Phase 3B, randomized, open-label, safety study of dapivirine vaginal ring and oral emtricitabine 200mg/tenofovir disoproxil fumarate 300mg tablet in breastfeeding mother-infant pairs

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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 in absence of PrEP).[2]
  - Recently re-affirmed in 2022 WHO postnatal care guidelines.[3]
- **WHO recommends the 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.**[6]
  - 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), and 36.25 ng/mg in cervicovaginal fluid.
  - 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]

Methods

- **MTN-043 was a phase 3b, randomized, open-label trial, with 12 weeks exposure to DVR or oral 200 mg emtricitabine (FTC)/ 300mg tenofovir disoproxil fumarate (TDF) tablet.**
- Healthy, HIV-negative, exclusively breastfeeding mother-infant pairs 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: tablet) to facilitate collection of additional safety data among users of DVR.
- Adverse events (AEs) were collected throughout product exposure and two weeks following product discontinuation.
- Primary safety outcomes for mothers and infants included serious adverse events (SAEs) and Grade 3 or higher AEs in both arms.
- Part of a larger portfolio of studies assessing safety in pregnancy and breastfeeding to ensure that products are safe to use across the life course.
- Dapivirine ring provided by IPM; oral FTC/TDF tablets provided by Gilead.

MTN-043/ B-PROTECTED Site Countries

Results

- 197 mother-infant pairs enrolled (DVR: 148, oral PrEP: 49) across sites.
- Median age of mothers was 26 years and infants was 9 weeks.
- **Most AEs mild or moderate, no grade 4 or 5 AEs** (Table 1).
- Among DVR arm participants, two (1%) mothers experienced an SAE and three (2%) an AE of Grade 3 or higher; four (3%) infants experienced an SAE, and 10 (7%) an AE of Grade 3 or higher (Table 2).
- **No SAEs or Grade 3 or higher events in mothers were related to product.**
- **No infant AEs were related to product for either study arm.**
- Most common AE in mothers was decreased creatinine clearance (includes cases where serum creatinine was normal at time of event).
  - DVR arm, n=20 (13.5%), oral PrEP arm, n=13 (26.5%)
- Most common AE in infants was upper respiratory tract infection.
  - DVR arm, n=40 (27.0%), oral PrEP arm, n=11 (22.4%)

Table 1. Frequency of adverse events by severity and study arm

	Mothers			Infants		
	DVR (N=148)	Oral PrEP (N=49)	Both Arms (N=197)	DVR (N=148)	Oral PrEP (N=49)	Both Arms (N=197)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Participants with one or more AEs						
Grade 1: Mild	18 (12.2%)	8 (16.3%)	26 (13.2%)	26 (17.6%)	7 (14.3%)	33 (16.8%)
Grade 2: Moderate	72 (48.6%)	25 (51.0%)	97 (49.2%)	76 (51.4%)	24 (49.0%)	100 (50.8%)
Grade 3: Severe	3 (2.0%)	2 (4.1%)	5 (2.5%)	10 (6.8%)	1 (2.0%)	11 (5.6%)
Total	93 (62.8%)	35 (71.4%)	128 (65.0%)	112 (75.7%)	32 (65.3%)	144 (73.1%)

Table 2. Primary safety outcomes among breastfeeding mothers and infants enrolled in MTN-043

	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 Vaginal Ring	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)

Conclusions

In this first evaluation of DVR safety during breastfeeding, few SAEs or AEs of Grade 3 or higher occurred among mothers and infants in either study arm. Most AEs were mild or moderate, and all infant AEs were unrelated to study product use. **This favorable safety profile and previous data demonstrating low drug transfer to breastmilk support updates of WHO and national guidelines to include breastfeeding people when recommending the DVR as an HIV prevention choice.** Additional analyses are forthcoming on adult and infant drug levels, adherence, acceptability, and genital microenvironment changes associated with study product use. Increased risks of HIV acquisition postnatally and of HIV transmission to infants with incident HIV infection during breastfeeding are ethical and scientific rationales to improve access for breastfeeding people to safe and effective HIV prevention methods such as the DVR.

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