Global PrEP Learning Network

New Data, New Opportunities: The Expanding Evidence Base for the PrEP Ring

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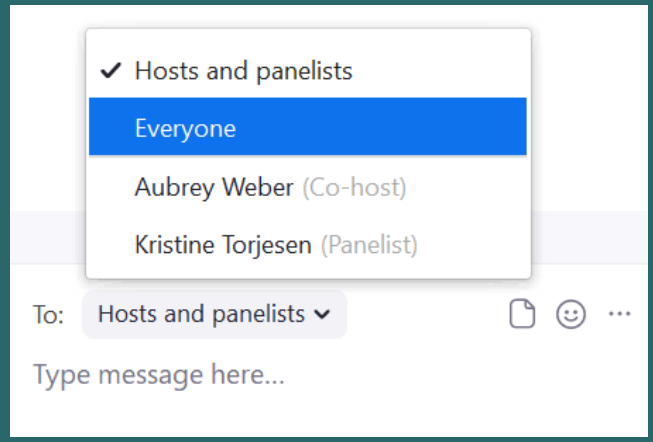
The webinar will begin shortly...

Please introduce yourself in the chat!

- Name
- Organization
- Country

Feel free to ask questions and add comments to the chat box at any point during today's session. We will dedicate time to Q&A at the end of the webinar.

Don't forget to select "Everyone"



Global PrEP Learning Network

New Data, New Opportunities: The Expanding Evidence Base for the PrEP Ring

- Welcome & Introductions
- Framing of Today's Agenda
- REACH Study: PrEP ring use for adolescent girls and young women
- DELIVER Study: PrEP ring safety data during pregnancy
- B-PROTECTED Study: Results of a randomized trial of PrEP ring and oral PrEP use for HIV prevention during breastfeeding
- WHO reflections on ring study implications for national PrEP policies and programs

Today's facilitators

Kristine Torjesen, MD, MPH, she/her

MOSAIC Project Director, FHI 360

Kristine Torjesen is a pediatrician and Project Director for the USAID-funded Maximizing Options to Advance Informed Choice for HIV Prevention (MOSAIC) project. Dr. Torjesen leads a consortium of international and country-based organizations working to accelerate market introduction of new biomedical HIV prevention products in sub-Saharan Africa.

@MOSAICproj

Nhlamulo Chantel Manganye, she/her

Community Liaison Officer & NGS Member, Wits Reproductive Health Institute

Nhlamulo Chantel Manganye is an HIV Prevention Ambassador, a member of the MOSAIC NextGen Squad, and a former participant on the REACH study. She supports the Demand Creation and Mobilization, Implementation Research, Gender Integration, and Civil Society Advocacy teams as part of MOSAIC.

Today's presenters

Carolyne A. Akello, MD, she/her

MOSAIC Project Director, FHI 360 Uganda

Carolyne A. Akello is a medical doctor, epidemiologist, and MOSAIC project director in Uganda. Prior to joining FHI 360, Akello was an investigator with the REACH/MTN-034 study. She has worked in various capacities on several studies of PrEP products for HIV prevention under the MTN and the HPTN.

Katherine Bunge, MD, she/her

Associate Professor, Department of Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh

Katie Bunge is a practicing obstetrician and gynecologist at the University of Pittsburgh. She served as a safety physician with the Microbicide Trials Network for the PrEP ring clinical trials and is currently acting as one of the protocol chairs for DELIVER/MTN-042. Within the last year she has taken on roles within the MOSAIC and Matrix programs.

Today's presenters

Lisa Noguchi, PhD, she/her

Director, Maternal and Newborn Health, Jhpiego/Johns Hopkins University

Lisa Noguchi is Director for Maternal and Newborn Health at Jhpiego. She is a nurse-midwife, infectious disease epidemiologist, and Certified Professional in Patient Safety. She was Protocol Co-Chair for the B-PROTECTED/MTN-043 study and is a member of WHO's Antenatal Care Guideline Development Group.

Michelle Rodolph

Technical Officer, ARV based prevention, World Health Organization

Michelle Rodolph is a technical officer with the HIV testing, prevention, and populations team of the Global HIV, Hepatitis and STI Programmes at the World Health Organization. She leads the ARV-based HIV prevention work for WHO, including the development of new policy and guidance on PrEP, PEP, and future prevention products.

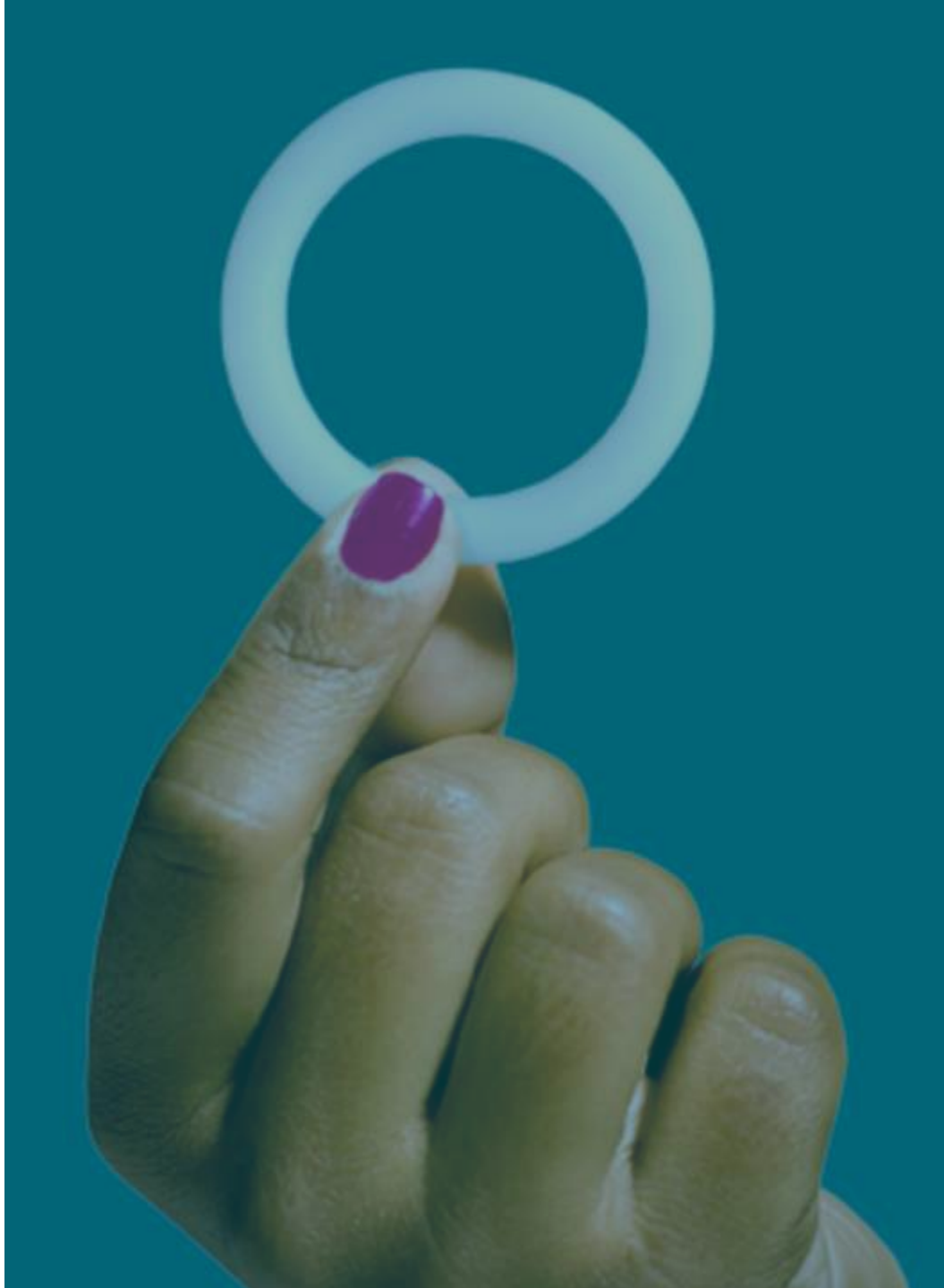
Framing Today's Agenda

Kristine Torjesen, MD
FHI 360

Dapivirine vaginal ring (PrEP ring)

Vaginal ring which releases dapivirine over one month

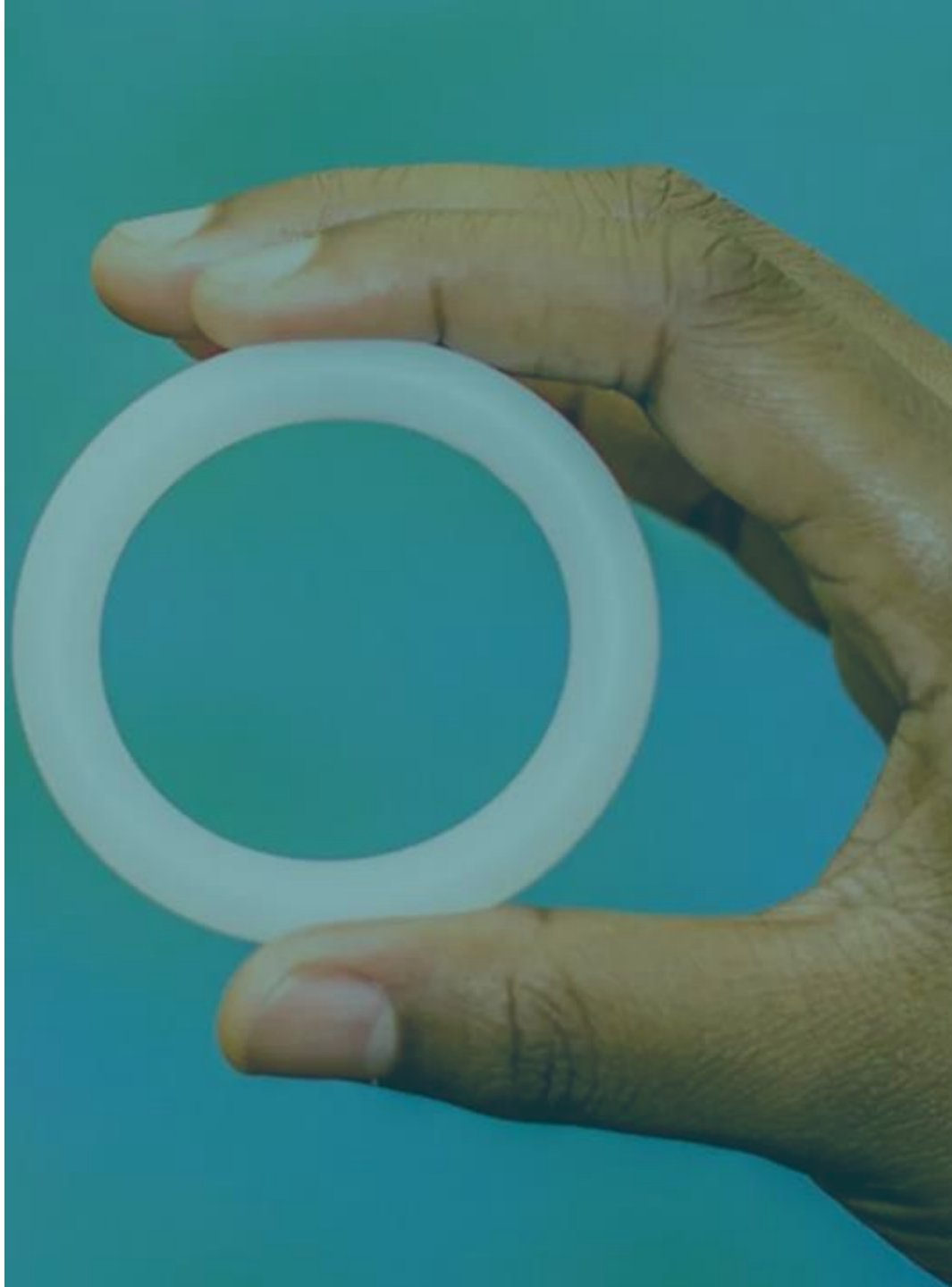
- **Flexible silicone vaginal ring** developed by the International Partnership for Microbicides (IPM), which slowly releases the antiretroviral drug dapivirine over one month.
- **Self-inserted monthly**
- **Reduced HIV risk in Phase III trials:** 35% in The Ring Study, 27% in ASPIRE, and demonstrated a strong safety profile.
- **Open-label extension studies** saw increased adherence and suggested risk reduction may be greater than 50% with consistent use.
- Brown et al, JIAS 2020: **Exploratory analyses** estimated 75% to 91% HIV-1 risk reduction with >4 mg dapivirine released when compared to placebo.
- Stored at room temperature (no cold chain); five-year shelf life.



Dapivirine vaginal ring (PrEP ring)

Current regulatory and procurement status

- **Recommended for cisgender women aged 18 and older** at substantial risk of HIV and who are unwilling or unable to use oral PrEP *(2021 World Health Organization recommendation).*
- **Approved by multiple regulatory agencies in Africa**
- **FDA application voluntarily withdrawn by IPM** based on feedback that current data are unlikely to support US approval given the context of the HIV prevention landscape for women in the United States.
- **PEPFAR currently supports ring procurement for research** only, not for program delivery.
- **The Global Fund supports ring procurement** for program delivery.
- Multiple planned and ongoing **implementation studies** include PrEP ring.



Women and girls bear a disproportionate burden of HIV in sub-Saharan Africa

Globally 46% of all new HIV infections were among women and girls in 2022.

Every week, 4000 adolescent girls and young women aged 15–24 years became infected with HIV globally in 2022. 3100 of these infections occurred in sub-Saharan Africa.

Source: UNAIDS fact sheet

Women of reproductive age are a growing population in Africa, the continent most impacted by HIV transmission

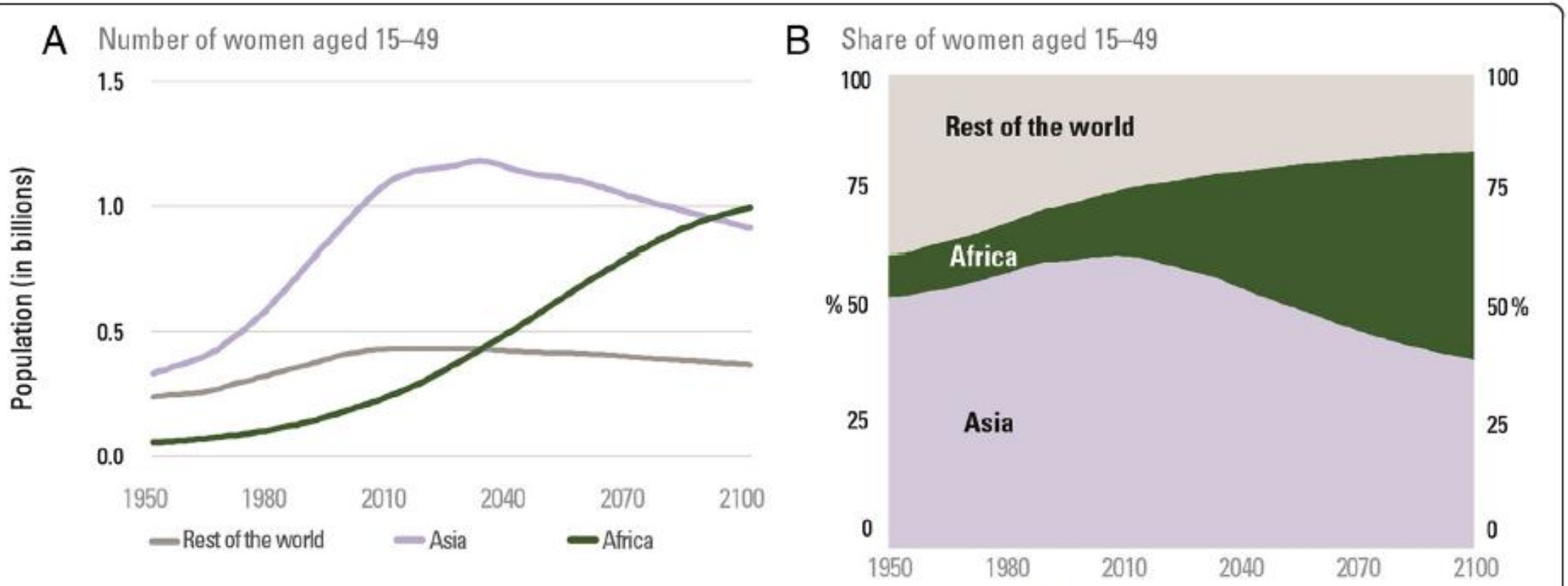
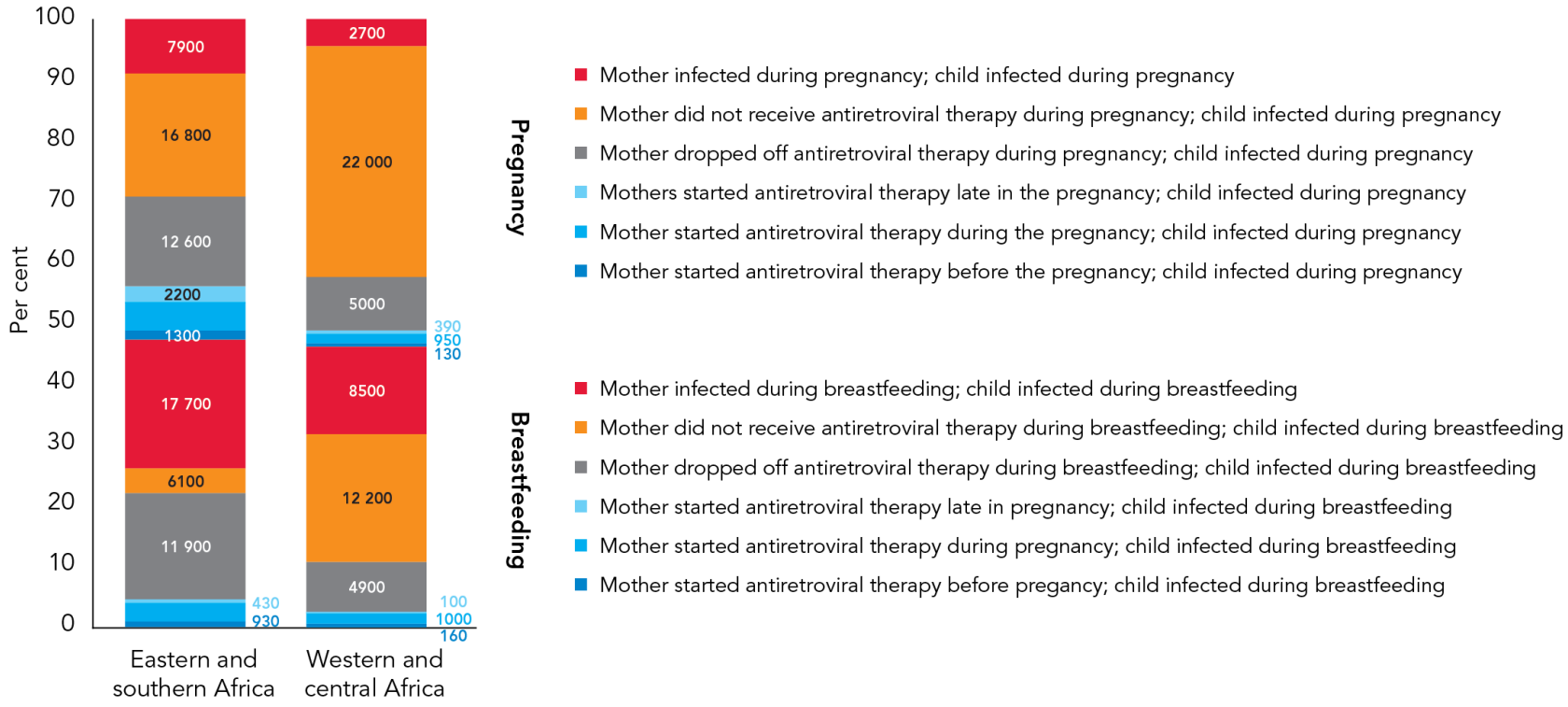


Figure 1 Africa's population of women of reproductive age is projected to more than double between 2015 and 2050. Women of reproductive age by region, 1950–2100 (**A**. Number of women aged 15-49. **B**. Share of women aged 15-49). Source: UNICEF: *Generation 2030 Africa*. New York: UNICEF; 2014.

Incident HIV infections during pregnancy and breastfeeding contribute to a substantial proportion of vertical transmissions

The causes of vertical transmission of HIV in Africa

Distribution of new child infections by cause, eastern and southern Africa and western and central Africa, 2018



Source: UNAIDS 2019 estimates.

PrEP options currently vary in terms of safety data for pregnant and breastfeeding populations

Largest amount of safety data for oral PrEP (FTC/TDF)

Strong safety data in pregnancy and breastfeeding

Limited but growing safety data

Oral PrEP

No evidence of negative impact on pregnancy or infant outcomes.

Full WHO recommendation during pregnancy and breastfeeding in place.

Ring PrEP

No evidence of negative impact on pregnancy or infant outcomes.

WHO recommendation does not (yet!) include people who are pregnant or breastfeeding.

CAB PrEP

Least amount of safety data during pregnancy, but no concerns identified (more data needed). No published breastfeeding safety data.

WHO actively seeking review of pregnancy data.

Restrictions around PrEP ring use by population

Country	Ring allowed during pregnancy	Ring allowed while breastfeeding	Ring allowed <18 years
Eswatini	No	No	No
Kenya	Yes	Yes	No
Lesotho	Yes	Yes	No
South Africa	No	No	No
Uganda	No	No	No
Zimbabwe	No	Yes	No

ACKNOWLEDGMENTS

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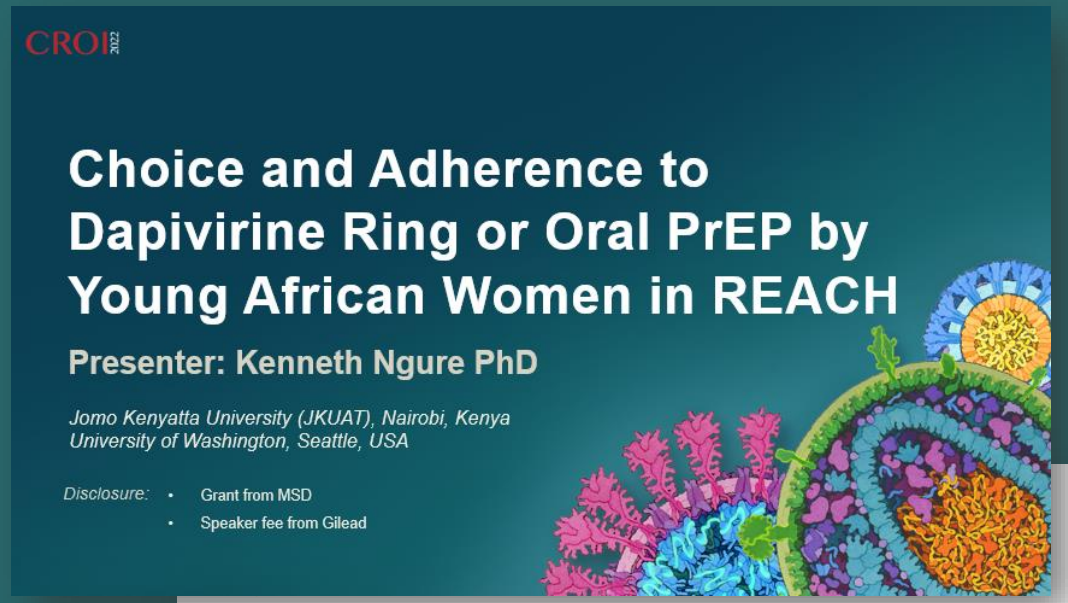
Photo Credit: MOSAIC Consortium

REACH Study Findings

Carolyne A. Akello, MD
FHI 360

PrEP Ring Use for Adolescent Girls and Young Women

DATA FROM MTN-034
(AS PRESENTED AT IAS 2021 & CROI 2022)



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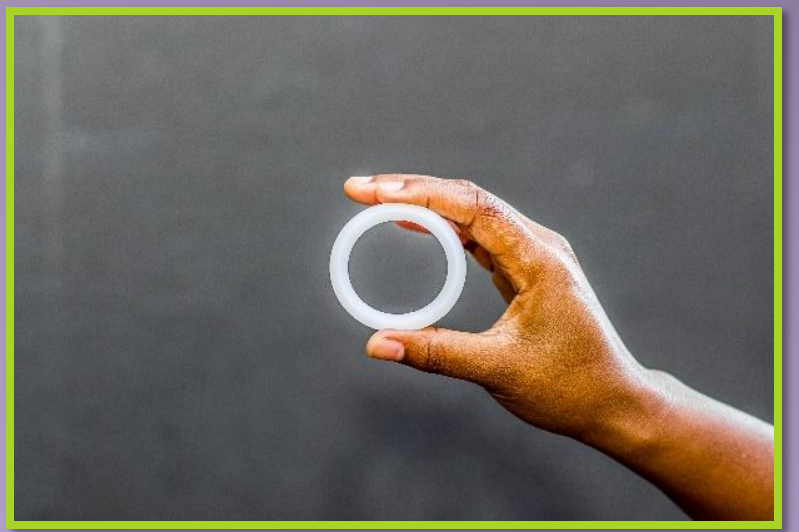
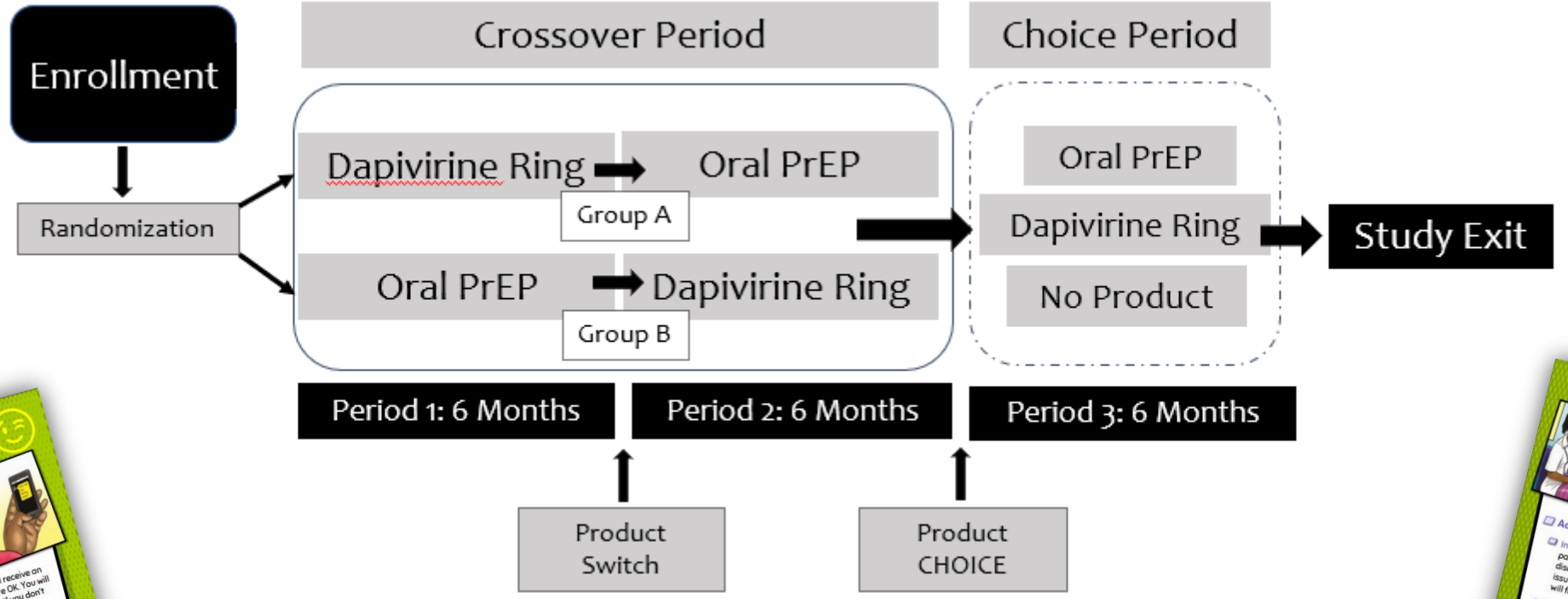
Introduction

- Adolescent girls and young women (AGYW) account for most new HIV acquisitions in Africa
- WHO recommends daily oral PrEP and the monthly dapivirine vaginal ring (ring) for women at risk of HIV acquisition
- A safety study of the PrEP ring among AGYW demonstrated a similar safety profile among this group as among older trial participants*
- Given low adherence among AGYW in efficacy trials, we assessed safety, product choice and adherence to the ring and oral PrEP among African AGYW in the MTN-034/REACH trial

*MTN-023 Results



REACH Study Design



A randomized crossover study offering a diverse menu of adherence support options to all participants in South Africa, Uganda, and Zimbabwe.

Participant Baseline Characteristics

	Cape Town, South Africa N=60	Harare, Zimbabwe N=60	Johannesburg, South Africa N=67	Kampala, Uganda N=60	Total N=247
Age	18.3	17.9	18.3	18.2	18.2
Not married	60 (100%)	36 (60%)	65 (97%)	53 (88%)	214 (87%)
Ever been pregnant	5 (8%)	41 (68%)	21 (31%)	32 (53%)	99 (40%)
Contraceptive commenced in last 70 days	17 (29%)	28 (47%)	22 (33%)	26 (46%)	93 (38%)
Secondary school	55 (92%)	55 (93%)	57 (85%)	22 (37%)	189 (77%)
In school	33 (55%)	14 (23%)	36 (54%)	9 (15%)	92 (37%)
Earns own income	2 (3%)	14 (23%)	6 (9%)	31 (52%)	53 (21%)

At screening, participants were assumed to have been assigned female sex at birth and were not asked to report their gender identity. However, required safety pelvic exams that occurred during the screening process would later confirm sex at birth.

Adverse Events in REACH

- 54% of participants experienced at least 1 product-related AE
- No difference in total number of reportable AEs experienced during ring use and oral PrEP use
- No AE-related product holds, discontinuations or related SAEs
- Most commonly reported AEs: decreased creatinine clearance, chlamydia and headache

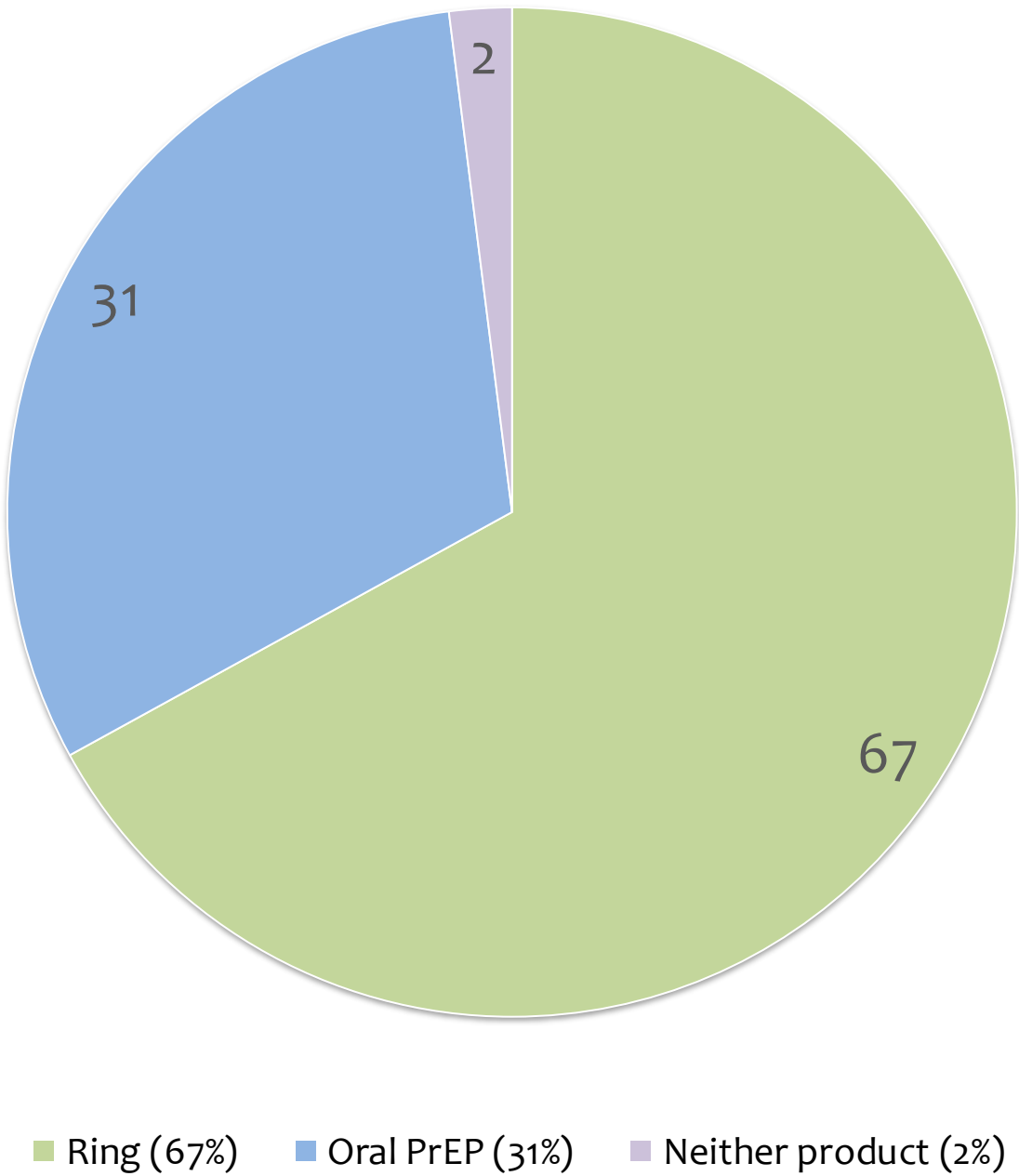
	Dapivirine Ring	Oral PrEP	Overall
At least 1 AE / participant	211 (88%)	222 (91%)	234 (95%)
At least 1 related AE per ppt	79 (33%)	131 (53%)	133 (54%)
Average number of AEs per ppt (SD)	2.9 (2.3)	3.5 (2.8)	5.1 (3.6)
Average number of related AEs per ppt (SD)	0.5 (1.0)	1.2 (1.6)	1.3 (1.7)

PrEP ring side effects in REACH were mild to moderate, and similar to those seen in the Phase III trials.

Product Choice in Period 3

Randomization sequence in the crossover period was not associated with product choice

Of 227 (92%) participants who reached the choice period, more than 2/3 (152) chose the ring



Evaluating Adherence

Ring adherence

Based on estimated dapivirine release calculated using residual drug (RD) levels in returned rings

Non-use

- RD levels showing release of <0.9mg

Some use

- RD levels showing release of 0.9 to <4.0mg

Consistent with 28 days of use

- RD levels showing release of ≥4.0mg

Oral PrEP adherence

Measured via tenofovir diphosphate (TFV-DP) levels in dried blood spots (DBS)

Non-use

- TFV-DP levels of <16fmol/DBS punch

Some use

- TFV-DP levels of 16-700fmol/DBS punch

High adherence

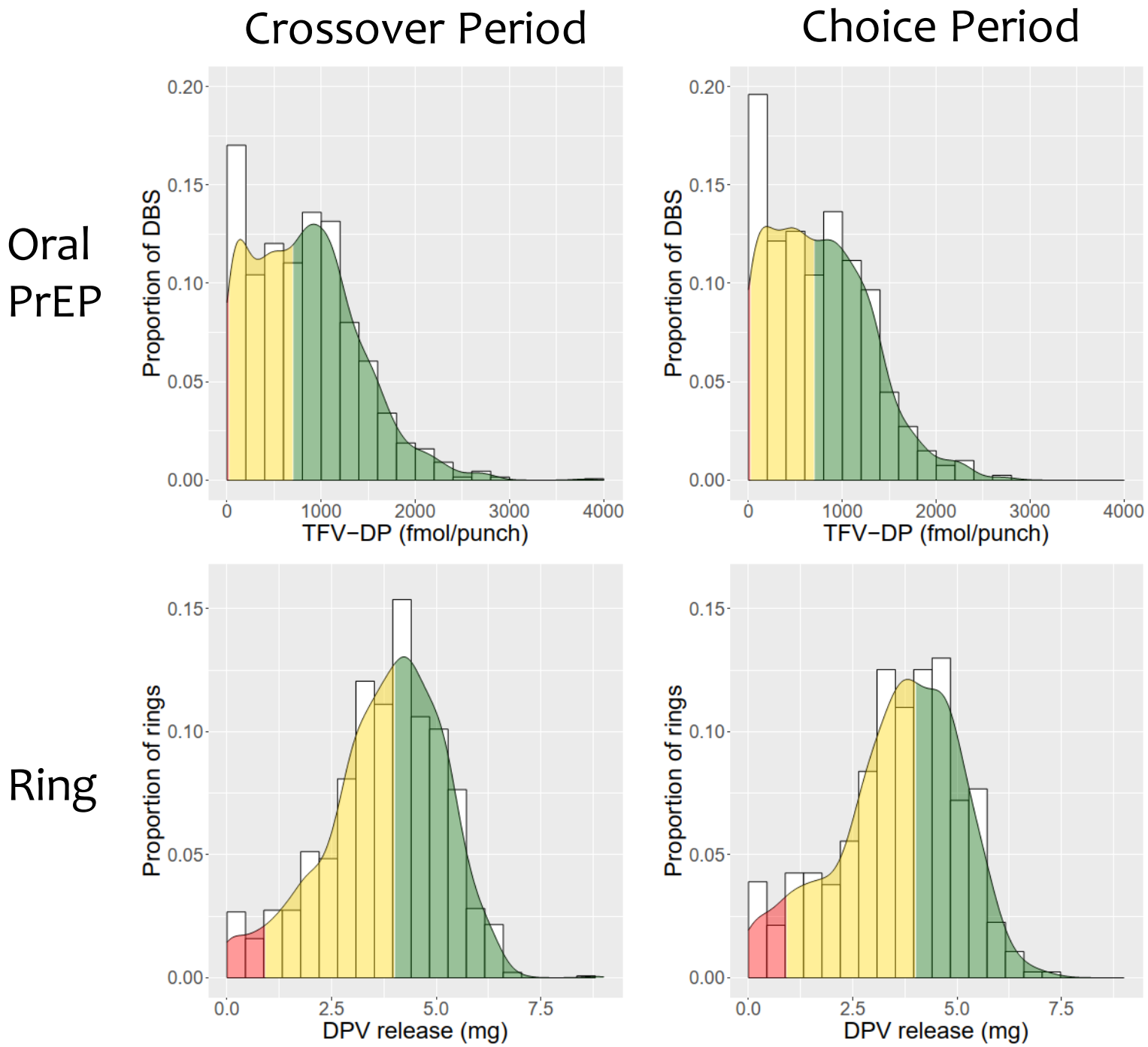
- TFV-DP levels of ≥ 700fmol/DBS punch

We compared the proportion of visits with high adherence between the crossover and choice periods for each product

PrEP ring and oral PrEP adherence during the crossover and choice periods

Overall, participants used both the ring and oral PrEP consistently in the crossover and choice periods, with "some" to "high" adherence.

Fewer than 5% of visits were categorized as no or low adherence to study product



Adherence during the crossover period and subsequent product choice

Oral PrEP adherence	Chose oral PrEP	Chose ring/neither	p-value
Red/yellow at least once	32 (20%)	129 (80%)	<0.001
Always green	39 (58%)	28 (42%)	

Non-use (red): TFV-DP levels of <16fmol/DBS punch
Some use (yellow): TFV-DP levels of 16-700fmol/DBS punch
High adherence (green): TFV-DP levels of ≥ 700fmol/DBS punch

Ring adherence	Chose ring	Chose oral PrEP/neither	p-value
Red/yellow at least once	134 (67%)	65 (33%)	0.85
Always green	19 (66%)	10 (35%)	

Non-use (red): RD levels showing release of <0.9mg
Some use (yellow): RD levels showing release of 0.9 to <4.0mg
Consistent with 28 days of use (green): RD levels showing release of ≥4.0mg

High adherence to oral PrEP in the crossover period was strongly associated with choice of oral PrEP (p<0.001)

No such association was observed for ring choice (p=0.85)

Conclusions

- Both PrEP products were well-tolerated and highly acceptable
- Among African AGYW who had experience with both ring and oral PrEP use, about 2/3 opted to use the ring when given a choice of products
- Participants with high adherence to oral PrEP in the crossover period were more likely to choose oral PrEP when given a choice
- Drug levels throughout the crossover and choice periods indicate partial to high adherence for both products – higher than in previous studies
- AGYW can make informed choices about HIV prevention products and can use products effectively with proper support

Acknowledgements

MTN-034/REACH Site staff and participants

- Desmond Tutu HIV Foundation (DTHF) Emavundleni Clinical Research Site
- Wits Reproductive Health and HIV Institute (WRHI)
- Makerere University-JHU Research Collaboration(MU-JHU)
- University of Zimbabwe Clinical Trials Research Centre (UZ-CTRC) Spilhaus clinical research site

Authors (Interim Results)

G Nair, D Szydlo, M Garcia, CA Akello, P Macdonld, B Siziba, T Palanee-Phillips, T McClure, S Johnson, L Levy, K Ngure, LE Soto-Torres, ER Brown, S Hillier, C Cellum, on behalf of the REACH Protocol Team

Authors (Final Results)

K Ngure, G Nair, D Szydlo, ER Brown, CA Akello, P Macdonald, T Palanee-Phillips, B Siziba, SL Hillier, M Garcia, S Johnson, L Levy, T McClure, L Soto-Torres, C Celum, on behalf of the REACH Protocol Team

The MTN-034/REACH Management Team

The International Partnership for Microbicides developed the dapivirine ring and supplied rings for this trial. FTC/TDF tablets were supplied by Gilead Sciences, Inc.

The study was designed and implemented by the Microbicide Trials Network (MTN). From 2006 until November 30, 2021, the MTN was an HIV/AIDS clinical trials network funded by the National Institute of Allergy and Infectious Diseases through individual grants (UM1AI068633, UM1AI068615 and 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.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

DELIVER Study Findings

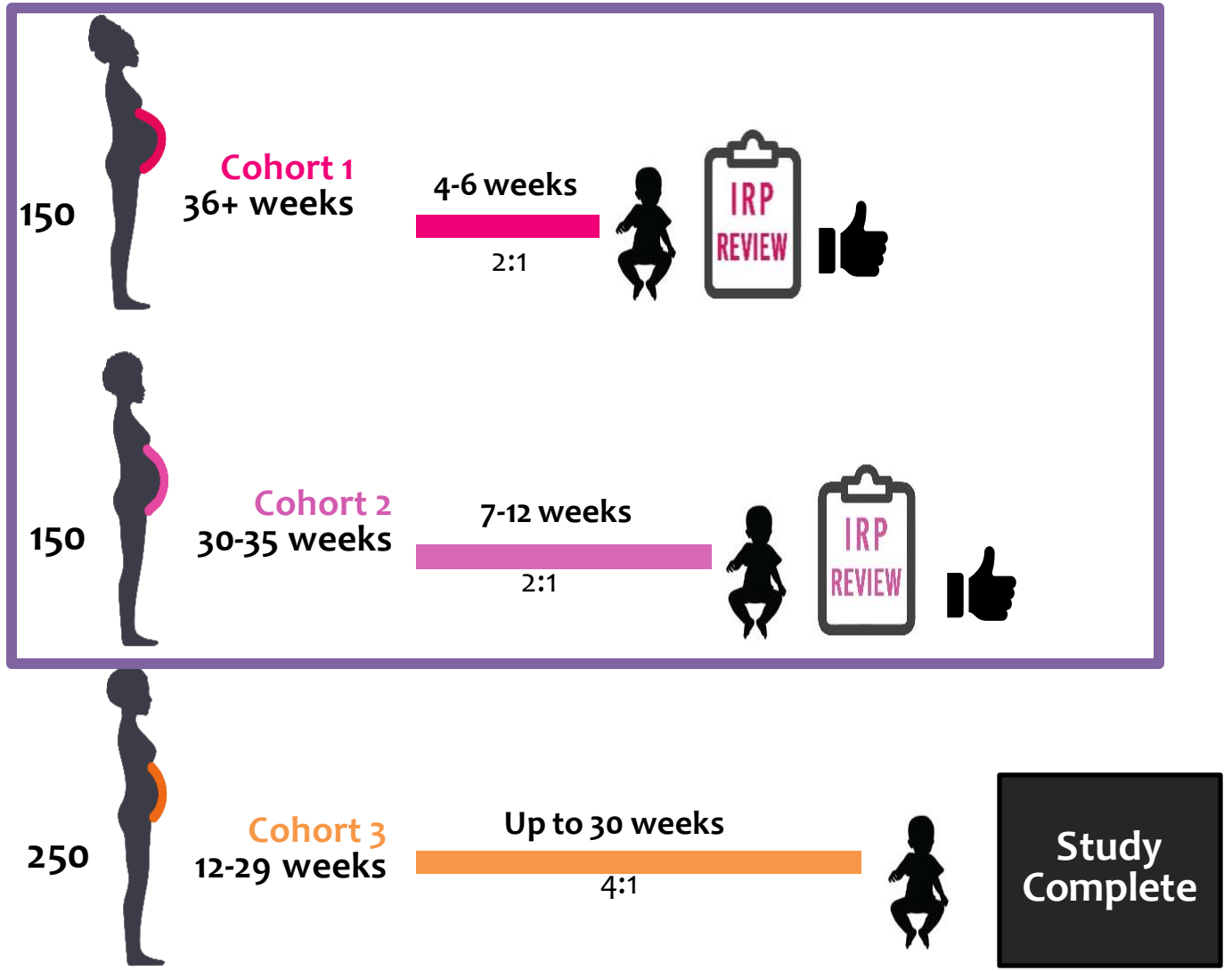
Katherine Bunge, MD
University of Pittsburgh

PrEP ring safety data during pregnancy

Dr. Katherine Bunge
University of Pittsburgh

MTN-042 Protocol Summary

- Conducted in a step-wise fashion, enrolling one cohort at a time, beginning with later gestational age
- Key eligibility criteria include 18-40 years old, singleton pregnancy, ultrasound confirmed gestational age, no history of pregnancy complications
- Participants randomly assigned to use either the monthly PrEP ring or daily TDF/FTC until delivery
  - 2:1 randomization for cohorts 1 and 2
  - 4:1 randomization for cohort 3
- Interim safety reviews by an independent panel conducted before moving to the next cohort



MTN-042 Study Sites

Uganda (Kampala)

MU-JHU Research Collaboration

Malawi (Blantyre)

College of Medicine- JHU Research Project

Zimbabwe (Harare)

University of Zimbabwe College of Health Sciences Clinical Trials Research Center- Zengeza

South Africa (Johannesburg) Wits-RHI Shandukani Research Centre- Wits RHI Hillbrow CRS

MTN-042 Methods

- Pregnancy outcomes and complications reported up to 6 weeks post delivery were assessed and summarized using descriptive statistics
  - Participants returned for in-person visits every two weeks alternating with telephone visits until delivery
  - A post-pregnancy outcome visit was scheduled in the clinic for both maternal and infant participants within two weeks of delivery
  - Mothers were exited from the study at 6 weeks post delivery
- Pregnancy outcomes and complications were compared to local background rates obtained through a systematic chart review (MTN-042B)*

* Balkus et al, Assessing pregnancy and neonatal outcomes in Malawi, South Africa, Uganda, and Zimbabwe: Results from a systematic chart review. PLoS One. 2021

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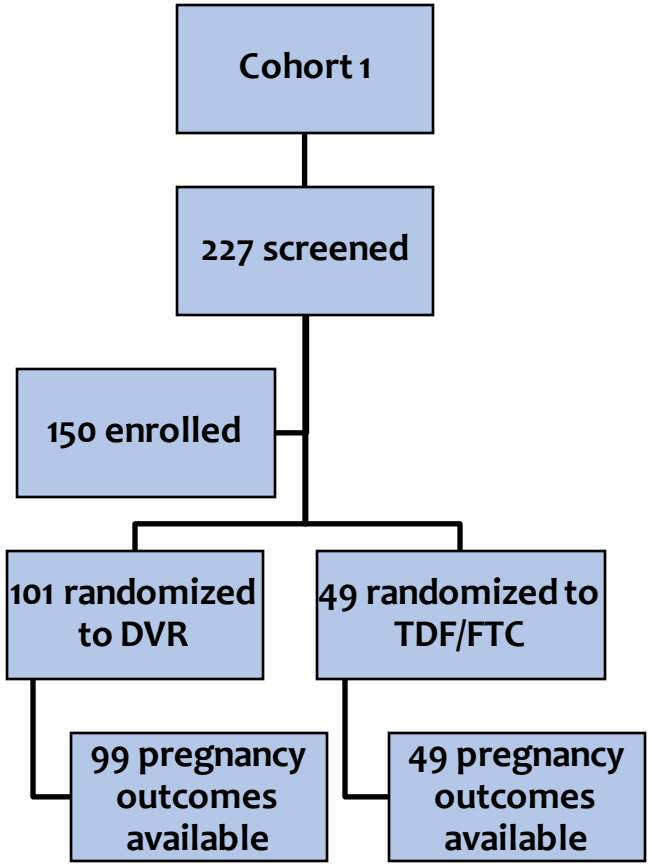
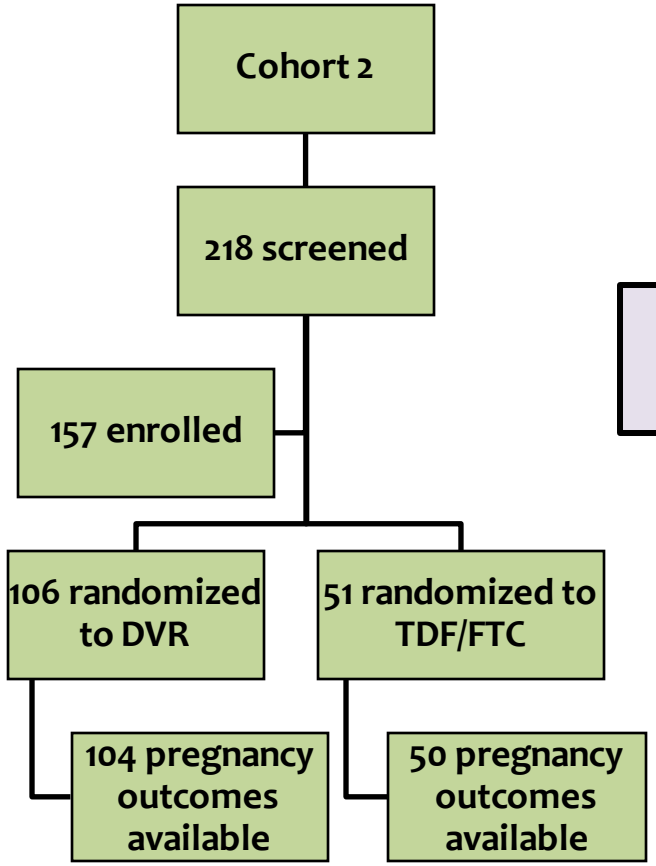
MTN-042 Study Population and Retention





> 95% expected maternal visits completed

Demographic and clinical characteristics were similar by study arm for each cohort

Pregnancy Outcomes

Cohort 1	DVR arm (n=99)* n (%)	TDF/FTC arm (n=49) n (%)	Both arms (n=148) n (%)
Live births	99 (100)	48 (98)	147 (99)
Fu			
Pr			
Stillbirth/intrauterine fetal demise	0 (0)	1 (2)	1 (1)
Cohort 2	DVR arm (n=104)* n (%)	TDF/FTC arm (n=50) n (%)	Both arms (n=154) n (%)
Live births	103 (99)	51 (100)**	154 (99)
Full term (≥ 37weeks)	97 (94)	47 (92)	144 (94)
Premature (<37 weeks)	6 (6)	4 (8)	10 (6)
Stillbirth/intrauterine fetal demise	1 (1)	0 (0)	1 (1)

No difference in preterm labor or still births

**51 live births amongst 50 participants due to an undiagnosed twin gestation

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Pregnancy Complications

Pregnancy complication	Cohort 1		Cohort 2		Local background frequencies (95% CI) of pregnancy complications
	Dapivirine arm (n=99) n (%)	TDF/FTC arm (n=49) n (%)	Dapivirine arm (n=106) n (%)	TDF/FTC arm (n=51) n (%)	
Any hypertensive disorder of pregnancy	3 (3)	4 (8)	9 (8)	5 (10)	10.5% (10.0,11.3)
Gestational hypertension	3 (3)	2 (4)	6 (6)	5 (10)	4.4% (4.0,4.8)
Pre-eclampsia					
Pre-eclampsia with severe features					
Eclampsia	0 (0)	0 (0)	0 (0)	0 (0)	0.6% (0.5,0.8)
Peripartum/Antepartum hemorrhage	0 (0)	1 (2)	2 (2)	2 (4)	--
Postpartum hemorrhage	2 (2)	1 (2)	2 (2)	0 (0)	3.2% (2.9,3.6)
Fever of unclear etiology	0 (0)	0 (0)	0 (0)	0 (0)	0.1% (0.1-0.2%)
Chorioamnionitis	0 (0)	0 (0)	1 (1)	0 (0)	0.2% (0.1-0.3%)
Postpartum endometritis	0 (0)	0 (0)	0 (0)	1 (2)	0.4% (0.3-0.5%)
Puerperal sepsis	0 (0)	0 (0)	0 (0)	2 (4)	-

No difference in pregnancy complications

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MTN-042 Maternal and Infant Safety Overview

- No HIV seroconversions to date
- No maternal deaths
- Maternal and infant serious adverse events and grade 3 or higher AEs by study arm and cohort were comparable
- 1 infant deaths in Cohort 1
  - Infant of mother randomized to TDF/FTC
  - Maternal participant experienced a placental abruption
  - Deemed not related to study product
- 1 infant deaths in Cohort 2
  - Infant of mother randomized to DVR
  - Born via cesarean section at 34 weeks and 6 days due to fetal distress
  - Noted to have multiple dysmorphic features involving the eyes, head shape and tongue
  - Deemed not related to study product

MTN-042 Acceptability and Adherence

- Pregnant people are like other people!
  - The vaginal PrEP ring is a new formulation for this population, but participants were able to use the ring without issue and fears regarding the ring diminished after the first use
  - Education and counseling from providers and past ring users helped alleviate concerns
- Preliminary adherence data are encouraging

MTN-042 Limitations, Strengths and the Bottom Line

- Limitations
  - Only uncomplicated singleton pregnancies in urban/ peri-urban settings were included
  - By design, drug exposure in both cohorts was short
  - Numbers are too small to detect rare pregnancy complications
- Strengths
  - MTN-042B provided complete background rates of pregnancy outcomes and complications for comparison
  - Site staff used standardized definitions based on the Global Alignment of Immunization safety Assessment in pregnancy (GAIA) guidelines*
  - Excellent retention in the setting of the global pandemic of COVID-19
- **Bottom Line:**
  - **The PrEP ring is safe and acceptable for use during pregnancy. There were no HIV seroconversions in either arm.**

* Bonhoeffer et al. The Brighton Collaboration: addressing the need for standardized case definitions of adverse events following immunization (AEFI), Vaccine, 2002

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Thank You

- **Participants** for their time, commitment, and trust
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- **Interim review panel**: Deborah M. Money, MD, FRCSC; Annie Lyerly, MD, MA; Richard Adanu, PhD; Professor Ellen Chirwa, PhD MRNM; Paige Williams, PhD, MS; Charles Shey Wiysonge, MD, PhD; Dorothy Mbori-Ngacha, MBChB, MMed, MPH
- **Study Products:** The dapivirine vaginal rings used in this study were developed and supplied by the International Partnership for Microbicides (IPM). Oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) was donated by Gilead Sciences.
- **Funders:** The study was designed and implemented by the Microbicide Trials Network (MTN). From 2006 until November 30, 2021, the MTN was an HIV/AIDS clinical trial network funded by the National Institute of Allergy and Infectious Diseases (UM1AI0686 33, 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 (NIH). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

MTN
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B-PROTECTED Study Findings

Lisa Noguchi, PhD
Jhpiego

Results of a multi-country, Phase 3B randomized trial of dapivirine vaginal ring and oral pre-exposure prophylaxis use for HIV prevention during breastfeeding

Lisa Noguchi, PhD, CNM, CPPS

Director, Maternal and Newborn Health

Jhpiego, Johns Hopkins University

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In your community, what options do HIV-negative women have to prevent getting an HIV infection while they are breastfeeding?

Why is breastfeeding so important?

- Undernutrition is a leading cause of child deaths (45%)
- 820,000 deaths of children <5 years old could be saved yearly via optimal breastfeeding
    - Benefits for infants
        - Provides complete nutrition
        - Fewer gastrointestinal infections
        - Reduced risk of infections (ear, respiratory, etc.)
        - Decreased SIDS risk
    - Benefits for mothers
        - Reduced risk of ovarian and breast cancer
        - Can help with pregnancy spacing
        - Healthier babies = healthier families

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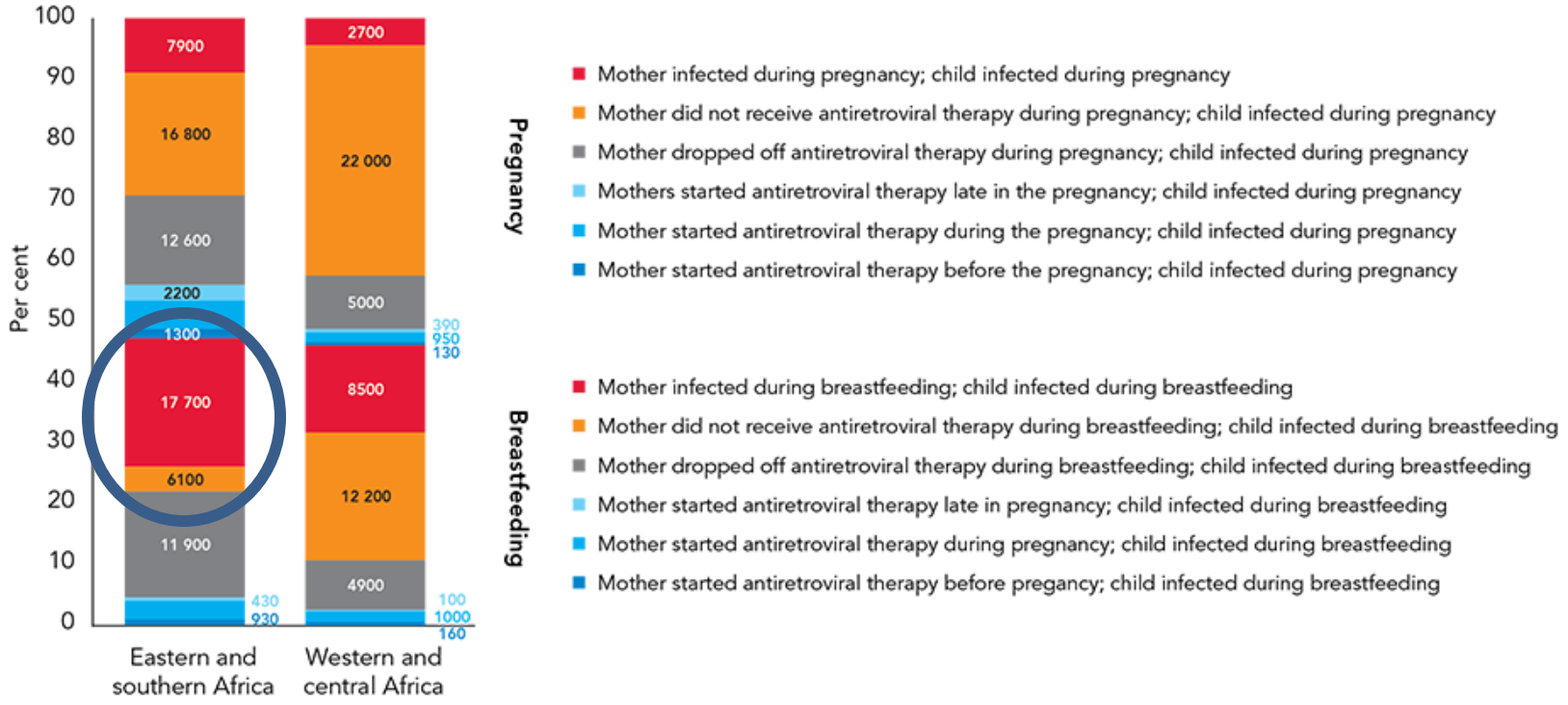
Incident HIV infection during breastfeeding is responsible for ~23% of vertical HIV transmission in eastern and southern Africa



UNAIDS, 2019

Incident HIV infection during the postnatal period is high and is associated with a higher risk of vertical transmission

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Not all effective biomedical HIV prevention strategies are available to breastfeeding populations

WHO guidance supports oral pre-exposure prophylaxis (PrEP) use for breastfeeding persons at substantial risk of HIV acquisition

200mg emtricitabine (FTC)/300mg tenofovir disoproxil fumarate (TDF) tablet (oral PrEP)

In 2021, WHO recommended dapivirine VR ("PrEP ring") for HIV prevention

Silicone matrix vaginal ring, 25 mg dapivirine

Now approved in multiple countries

Guidelines do not yet include pregnant or breastfeeding populations due to data gaps

Injectable long-acting cabotegravir: While the very limited data available from the small number of women who became pregnant during studies suggest that CAB-LA may be safe during pregnancy and breastfeeding, more research and safety surveillance in pregnancy are needed.

B-PROTECTED Phase 3B randomized trial

Healthy, HIV-, breastfeeding mother-infant pairs, randomized 3:1

(VR: PrEP)

Monthly dapivirine vaginal ring

(VR)

Daily oral 200mg FTC/300mg TDF

(oral PrEP)

12-week exposure to study product

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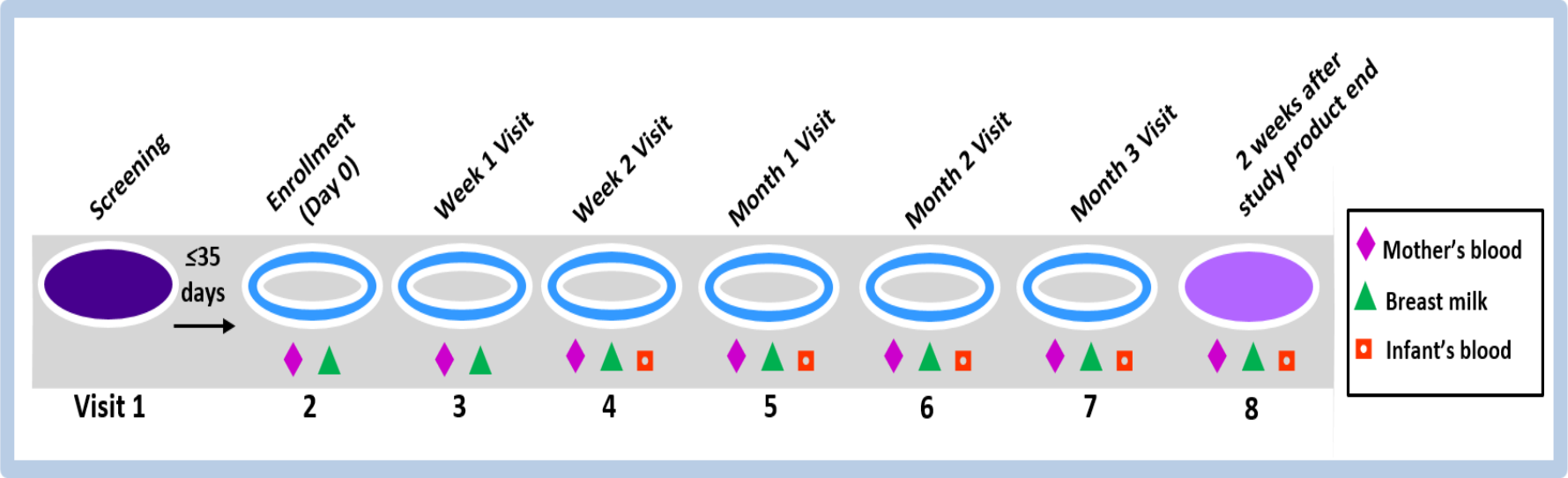
Study Visit Schedule



- Serious adverse events (SAEs) and adverse events (AEs) collected
- Drug concentrations in maternal blood/plasma, breast milk, infant blood/plasma; residual in VR
- Acceptability assessed via questionnaire

Adverse events defined by Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017 and/or Addendum 1 (Female Genital Grading Table for Use in Microbicide Studies [Dated November 2007]) in both trial groups.

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Objectives and Endpoints

Objectives		Endpoints
Primary	Maternal safety	All serious adverse events (SAEs) and grade 3 or higher AEs
Primary	Infant safety	All SAEs and grade 3 or higher AEs
Primary	Study drug detection and concentrations	Maternal plasma dapivirine, dried blood spot (DBS) emtricitabine triphosphate (FTC-TP) and TFV-DP (tenofovir diphosphate) Maternal breast milk dapivirine or FTC-TP and TFV-DP Infant plasma dapivirine Infant DBS FTC-TP and TFV-DP
Secondary	Willingness to use Acceptability	During breastfeeding in the future Proportion who find product at least as acceptable as other HIV prevention methods
Secondary	Adherence	Reported frequency of study product use (e.g., missed doses, VR removal/expulsions) Residual drug levels in returned VRs Maternal plasma dapivirine, DBS FTC-TP, and TFV-DP

Bottom line: Was it safe for mom and baby? How much medication passed to babies? Did users like and use the products?

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Why was exclusive breastfeeding so important for MTN-043 objectives?

Safety

Risk of food-borne illness increases once complementary foods are started – can be confused with adverse events related to study product exposure

Pharmacokinetics

Understand likely maximum potential drug exposure for infant, and infant PK may vary with amount and type of complementary food(s), e.g., fat intake

Impact on breastfeeding

More accurate estimate before starting complementary foods, which decrease milk supply (FDA requires drug label to summarize effect on milk production)

Baseline Demographic Characteristics

	Dapivirine Ring Group n=148		Oral PrEP Group n=49		All Participants N=197	
Mothers						
Age (years)*	26	(18, 43)	25	(18, 38)	26	(18, 43)
# of live births	2	(1, 6)	2	(1, 5)	2	(1, 6)
Has a primary partner	144	97%	48	98%	192	97%
Infants						
Age (weeks)						
6 to 9 weeks	87	59%	34	69%	121	61%
>9 to 12 weeks	61	41%	15	31%	76	39%
Female sex at birth	84	57%	24	49%	108	55%

Bottom line: On average, the groups of women who used the PrEP ring and who used oral PrEP were pretty similar.

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Excellent Safety Profiles for Mothers and Infants

	Mothers				Infants			
	Serious Adverse Events		Grade 3 or Higher Adverse Events		Serious Adverse Events		Grade 3 or Higher Adverse Events	
	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)
Dapivirine VR	2/148	1% (0, 5)	3/148	2% (0, 6)	4/148	3% (1, 7)	10/148	7% (3, 12)
Oral PrEP	0/49	0% (0, 7)	2/49	4% (1, 14)	0/49	0% (0, 7)	1/49	2% (0, 11)

Uterine leiomyoma
Appendiceal abscess

Bronchiolitis (n=2)
Dysentery
Pneumonia

No SAEs or grade ≥3 AEs were related to study product for mothers and infants

Bottom line: Both oral PrEP and PrEP ring were extremely safe.

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Dapivirine Quantification and Concentrations in Maternal Plasma, Breast Milk, and Infant Plasma

	Maternal Plasma		Breast Milk		Infant Plasma	
	Quantification (%)	Median (IQR) pg/mL	Quantification (%)	Median (IQR) pg/mL	Quantification (%)	Median (IQR) pg/mL
Week 1	99%	374.0 (285.0, 448.0),	99%	656.0 (407.0, 878.0)	--	--
Week 2	98%	388.5 (299.0, 469.0)	99%	611.0 (407.0, 877.0)	15%	BLQ (BLQ, BLQ)[a]
Month 1	99%	326.0 (241.0, 402.0)	99%	559.0 (339.5, 811.0)	14%	BLQ (BLQ, BLQ)
Month 2	96%	316.5 (234.5, 428.0)	97%	545.0 (315.0, 719.0)	10%	BLQ (BLQ, BLQ)[a]
Month 3	98 %	311.0 (212.0, 406.0)	98%	558.5 (282.0, 778.0)	5%	BLQ (BLQ, BLQ)[a]
2 weeks post-use	34 %	BLQ (BLQ, 29.7)[a]	66%	16.7 (BLQ, 49.1)[a]	0%	BLQ (BLQ, BLQ)[a]

BLQ= below lower level of quantification; LLOQ= lower level of quantification. [a] LLOQ of dapivirine in plasma and breast milk were 20 pg/mL and 10 pg/mL, respectively. Drug concentrations below LLOQ are identified as "BLQ".

Bottom line: Very little dapivirine passed to milk and even less to babies.

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TFV-DP and FTC-TP Quantification and Concentrations in Maternal and Infant Dried Blood Spots

	Quantification and Concentrations of TFV-DP				Quantification and Concentrations of FTC-TP			
	Maternal DBS		Infant DBS		Maternal DBS		Infant DBS	
	Quantification (%)	Median (IQR) fmol/ punch	Quantification (%)	Median (IQR) fmol/ punch	Quantification (%)	Median (IQR) pmol/ punch	Quantification (%)	Median (IQR) pmol/ punch
Week 1	100%	263 (193, 363)	n.a.	n.a.	96%	0.34 (0.27, 0.45)	n.a.	n.a.
Week 2	100%	463 (270.5, 613)	0%	BLQ (BLQ, BLQ)[a]	96%	0.37 (0.26, 0.47)	9%	BLQ (BLQ, BLQ)[a]
Month 1	96%	675.5 (380, 983)	0%	BLQ (BLQ, BLQ)[a]	83%	0.33 (0.19, 0.46)	4%	BLQ (BLQ, BLQ)[a]
Month 2	100%	612.5 (327.5, 1041)	0%	BLQ (BLQ, BLQ)[a]	77%	0.30 (0.17, 0.41)	4%	BLQ (BLQ, BLQ)[a]
Month 3	100%	777 (381, 1241)	0%	BLQ (BLQ, BLQ)[a]	81%	0.31 (0.19, 0.39)	2%	BLQ (BLQ, BLQ)[a]
2 weeks post-use	98%	410.5 (216, 674)	0%	BLQ (BLQ, BLQ)[a]	2%	BLQ (BLQ, BLQ)[a]	0%	BLQ (BLQ, BLQ)[a]

BLQ= below lower level of quantification; DBS= dried blood spots; FTC-TP = emtricitabine triphosphate; TFV-DP = tenofovir diphosphate; LLOQ= lower level of quantification. [a] LLOQ of TFV-DP and FTC-TP in DBS were 31.3 fmol/punch and 0.125 pmol/punch, respectively.

Bottom line: No significant transfer of oral PrEP medications to infants via breastfeeding.

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Adherence

Use Category	DVR n (%)	Use Category	Oral FTC/TDF n (%)
Month1	141 (95.3)	Month 1	46 (93.9)
Low/No use	16 (11.3)	Low/No use	2 (4.3)
Some release	108 (76.6)	Some use	22 (47.8)
High release	17 (12.1)	High use	22 (47.8)
Month 2	143 (96.6)	Month 2	44 (89.8)
Low/No use	28 (19.6)	Low/No use	0
Some release	99 (69.2)	Some use	24 (54.5)
High release	16 (11.2)	High use	20 (45.5)
Month 3	132 (89.2)	Month 3	47 (95.9)
Low/No use	29 (22.0)	Low/No use	0
Some release	89 (67.4)	Some use	23 (48.9)
High release	14 (10.6)	High use	24 (51.1)

Bottom line: Drug levels were consistent with product use.

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High User Acceptability for Both Products

Most found both products acceptable

Overall 97%

VR 97%

Oral PrEP 98%

Most willing to use assigned product when breastfeeding in the future

Overall 98%

VR 98%

Oral PrEP 100%

Most preferred study product to which they were assigned

No difference between acceptability of the two study products for both acceptability aspects above

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First study of dapivirine VR use during breastfeeding

Both PrEP ring and oral PrEP have favorable safety profile among breastfeeding mothers-infant pairs

Adherence and acceptability generally **high**

Drug levels in breast milk and infant samples **low**

Expand HIV prevention choices during breastfeeding to include dapivirine vaginal ring

Ample evidence to warrant update of dapivirine ring guidelines to include breastfeeding individuals

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Thank-you


A mother's
breastmilk
supplies the
essential nutrients
a newborn
needs to thrive.
Photo by Kate Holt/Jhpiego

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Discussion & Reflection

Michelle Rodolph, World Health Organization

Discussion & Reflection

- How will WHO respond to these new findings?
- What is the usual process and timeline for updating WHO PrEP guidance?
- Will the next update include guidance on ring use during pregnancy, breastfeeding, and adolescence?

Upcoming Sessions

The MOSAIC Global PrEP Learning Network takes place **quarterly.**

The next session will be in **early 2024**.

Visit PrEP Watch

This webinar will be accessible on PrEPWatch next month.

Complementary resources, relevant articles, tools, and **registration for upcoming webinars** can also be found on PrEPWatch.

Visit https://www.prepwatch.org/global-prep-learning-network/ for more.

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