



B-Protected (MTN-043)



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Overview

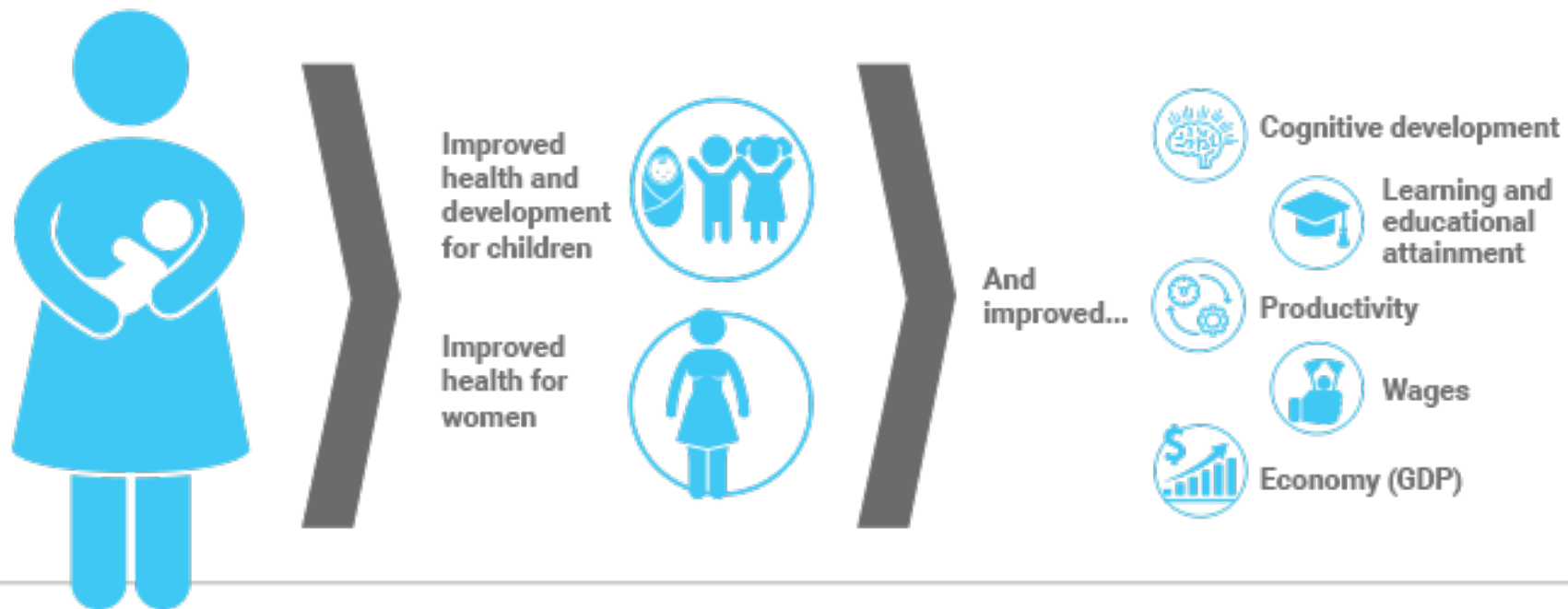
- Breastfeeding in the context of HIV prevention
- What do we know about oral PrEP and the dapivirine vaginal ring in breastfeeding women?
- B-Protected



Maxensia Owor, MBChB MMed
B-Protected Protocol Chair

Breastfeeding is one of the most effective ways to promote child health and survival

Improved rates of breastfeeding lead to...



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; and
 - Breastfeeding should continue up to two years of age and beyond, along with appropriate complementary foods





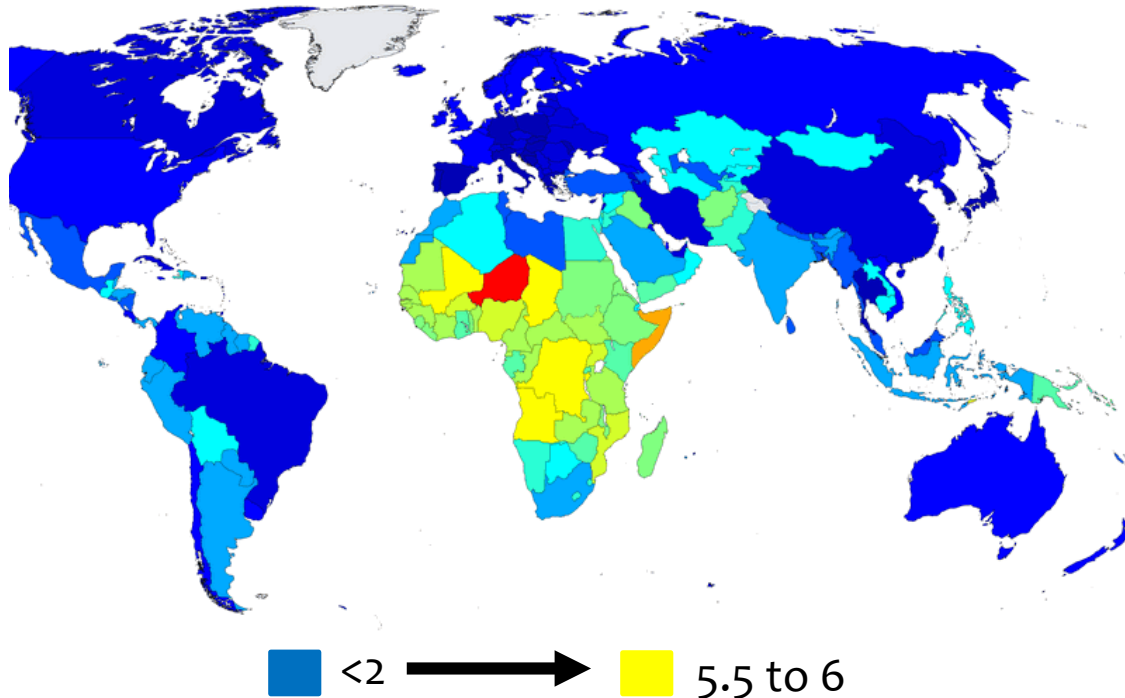
Global Targets 2025: To improve maternal, infant and young child nutrition



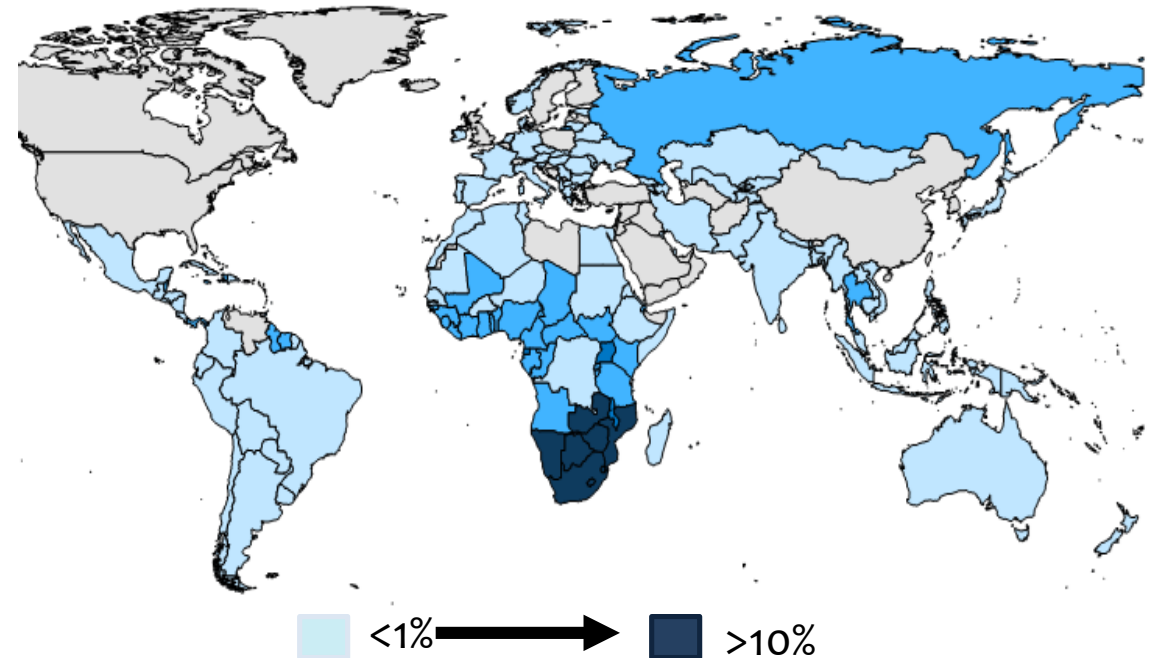
- To increase the rate of exclusive breastfeeding in the first six months up to at least 50%
- Countries that have already surpassed this target are encouraged to continue progressing towards higher rates

Synergy between fertility rates and HIV prevalence

Total fertility rate

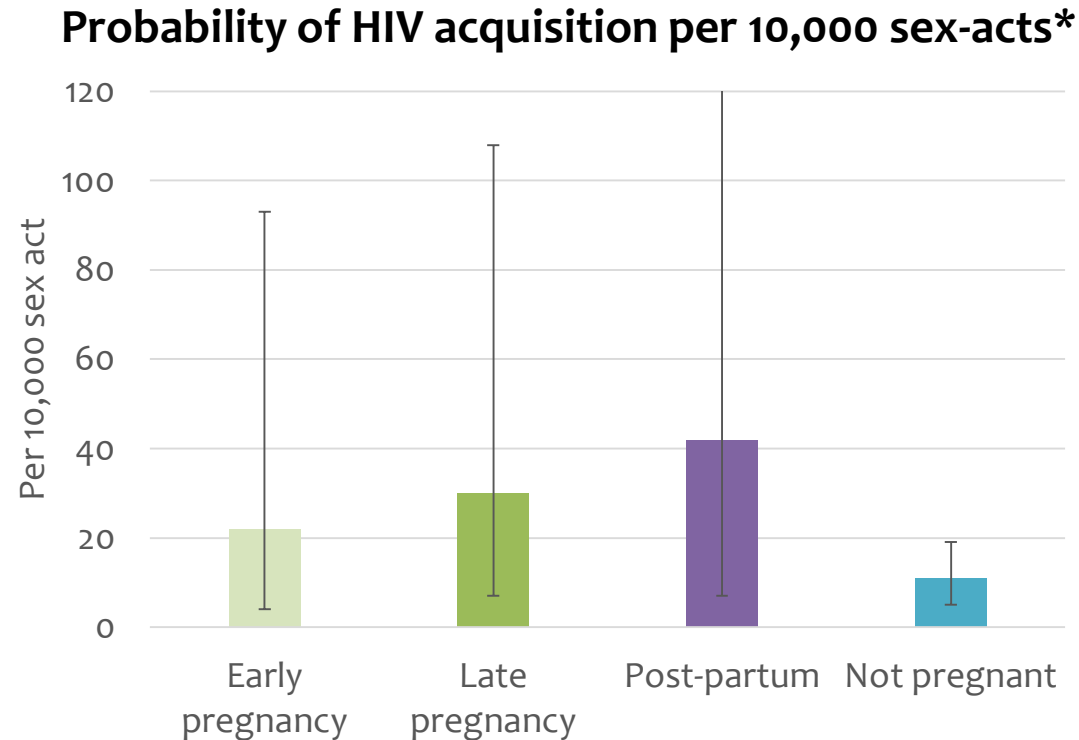


Adult HIV prevalence - 2017



Significant overlap exists between high-parity countries where extended breastfeeding is the norm and those most impacted by the HIV epidemic

Postpartum women are at increased risk of HIV-1 acquisition



- HIV-1 incidence in pregnant and postpartum women is similar to incidence among non-pregnant women
- However, pregnant and postpartum women may have less frequent sex
- As a result, the probability of acquisition at each sex act may be higher than compared to non-pregnant women

*For a 25-year-old woman not taking PrEP, the HIV acquisition probability per condomless sex act with an HIV-infected male partner with a viral load of 10,000 copies/mL

Long cumulative duration of heightened HIV-1 risk

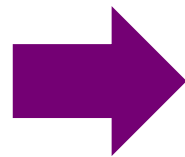
	Malawi	South Africa	Uganda	Zimbabwe
Average Life expectancy	63 years	63 years	60 years	61 years
Total fertility rate	4.6	2.5	5.6	3.8
Total years pregnant/lactating*	8 years	4.4 years	9.8 years	6.7 years
	~26% of reproductive years	~12% of reproductive years	~29% of reproductive years	~20% of reproductive years
HIV prevalence in adult women	12.8%	23.7%	7.3%	16.1%

*Assuming 1.75 years pregnant & lactating per pregnancy

Urgent need to understand the impact of HIV prevention products in breastfeeding women

- Breastfeeding women do not represent a separate, special population at risk for HIV, but a very significant proportion of the general population of women at any given time
- That said, investigational products need to specifically be evaluated in breastfeeding women

Does the
investigational
product...



Impact milk supply

Pass into breastmilk

Get orally absorbed by
the infant

Have adverse effects
on the infant

Reassuring data from Kenya and Uganda about the use of oral PrEP in breastfeeding women



RESEARCH ARTICLE

Pre-exposure Prophylaxis Use by Breastfeeding HIV-Uninfected Women: A Prospective Short-Term Study of Antiretroviral Excretion in Breast Milk and Infant Absorption

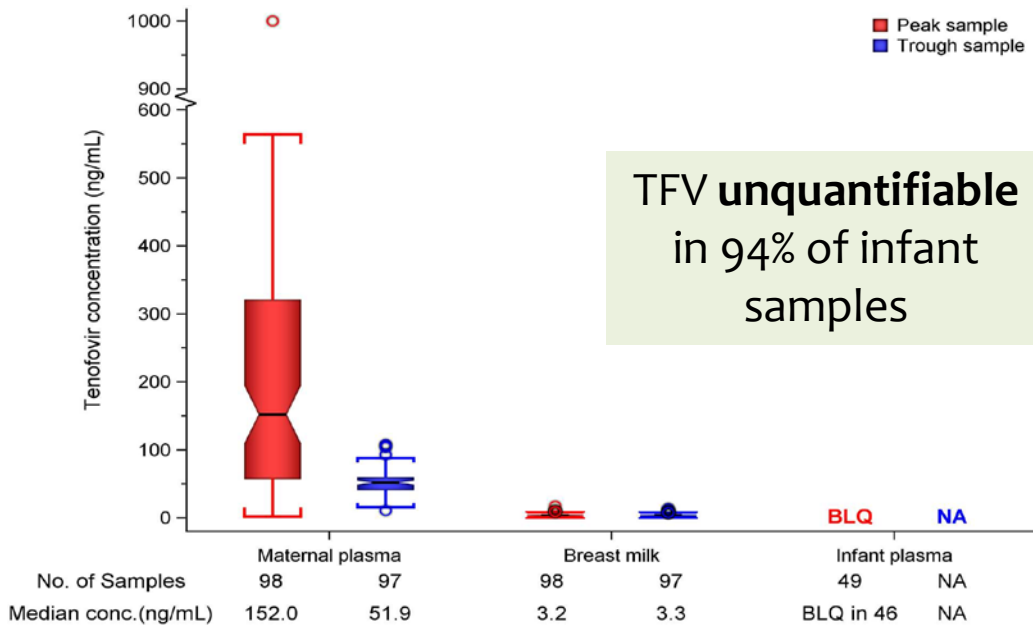
Kenneth K. Mugwanya^{1,2,3*}, Craig W. Hendrix⁴, Nelly R. Mugo^{2,5}, Mark Marzinke⁴, Eilly T. Katabira⁶, Kenneth Ngure^{2,7}, Nulu B. Semiyaga⁸, Grace John-Stewart^{1,2,9,10}, Timothy R. Muwonge⁸, Gabriel Muthuri¹¹, Andy Stergachis^{2,12}, Connie L. Celum^{1,2,9}, Jared M. Baeten^{1,2,9}

ClinicalTrials.gov Identifier: NCT02776748

- Prospective open-label, daily oral FTC/TDF for 10 days via directly observed therapy (DOT)
- 50 HIV-uninfected mother–infant pairs between 1–24 weeks postpartum
- Aimed to quantify steady-state TFV and FTC levels in infant plasma
 - Maternal plasma and breast milk drug concentration steady states (days 7 & 10)
 - Single infant plasma sample obtained on day 7

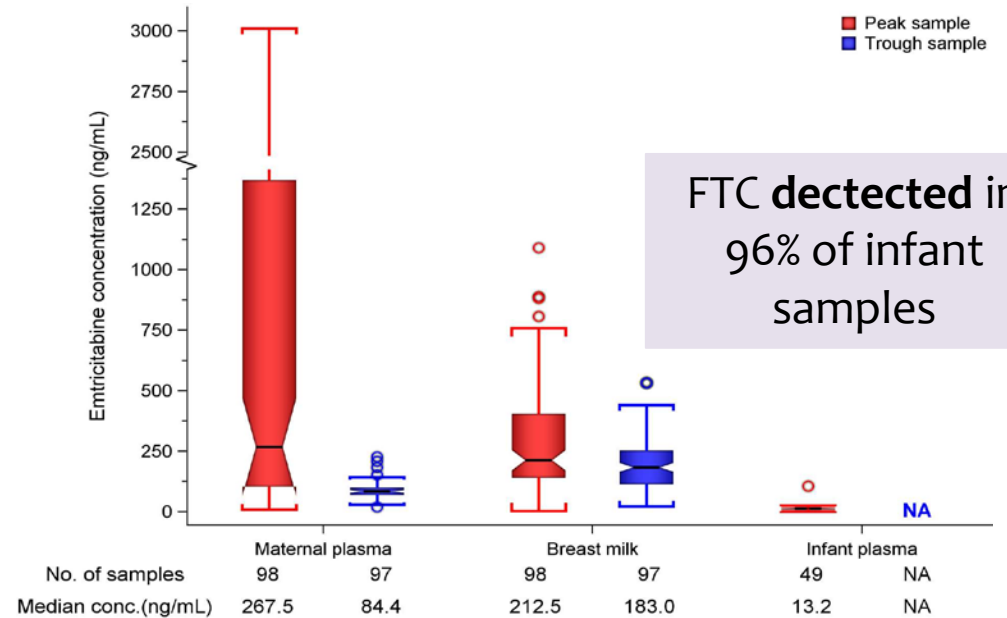
Concentrations of TFV and FTC in maternal plasma, breast milk and infant plasma were very low

TFV concentrations



TFV= 0.47 $\mu\text{g}/\text{kg}$ (IQR 0.35 to 0.71) infant exposure

FTC concentrations



FTC = 31.9 $\mu\text{g}/\text{kg}$ (IQR 21.0 to 60.8) infant exposure

Infant exposure via daily breastfeeding results in a very small fraction of the 6 mg/kg dose (<0.01% and 0.5%) used in infant HIV treatment and prevention of infant postnatal HIV, which is considered safe

Bottom Line

- Estimated infant doses from breast milk for TFV and FTC were very low
- Suggests PrEP can be safely used during breast feeding with minimal infant drug exposure



What about the dapivirine vaginal ring?



Congratulations, MTN-029/IPM 039 Team!



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Antiviral Agents

Pharmacokinetics of Dapivirine Transfer into Blood Plasma, Breast Milk, and Cervicovaginal Fluid of Lactating Women using the Dapivirine Vaginal Ring

Lisa M. Noguchi, Craig Hoesley, Cliff Kelly, Rachel Scheckter, Katherine Bunge, Annalene Nel, Mark A. Marzinke, Craig W. Hendrix, Charlene S. Dezzutti, Sharon L. Hillier, Debra L. Bogen, Jeanna M. Piper, Richard H. Beigi

MTN-029/IPM 039

- Phase 1, open-label study of DPV VR among 16 healthy adult lactating women
 - All women had recently weaned infants
 - Infants were not participants!
- Women instructed to use VR for 14 days
- Collected milk, plasma, and cervicovaginal fluid samples
- Estimated infant exposure based on milk drug levels (no actual infant exposure)

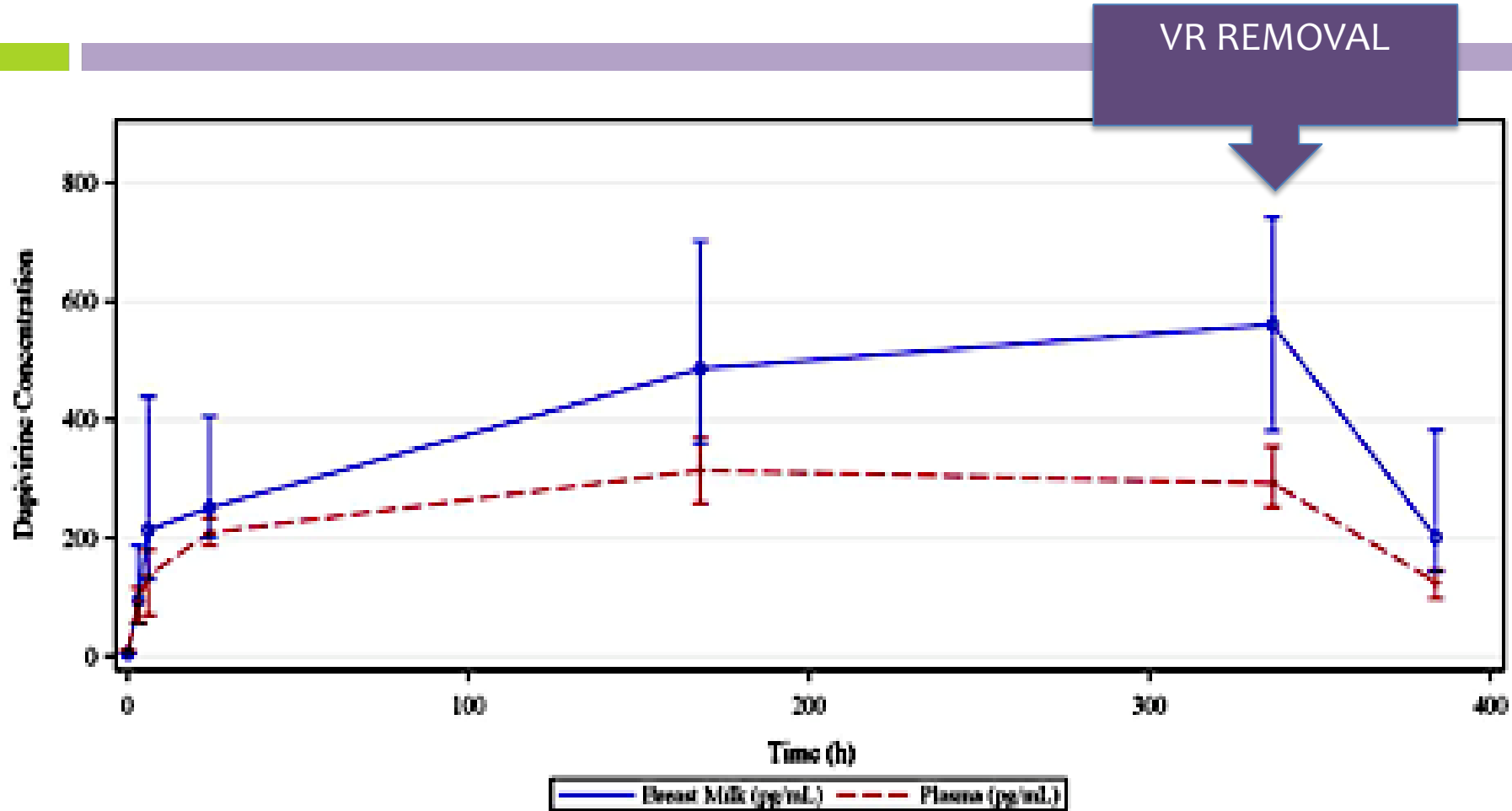
Safe and Well-tolerated

- 10 adverse events (AEs) reported from 6 participants
 - 8 Grade 1, 2 Grade 2 (no Grade 3 or higher)
- Two AEs deemed related to VR
 - Grade 1 vaginal discharge and vaginal odor (in same participant)
- Two abnormal pelvic exam findings
 - Vaginal spotting and vaginal abrasion

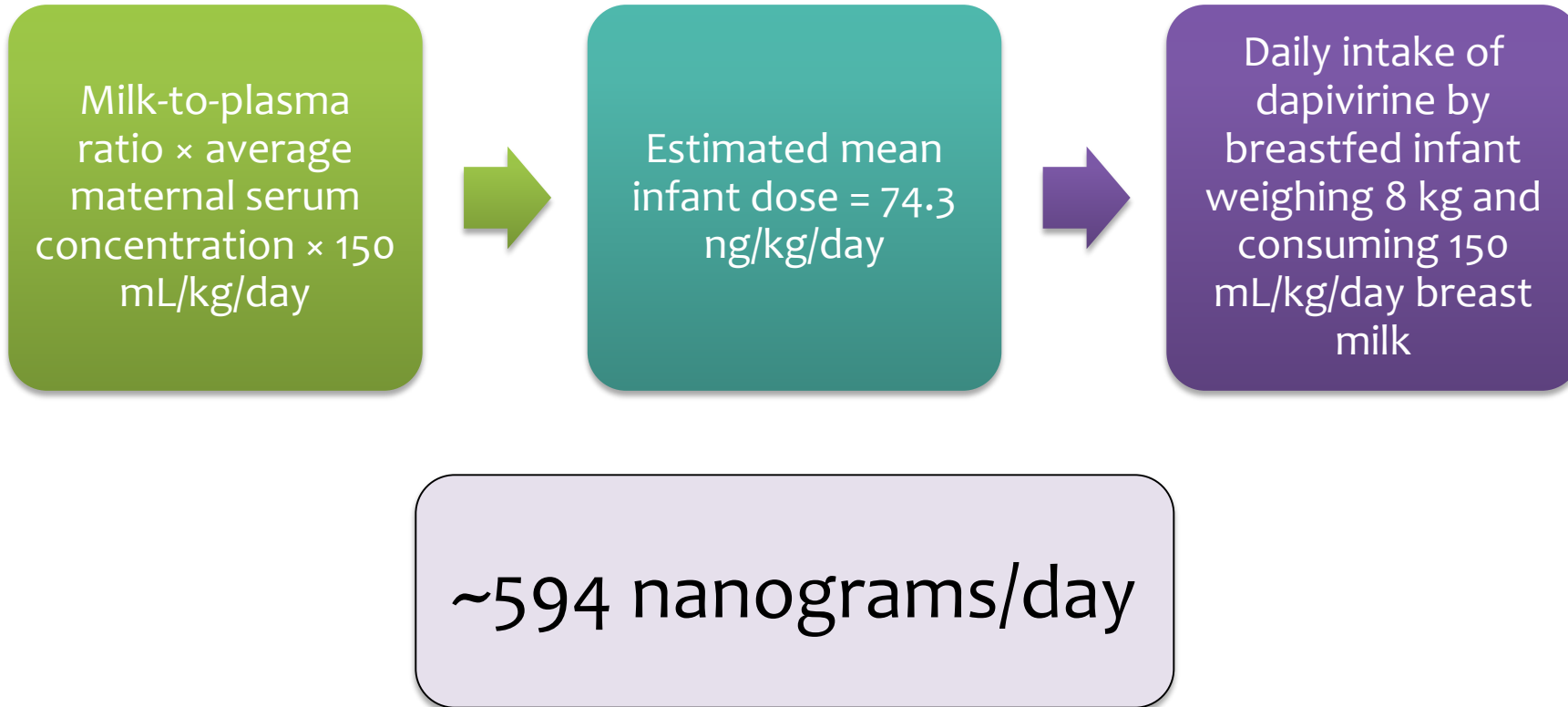
DPV Levels in MTN-029/IPM 039

- Median DPV levels
 - 676 pg/mL in breast milk
 - 327 pg/mL in plasma (milk:plasma ~2.0)
 - 36.25 ng/mg in cervicovaginal fluid

Absolute Levels in Milk Were Low



What does this mean for possible infant exposure?



594 nanograms of dapivirine per day for the rest of your life would still add up to less than one grain of rice.



Bottom Line



- Favorable safety profile
- Low levels in milk and plasma
- Some DPV accumulation in milk
 - Absolute levels very low
- $\frac{1}{2}$ of drug gone from blood and milk <2 days after VR removal
- Estimated potential daily levels of infant exposure very low



B ♥ Protected



- **B**reastfeeding
- **P**rEP &
- **R**ing
- **O**pen-label
- **T**rial to
- **E**nsure
- **C**ollection of
- **T**imely and
- **E**ssential
- **D**ata

Study Population



200 breastfeeding mother-infant pairs

Sites



- Blantyre
- MU-JHU
- Wits
- Zengeza



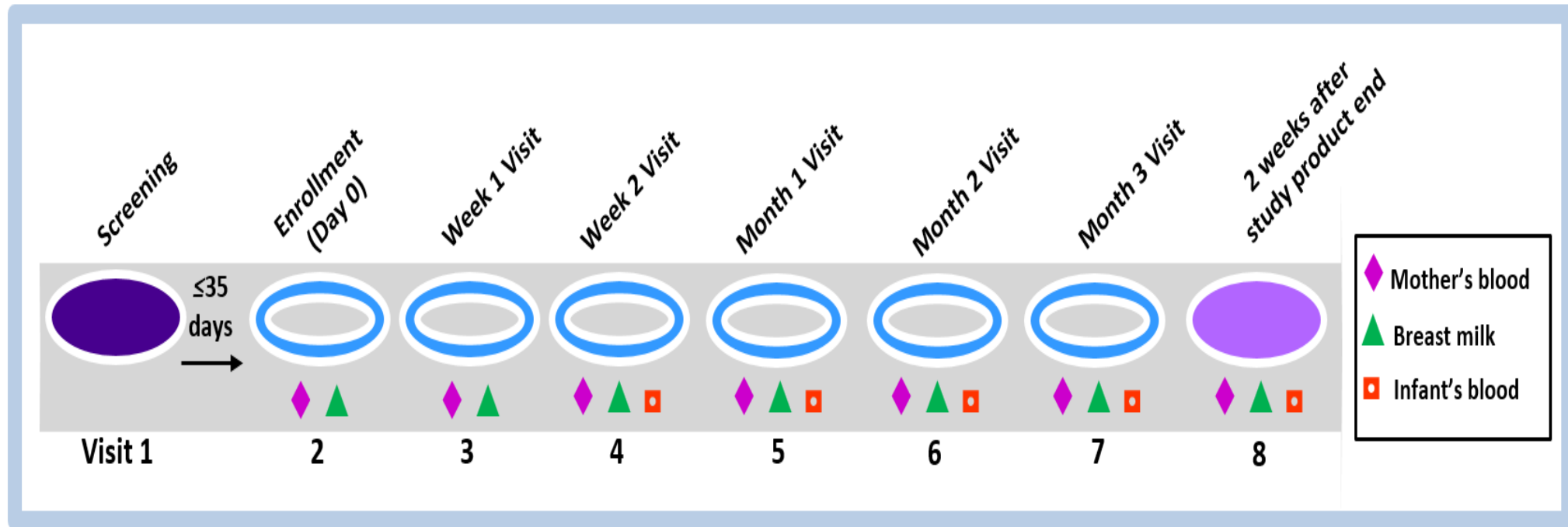
Study Hypotheses

- Study products will be safe and well-tolerated by mothers and breastfeeding infants
- Study drugs will be detectable at low levels in milk
 - Dapivirine
 - FTC-TP (emtricitabine) and TFV-DP (tenofovir)
- Study drugs will be detectable in blood of some breastfeeding infants

Overview

Design	Phase 3B, randomized (3:1 ring to PrEP), open-label
Duration	Each mother-infant pair followed up to ~3.5 months
Regimen	DPV 25 mg VR replaced each month for 12 weeks or Truvada one tablet by mouth daily for 12 weeks
PK	Maternal blood and milk, infant blood concentrations assessed at multiple time points

Study Visit Schedule



Primary Objectives

- Maternal safety profile
 - All SAEs and grade 3 or higher AEs
- Infant safety profile
 - All SAEs and grade 3 or higher AEs
- Study drug detection and concentration
 - Maternal plasma DPV or blood FTC-TP and TFV-DP
 - Maternal breast milk DPV or FTC-TP and TFV-DP
 - Infant plasma DPV concentrations or blood FTC-TP and TFV-DP concentrations

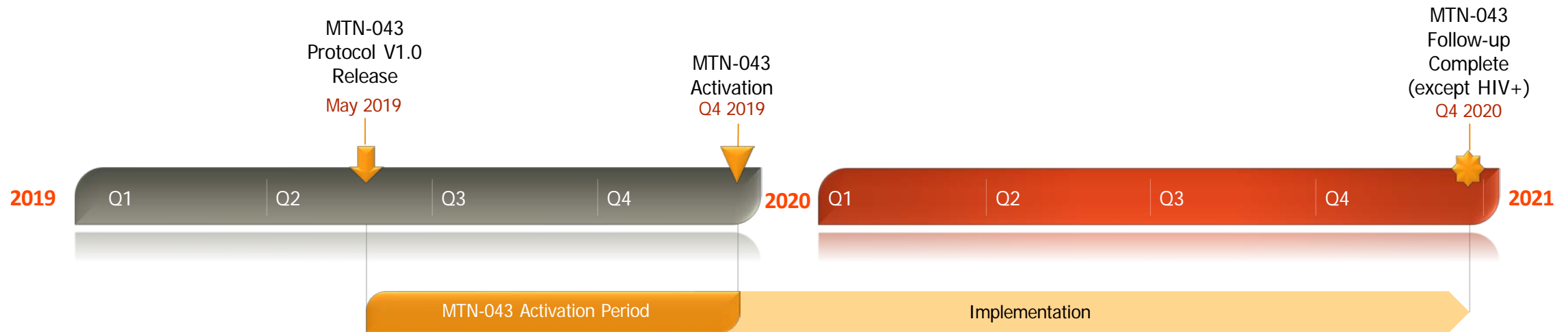
Secondary Objectives

- Adherence
 - Reported frequency of study product use (e.g., missed doses, VR removal/expulsions)
 - Residual drug levels in returned VRs
 - Maternal plasma DPV, blood FTC-TP and TFV-DP
- Willingness to use study product
 - During breastfeeding in the future
 - Proportion who find study product at least as acceptable as other HIV prevention methods

Exploratory Objectives

- Acceptability
 - Experiences with study products and preferences for product attributes
 - Attitudes about study products, and perceived attitudes of key influencers
- Genital Microenvironment
 - Gram stain and quantitative PCR, biomarkers
- Breastfeeding
 - Duration, weaning, supplementation

Timeline



- Anticipate release of Protocol V1.0 in May 2019
- First activation targeted for end of Q4 2019, with enrollments starting early Q1 2020
- Accrual and follow-up expected to last 8-10 months at each site. Depending on activation spread across sites, may complete follow-up by Q4 2020

What are the risks of not breastfeeding and early weaning?

Mothers

- Breast cancer
- Ovarian cancer
- Diabetes
- Hypertension
- Myocardial infarction

Infants

- Diarrhea
- Malnutrition
- Otitis media
- Lower respiratory tract infection
- SIDS
- Leukemia
- Type 1 diabetes



#breastfeeding

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

Thank you!



Acknowledgements

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MTN-041, 042, and 043 Protocol Teams

MTN CWG, BSWG, and BRWG

Photo credits: Jhpiego, UNICEF