Update on Pregnancy and Lactation Research: MTN-008

Richard H. Beigi, MD, MSc., Lisa Noguchi, CNM, MSN
University of Pittsburgh
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GOALS – Pregnancy & Lactation

- Proactively investigate HIV prevention agents
  - Delineate **Safety Profile** in real-time
  - Enable **Informed Global Use** during preg/lact
  - Delineate a **Paradigm Change** for studying therapeutics in pregnancy/lactation
    - Challenge status quo
      - Does not serve women well
  - MTN-002
  - **MTN-008**, MTN-016

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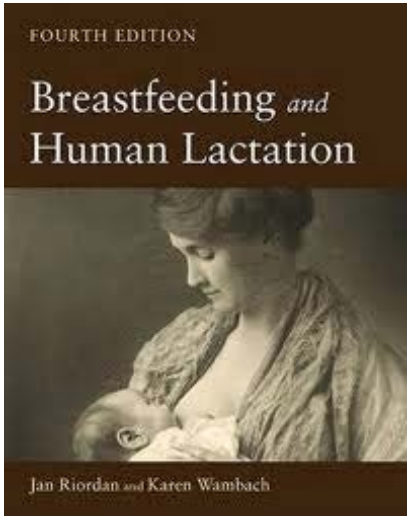
MTN-008

- **Expanded Safety Investigation of Tenofovir 1% Gel in Pregnancy and Lactation**
  - **UAB, PITT**



- **Primary Objectives: Today**
  - **Safety & tolerability** of TFV gel for 7 days
  - **PK** of TFV gel for 7 days
- **Secondary Objectives:**
  - **Infant TFV**
  - TFV gel impact on select organisms associated with neonatal sepsis → Pregnancy Cohort, (e.g., GBS, *E. coli*)
  - Adherence & acceptability TFV gel
- **Exploratory Objectives**
  - Measure vaginal flora changes with daily TFV gel
  - TFV gel effects on vaginal and cervical biomarker expression

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MTN-008 Study Population

- Pregnancy Cohort
  - Healthy, 3rd trimester gestation, HIV-uninfected, pregnant women, 18 – 40 years old, without current evidence of maternal/fetal complications
  - RCT, placebo controlled, Blinded (HEC gel)
    - 2:1 Active/Placebo → 30:15 TFV/HEC
      - PK day 0 & 7 (0-8 hrs)
- **Group 1**: 45 participants between 37 0/7 weeks and 39 1/7 weeks gestation (inclusive)
  - Enrolled 51→ 45 evaluable: (34 TFV, 17 HEC)
- **Group 2**: 45 participants between 34 0/7 and 36 6/7 weeks gestation
  - Enrolled 47 → 46 evaluable: (32 TFV, 15 HEC)

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MTN-008 Endpoints

- Pregnancy Safety and Tolerability – Maternal
- Grade 2 or higher adverse events in the following categories
  - Specific laboratory abnormalities
    - ALT
    - AST
    - Creatinine
  - Specific genital/pelvic signs/symptoms
    - Dyspareunia
    - Pain (vulvar, vaginal, and/or pelvic)
    - Tenderness (vulvar, vaginal, and/or pelvic)
    - Itching (vulvar and/or vaginal)
    - Edema (vulvar, vaginal, and/or cervical)
    - Erythema (Vulvar, vaginal, and/or cervical)
    - Lesions (vulvar, vaginal, and/or cervical)
    - Vulvar rash
    - Vaginal dryness
    - Dysuria
    - Vulvovaginitis
    - Cervicitis

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MTN-008 Major Endpoints

- Specific pregnancy complications
  - Postpartum hemorrhage
  - Postpartum endometritis
  - Chorioamnionitis
  - Third trimester bleeding
  - Preterm premature rupture of membranes (prior to labor onset)
  - Term premature rupture of membranes (prior to labor onset)
  - Spontaneous preterm delivery

For adverse events not included, Grade 3 or higher adverse events judged by the investigator to be related to the study gel or applicator

MTN-008 Endpoints

- Pregnancy Safety and Tolerability – Infant
- Infant diagnosed (and confirmed) with any of the following during the 7 days following delivery
  - Intensive care admission greater than 24 hours
  - Sepsis

- <u>TIMELINE</u>
  - MTN-008 1.0: 4-2010
  - 1st enrollment: 4-2011
  - Interim review Cohort #1 (term): 8-2012
  - Final f/u cohort #2: 9-2013

Demographics

Cohort 1

	All Arms	HEC Placebo Gel	Tenofovir Gel
Participants Enrolled	51	17	34
Age (years)			
N	51	17	34
Mean (SD)	24.2 (4.5)	25.4 (3.8)	23.6 (4.7)
Median	23.0	25.0	22.0
25th, 75th %tile	21.0, 27.0	23.0, 27.0	20.0, 26.0
Min, Max	18.0, 40.0	20.0, 33.0	18.0, 40.0
Age (years)			
18-19	3 (6%)	0 (0%)	3 (9%)
20-24	28 (55%)	8 (47%)	20 (59%)
25-29	13 (25%)	6 (35%)	7 (21%)
30-34	6 (12%)	3 (18%)	3 (9%)
35-40	1 (2%)	0 (0%)	1 (3%)
Latina or of Hispanic Origin			
Yes	1 (2%)	0 (0%)	1 (3%)
No	50 (98%)	17 (100%)	33 (97%)
Race			
Black or African American	37 (73%)	10 (59%)	27 (79%)
White	10 (20%)	5 (29%)	5 (15%)
Black or African American, White	2 (4%)	1 (6%)	1 (3%)
Asian, White	1 (2%)	1 (6%)	0 (0%)
American Indian or Alaskan Native, Black or African American, White	1 (2%)	0 (0%)	1 (3%)

Cohort 2

	All Arms	HEC Placebo Gel	Tenofovir Gel
Participants Enrolled	47	15	32
Age (years)			
N	47	15	32
Mean (SD)	23.5 (4.7)	22.8 (4.2)	23.9 (4.9)
Median	22.0	21.0	22.5
25th, 75th %tile	20.0, 26.0	20.0, 26.0	20.0, 26.5
Min, Max	18.0, 38.0	18.0, 34.0	19.0, 38.0
Age (years)			
18-19	9 (19%)	3 (20%)	6 (19%)
20-24	22 (47%)	7 (47%)	15 (47%)
25-29	11 (23%)	4 (27%)	7 (22%)
30-34	4 (9%)	1 (7%)	3 (9%)
35-40	1 (2%)	0 (0%)	1 (3%)
Latina or of Hispanic Origin			
No	47 (100%)	15 (100%)	32 (100%)
Race			
Black or African American	40 (85%)	13 (87%)	27 (84%)
White	4 (9%)	1 (7%)	3 (9%)
Other	1 (2%)	0 (0%)	1 (3%)
Black or African American, White	2 (4%)	1 (7%)	1 (3%)

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Adverse Events (N=98)

- Mothers:
  - Total: 377 AE's (Cohort 1&2 ~ identical #'s)
    - 85% grade 1-2
    - 93% NR, no grade 3-4 related
      - Delivery-related pain, local irritation, preg complications
- Infants:
  - Total: 63 AE's (Cohort 1&2 ~ identical #'s)
    - 87% grade 1-2, 7 grade 3 & 1 grade 4
    - 100% NR
- No concerning signals!
  - Moms and babies

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Safety & Tolerability by Arm – 1^0 Endpoints

	HEC Placebo Gel	Tenofovir Gel
Specific laboratory abnormalities[1]		
ALT	0	0
AST	0	0
Creatinine	0	0
Specific genital and pelvic signs and symptoms[1]		
Dyspareunia	0	0
Pain (vulvar, vaginal, and/or pelvic)	14 (43.8%)	25 (37.9%)
Tenderness (vulvar, vaginal, and/or pelvic)	0	0
Itching (vulvar and/or vaginal)	0	0
Edema (vulvar, vaginal, and/or cervical)	0	0
Erythema (vulvar, vaginal, and/or cervical)	0	0
Lesions (vulvar, vaginal, and/or cervical)	1 (3.1%)	2 (3.0%)
Vulvar rash	0	0
Vaginal dryness	0	0
Dysuria	0	0
Vulvovaginitis	0	1 (1.5%)
Cervicitis	0	0
Specific pregnancy complications[2]		
Postpartum hemorrhage	4 (12.5%)	13 (19.7%)
Postpartum endometritis	0	1 (1.5%)
Chorioamnionitis	2 (6.3%)	1 (1.5%)
Third trimester bleeding	1 (3.1%)	1 (1.5%)
Preterm premature rupture of membranes	0	0
Term premature rupture of membranes	6 (18.8%)	15 (22.7%)
Spontaneous preterm delivery	3 (9.4%)	2 (3.0%)

[1]Grade 2 or higher AEs.

[2]Events of any grade.

Safety & Tolerability - 1^0Outcomes

MOTHER

	n/N (%)	p-value[1]
Tenofovir Gel	48/66 (72.7%)	
HEC Placebo Gel	22/32 (68.8%)	
Tenofovir Gel vs. HEC Placebo Gel		0.81

INFANT

	n/N (%)	p-value[1]
Tenofovir Gel	3/66 (4.5%)	
HEC Placebo Gel	2/32 (6.3%)	
Tenofovir Gel vs. HEC Placebo Gel		0.66

[1] Fisher's exact test

Preliminary PK Highlights (N=65)

- 100% women -> Detectable levels of TFV
  - 45% women -> Undetectable @ pre-gel day 7

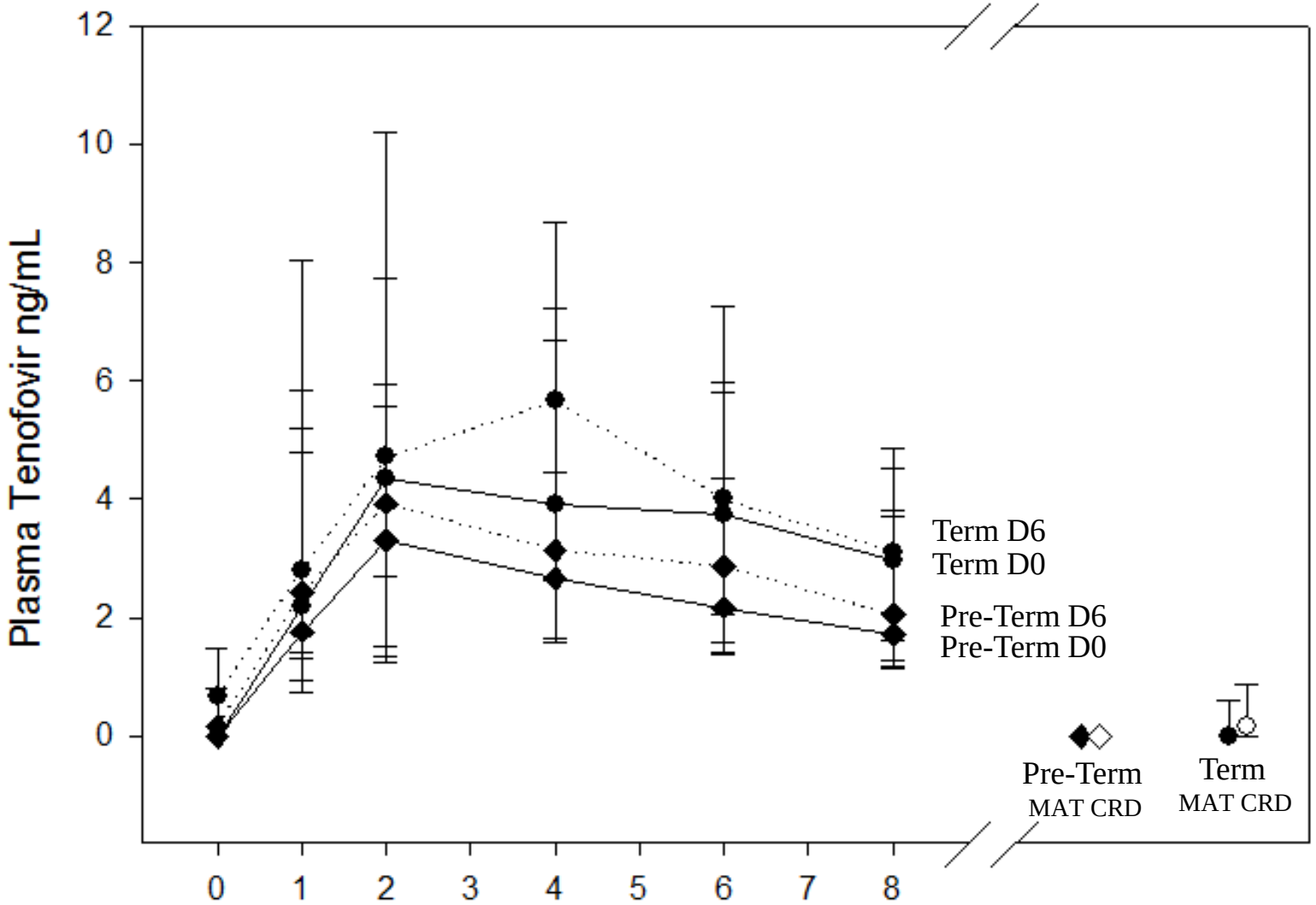
- 84% women -> Undetectable TFV @ delivery
- 75% babies -> Undetectable TFV in cord blood
  - Median 15 days(0-41): dosing → delivery
  - 25 days longest detection (cord)

- Zero women with detectable PBMC TFV-DP
  - Cut-point for evaluation = TFV 10 ng/ml

Preliminary PK Analysis

PK Parameter	Term Cohort	Pre-term Cohort	Non-Pregnant (*MTN 001)
Cmax, Day 0,TFV ng/ml, **Median** (25-75% IQR)	**4.4*** (1.8-9.0)	**3.5*** (2.3-6.8)	**3.9** (2.2–7.9)
Cmax, Day 6, TFV ng/ml, **Median** (25-75% IQR)	**6.3*** (3.1-10.2)	**5.1*** (2.0-8.7)	
Tmax, Day 0, Hours (Std. Dev)	**4.0** (2.0)	**2.0** (1.7)	**2.1** (1.9–4.6)
Tmax, Day 6, Hours (Std. Dev)	**2.0** (1.9)	**2.0** (2.0)	
AUC_{0-8} ng*h/ml Day 0 **Med** (Std. Dev)	**26.6*** (39.4)	**18.6*** (30.8)	
AUC_{0-8} ng*h/ml Day 6, **Med** (Std. Dev)	**38.3*** (43.0)	**27.4*** (38.6)	
Pre-dose , TFV ng/ml,7 **Median** (IQR)	**0.67** (BLQ-1.6)	**0.35** (BLQ-0.8)	**0.67** (0.3–2.09)
Mat Deliv TFV ng/ml **Median** (IQR)	**BLQ** (0.0)	**BLQ** (0-0.58)	
Cord Blood TFV ng/ml **Median** (IQR)	**BLQ** (0-0.85)	**BLQ** (0.0)	

TFV Concentration vs. Time



Pregnancy Summary

- Daily TFV gel well tolerated among:
  - Term & near-term pregnant women & their infants
- AE's: No concerning signals
  - Majority 2^0 to pregnancy:
    - Model for research
- PK of daily TFV gel in pregnancy:
  - Low levels overall
    - Minimal detectable accumulation in mothers & babies
  - Similar to non-pregnant women
- Analyses ongoing for all objectives

MTN-008 LACTATION COHORT

Postpartum sexual abstinence

- Extended postpartum abstinence prevalent in Central & West Africa
- Traditional belief
  - Thought to improve health of mothers and nursing babies
  - Applies only to women
- Potentially higher probability of male unprotected sex outside primary partnership
- Postpartum period may be time of increased HIV risk for women

Background

- Tenofovir (TFV): nucleotide reverse transcriptase inhibitor
- Extensive safety/pharmacokinetic (PK) data – oral, topical
- US FDA requested TFV gel data in breastfeeding (BF)

Recent & ongoing studies of tenofovir 1% gel in women			
	Regimen	Results	Breastfeeding
CAPRISA 004 (2010)	Peri-coital	39% reduction HIV-1, ~50% reduction HSV-2	Not excluded No BF data collected
VOICE (2013)	Daily	No significant reduction in HIV-1	BF specifically excluded
FACTS 001 (2014)	Peri-coital	Pending	Not excluded No BF data collected
CAPRISA 008 (2015)	Peri-coital	Pending	Not excluded No BF data collected

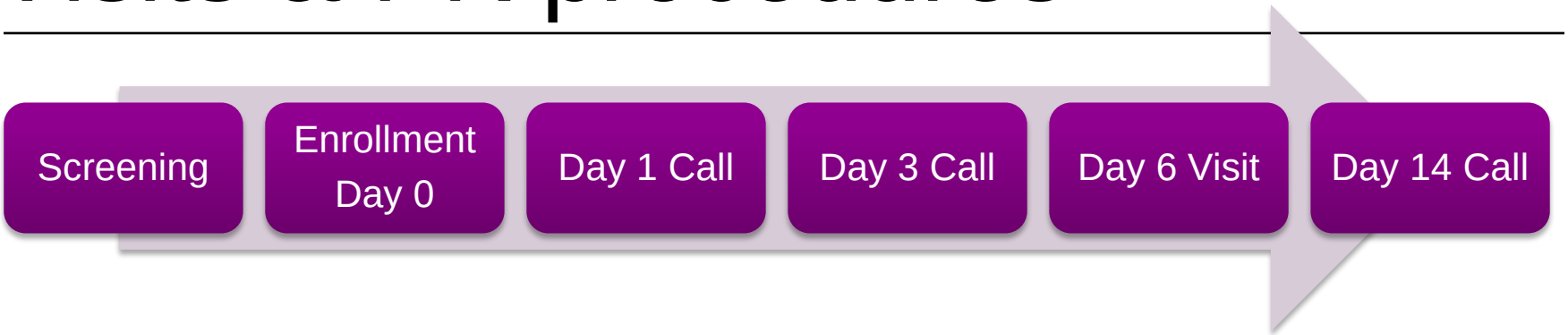
Topical tenofovir and breastfeeding

- When is a drug likely detectable in milk?
  - High maternal serum concentration of drug
  - Small molecule, lipid soluble, not highly protein bound
- Impact of prolactin on estrogen levels
- TFV form – no substantial oral bioavailability
- Hypotheses
  - Topical dosing in BF women with potentially hypoestrogenic vaginal epithelium may alter safety, tolerability, and/or PK profile of TFV gel
  - Very limited detectable TFV in milk or infants with daily topical dosing

Design and aims

- Open-label IND, daily 1% TFV gel, 7 days
- 16 mother-infant pairs (target met Q4 2012)
  - Healthy, BF HIV- women, 18-40 years, infant 4-26 wks
  - Birmingham & Pittsburgh
- Aims
  - Safety & tolerability
  - Maternal & infant PK
  - Adherence & acceptability
  - Vaginal flora & biomarker expression
  - Breast milk pharmacodynamics

Visits & PK procedures



	0h	1h	2h	4h	6h	8h
Maternal blood	✔ (Day 6)	✔	✔	✔	✔	✔
Breast milk	✔ (Day 6)		✔	✔	✔	

- Infant blood collected 6 hr after dosing (~1-4 hr post-BF)
- Two other milk specimens collected on two interim days
- TFV and TFV diphosphate (TFV-DP) by LC-MS/MS, LLOQ: 0.31 ng/mL (serum) and 1.0 ng/mL (milk)

Enrolled participants (N = 17)

	Median (IQR)
Mothers	
Age (years)	27.0 (23-29)
Weight (kg)	75 (63-90)
Creatinine clearance	122 (98-156)
Infants	
Age (weeks)	10.0 (8.1-13.3)
Weight (kg)	6 (5-6)

- Screen-to-enroll ratio = 1.9 : 1
- Race/ethnicity: 7 (43.8%) Black, 7 (43.8%) white, 2 (12.4%) other
- 94% retention to Day 6 visit, 88% to Day 14 phone call

Median (IQR) TFV PK parameters in maternal serum, breast milk, and infant serum after single and multiple maternal dosing

	Maternal serum	Breast milk	Infant serum
Day 0 (n=16)			
Detectable post-: n (%)	16 (100%)	4 (25%)	6 (37.5%)
T_{max} (h)	3.0 (2.0 – 4.5)	5.0 (4.1 – 6.0)	
C_{max} (ng/mL)	7.5 (4.3 – 47.3)	0.0 (0.0 – 0.3)	
AUC	40.6 (24.5 – 157.4)	0.0 (0.0 – 1.4)	
Heel stick (ng/mL)			0.0 (0.1 – 1)*
Day 6 (n=16)			
Detectable pre-: n (%)	9 (56.3%)	2 (12.5%)	
Detectable post-: n (%)	16 (100%)	6 (37.5%)	12 (75.0%)
T_{max} (h)	3.9 (1.7 – 4.0)	4.9 (2.4 – 5.9)	
C_{max} (ng/mL)	5.6 (4.1 – 22.6)	0.0 (0.0 – 1.6)	
AUC	30.2 (21.2 – 92.0)	0.0 (0.0 – 2.6)	
Heel stick (ng/mL)			2.4 (0.8 – 4)*

*Wilcoxon rank-sum test of Day 0 vs. Day 6 infant serum, p = 0.01

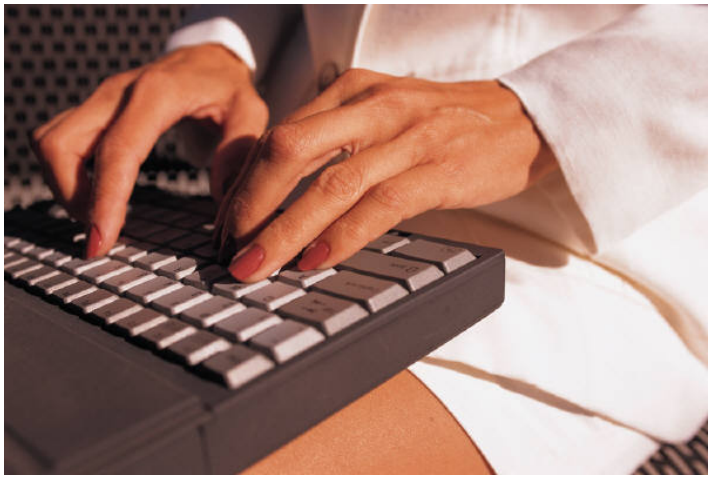
Safety

- No SAEs or product holds due to safety issues
- Nine mothers had one or more AEs
  - Total: 20
  - All mild, 60% unrelated
  - Related: genital burning, spotting, diarrhea
- Four infants had one or more AEs
  - Total: 8
  - One moderate (unrelated rash), all others mild
  - Related: diarrhea

Adherence by CASI

Q2 – 2:
How many days did you insert the study gel at home?

Days	Frequency (%)
4	2 (13.3)
5	11 (73.3)
6	2 (13.3)
	15 (100.0)



Summary and next steps

- Pharmacokinetics
  - TFV transfers into milk following topical vaginal dosing
  - Despite low oral bioavailability, TFV detectable in some infants
  - Possible accumulation in infants but overall levels very low
- Safety
  - Repeat dosing well-tolerated overall by mothers and infants
  - AEs in BF women similar to non-BF women
- Inferences limited by small sample size, potential gaps in adherence and non-randomized, open-label design
- Ongoing work on adherence/acceptability, pharmacodynamics & vaginal microenvironment

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