Safety and Pharmacokinetics of Dapivirine Ring Use during Lactation

Lisa Noguchi, CNM, PhD

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

20 September 2017

MTN 2017 Regional Meeting, Cape Town, South Africa
Dapivirine Vaginal Ring

**The NEW ENGLAND JOURNAL of MEDICINE**

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


*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%

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/.


**Prevention Can’t Exclude Pregnant and Breastfeeding Women**

<table>
<thead>
<tr>
<th></th>
<th>Total Fertility Rate (births/woman)</th>
<th>% infants ever breastfed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malawi</td>
<td>5.1</td>
<td>97.7</td>
</tr>
<tr>
<td>South Africa</td>
<td>2.4</td>
<td>87.4</td>
</tr>
<tr>
<td>Uganda</td>
<td>5.8</td>
<td>98.2</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>3.9</td>
<td>98.1</td>
</tr>
</tbody>
</table>

TFR, World Bank, 2014; Malawi, 2015-6 DHS; South Africa, 1998 DHS; Uganda, 2011 DHS; Zimbabwe, 2015 DHS
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.
What impacts risk for baby?

- Timing of exposure
- Toxicity
- Age of infant
- Relative infant dose
- Volume of milk
- Oral bioavailability
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
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
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
Methods

Day 0
Enrollment

Day 7
Between visits: Self-collection of milk twice daily

Day 14
VR removal

Day 0:
Milk, blood plasma
Day 0: 0, 3, 6 hr
Day 1: 24 hr

Day 14:
Day 14: Milk, blood plasma
Day 14: Milk, blood plasma

Day 16:
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

\[ t_{1/2} = \frac{\ln(2)}{\ln \left( \frac{C_{\text{Day14}}}{C_{\text{Day16}}} \right) / (t_{\text{Day16}} - t_{\text{Day14}})} \]
Estimated Infant DPV Intake

Milk-to-plasma ratio (M/P) \[\times\] Average maternal plasma concentration \[\times\] 150 mL/kg/day

Estimated intake in ng/kg/day

\[M/P = \text{ratio of } AUC_m \text{ to } AUC_p\]
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

<table>
<thead>
<tr>
<th></th>
<th>Pittsburgh</th>
<th>Birmingham</th>
<th>Both Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled</td>
<td>8</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>27.5</td>
<td>32.5</td>
<td>29.5</td>
</tr>
<tr>
<td>Hispanic ethnicity</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>White</td>
<td>5</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Black, White</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>
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
# Primary PK Results

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

- \( C_{\text{max}} \): peak concentration
- \( T_{\text{max}} \): time to peak concentration
- \( \text{AUC} \): area under the concentration-time curve
- \( t_{1/2} \): terminal half-life
- IQR: interquartile range
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
Estimated Infant Exposure

- Tenofovir (TFV) 3.76 μg/day
- Emtricitabine (FTC) 255.2 μg/day
- DPV 594.4 ng/day (or <1 μg/day)

Molar ratios
- TFV : DPV = 7.25
- FTC : DPV = 572

Oral PrEP

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

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
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
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

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.

Study rings were developed and provided by the International Partnership for Microbicides.

We thank all MTN-029/IPM 039 study participants and team members, including our Community Working Group Members.