Dapivirine Vaginal Ring Safety and Drug Detection in Breastfeeding Mother-Infant Pairs

Poster# 785

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Background

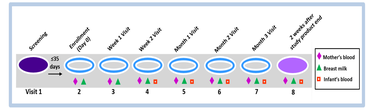
- Research suggests probability of HIV acquisition per condomless sex act may be highest during the postnatal period[1]
- World Health Organization (WHO) guidance supports provision of oral pre-exposure prophylaxis (PrEP) for breastfeeding people at substantial risk of HIV acquisition (living in communities with HIV incidence >3/100 person-years)[2]
  - Recently re-affirmed in 2022 WHO postnatal care guidelines[3]
- **WHO recommends the 25 mg dapivirine vaginal ring (DVR) as an additional HIV prevention choice as part of combination prevention approaches[2]**
  - Approved by Medicines Control Authority of Zimbabwe[4], Uganda National Drug Authority[5], and South African Health Products Regulatory Authority[6]
- **A previous DVR study, MTN-029/IPM 039, found a positive safety profile in lactating persons and low likelihood of significant drug transfer to infants[7]**
  - DVR use was safe and well tolerated among individuals who had weaned infants but were still able to produce milk
  - Median dapivirine concentrations were 676 pg/ml in breast milk, 327 pg/ml in plasma (milk/plasma ratio ~2.0)
  - Estimated mean daily infant exposure was extremely low (74.3 ng/kg/day)
- **Additional research has been recommended to evaluate safety of DVR use for breastfeeding individuals and their infants[2]**

In this first evaluation of the dapivirine vaginal ring safety and drug detection during breastfeeding, we report a favorable safety profile and low dapivirine transfer to infants.

These data support updates to WHO and national guidelines to include breastfeeding people when recommending the dapivirine vaginal ring as an additional HIV prevention choice.

Methods

- **MTN-043 was a phase 3b, randomized, open-label trial, with 12 weeks exposure to 25mg DVR or oral PrEP [200mg emtricitabine (FTC)/300mg tenofovir disoproxil fumarate (TDF)]**
- Healthy, HIV-negative, exclusively breastfeeding mother-infant pairs (cisgender women) enrolled from September 2020 to July 2021 at sites in Malawi, South Africa, Uganda, and Zimbabwe
- Participants were randomized in a 3:1 ratio (DVR: PrEP) to facilitate collection of additional safety data among DVR users
- Adverse events (AEs) were collected throughout product exposure and two weeks following product discontinuation



MTN-043/ B-PROTECTED Site Countries

Malawi = 39
South Africa = 36
Uganda = 55
Zimbabwe = 67

- Primary safety outcomes for mothers and infants included serious adverse events (SAEs) and Grade 3 or higher AEs in both study arms
- The following drug measurements were performed:
  - Dapivirine (DPV) – maternal plasma, infant plasma, breast milk
  - Tenofovir (TFV) – breast milk; TFV-diphosphate(TFV-DP) – maternal dried blood spot (DBS), infant DBS

Results

- 197 mother-infant pairs enrolled (DVR: 148; oral PrEP: 49) across sites
- At enrollment, median age of mothers was 26 years and infants was 9 weeks

Safety

- Most AEs mild or moderate, no grade 4 or 5 AEs
  - Among DVR arm participants, two (1%) mothers experienced an SAE and three (2%) an AE of ≥Grade 3; four (3%) infants experienced an SAE and 10 (7%) an AE of ≥Grade 3
- No SAEs or ≥Grade 3 in mothers were related to product
- No infant AEs were related to product for either study arm

Drug measurement

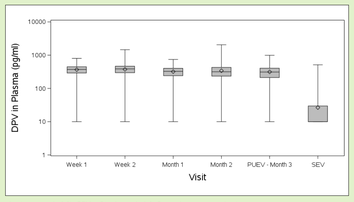
- There was high uptake of study product in both arms with extremely low concentrations of dapivirine (DVR arm) detected in infant plasma samples (see Table and Figures)
- In the oral PrEP arm, tenofovir diphosphate concentrations from infant DBS were all below the lower limit of quantitation

Drug concentrations in maternal plasma, maternal DBS, breastmilk, and infant plasma by study arm and visit

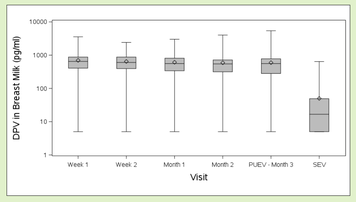
	Dapivirine arm						Oral PrEP arm*			
	Maternal plasma		Breast milk		Infant plasma		Maternal DBS		Breast milk	
	Detection (%)	Mean (pg/ml)	Detection (%)	Mean (pg/ml)	Detection (%)	Mean (pg/ml)	Detection (%)	Mean (fmol/punch)	Detection (%)	Mean (ng/ml)
Week 1	99.3%	367.0	99.3%	698.3	--	--	100.0%	293.2	97.9%	7.0
Week 2	97.1%	374.6	98.6%	646.4	15.0%	14.5	100.0%	492.4	93.6%	5.3
Month 1	98.6%	320.0	98.6%	612.4	14.4%	12.4	95.7%	680.6	89.4%	4.5
Month 2	95.8%	340.6	97.2%	590.8	9.8%	11.8	100.0%	720.1	88.4%	5.1
Month 3	97.8%	314.3	97.8%	596.1	5.1%	10.7	100.0%	908.1	82.6%	3.6
2 weeks post-use	33.8%	26.6	66.2%	50.1	0%	BLQ	97.8%	505.7	6.5%	2.9

*Detection and concentration of tenofovir diphosphate (TFV-DP) reported for maternal DBS and tenofovir (TFV) reported for breast milk.
Detection = a value above the lower limit of quantitation (LLOQ) for the assay. To summarize mean concentration, samples with concentrations below the LLOQ were assigned a value equivalent to half the LLOQ (see below for LLOQ for each assay). BLQ = below the lower limit of quantitation. LLOQ for dapivirine in plasma = 20 pg/ml and breast milk = 10 pg/ml; LLOQ for TFV-DP in DBS = 31.3 fmol/punch; LLOQ for TFV in breast milk = 1 ng/ml .

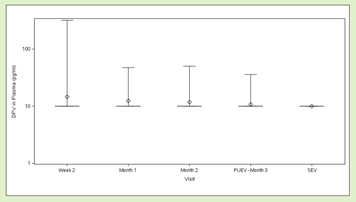
Maternal Dapivirine Concentrations in Plasma by Visit



Dapivirine Concentrations in Breastmilk by Visit



Infant Dapivirine Concentrations in Plasma



PUEV = Product use end visit; SEV = Study end visit 2 weeks post-product use

Conclusions

- In this first evaluation of DVR safety and drug detection during breastfeeding, few SAEs or ≥Grade 3 AEs occurred among mothers and infants and all infant AEs were deemed unrelated to study product
- Plasma and breastmilk DPV concentrations were consistent with prior studies. However, even though concentrations in breast milk were higher than maternal plasma, infant plasma concentrations remained low
- The favorable safety profile of the DVR, along with data demonstrating low dapivirine transfer to infants, supports updates to WHO and national guidelines to include breastfeeding people when recommending the DVR as an additional HIV prevention choice

References

1. Thomson KA et al. Increased Risk of HIV Acquisition Among Women Throughout Pregnancy and During the Postpartum Period: A Prospective Per-Coital-Act Analysis Among Women With HIV-Infected Partners. J Infect Dis. 2018 Jun 5;218(1):16-25.
2. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. Geneva: World Health Organization; 2021.
3. WHO recommendations on maternal and newborn care for a positive postnatal experience. Geneva: World Health Organization; 2022.
4. Medicines Control Authority of Zimbabwe. Dapiring/Dapivirine. Registration number: 2021/7.13/6148. Registration date: 07/06/2021. https://onlineservices.mcaz.co.zw/onlineregister/frmAllophaticRegister.aspx. Accessed 06/30/2022.
5. Uganda National Drug Authority. Dapiring/Dapivirine. Registration number:NDA/MAL/HDP/9805. Registration date: 05/10/2021. https://www.nda.or.ug/drug-register/. Accessed 07/12/2022.
6. IPM Global. South Africa Approves Dapivirine Vaginal Ring for Use by Women. https://www.ipmglobal.org/sites/default/files/media_block_files/south_africa_release_03.10_0.pdf. Accessed 06/28/2022.
7. Noguchi LM et al. Pharmacokinetics of Dapivirine Transfer into Blood Plasma, Breast Milk, and Cervicovaginal Fluid of Lactating Women Using the Dapivirine Vaginal Ring. Antimicrob Agents Chemother. 2019 Feb 26;63(3):e01930-18.

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