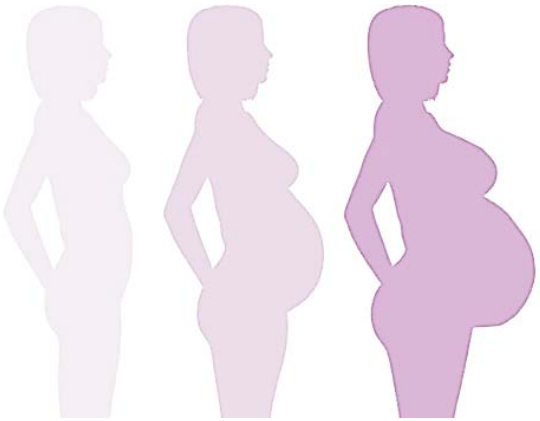
MTN-042: An Overview



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Stakeholders Consultation
5-6 April 2018
Johannesburg, South Africa

• Overview

- Background and rationale
- Design and objectives
- Who may participate and what's involved
- Safety monitoring
- Timeline

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Making a case for studies involving pregnant women

- Drugs are often contraindicated in pregnant women because data to support their use in this population is lacking
  - Usually, a woman in a clinical trial must not be pregnant and must use contraception throughout
  - She must immediately stop using the product if she gets pregnant
  - These measures are intended to avoid potential risk to the developing fetus
- Drugs are used during pregnancy anyway
  - Now the uncertainty sits with the health care provider

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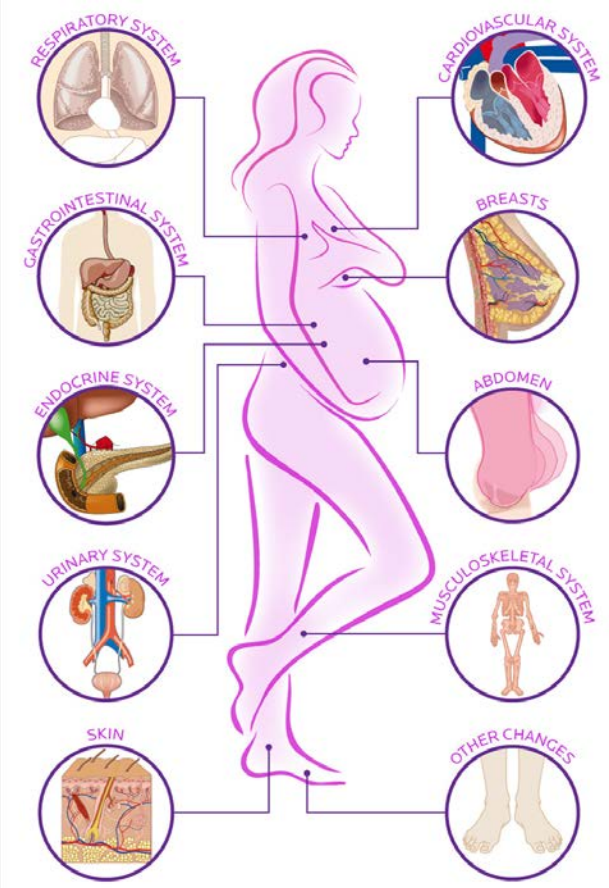
Why we should study drugs in pregnancy rather than leave safety to chance



- The body undergoes many changes during pregnancy
- A drug may work differently in a woman who's pregnant
- It may pass to the placenta and cause harm to the developing fetus or put the pregnancy (mother/fetus) at risk

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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)
  - Approved in a number of African countries
  - Guidelines differ: Some say it's OK during pregnancy, others want more data

- The dapivirine ring is used every month
  - Found safe and to reduce HIV risk in two Phase III trials – ASPIRE and The Ring Study
  - The International Partnership for Microbicides (IPM) is seeking its regulatory approval– would not be for pregnant women

- Regulators and national programs need information about the safety of a drug in pregnancy before deciding about its use in pregnant women

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 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?
- Conducted by the Microbicide Trials Network (MTN) and led by:
  - Protocol Chairs: **Katie Bunge** (University of Pittsburgh) and **Bonus Makanani** (College of Medicine, University of Malawi)
  - Protocol Co-Chair: **Lee Fairlie** (Wits Reproductive Health and HIV Institute)
- Funded by the US National Institutes of Health

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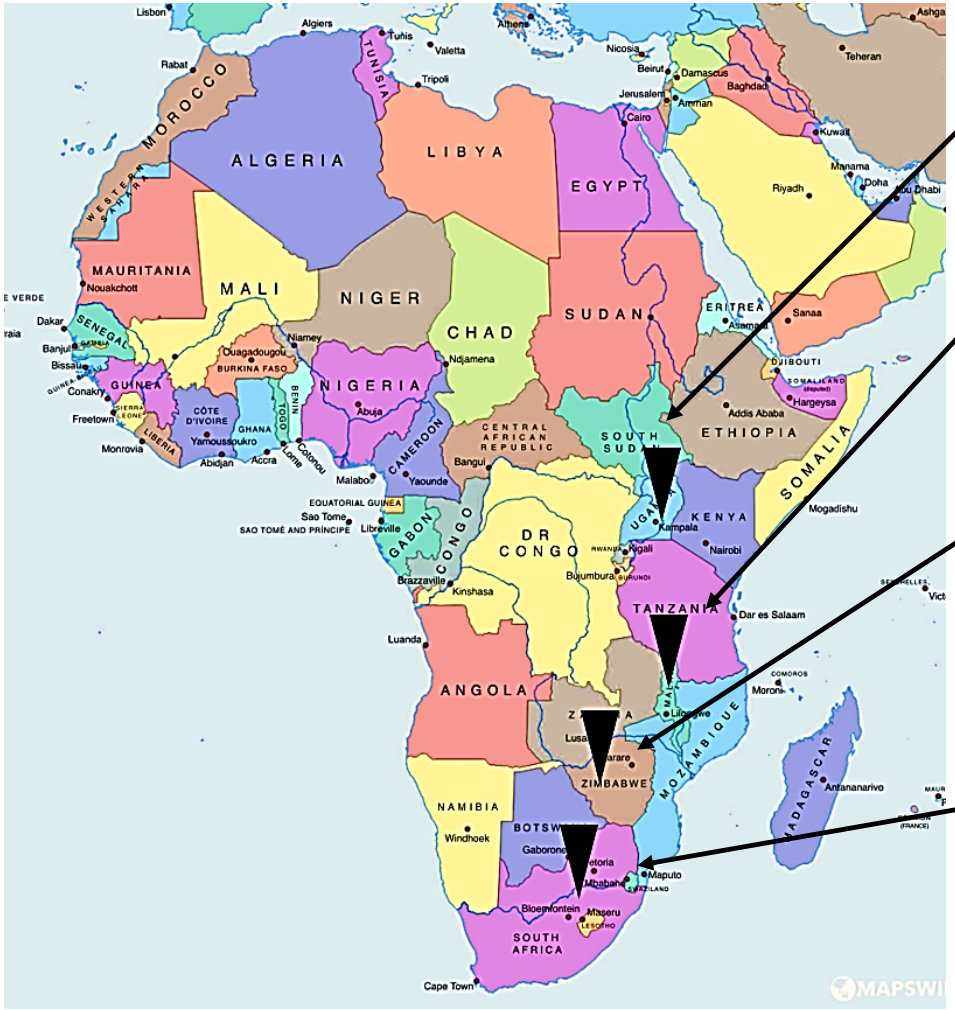
Will enroll 750 women at 4 sites in 4 countries



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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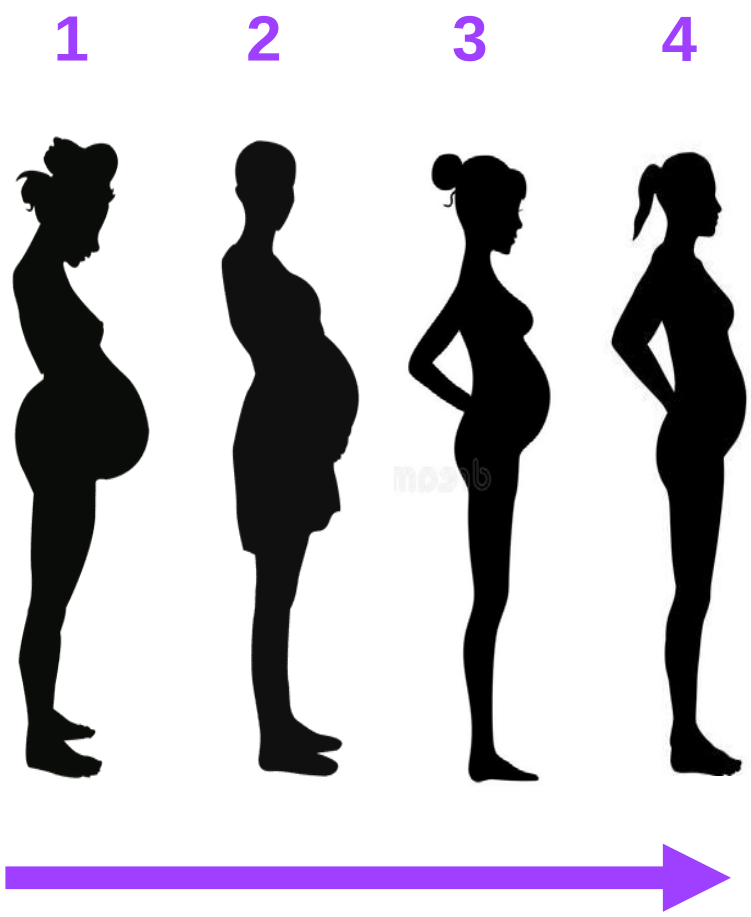
Study design



- 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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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

The study's primary objectives

Primary objectives are the main questions being asked

Primary Objective

- To describe the **maternal, peri-partum, and infant safety profile** associated with use of PrEP and the dapivirine ring during pregnancy

Getting the answer

- **Maternal safety**
  - Symptoms a participant reports (e.g. headache)
  - Problems that a clinician finds on exam (e.g. high blood pressure)
  - Abnormalities in lab tests (e.g. low hemoglobin)
- **Peri-partum complications**
- **Infant safety**
  - Problems the mother reports, clinician observes or found in lab tests

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Secondary Objectives

Secondary Objective #1

- To describe **pregnancy outcomes** associated with use of PrEP and the dapivirine ring during pregnancy

Getting the answer

- Document the number of:
  - Full term live births (≥37 weeks)
  - Premature live births (<37 weeks)
  - Stillbirths (≥20 weeks)
  - Spontaneous abortions (<20 weeks)

Secondary Objective #2

- To describe **how the body takes up the active drug** (pharmacokinetics) in PrEP and the dapivirine ring during pregnancy

Getting the answer

- Tenofovir drug concentrations in maternal blood plasma and red blood cells
- Dapivirine drug concentrations in maternal blood plasma
- Drug concentrations in infant blood

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Secondary Objectives

Secondary Objective #3

- To characterize **adherence –** how well women are able to use daily PrEP and the monthly dapivirine ring during pregnancy

Getting the answer

- Tests of blood to determine the presence of drug
- Tests of returned rings to determine amount of leftover drug remaining
- What participants report

Secondary Objective #4

- To characterize **acceptability –** do women find using PrEP and the ring acceptable during pregnancy?

Getting the answer

- Participants' attitudes as reported in questionnaires and interviews

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Exploratory Objectives

Exploratory Objective #1

- To describe the **vaginal microbiome (good and bad bacteria in the vagina)** in participants using oral PrEP and the vaginal ring during pregnancy

Getting the answer

- In genital swab samples, tests to determine whether there are changes in the balance of good and bad bacteria and markers of inflammation (immune system activity) that may be indicators of safety

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Who may participate?

- Healthy, HIV-uninfected women 18-45 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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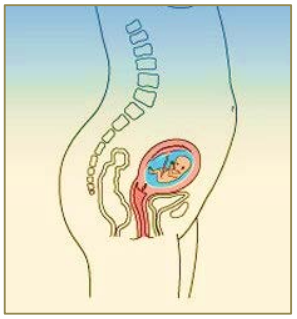
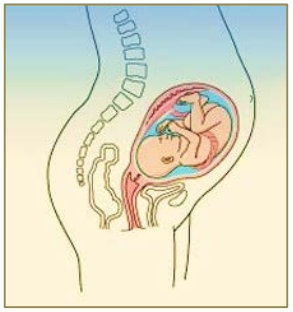
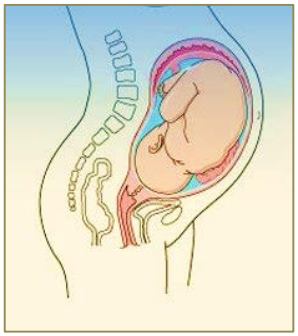
Why different groups? Different concerns at different stages



- 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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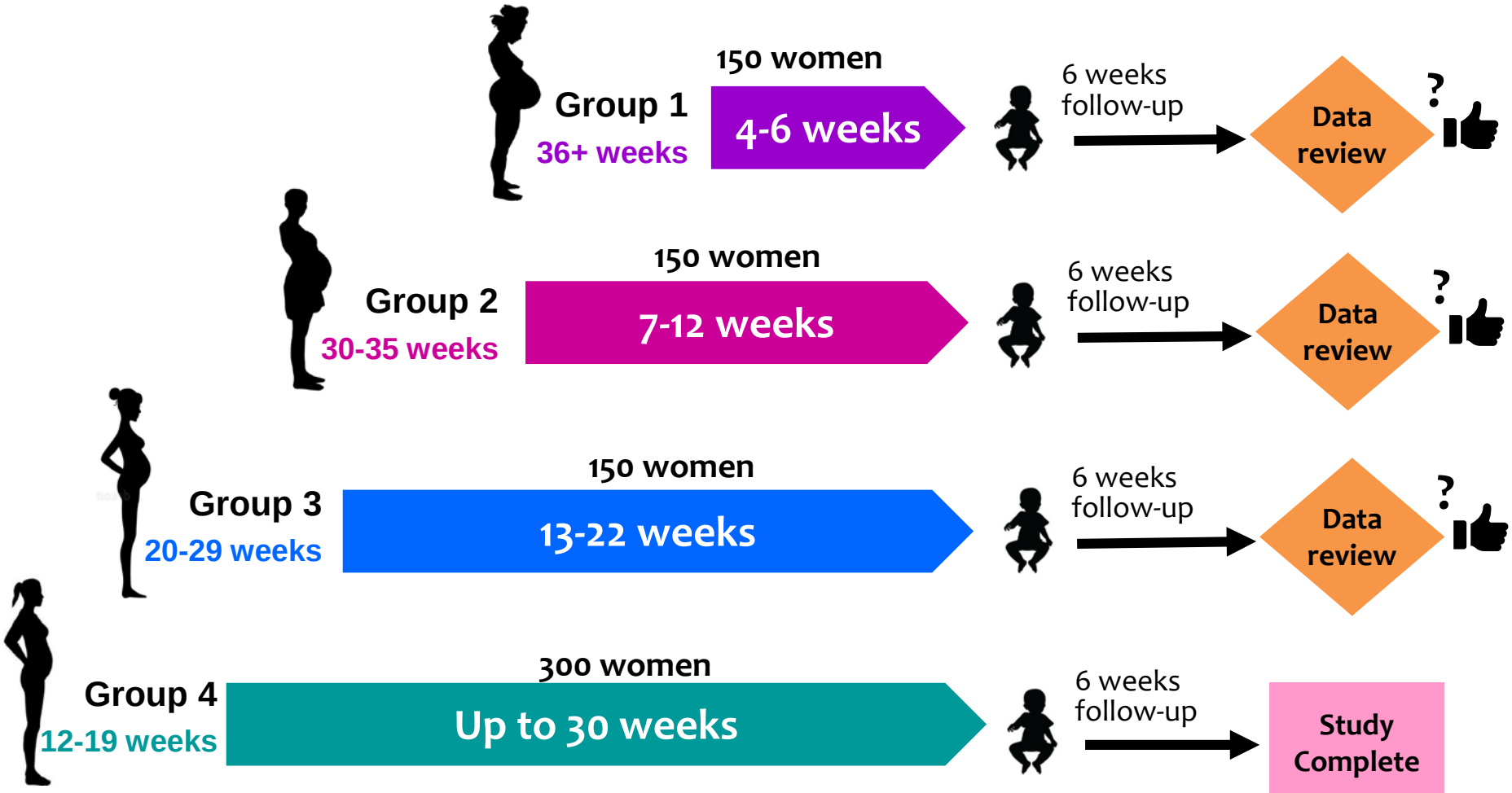
A stepwise approach with interim reviews



Study procedures and visits

- Women will be followed for up to 34 weeks, depending on when they enroll, including 1 and 6 weeks after delivery/pregnancy outcome
  - Interview
  - Physical exam
  - Laboratory testing (including HIV testing)
- Newborn infants will be followed for 6 weeks after birth
  - Physical exam
  - Dried blood spot for drug level within one week of birth (ideally at birth)
- Referrals as necessary for care not provided as part of the study

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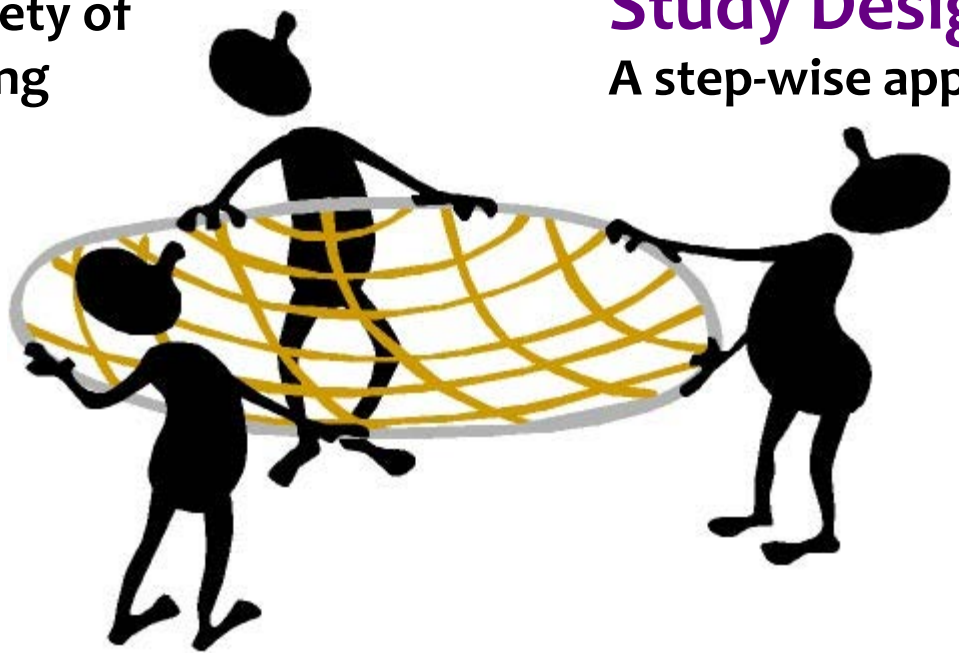
MTN-042: A Three-Way Safety Net for Two

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 their babies – and will ultimately protect them as well!

Timeline

- The study protocol is under development
- Protocol Development Team Meeting is taking place Monday and Tuesday (April 9-10) to discuss key issues
  - Views expressed at this Stakeholders Consultation will help inform the discussion and development of Version 0.3
- Expect Version 1.0 early Q4 –then sites will send to IRBs/ECs for review

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Thank you!

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