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A Study of PrEP and the Dapivirine Ring in Pregnant Women

Bonus Makanani MBBS, FCOG

Katie Bunge MD, MPH

Lee Fairlie, MBChB, FCPaeds

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Cape Town, South Africa

Two HIV prevention methods



- PrEP is daily use of an ARV tablet (Truvada)
 - Reduces risk of acquisition
 - Pregnant women excluded from PrEP trials
 - Many became pregnant while on study product
 - Most safety data come from HIV+ population



- The dapivirine vaginal ring is used every month
 - Reduces risk of acquisition
 - Only safety data are from early pregnancy

Can pregnant women use these methods?

- 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

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

- The dapivirine ring is a new HIV prevention method
 - Regulatory approval is being sought, although this would not be for pregnant women

MTN-042 (deliver) is born!

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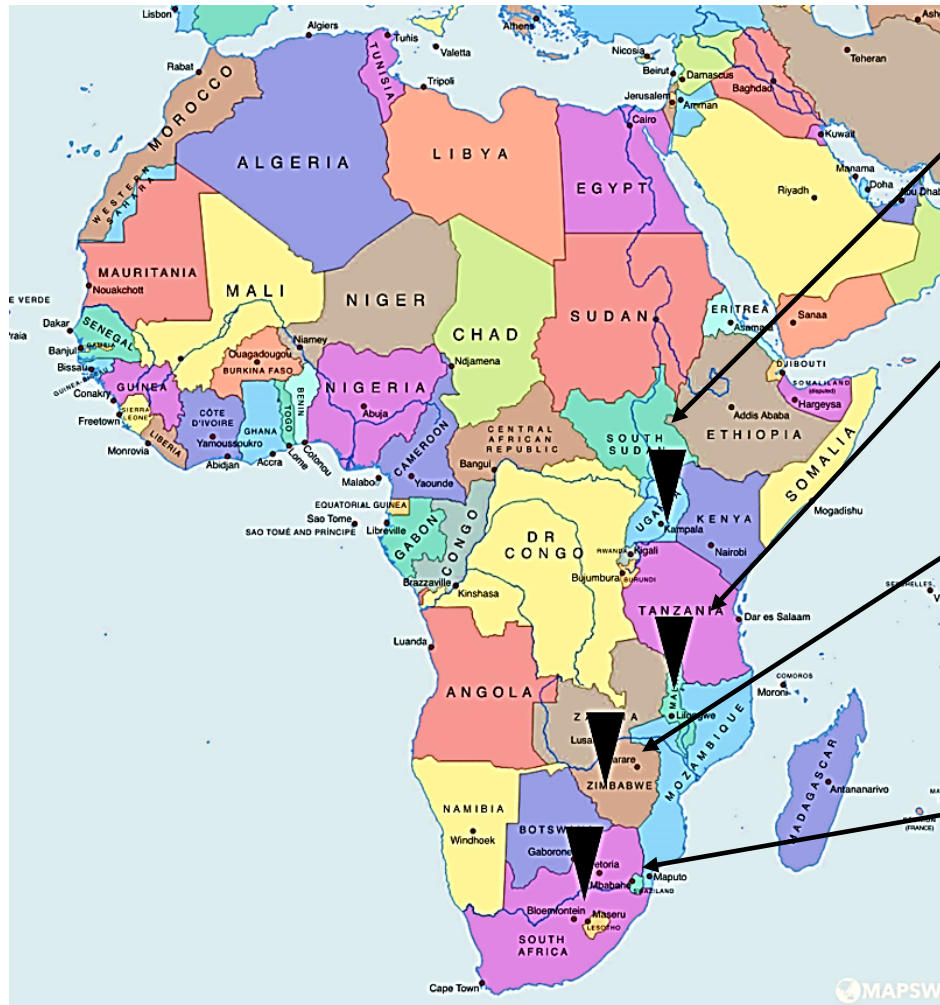
MTN-042 (deliver) is born!

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- Phase 3b, Randomized, open label safety trial of dapivirine vaginal ring and oral PrEP use in pregnancy
 - One of three pregnancy, breastfeeding studies (MTN-041,042,043)
- Primary question
 - Are these products safe for mother and infant
- Other questions
 - How are these drugs taken up in mother and infant
 - Are pregnant women able to be adherent to these products
 - Are these products acceptable to pregnant women
- Answer these questions in the safest, most efficient way possible

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

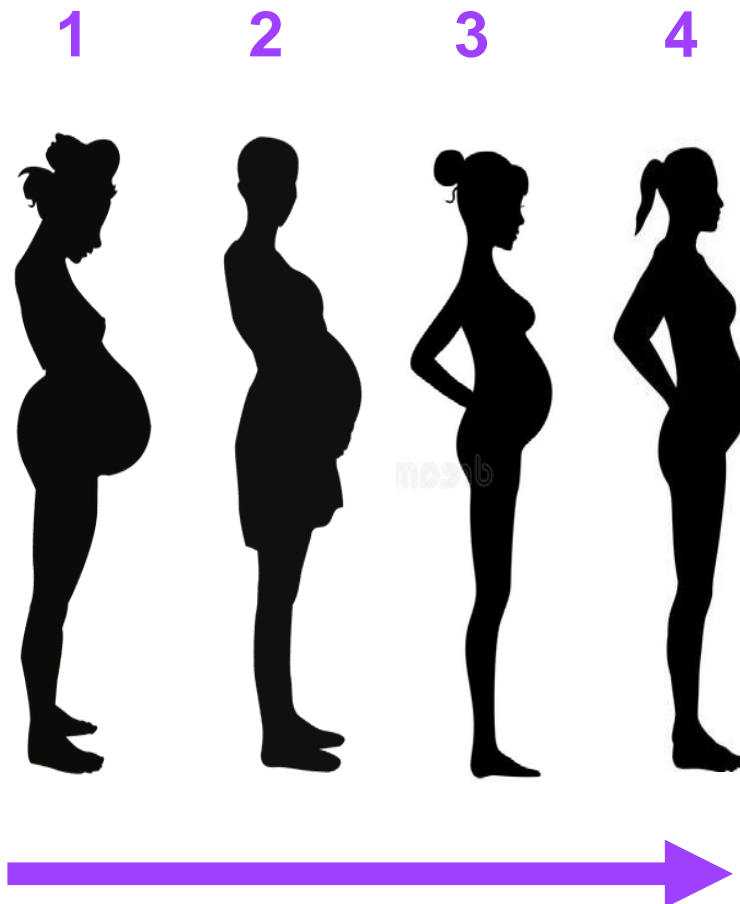
Zimbabwe (Harare)
University of Zimbabwe College of Health Sciences Clinical Trials Research Centre – Zengeza

South Africa (Johannesburg)
Wits RHI Shandukani Research Centre

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 – 36-37 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

Study design



- Women will be randomly assigned to the monthly ring or daily PrEP until delivery
 - 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
- Mothers followed for 6 weeks post partum
- Infants followed for one year

Primary objectives/ 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)

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

Secondary objectives/ endpoints





- Adherence

- Maternal blood TFV-DP and FTC-TP concentrations
- Maternal plasma DPV concentrations
- Participant report of frequency of study product use (e.g., missed doses for oral Truvada and VR removal/expulsions [voluntary and involuntary] and duration without VR in vagina)
- Residual drug levels in returned VRs

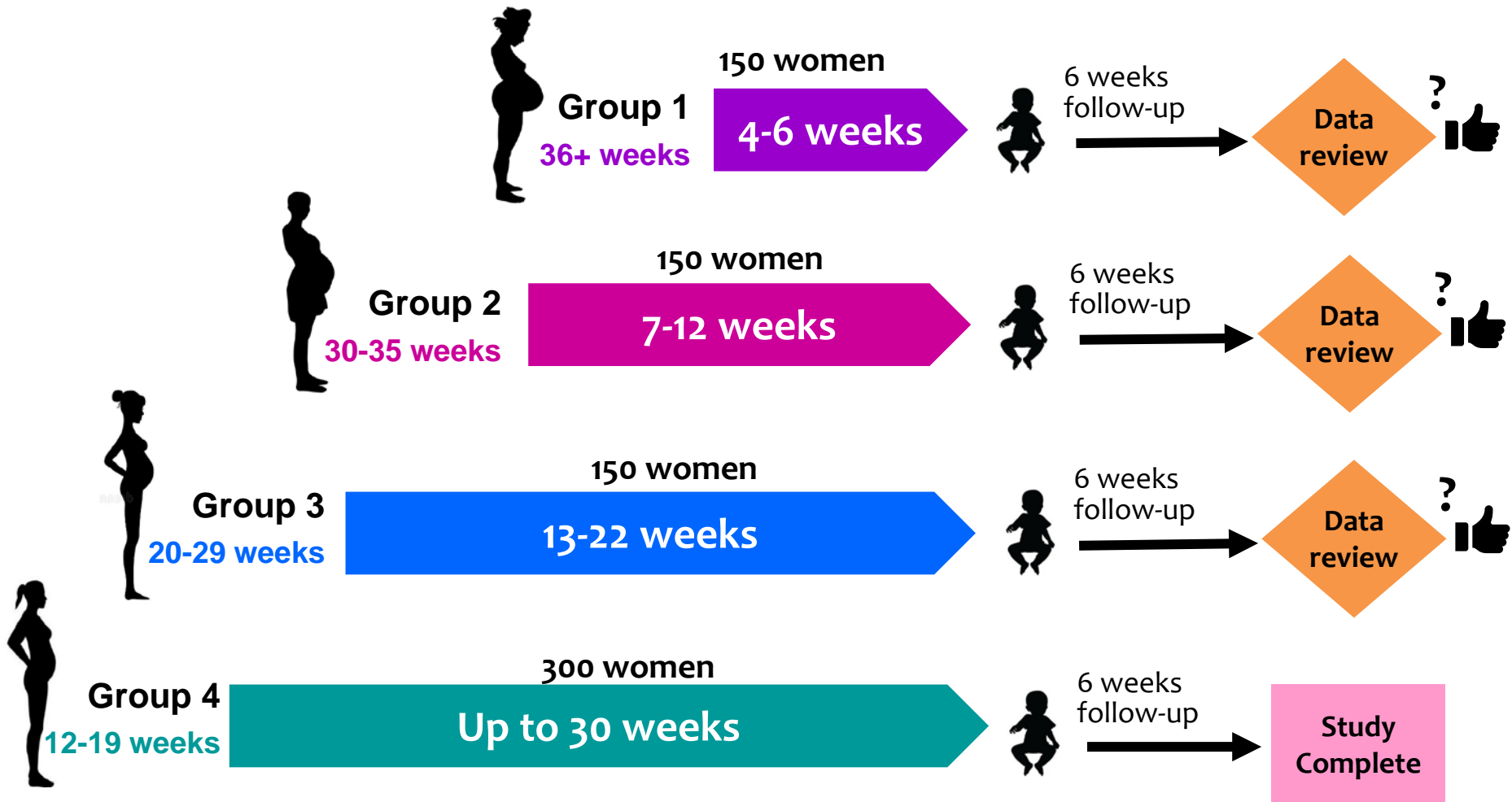
- Acceptability

- 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

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



MTN-042 Stakeholders Consultation

- Took place April 5-6, 2018 in Johannesburg – a few days before the MTN-042 protocol development meeting
- MTN hosted in partnership with AVAC



Who attended?

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

Support for the 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

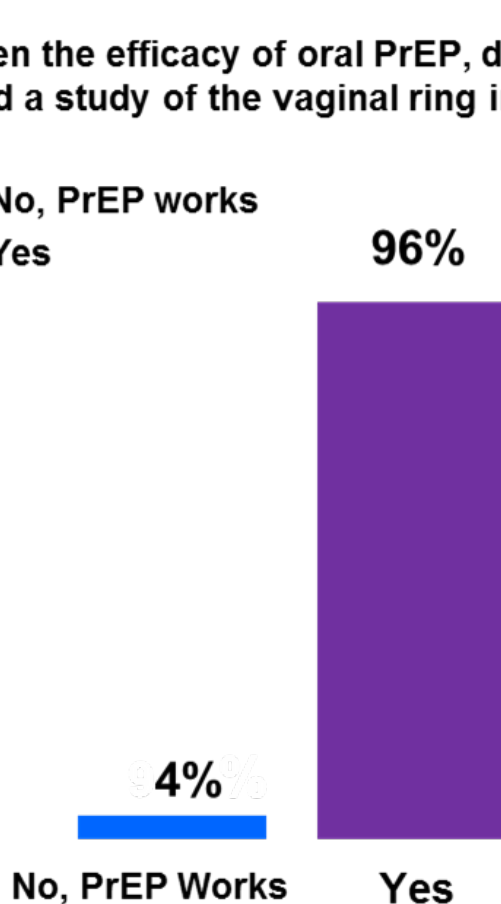


- Provided a number of specific suggestions which we discussed at the protocol development meeting a few days later

Do we need a study like MTN-042?

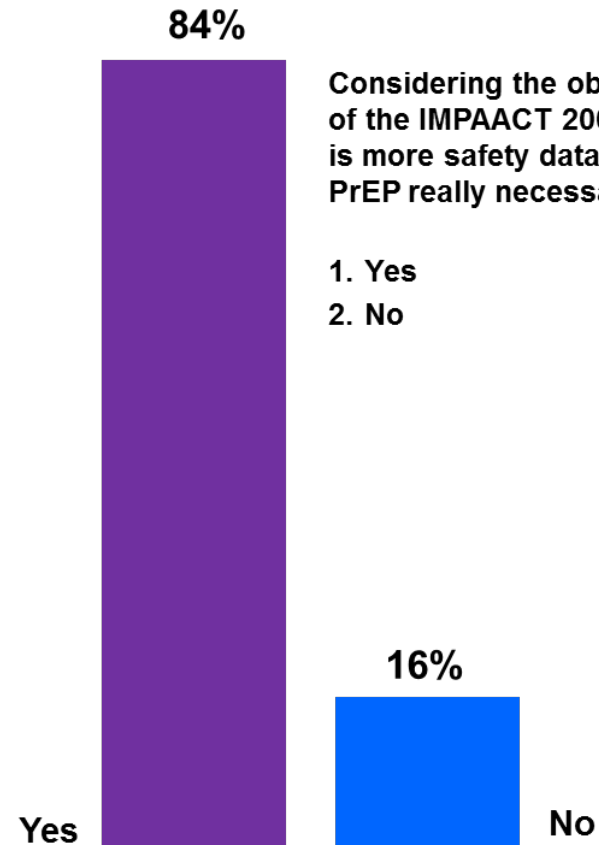
Given the efficacy of oral PrEP, do we even need a study of the vaginal ring in pregnancy?

1. No, PrEP works
2. Yes



Considering the objectives of the IMPAACT 2009 study, is more safety data on oral PrEP really necessary?

1. Yes
2. No



Messaging about the Study



- Messaging should emphasize how the study is focused on protecting women during pregnancy and ensuring their babies are born healthy
- Communications must be transparent and truthful about the risks and realities of pregnancy; that serious complications are a possibility — study or no study.
- Stakeholders must be kept informed throughout the study, especially before and after interim safety reviews

Recommendations

Considerations	y/n
Extend infant follow up to 1 year	√
Collect background pregnancy outcome data from the participating hospitals	√
Consider restricting enrollment to >21 years old	X
Facilitate autopsies	√
Adopt standardized definitions for pregnancy complications	√
Provide oral PrEP to mothers 6 week post partum	X
Include African experts in the Interim Safety Review	√*
Participants enrolling in later cohorts need to be informed of the results from previous cohorts	√

Stakeholders
Consultation
on MTN-042

Phase 3B open-label safety study of the dapivirine vaginal ring and oral PrEP used during pregnancy

MEETING REPORT



Timeline

- PSRC review complete
- Anticipate Version 1.0 by November 1, 2018
- Pre-implementation training February, 2019 (annual meeting)
- Additional in-country stakeholders meetings
- Earliest activation April, 2019

Funding

The Microbicide Trials Network is funded by the National Institute of Allergy and Infectious Diseases (UM1AI068633, UM1AI068615, UM1AI106707), with co-funding from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and the National Institute of Mental Health, all components of the U.S. National Institutes of Health.

Thank You

- Research sites
- Communities within which this research takes place
- Trial participants

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