

Two studies seeking answers: Overview of the DELIVER and B-PROTECTED Studies



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**Ensuring Safe HIV Prevention Methods for
Pregnant and Breastfeeding Women**

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The Need

- Pregnant and breastfeeding women deserve to be included in clinical trials of potentially beneficial drugs
 - Mothers benefit, infants benefit, clinicians benefit, science benefits
- Women may be pregnant or breastfeeding for a significant portion of their lives
- Pregnancy and breastfeeding represent periods of high HIV risk
- Preventing HIV infection in the mother protects her baby, too

Two HIV Prevention Methods



- PrEP is daily use of an ARV tablet (Truvada)
 - Approved in a number of African countries
 - Most information about safety during pregnancy and breastfeeding is from HIV-infected women taking Truvada as treatment.
 - WHO recommends PrEP during pregnancy and breastfeeding but guidelines on its use differ – some countries say more data is needed



- The dapivirine ring is used every month
 - Found to be well tolerated and to reduce HIV risk in two Phase III trials
 - ASPIRE and The Ring Study
 - We know less about the safety of the ring in pregnant and breastfeeding women (but information we do have is reassuring)
 - The International Partnership for Microbicides (IPM) is seeking its regulatory approval– would not be for pregnant/breastfeeding women

Regulators and national programs need information about the safety of a drug in pregnancy and breastfeeding before deciding about its use in these populations.

DELIVER and B-PROTECTED

- Are two studies that will evaluate the safety of PrEP and the ring in pregnant and breastfeeding women
 - DELIVER for pregnant women
 - B-PROTECTED in breastfeeding women

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- Both will be conducted by the National Institutes of Health-funded Microbicide Trials Network 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 (042/042B/043)
Wits RHI Hillbrow CRS (041)

DELIVER and B-PROTECTED in South Africa



Who's Who

deliver is being led by:

- Protocol Chairs:
 - **Bonus Makanani** (Malawi) and **Katie Bunge** (USA)
- Protocol Co-Chair:
 - **Lee Fairlie** (South Africa)



is being led by:

- Protocol Chair:
 - **Maxensia Owor** (Uganda)
- Protocol Co-Chairs:
 - **Jen Balkas** (USA) and **Lisa Noguchi** (USA)

What is similar about the two studies?

- Both studies are Phase IIIb “open-label” studies
 - Phase III b studies involve a product that has already been shown to be safe and effective
 - Open-label means all study participants will use a product with an active drug – there is no placebo ring or placebo tablet
- Women in both studies use either the monthly ring or daily PrEP during the time that they are in the study
 - Which product women use will be determined by chance (randomization) – like flipping a coin



or





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A Study of PrEP and the
Dapivirine Ring in Pregnant Women

Questions DELIVER seeks to answer

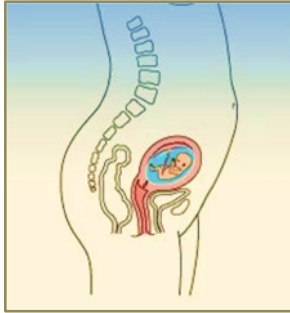
- DELIVER is designed to answer these and other questions:
 - Are PrEP and the dapivirine ring safe to use by women during pregnancy – safe for the pregnancy and for her baby’s development?
 - How is the drug in each product taken up in the body in pregnant women?
 - Will pregnant women use these products during pregnancy – and are they acceptable?

4 Groups of Women

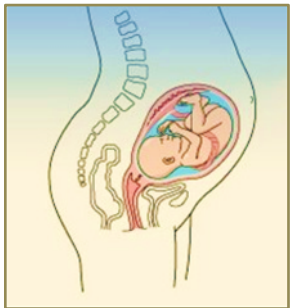
- Will enroll 750 pregnant women at different times during pregnancy
 - Group 1** – 36+ weeks pregnant (about 8-9 months)
 - Group 2** – 30-35 weeks pregnant (about 7-8 months)
 - Group 3** – 20-29 weeks pregnant (about 5-7 months)
 - Group 4** – 12-19 weeks pregnant (about 3-5 months)

Why Different Groups?

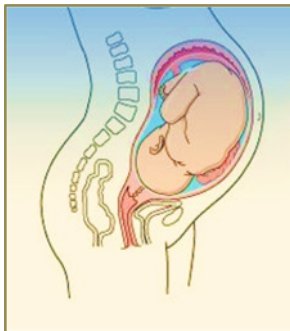
Different Concerns at Different Stages



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

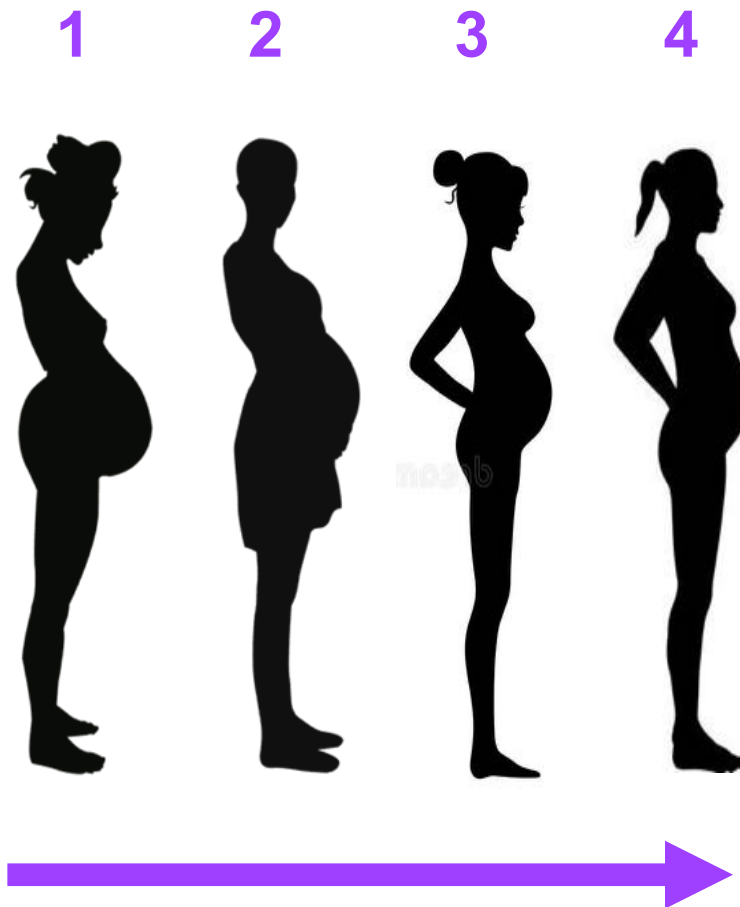


- Second Trimester – Weeks 13-28 (Months 4-6)
 - Baby grows
 - Potential concerns: poor growth, early delivery







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

Study Design at a Glance



- Will enroll one group at a time, beginning with women late in pregnancy
- Women will be randomly assigned to use either the monthly ring or daily PrEP until the time they deliver
 - Twice as many women will use the ring, because we need more safety data with the ring
- Interim reviews will be conducted before deciding to enroll the next group of women

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

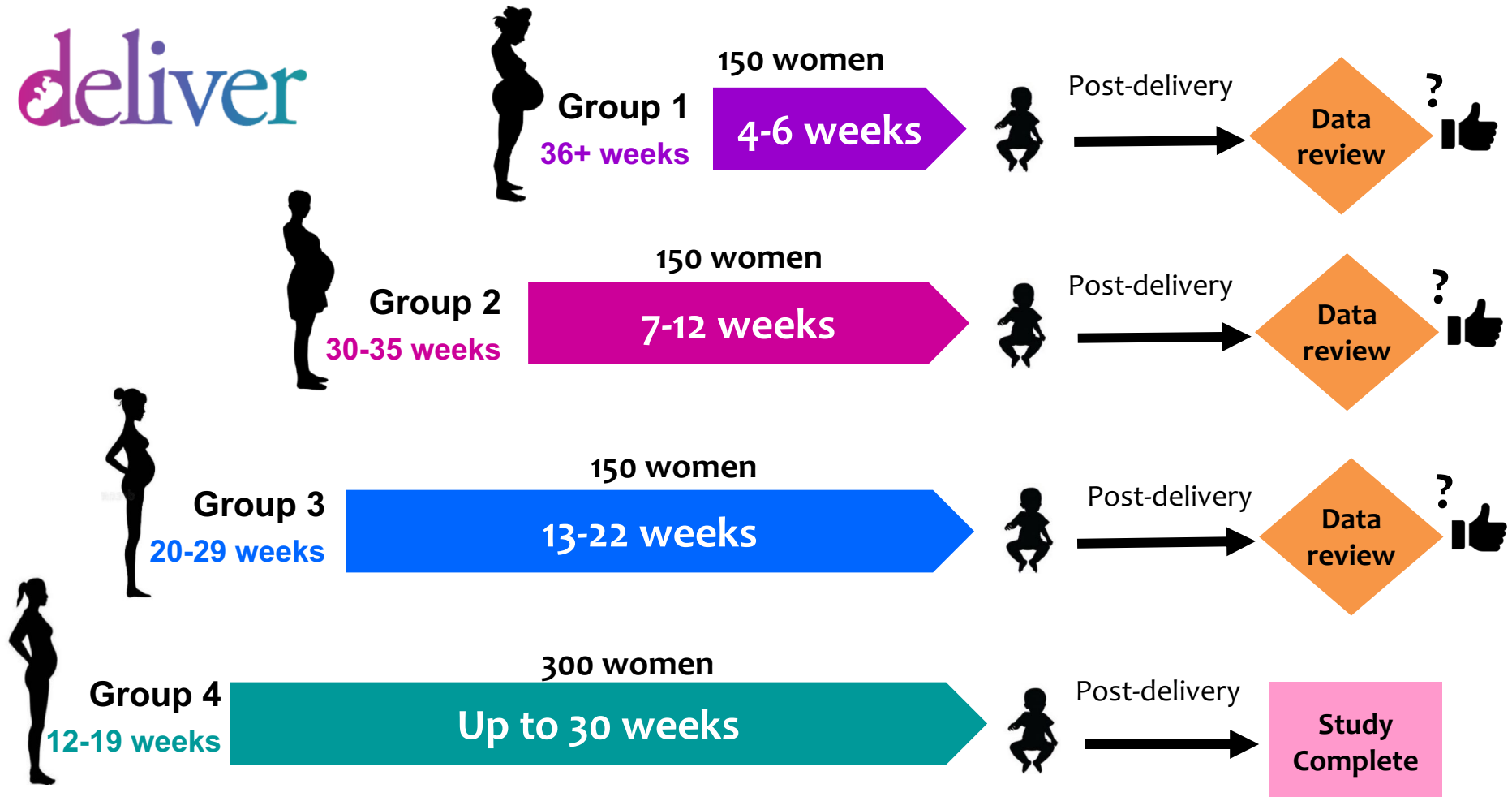
Ensuring safety at several levels

- Site clinicians will monitor the safety and wellbeing of women at each visit
 - MTN Study safety physicians will conduct frequent reviews of data
- Women will be followed for 6 weeks after delivery, and their babies for 1 year
- Ongoing oversight by local IRBs/ECs
- Study outcomes will be reviewed by an Interim Safety Review Panel after all women in each group have delivered. If there are no concerns, the study will proceed enrolling the next group



A stepwise approach with interim reviews

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Who may participate in deliver?

- 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
- Must be 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 – here in Johannesburg at Shandukani MOU, with possible referral to Charlotte Maxeke Johannesburg Academic Hospital



Global recommendations on breastfeeding

- WHO and UNICEF recommend:
 - Early initiation of breastfeeding within 1 hour of birth
 - Exclusive breastfeeding for the first 6 months of life
 - Breastfeeding should continue up to two years of age and beyond, along with appropriate complementary foods



Breastfeeding moms and their babies

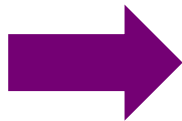


- The study will enroll 200 HIV-uninfected mothers who are breastfeeding a baby between the ages of 6-12 weeks
 - Their babies will also be enrolled in the study
- Women must be HIV-uninfected and be planning to exclusively breastfeed for the duration of the study
- Women will use either the ring or PrEP for 3 months and both women and their babies will be followed for an additional two weeks

Questions to answer in B-PROTECTED

- B-PROTECTED is designed to answer these and other questions:
 - Is use of the PrEP or the dapivirine ring during breastfeeding safe for the mother?
 - Is use of these products safe for their breastfed babies?

Does drug from either the ring or oral PrEP



Pass into breastmilk?

Get absorbed by the infant?

Have adverse effects on the infant?



Questions to answer in B-PROTECTED

- B-PROTECTED also wants to understand if women are willing to use either product during breastfeeding and whether they are able to use them as directed:



- A tablet once a day for oral PrEP
- Using the vaginal ring for a month at time

Safety Considerations in B-PROTECTED

- Breastfeeding has extensive health benefits for both mother and baby
- For the baby:
 - Provides all nutritional needs, promotes development, protects against diseases, and reduces infant mortality
- For the mother:
 - Contributes to health and well-being, helps to space children, reduces ovarian and breast cancer risk
- The study team has two very important priorities:
 - **Ensuring the safety of both the mother and her baby**
 - **Supporting mothers to exclusively breastfeed their babies**





#breastfeeding

No woman should have to choose between breastfeeding and protecting herself from HIV infection

What happens next?



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Dapivirine Ring in Pregnant Women

Timeline



- Will soon undergo review by the necessary ethics and regulatory committees in each trial site country.
- Pending approvals, it could begin at some sites before the end of this year (2019)



- B-PROTECTED will be ready for in-country ethics and regulatory reviews by mid-2019
- Pending approvals, the study could also begin before the end of this year

The Bottom Line

- Pregnant and breastfeeding women need HIV prevention tools that they know are safe for them and their babies
- Two products, PrEP and the dapivirine vaginal ring, are safe and can reduce the risk of HIV, but we need to know that they are safe to use by women during pregnancy and breastfeeding.
- Two studies—DELIVER and B-PROTECTED— will evaluate the safety of these drugs in pregnant and breastfeeding moms

In the end, it's about ensuring women can be protected against HIV with options they know are safe – safe for themselves, their pregnancies and for their babies.

Acknowledgements



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