Safety and Pharmacokinetics of Dapivirine Ring Use during Lactation

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on behalf of the MTN-029/IPM 039 Protocol Team

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Dapivirine Vaginal Ring

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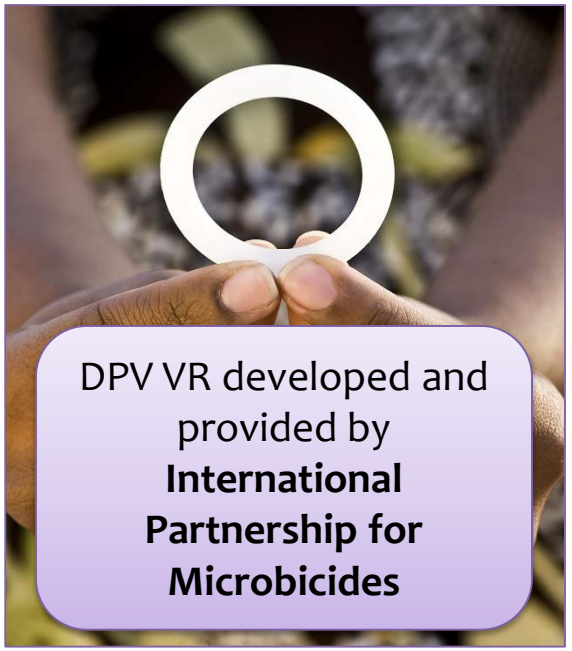
Use of a Vaginal Ring Containing Dapivirine for HIV-1 Prevention in Women

J.M. Baeten, T. Palanee-Phillips, E.R. Brown, K. Schwartz, L.E. Soto-Torres, V. Govender, N.M. Mgodi, F. Matovu Kiweewa, G. Nair, F. Mhlanga, S. Siva, L.-G. Bekker, N. Jeenarain, Z. Gaffoor, F. Martinson, B. Makanani, A. Pather, L. Naidoo, M. Husnik, B.A. Richardson, U.M. Parikh, J.W. Mellors, M.A. Marzinke, C.W. Hendrix, A. van der Straten, G. Ramjee, Z.M. Chirenje, C. Nakabiito, T.E. Taha, J. Jones, A. Mayo, R. Scheckter, J. Berthiaume, E. Livant, C. Jacobson, P. Ndase, R. White, K. Patterson, D. Germuga, B. Galaska, K. Bunge, D. Singh, D.W. Szydlo, E.T. Montgomery, B.S. Mensch, K. Torjesen, C.I. Grossman, N. Chakhtoura, A. Nel, Z. Rosenberg, I. McGowan, and S. Hillier, for the MTN-020–ASPIRE Study Team*



DPV VR developed and provided by **International Partnership for Microbicides**

25 mg dapivirine (DPV) vaginal ring (VR) reduced women's risk of acquiring HIV infection by ~27%

Baeten, J.M. et al, Use of a vaginal ring containing dapivirine for HIV-1 prevention in women. N Engl J Med. 2016;375:2121.

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Breastfeeding Data are Critical

- Many safety/pharmacokinetic (PK) studies exclude breastfeeding (BF)
- WHO recommends exclusive BF 6 months, then 2+ years
- Possible ↑ risk HIV acquisition
- High total fertility rates and long BF in areas with ↑HIV incidence
- FDA recommends BF studies

http://www.who.int/topics/breastfeeding/en/.

De Schacht, C. et al. High HIV incidence in the postpartum period sustains vertical transmission in settings with generalized epidemics: a cohort study in Southern Mozambique. JIAS. 2014; 17:18808.

https://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127505.pdf.

Prevention Can't Exclude Pregnant and Breastfeeding Women

	Total Fertility Rate (births/woman)	% infants ever breastfed
Malawi	5.1	97.7
South Africa	2.4	87.4
Uganda	5.8	98.2
Zimbabwe	3.9	98.1

TFR, World Bank, 2014; Malawi, 2015-6 DHS; South Africa, 1998 DHS; Uganda, 2011 DHS; Zimbabwe, 2015 DHS

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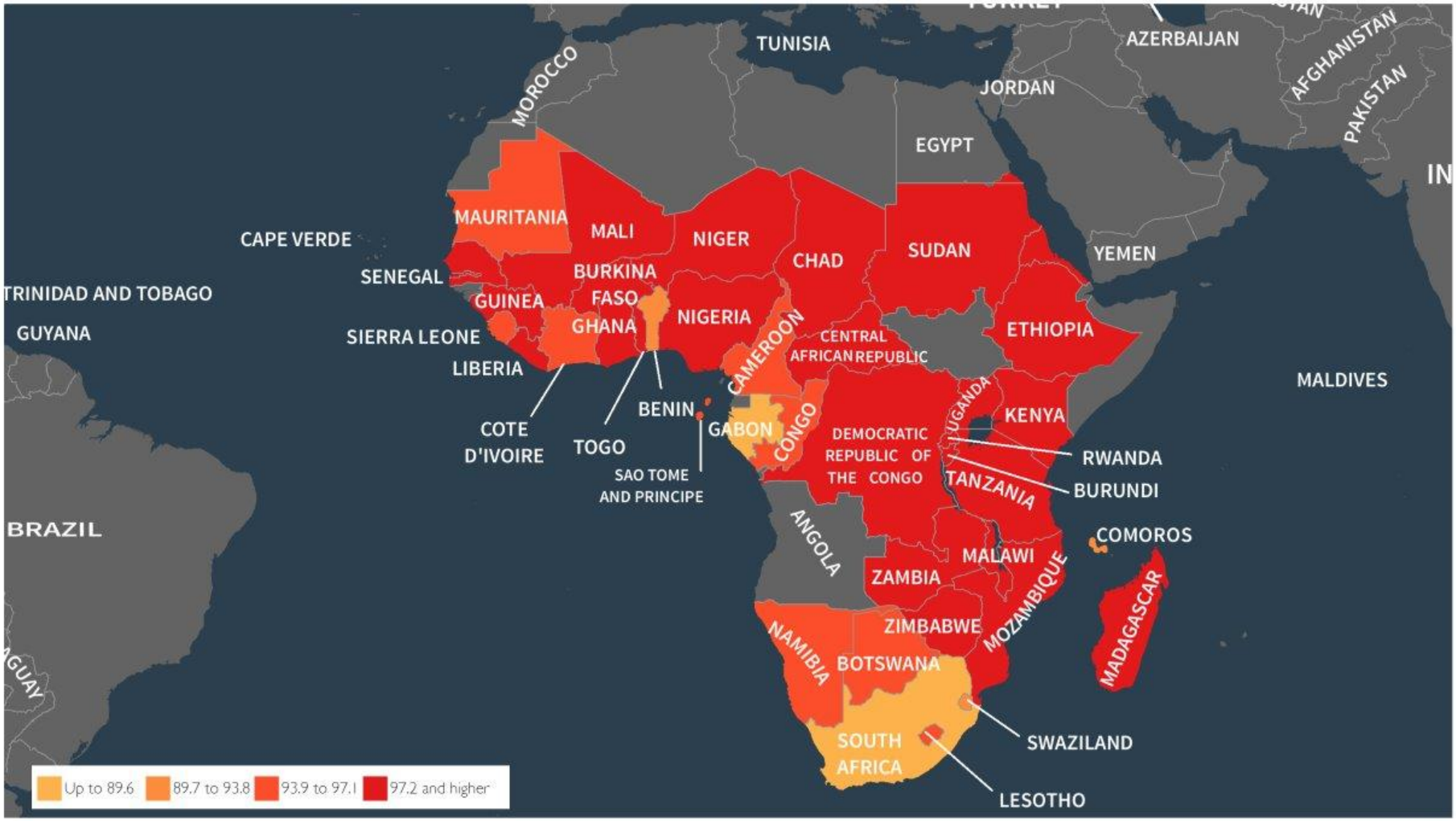
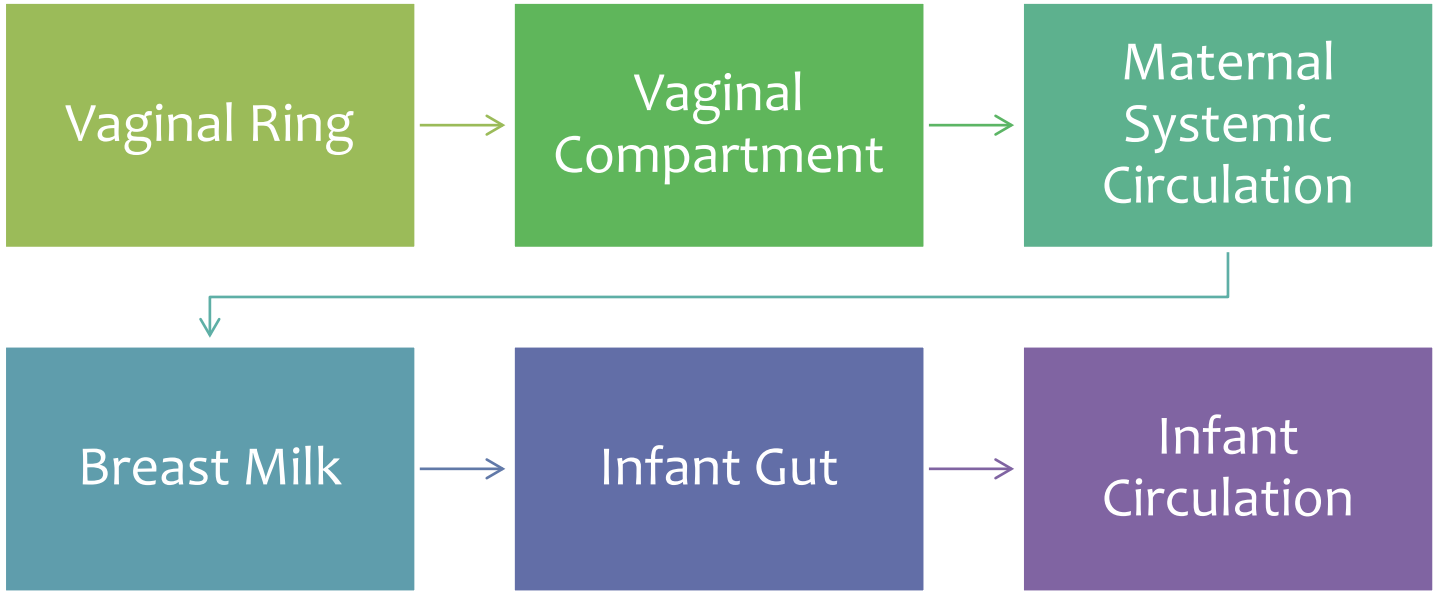
Children Ever Breastfed

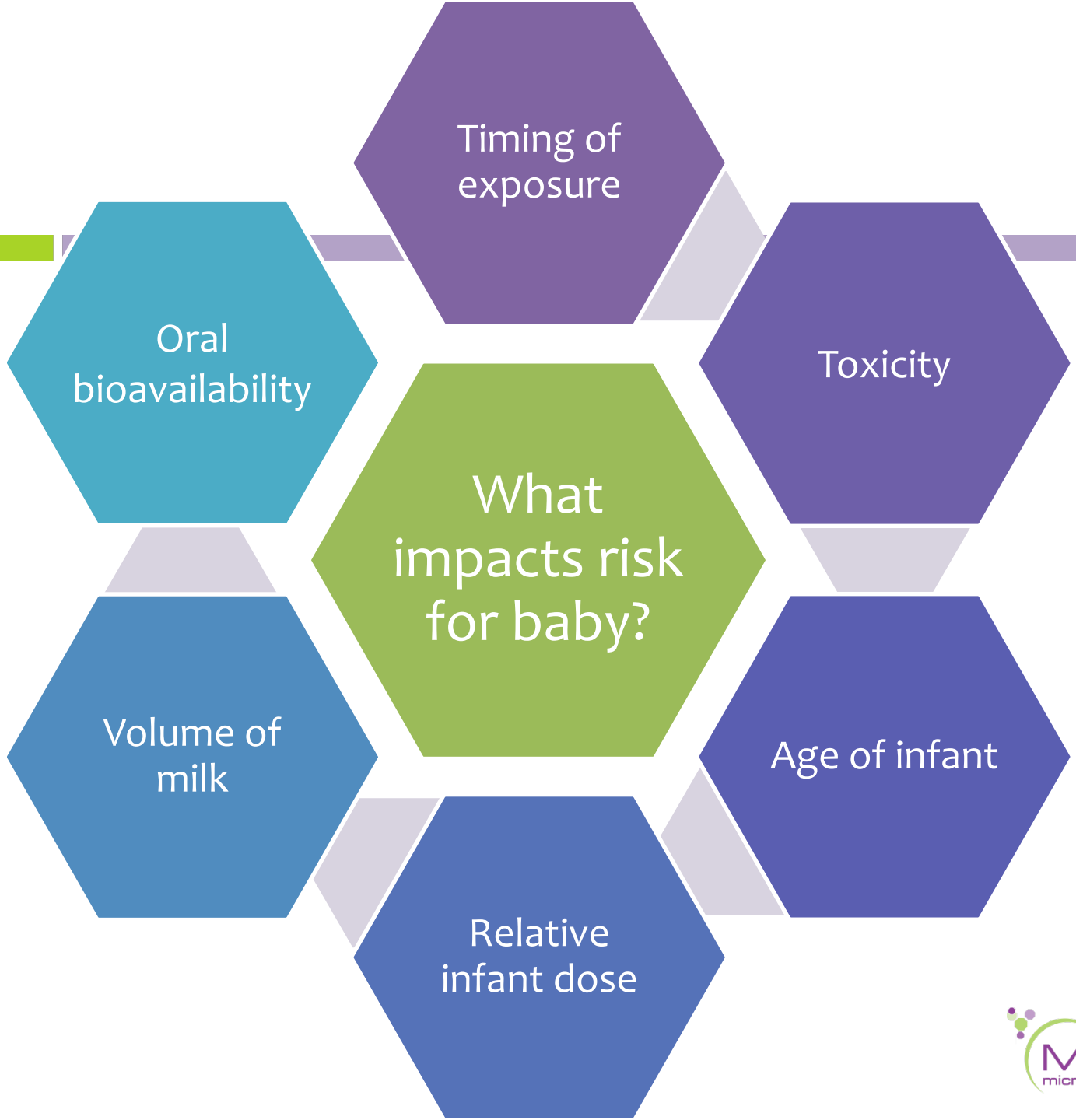


Most commonly used drugs are safe in breastfeeding, but many drugs have no breastfeeding safety data!

Drug transfer into milk: how and why?



Maternal plasma concentration, maternal plasma protein binding, molecule size, ionization, lipid solubility, and maternal pharmacogenomics can all impact drug transfer into milk.



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MTN-029/IPM 039

- Same 25 mg DPV VR used in Phase 3 studies
- 16 women at sites in Birmingham, AL and Pittsburgh, PA
  - 18+ years old
  - HIV-
  - >6 weeks postpartum
  - Lactating but **weaning completed**

MTN-029/IPM 039 Primary Objective

- To assess PK of DPV VR used for 14 consecutive days in lactating women
  - Blood plasma dapivirine concentrations
  - Breast milk dapivirine concentrations
  - Cervicovaginal fluid dapivirine concentrations

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Secondary Objectives

- To assess safety and tolerability of DPV VR used for 14 days in lactating women
  - Grade 2 or higher genitourinary AEs
  - All Grade 3 or higher AEs
- To assess adherence to DPV VR use
  - Blood DPV concentrations
  - Residual DPV concentrations in returned VRs

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Exploratory Objectives

- Describe changes in vaginal microbiota after 14 consecutive days of DPV VR use
  - Candidate biomarkers of vaginal microbiota
- Describe dapivirine anti-HIV activity in breast milk
  - TZM-bl assay

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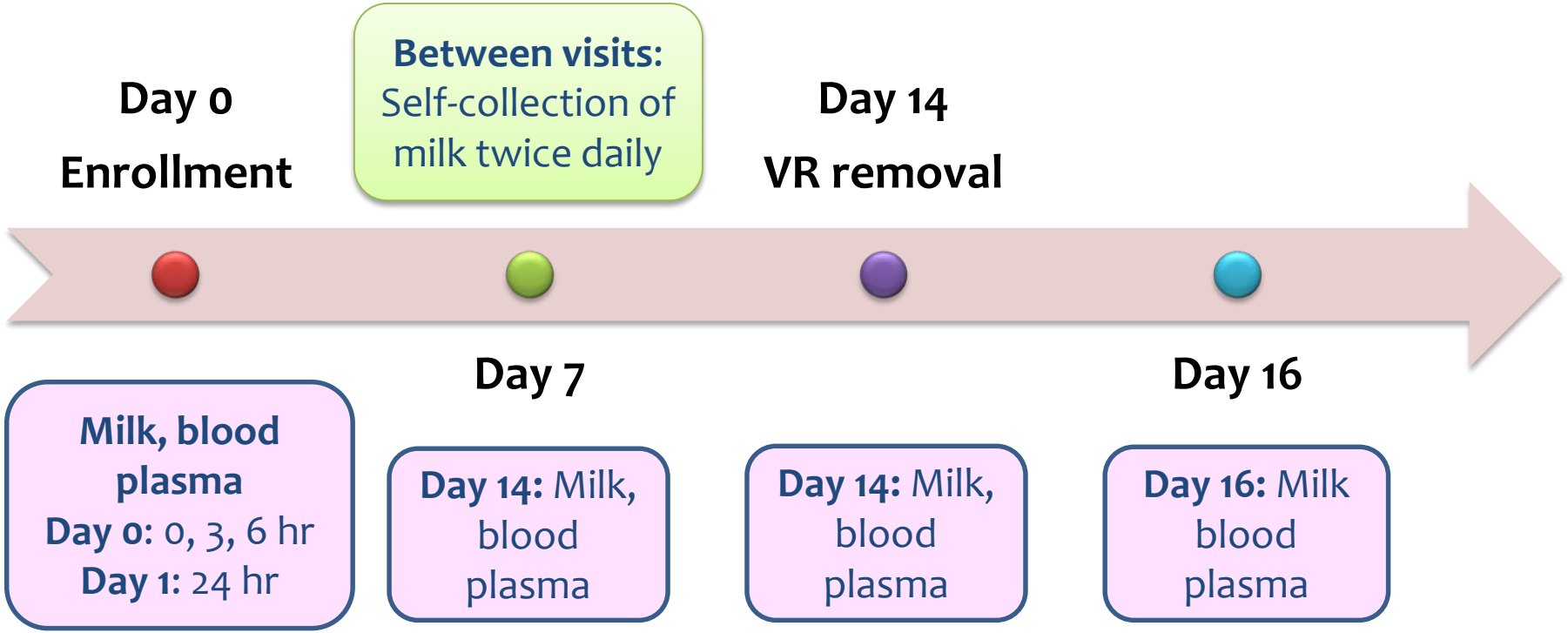
Methods


Day 0
Enrollment
Between visits:
Self-collection of milk twice daily
Day 14
VR removal
Day 7
Day 16
Milk, blood plasma
Day 0: 0, 3, 6 hr
Day 1: 24 hr
Day 14: Milk, blood plasma
Day 14: Milk, blood plasma
Day 16: Milk blood plasma

Laboratory and PK Methods

Validated LC-MS/MS assay

- Lower limits of quantification: 10 pg/mL (milk), 20 pg/mL (plasma)

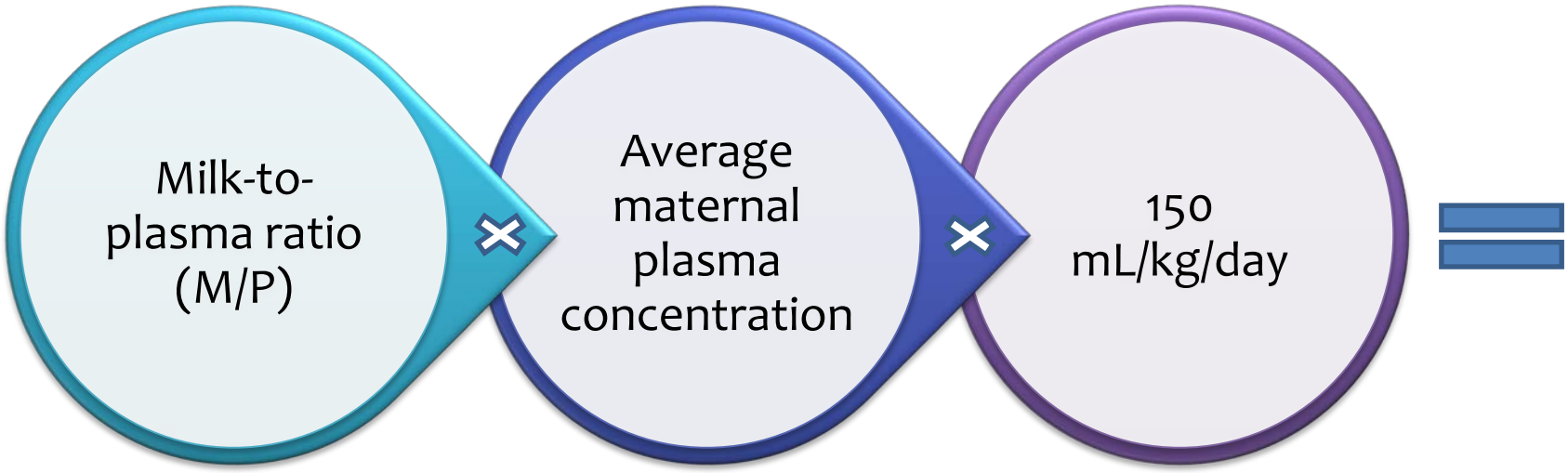
Area under curve (AUC) by trapezoidal method

- VR insertion time to removal time (Day 14, hr 336)

Estimated terminal concentration half-life

- $t_{1/2} = \ln(2) / [\ln (C_{Day14}/C_{Day16}) / (t_{Day16} - t_{Day14})]$

Estimated Infant DPV Intake



Estimated intake in ng/kg/day

M/P = ratio of AUC_m to AUC_p

Methods (cont.)

- Adverse events (AEs) collected at all contacts
  - US NIH Division of AIDS Table for Grading Adult and Pediatric Adverse Events, Version 2.0, November 2014
  - Female Genital Grading Table for Use in Microbicide Studies
- Regular clinical data and safety review

http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables

Results

	Pittsburgh	Birmingham	Both Sites
Enrolled	8	8	**16**
Median age (years)	27.5	32.5	29.5
Hispanic ethnicity	0	0	0
Race			
Black	1	3	4
White	5	5	10
Black, White	2	0	2

Results

- Retention
  - 100% participant retention and visit adherence
  - Nearly 100% procedure adherence
- Safety
  - Six of 16 (38%) women had total of eight AEs
  - 6/8 AEs were mild and deemed unrelated to VR

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Primary PK Results

PK Parameter	Milk Median (IQR)	Blood Plasma Median (IQR)	Milk : Plasma Median (IQR)
C_{max} (pg/mL)	676.0 (443.0, 924.5)	327.0 (274.5, 378.0)	2.0 (1.5, 2.5)
T_{max} (hours)	335.4 (171.1, 339.0)	172.0 (169.0, 333.8)	
AUC_{0-336} (pg*h/mL)	152604.9 (119122.5, 191806.4)	93717.7 (77318.8, 106607.9)	1.7 (1.4, 1.9)
$t_{1/2}$ (hours)	39.0 (27.1, 53.4)	35.2 (29.8, 46.4)	

C_{max}: peak concentration
T_{max}: time to peak concentration
AUC: area under the concentration-time curve
$t_{1/2}$: terminal half-life
IQR: interquartile range

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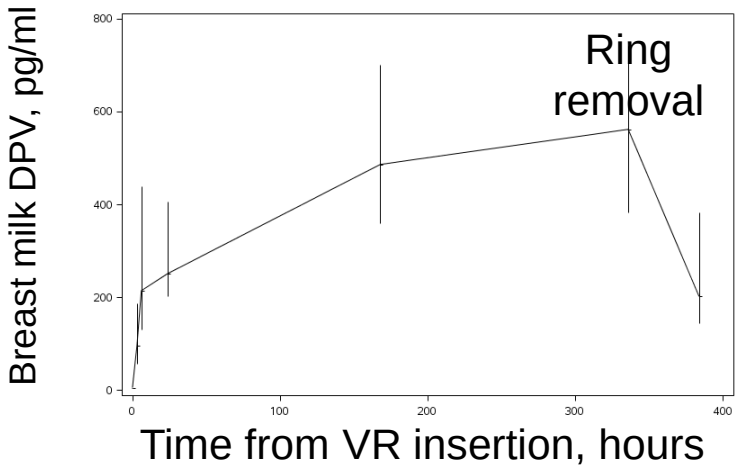
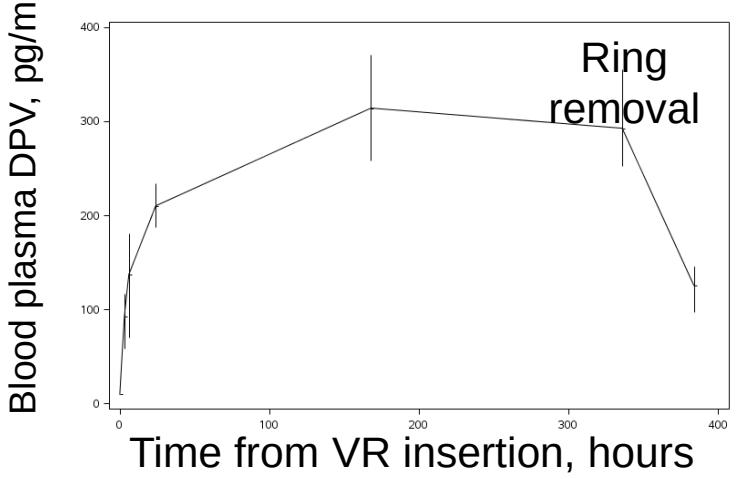
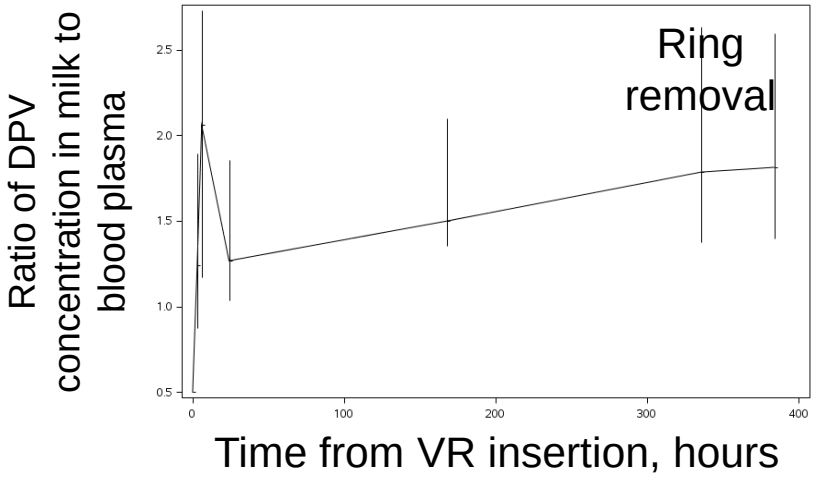
Breast milk DPV concentration over time



Blood plasma DPV concentration over time

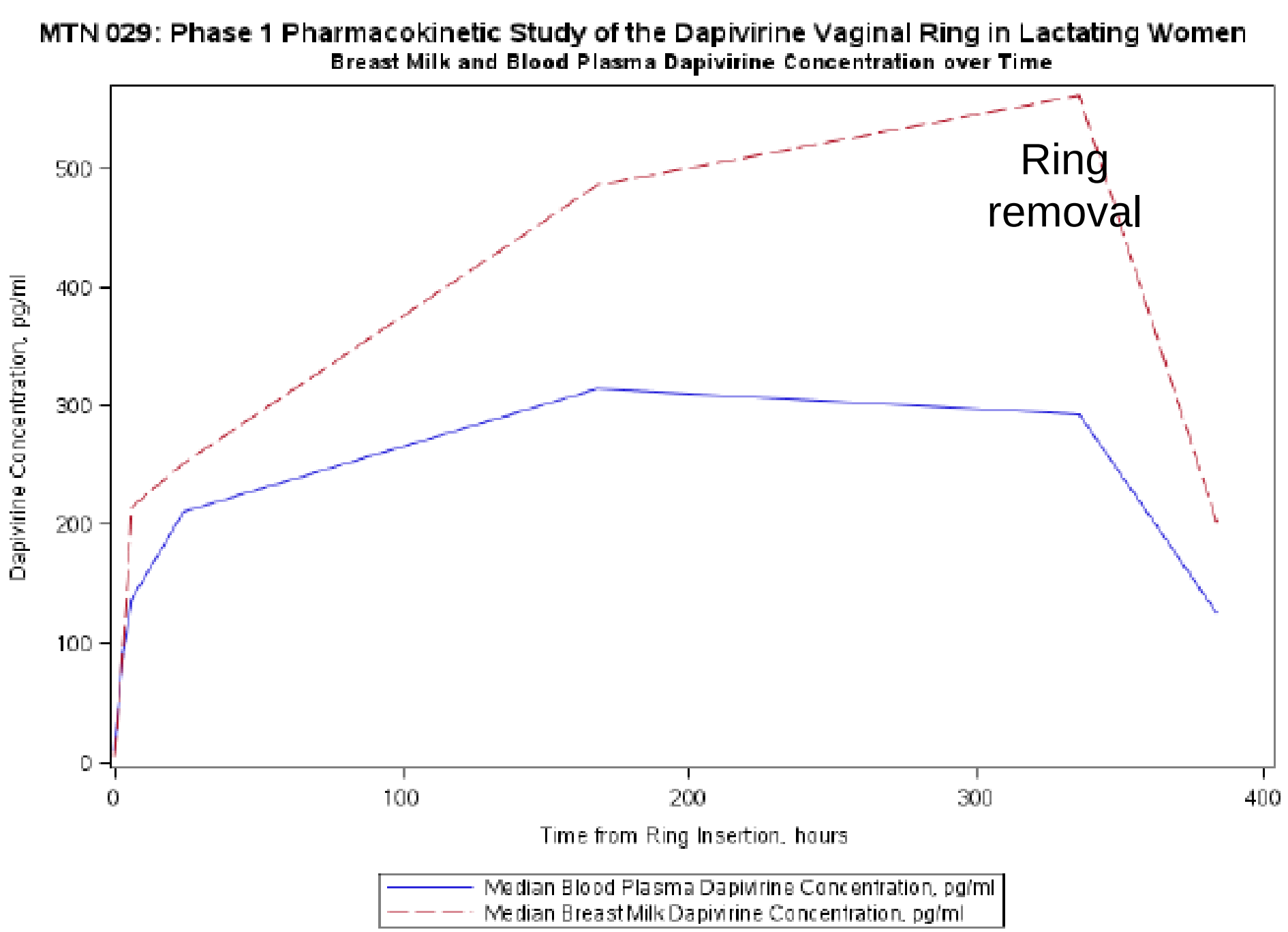


Ratio of milk to blood plasma DPV concentration over time



Median DPV concentration in breast milk increased over 14 days, but absolute values remained very low.

For all figures: median values joined by line, vertical lines 25th to 75th %ile.


MTN 029: Phase 1 Pharmacokinetic Study of the Dapivirine Vaginal Ring in Lactating Women
Breast Milk and Blood Plasma Dapivirine Concentration over Time
Ring removal
Dapivirine Concentration, pg/ml
0
100
200
300
400
500
Time from Ring Insertion, hours
0
100
200
300
400
Median Blood Plasma Dapivirine Concentration, pg/ml
Median Breast Milk Dapivirine Concentration, pg/ml

Estimated Infant Exposure

- Tenofovir (TFV) **3.76 µg/day**
- Emtricitabine (FTC) **255.2 µg/day**

Oral PrEP

Molar ratios

TFV : DPV = **7.25**

FTC : DPV = **572**

- DPV 594.4 ng/day (or **<1 µg/day**)

Dapivirine Ring

Assumptions:

TFV 0.47 µg/kg and FTC 31.9 µg/kg (Mugwanya et al, 2016); 8 kg BF infant (median weight for ~6 month old male by WHO Child Growth Standards)

http://www.who.int/childgrowth/standards/cht_wfa_boys_p_0_6.pdf?ua=1.

Mugwanya KK et al. (2016) Pre-exposure Prophylaxis Use by Breastfeeding HIV-Uninfected Women: A Prospective Short-Term Study of Antiretroviral Excretion in Breast Milk and Infant Absorption. PLoS Med 13(9).

Strengths and Limitations

- Strengths
  - 100% participant and 99% procedure retention
  - Sensitive, validated assays
  - Answered primary study question without infant exposure
- Limitations
  - PK profiles in weaning vs. BF women may differ
  - Lack of placebo control for safety outcome; however, few safety events noted

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Conclusions

- First study of DPV exposure in lactating women
- Unusual but feasible design for evaluation of investigational drug PK during lactation
- Low detectable DPV concentrations in milk, plasma
- Very favorable safety profile in lactating women

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Conclusions (continued)

- Low estimated DPV intake for infants
  - Suggests safe during BF, minimal DPV exposure
- Possibly less drug exposure vs. oral PrEP
  - Other relevant issues, e.g., bioavailability
  - No adverse effects associated with BF during PrEP use
- Future analyses
  - Total milk lipids, residual DPV concentrations in VR, vaginal microbiota, HIV pharmacodynamics
- **Follow-up study needed to evaluate longer DPV VR use among BF mother-infant pairs**

MTN-043

- Open label, multi-site study
  - Assess PK of dapivirine VR when used during BF
- ~100 healthy, HIV-uninfected, BF women and their healthy infants between 6-12 weeks old
  - VR use for ~12 weeks
  - Mother-infant pairs followed up for up to 3.5 months

Acknowledgements

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University of Pittsburgh

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