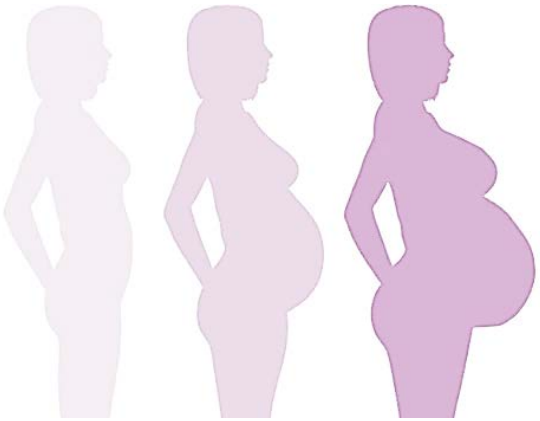
MTN-042: DELIVER



Katie Bunge MD, MPH
On behalf of the MTN-042 protocol team
MTN Annual Meeting
February 11, 2019

HIV prevention during pregnancy: We know there's a need

- Women are at very high risk of acquiring HIV during pregnancy
- They need methods of protection that they know will be safe to both them and their babies
- Protecting mothers from getting infected also means protecting against mother-to-child transmission

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Two HIV prevention methods

- PrEP is daily use of an ARV tablet (Truvada)
  - PrEP is approved in a number of African countries, though guidelines differ with respect to use during pregnancy
    - WHO supports its use in pregnancy
    - South Africa is hesitant to recommend until more data is available
- The dapivirine ring is used every month
  - Regulatory approval is being sought, although this would not be for pregnant women

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Phase III Pooled Analysis: Pregnancy*

Pregnancy Outcome	Dapivirine Vaginal Ring n (%)	Placebo Vaginal Ring n (%)
Number of pregnancies	137	117
Live birth	80 (58.4%)	72 (61.5%)
Spontaneous abortion	28 (20.4%)	24 (20.5%)
Non-therapeutic abortion/elective termination of pregnancy	22 (16.1%)	15 (12.8%)
Stillbirth/intrauterine death	2 (1.5%)	3 (2.6%)
Ectopic Pregnancy	2 (1.5%)	1 (0.9%)
Maternal death	None	1 (0.9%)
Unknown	3 (2.2%)	1 (0.9%)

*As of 30 Sept 2017

Courtesy J. Steytler, IPM

Phase III Data: Congenital Anomalies

Anomaly Medical Concept	IPM 027		MTN-020	
	DPV Ring N=45 n (%)	PLA Ring N=21 n (%)	DPV Ring N=92 n (%)	PLA Ring N=96 n (%)
• Congenital inguinal hernia (bulge in the groin area)			1 (1.1%)	
• Congenital umbilical hernia (bulge at the belly button)			3 (3.3%)	3 (3.1%)
• Multiple congenital abnormalities		1 (4.8%)		
• Plagiocephaly (flattening of the head)			1 (1.1%)	
• Polydactyly (extra fingers or toes)	1 (2.2%)			1 (1%)
• Skeletal dysplasia (short legs and arms)			1 (1.1%)	

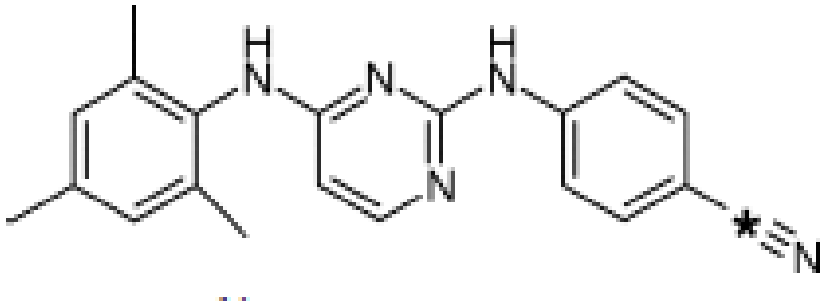
Abbreviations:
DPV = dapivirine
PLA = placebo
N = overall number of pregnancies per treatment group
n = number of pregnancies with anomaly

*As of 30 Sept 2017

Courtesy J. Steytler, IPM

The dapivirine ring and pregnancy

- The drug



- The physical ring

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The drug

- Animal studies are reassuring
  - No effects on embryo-fetal development in rabbits up to 90mg/kg or maternally non-toxic doses up to 20mg/kg in rats
    - Exposure levels > 1000-fold higher than expected human systemic exposure
- Systemic exposure with the vaginal ring is minimal
  - Plasma dapivirine concentrations after a month of use are measured in pg/mL

The physical ring

- No reason to think that a physical silicone ring should cause a problem
- Theoretical concerns center around change in microflora and cervical disruption
  - MTN-023 and MTN-024 demonstrate no concerning changes in microflora with dapivirine vaginal ring use
  - Pessaries (vaginal silicone products) are currently used during pregnancy (and have been used since the 1960s!)

MTN-042 at a glance

- A Phase 3B open-label study designed to answer these and other questions:
  - Are PrEP and the dapivirine ring safe to use for women during pregnancy?
  - How is the active drug in each product taken up in the body in pregnant women?
  - Is use of these products during pregnancy safe for the pregnancy and babies?
- Conducted by the Microbicide Trials Network (MTN) and led by:
  - Protocol Chairs: **Bonus Makanani** (College of Medicine, University of Malawi) and **Katie Bunge** (University of Pittsburgh) Protocol Co-Chair: **Lee Fairlie** (Wits Reproductive Health and HIV Institute)
- Funded by the US National Institutes of Health

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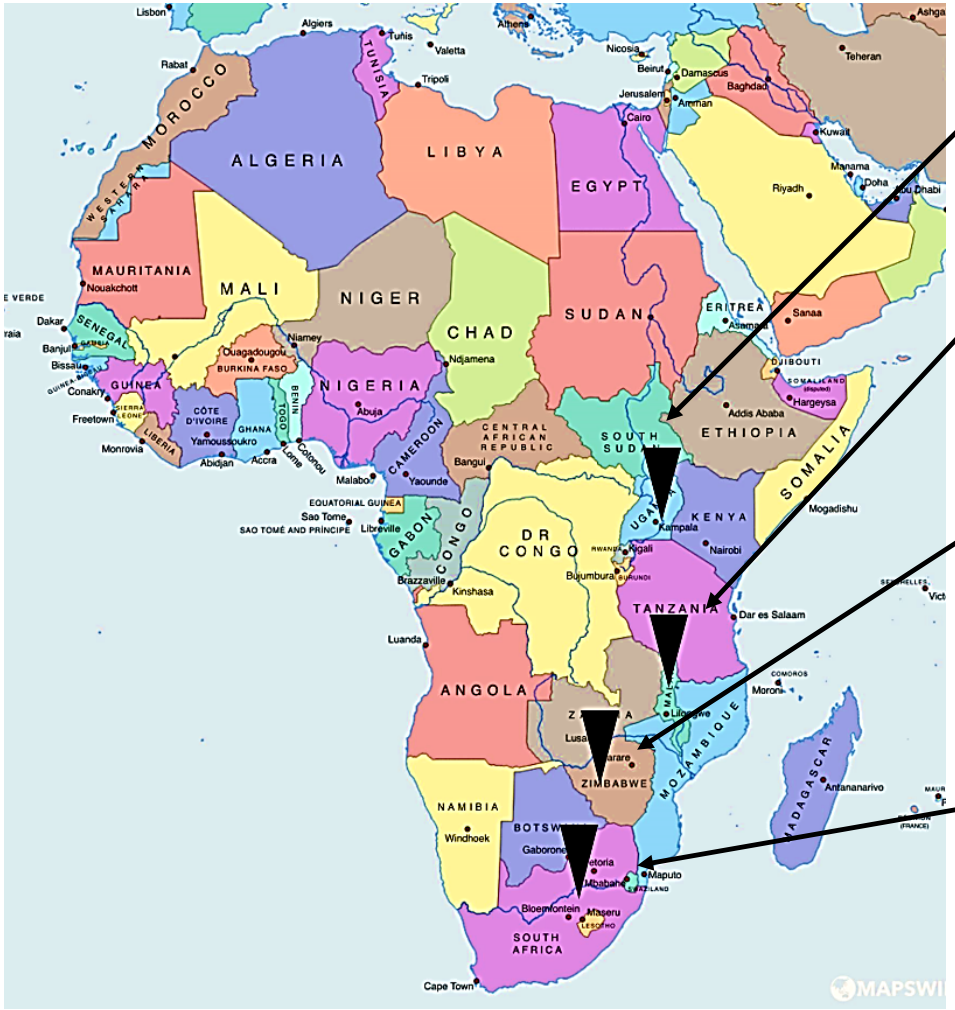
Will enroll 750 women at 4 sites in 4 countries



Uganda (Kampala)
MU-JHU Research Collaboration

Malawi (Blantyre)
College of Medicine-John Hopkins University Research Project

Zimbabwe (Harare)
University of Zimbabwe College of Health Sciences Clinical Trials Research Centre – Zengeza

South Africa (Johannesburg)
Wits RHI Shandukani Research Centre

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Primary objectives and endpoints

- Maternal safety
  - All serious adverse events and all Grade 3 or higher adverse events
- Infant safety
  - All serious adverse events and all Grade 3 or higher adverse events
- Pregnancy outcomes
  - Full term live birth (≥37 0/7 weeks)
  - Premature live birth (<37 0/7 weeks)
  - Pregnancy loss (≥20 0/7 weeks)
  - Pregnancy loss (<20 0/7 weeks)

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Secondary objectives and endpoints

- Frequency of the following pregnancy complications
  - Hypertensive disorders of pregnancy
  - Chorioamnionitis
  - Puerperal sepsis and endometritis
  - Peripartum and postpartum hemorrhage
  - Preterm premature rupture of membranes (PROM)
  - Fever of unclear etiology

- Infant Drug Levels
  - Infant blood tenofovir diphosphate (TFV-DP) and emtricitabine triphosphate (FTC-TP) concentrations
  - Infant plasma DPV concentrations

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Secondary objectives and endpoints

- Adherence
  - Maternal blood TFV-DP and FTC-TP concentrations
  - Maternal plasma DPV concentrations
  - Participant report of frequency of study product use
  - Residual drug levels in returned VRs
- Acceptability
  - Self-reported attitudes about study product attributes and willingness to use study product during pregnancy
  - Proportion of participants who find the study product to be at least as acceptable as other HIV prevention methods

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Who may participate?

- Healthy, HIV-uninfected women 18-40 years old with an uncomplicated pregnancy
- Must be within the window of the particular gestational age being enrolled at that time
  - Group 1 – 36+ weeks pregnant
  - Group 2 – 30-35 weeks pregnant
  - Group 3 – 20-29 weeks pregnant
  - Group 4 – 12-19 weeks pregnant
- Must be will willing to be randomized to use either daily PrEP or the monthly vaginal ring during the study
- May not plan to access and/or use oral PrEP outside the study
- Must be planning to deliver her baby at a health center or hospital

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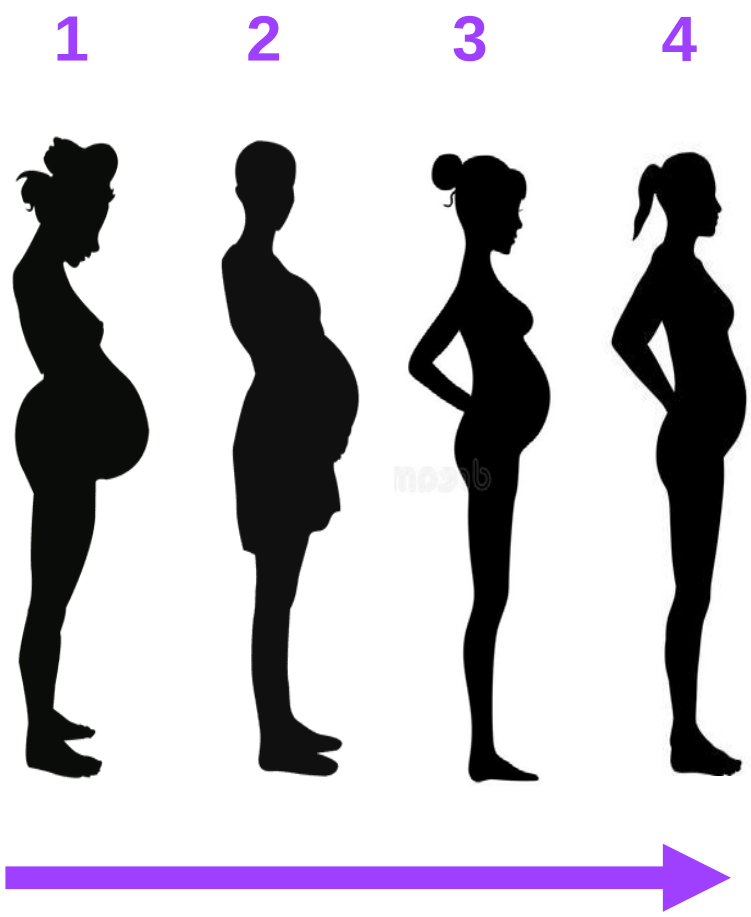
Study design



- Women will be randomly assigned to use either the monthly ring or daily PrEP
  - For every one woman assigned to use PrEP, two will use the ring
- Will be conducted in a stepwise fashion starting with women late in pregnancy
- Interim reviews will be conducted before deciding to enroll the next group of women

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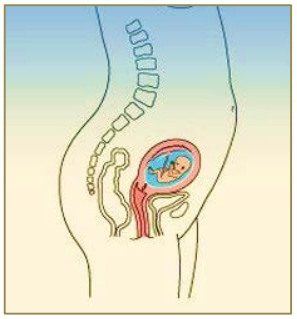
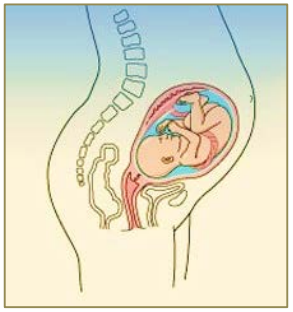
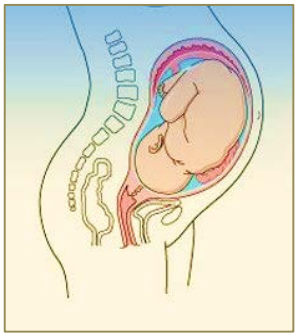
Why Different Groups? Different Concerns at Different Stages



- First Trimester – Weeks 1- 12 (Months 1-3)
  - Conception and baby's organs develop
  - Potential concerns: miscarriage, birth defects



- Second Trimester – Weeks 13-28 (Months 4-6)
  - Baby grows
  - Potential concerns: poor growth, early delivery



- Third Trimester – Weeks 28+ (Months 7-9)
  - Baby grows, labor
  - Potential concerns: early delivery, infection, blood pressure issues

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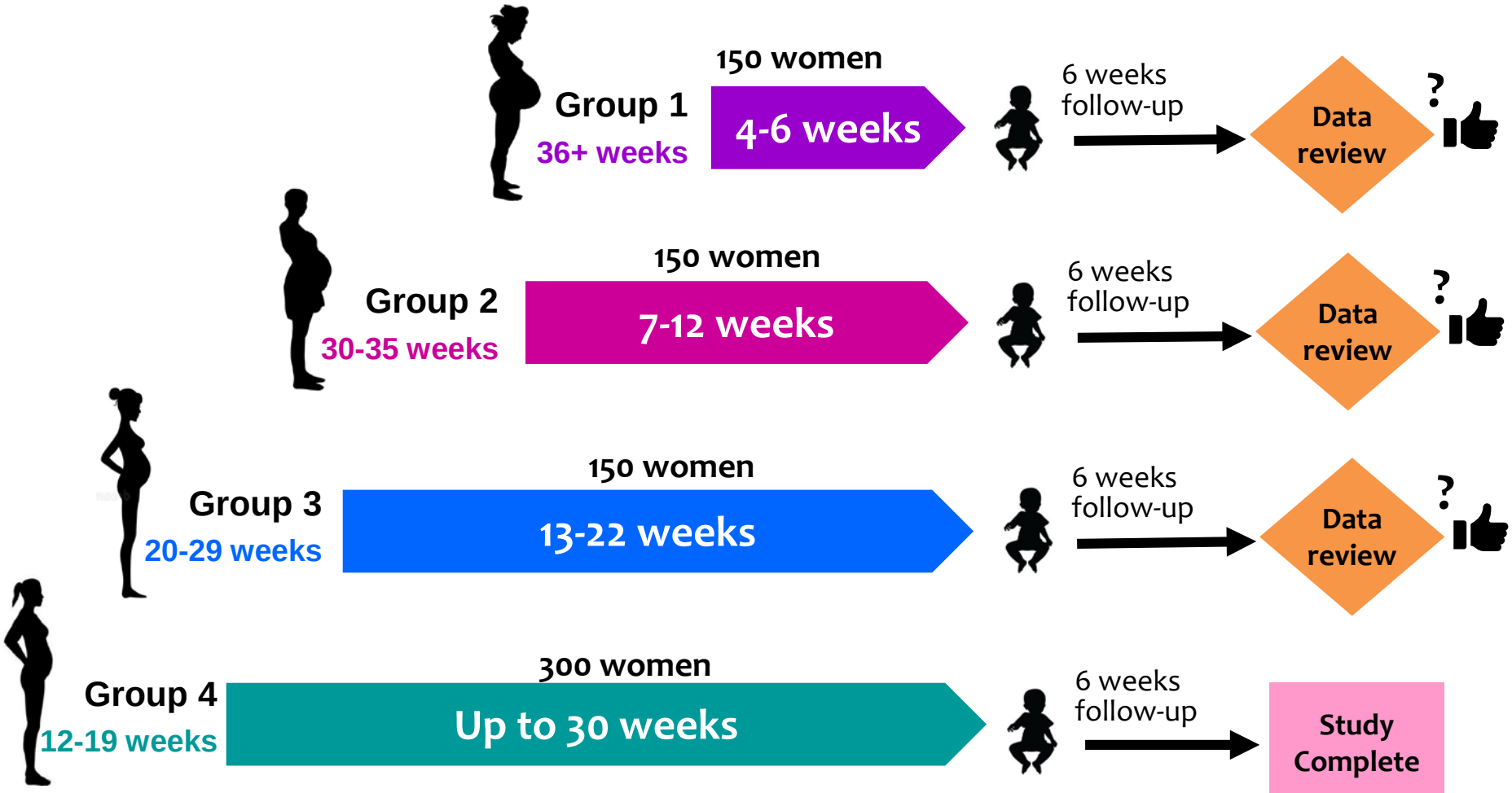
Each group will use the ring or PrEP a longer time

		number	Ring or PrEP?	Approximately how long?
Group 1 **36+ weeks**		150	100 will use the ring 50 will use PrEP	4-6 weeks
Group 2 **30-35 weeks**		150	100 will use the ring 50 will use PrEP	7-12 weeks
Group 3 **20-29 weeks**		150	100 will use the ring 50 will use PrEP	13-22 weeks
Group 4 **12-19 weeks**		300	200 will use the ring 100 will use PrEP	Up to 30 weeks

A stepwise approach with interim reviews



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

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Ensuring safety at several levels

- Site clinicians will monitor the safety and wellbeing of participants at each visit
  - MTN Study safety physicians will conduct frequent reviews of data
- Ongoing oversight by local IRBs/ECs
- For MTN-042, study outcomes will be reviewed by an Interim Safety Review Panel at the conclusion of each cohort, and enrollment of the next group will not proceed if there are any concerns

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Seeking Feedback

- Stakeholders meeting, Johannesburg April 5-6, 2018
- MTN hosted in partnership with AVAC
- Reviewed existing safety data on two products and an early version of the protocol

Who attended?

- Stakeholders from each trial site country:
  - EC/IRB Chairs and Members
  - Ministries of Health representatives
  - National Drug Regulatory Authority representatives
  - Civil society representatives
- Global and regional stakeholders:
  - WHO
  - Leading researchers
- As well as:
  - IPM
  - MTN-041 Protocol Chair and Co-Chair
  - MTN-042 site IoRs

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Major feedback received

- General support for the MTN-042 study
- General agreement that more data is needed to support the safety of oral PrEP
- General agreement that the dapivirine ring should be studied in pregnant women, and the time is right to move forward
- Lots of specific suggestions

Major feedback incorporated

- Follow infants through a year of life
- Require ultrasound for gestational age determination
- Create strong linkages with care providers to ensure that "influencers" are aware of the study and do not advise women not to use study products
- Include mental health evaluation as part of the health evaluation
- Harmonize the definitions of maternal and neonatal outcomes with standardized definitions developed for maternal vaccination studies
- Prepare for poor obstetrical outcomes by sensitizing the community and understanding back ground rates

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Next steps

- Anticipated release of Protocol V1.0 in February 2019
- Activation of first site targeted for end of Q3/beginning of Q4 2019
- Goal will be to work expeditiously at sites to resolve data queries prior to the pause periods and then provide safety data for the Interim Review Panel as soon quickly as possible

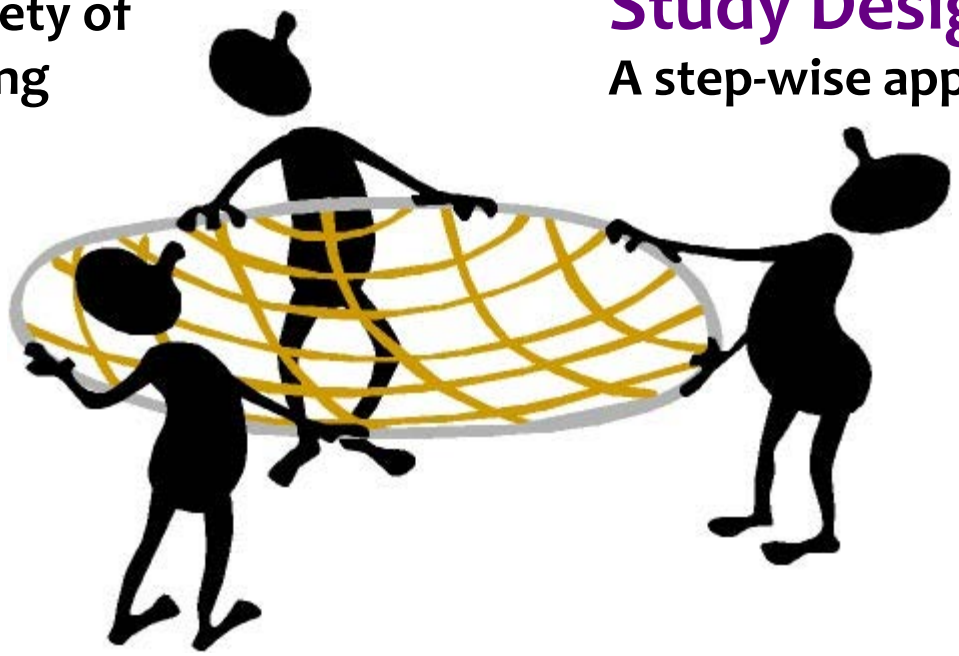
MTN-042: A Three-Way Safety Net for Two

Study Objective

Understanding the safety of PrEP and the ring during pregnancy

Study Design

A step-wise approach



Study Conduct

Multiple measures to ensure safe participation

So that women can be protected against HIV at all times, including during pregnancy, with methods that are safe for them and their babies

Acknowledgements

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