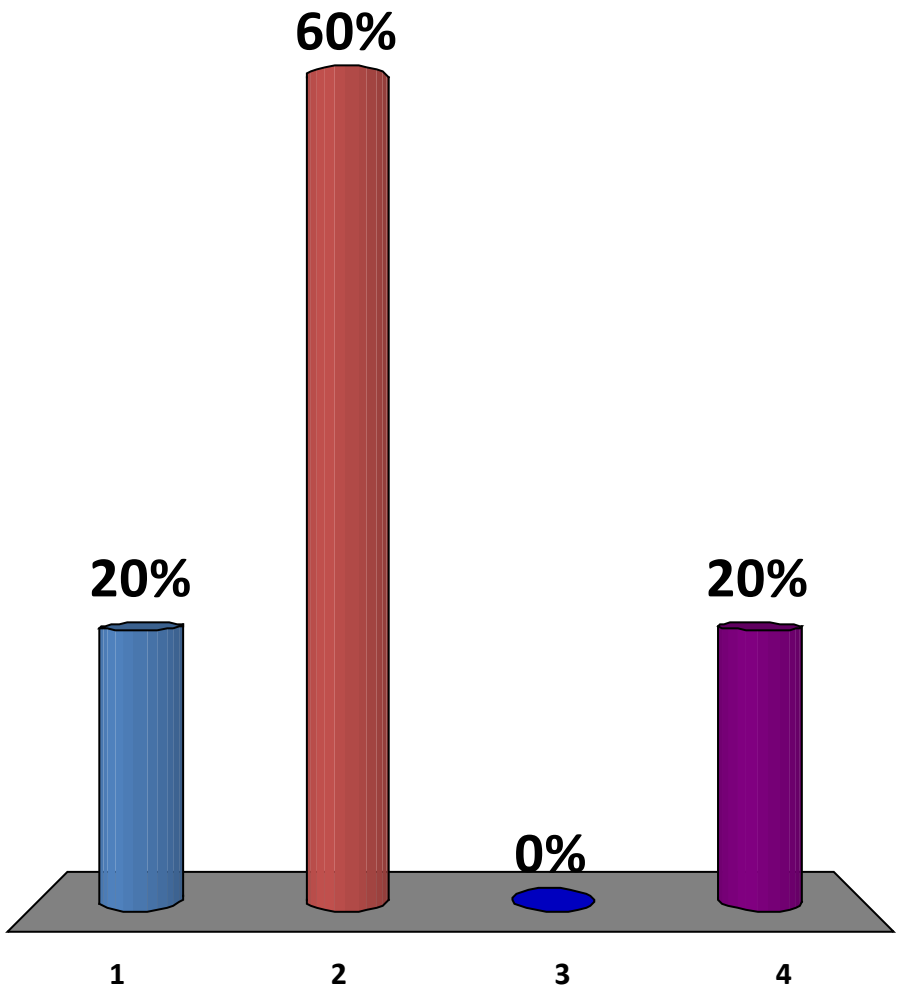
Audio Response System

- Do you see a green light on your card?
- To vote, point the card at the computer and press a button.
- One person, one vote!
- You can change your mind. The last response will be recorded

Let's Practice

Before coming to this meeting, I….

1. Read every word of the protocol front to back
2. Looked at the summary page only
3. Printed the document (It's a start!)
4. I have more interesting things to read



MTN-042:
What do you think?

Context

- Women are at very high risk of acquiring HIV during pregnancy
- PrEP is approved in a number of African countries, though guidelines differ with respect to use during pregnancy
  - WHO supports its use, and some countries have guidelines that are in accordance
  - South Africa is hesitant to recommend until more data is available
  - Use of PrEP during pregnancy is considered off-label – there is not a labeling indication.
- The dapivirine ring is a new HIV prevention method
  - Regulatory approval is being sought, although this would not be for pregnant women

MTN-042

- MTN-042 intends to evaluate both PrEP and the vaginal ring in women during pregnancy
- Main questions to be asked:
  - Are PrEP and the dapivirine ring safe to use by women during pregnancy?
  - How is the active drug in each product taken up in the body in pregnant women? (i.e., pharmacokinetics, or PK)
  - Is use of these products during pregnancy safe for the pregnancy and babies?
- Another study – IMPAACT 2009 – will evaluate PrEP among pregnant adolescent girls and young women

MTN microbicide trials network

IMPAACT 2009
n= 300 (200 on TDF/FTC)

MTN 042
n=750 (n=250 on TDF/FTC, 500 on ring

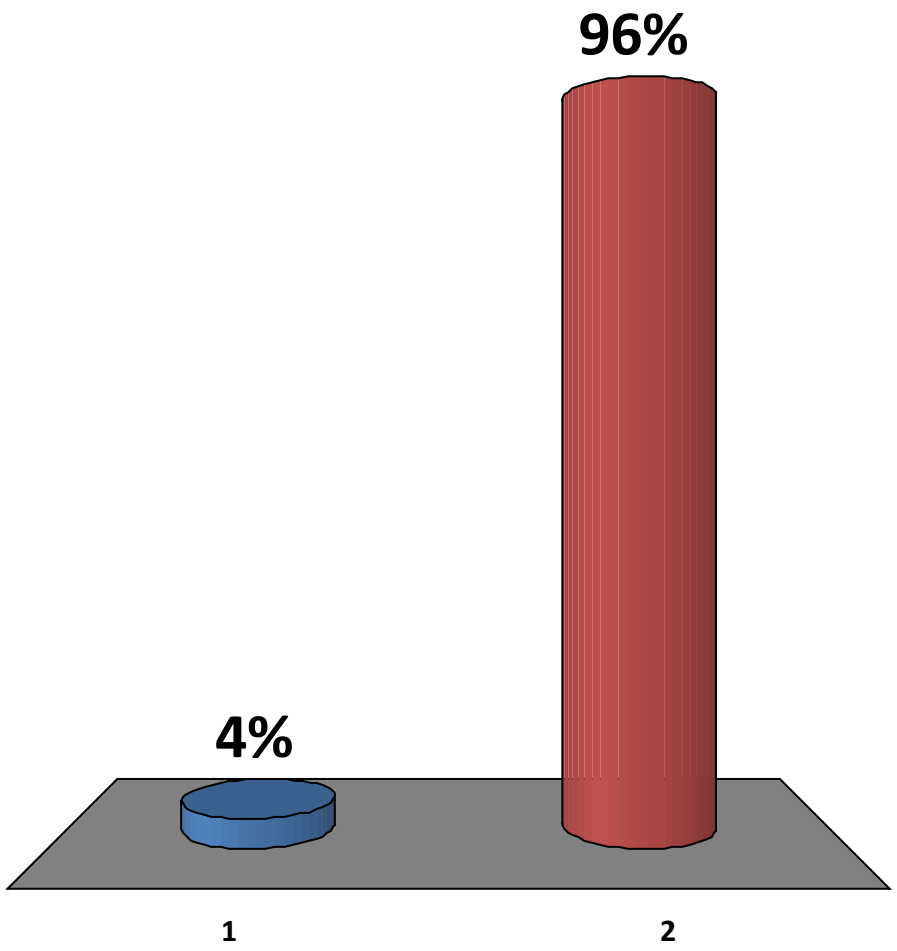
Both studies evaluate safety, adherence, PK , feasibility, acceptability
Both contribute to the body of evidence required around oral PrEP in pregnancy/postpartum

- PK and adherence component (40 women) more intense-observed dosing
- Pregnancy and postpartum cohort
- Young women 16-24 years
- Women self-select using PrEP or not (control group)
- Enrollment 14-24 weeks & 6-12 weeks post partum
- Bone scans of women & infants
- Study completion 26 weeks postpartum
- Evaluation of impact on microbiome

- PK and adherence evaluated-self report, plasma and ring levels
- All women 18-40 years
- Gestational age de-escalating to 12 weeks
- Randomisation 2:1 to dapivirine ring and oral PrEP (truvada)
- Control group=PrEP:
- Expanded birth outcomes of interest given local vaginal product
- DPV levels in pregnant women and infants
- Study completion 6 weeks postpartum

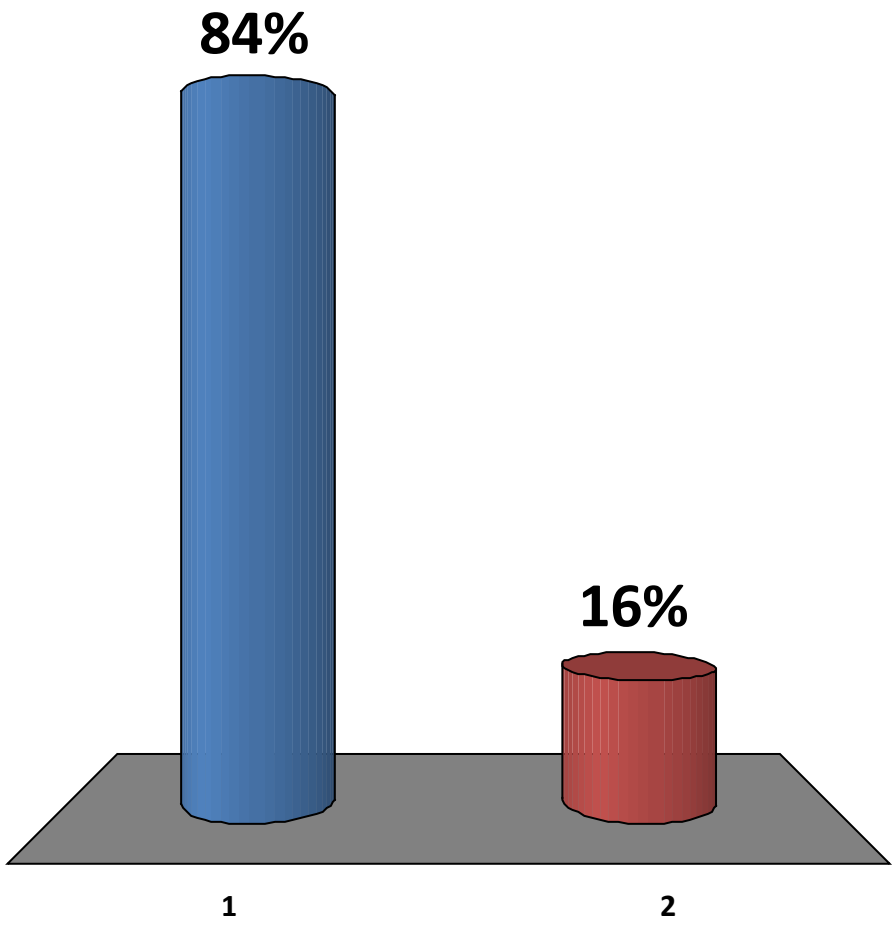
Given the efficacy of oral PrEP do we even need a study looking at the vaginal ring in pregnancy?

1. No, PrEP works
2. Yes



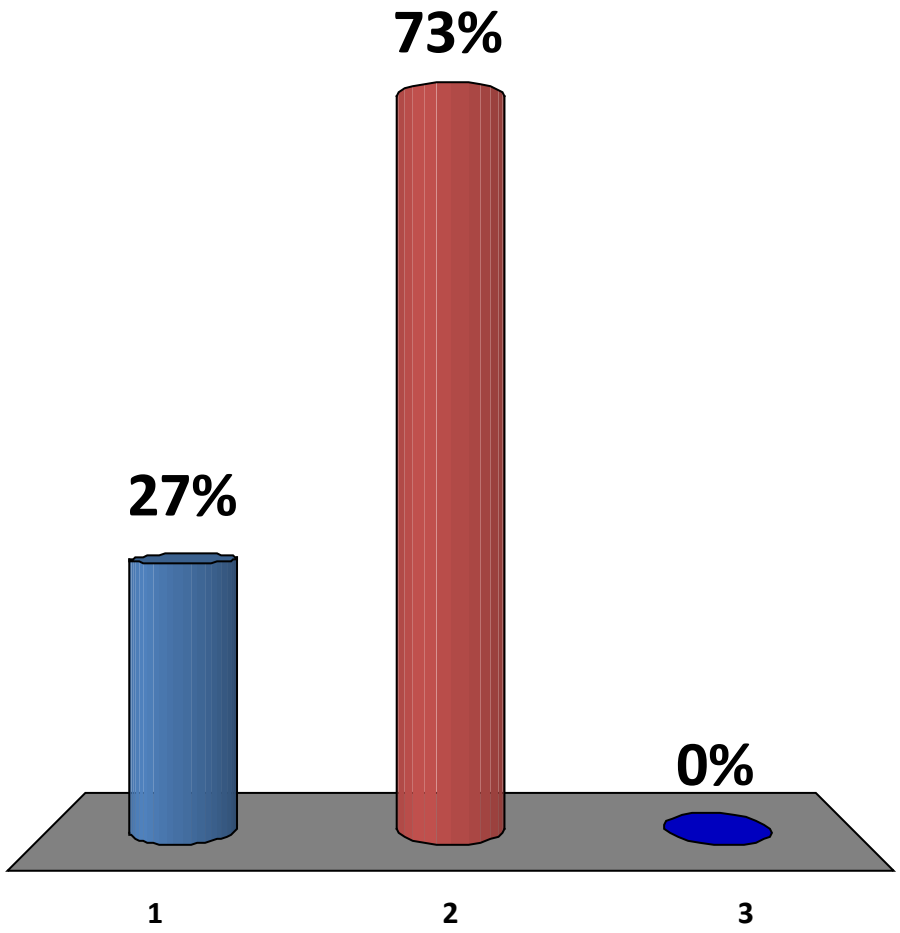
Considering the objectives of IMPAACT, is *more* safety data on oral PrEP *really* needed?

1. Yes
2. No



Are we asking the right questions in MTN-042?

1. Yes
2. For the most part
3. No, the study is way off base



Safety

Layers of safety

- Safety monitoring of participants begins at the site level
- A Protocol Safety Review Team (PSRT) is responsible for overseeing safety of trial participants on a regular and expedited basis as needed
  - Significant symptoms and findings identified at site are submitted to the Data Center
  - Once a month the PSRT reviews the events submitted over the past month looking for trends or concerns
  - Serious events (adverse events) are flagged by the Data Center and the PSRT is notified immediately

Layers of safety (continued)

- For MTN-042, an Interim Review Panel will conduct reviews of safety data between each cohort before deciding whether to proceed
  - Specific criteria are under discussion, but are likely to include
    - Gestational age at delivery
    - Uterine infections
    - Hemorrhage
    - Pre-eclampsia
    - Neonatal death
    - Maternal death
    - Serious adverse events for mother or baby

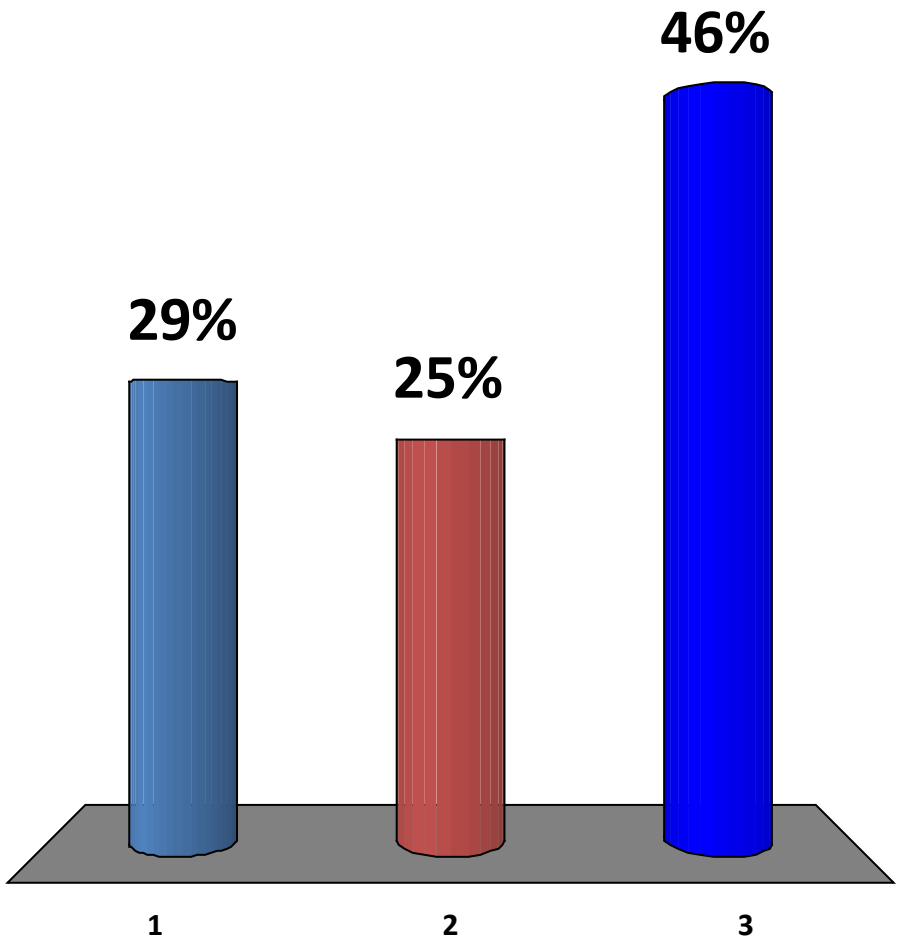
Assessing safety between cohorts

Challenges:

- There is no placebo arm
- Rates of adverse events (participant complaints, findings, lab abnormalities) will be assessed between the ring and PrEP group
- Rates of adverse events (participant complaints, findings, lab abnormalities) will be considered in light of known complication rates, though these data are lacking

Does the study provide enough safety oversight?

1. Yes
2. No, much more is needed
3. It is a start, but more could be done.



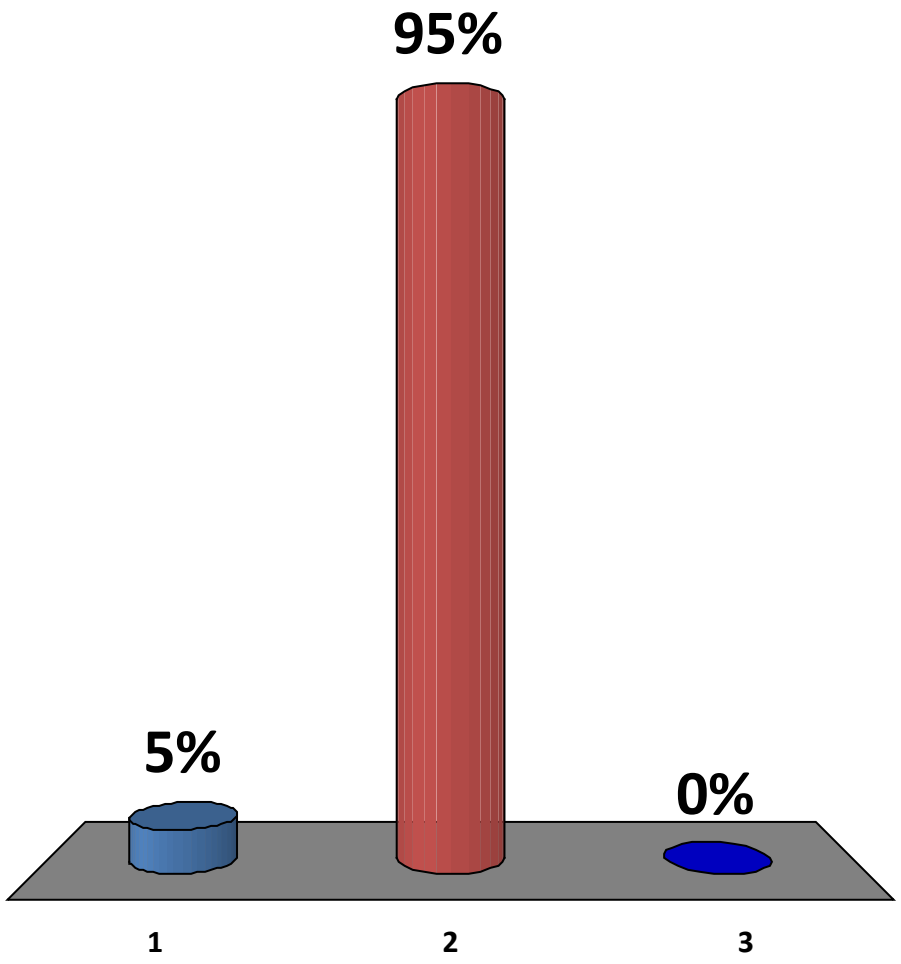
The Interim Review Panel

Currently, the suggested makeup is:

- 1 community representative
- 1 obstetrician from Sub-Saharan Africa
- 1 obstetrician from the United States
- 1 pediatrician from Sub-Saharan Africa or the United States
- 1 ethicist
- 1 statistician
- 1 maternal-child health expert from the public health sector

I think……

1. This composition is perfect
2. I would suggest an addition
3. An Interim Review Panel is unnecessary



Interim review findings

- Interim review findings will be reported to IRBs/ECs, potential participants enrolled into the next cohort, community and other stakeholders

  - Other expectations?
  - What will be the obligations of the study team?
  - Will consents need to be modified?

Imagine these scenarios…

- A participant presents to the clinic for a study visit and a fetal heart tones are absent. She is diagnosed with a stillbirth at 38 weeks. She delivers a normally appearing baby boy. There is no clear explanation for the fetal death.
- A participant at 38 weeks is found to have very high blood pressure and protein in her urine. She is referred to the local clinic for evaluation of pre-eclampsia and is induced later that day.

Known complications of pregnancy

- To what extent do you think this will be a problem in terms of perceptions of community members, health care providers and participants themselves?

- How can we mitigate concerns?