MTN 005: Preliminary Safety, Adherence, and Acceptability Data

MTN Annual Meeting

February 11th, 2013

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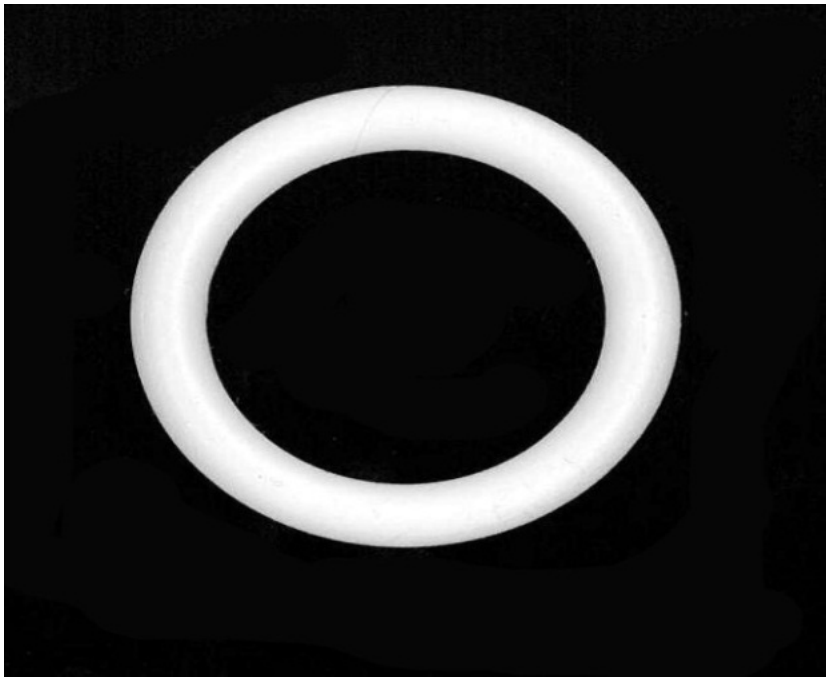
Study design

- Expanded safety and adherence study of a non-medicated intravaginal ring (IVR)
  - Randomized (2:1, IVR: no IVR), controlled trial of sexually active, HIV-uninfected women
- 3 sites (Birmingham, Bronx, Pune)
- Planned enrollment – 252 women
  - NARI – 150
  - UAB – 51
  - Bronx-Lebanon Health Center -51

Study Product

- Silicone elastomer ring
  - Manufactured by Andromaco for the Population Council (IND holder)



Study Schema

	Screening	Enrollment	4-Week	8-Week	12-Week	16-Week
	↓	↓	↓	↓	↓	↓
GROUP						
A		**[**	**STUDY IVR USE PERIOD**		**]**	**TERMINATION**
B		**[NO IVR (SAME STUDY VISITS AS GROUP A)]**				

Primary Objectives

- Evaluate the safety of the study IVR in HIV-uninfected women over 12 weeks of use

- Evaluate the adherence to the study IVR in HIV-uninfected women over 12 weeks of use

Primary Endpoints

- Grade 2 or higher genitourinary events
- For women in IVR group, participant report of IVR removal and duration without IVR over 12 weeks of use

Secondary Objectives

- Evaluate the acceptability of the study IVR in HIV-uninfected women over 12 weeks of use
- Measure vaginal flora characteristics, and descriptively examine changes in these characteristics over the course of study IVR use

Secondary Endpoints

- For IVR arm, participant report of acceptability including genitourinary discomfort, ring insertion/removal issues, expulsions, and changes in participant and/or partner sexual feeling
- Changes in vaginal flora from enrollment to week 12 as measured by Gram stain Nugent score and quantitative culture

Study Timeline

- June 2011
  - First participants enrolled at UAB, BLHC
- January 2012
  - Last participants enrolled at UAB, BLHC
- February 2012
  - First participant enrolled at NARI
- April 2012
  - Last U.S. participant exited the study

Study Timeline (2)

- May 30, 2012
  - NARI investigators noted “spots” on 3 rings
    - Observed during scheduled assessments
    - Not related to adverse event
- June 4, 2012 – 8 spotted rings noted
  - No adverse events related to findings
  - Protocol team notes spotted rings not detected at U.S. sites

Study Timeline (3)

- June 7-11, 2012 – NARI IRB and MTN recommended suspending enrollment, ring removal
  - 93 (of 150) women enrolled
  - Collect used and unused rings
  - Follow enrolled participants in IVR arm for 4 additional weeks as outlined in protocol
- June 20, 2012 – PSRT review call
- September 2012
  - Last participant visit
- October 2012
  - Used rings shipped to NL, unused rings shipped to Population Council for further assessment

Study Population - Demographics

	All sites	NARI	BLHC	UAB
Participants enrolled	**195**	**93**	**51**	**51**
Mean age (years)	**31.3**	**32.2**	**31.2**	**29.6**
Married (N, %)	**123 (63)**	**92 (99)**	**10 (20)**	**21 (41)**
Unmarried, w/ primary sex partner	**70 (36)**	**1 (1)**	**40 (78)**	**29 (57)**
Highest level of education (N, %)				
Secondary school complete	**39 (20)**	**19 (20)**	**15 (29)**	**5 (10)**
Attended university/college	**107 (55)**	**31 (33)**	**30 (59)**	**46 (90)**
Earns own income (N, %)	**103 (67)**	**66 (71)**	**27 (53)**	**37 (73)**
Partner provides financial support (N, %)	**156 (81)**	**91 (98)**	**37 (74)**	**28 (56)**

Safety Analysis – Adverse Events

	Not Related	Related	Total
Severity Grade	**N (%)**	**N (%)**	**N (%)**
Grade 1 – Mild	**218 (74.7)**	**74 (25.3)**	**292 (79.1)**
Grade 2 – Moderate	**49 (67.1)**	**24 (32.9)**	**73 (19.8)**
Grade 3 – Severe	**4 (100)**	**0**	**4 (1.1)**
Grade 4 – Life threatening	**0**	**0**	**0**
Grade 5 – Death	**0**	**0**	**0**
Total	**271 (73.4)**	**98 (26.6)**	**369 (100)**

Safety Analysis – Grade 3 Events

- Four Grade 3 events in 3 participants
  - Vomiting and Gastritis
    - Two distinct events
    - Not related
  - Hypotension
    - Not related
  - Vertigo
    - Not related
- No Grade 3 GU events

Safety Analysis (ITT) – All Sites

Arm	Enrolled	No. participants with ≥1 Grade 2 or higher GU event	Rate (Exact 95% CI)	p-value
IVR	**131**	**27**	**0.206 (0.140, 0.286)**	**--**
No IVR	**64**	**9**	**0.141 (0.066, 0.250**	**--**
Difference	**--**	**--**	**0.066 (-0.086, 0.215)**	**0.33**

Safety Analysis (ITT) – UAB

Arm	Enrolled	No. participants with ≥1 Grade 2 or higher GU event	Rate (Exact 95% CI)	p-value
IVR	**34**	**12**	**0.353 (0.198, 0.535)**	**--**
No IVR	**17**	**4**	**0.235 (0.068, 0.499)**	**--**
Difference	**--**	**--**	**0.118 (-0186, 0.408)**	**0.53**

Safety Analysis (ITT) – BLHC

Arm	Enrolled	No. participants with ≥1 Grade 2 or higher GU event	Rate (Exact 95% CI)	p-value
IVR	**34**	**12**	**0.353 (0.198, 0.535)**	**--**
No IVR	**17**	**4**	**0.235 (0.068, 0.499)**	**--**
Difference	**--**	**--**	**0.118 (-0.186, 0.408)**	**0.53**

Safety Analysis (ITT) – NARI

Arm	Enrolled	No. participants with ≥1 Grade 2 or higher GU event	Rate (Exact 95% CI)	p-value
IVR	**63**	**3**	**0.048 (0.010, 0.133)**	**--**
No IVR	**30**	**1**	**0.033 (0.001, 0.172)**	**--**
Difference	**--**	**--**	**0.014 (-0.202, 0.229)**	**1.00**

Safety Analysis (PP*) – All Sites

Arm	Enrolled/ Adherent	No. participants with ≥1 Grade 2 or higher GU event	Rate (Exact 95% CI)	p-value
IVR	**127**	**27**	**0.213 (0.145, 0.294)**	**--**
No IVR	**64**	**9**	**0.141 (0.066, 0.250)**	**--**
Difference	**--**	**--**	**0.072 (-0.080, 0.219)**	**0.25**

*Per-protocol analysis was performed by excluding visits of non-adherent participants

Product holds

	All Sites	NARI	BLHC	UAB
Participants enrolled	**195**	**93**	**51**	**51**
Ppts with ≥ 1 product hold (N, %)	**52 (27)**	**49 (53)**	**1 (2)**	**2 (4)**
Number of product holds	**54**	**51**	**1**	**2**
Reasons for product hold (N, %)				
HIV +	**--**	**--**	**--**	**--**
Pregnancy	**1 (2)**	**1 (2)**	**--**	**--**
AE	**4 (7)**	**2 (4)**	**1 (100)**	**1 (50)**
Other*	**49 (91)**	**48 (94)**	**--**	**1 (50)**
Product resumed (N, %)				
Yes	**1 (2)**	**--**	**--**	**1 (50)**
No	**53 (98)**	**51 (100)**	**1 (100)**	**1 (50)**

*** 1 participant co-enrolled in another study, 1 participant opted to discontinue participation in study, 47 participants' product held due to protocol team guidance**

Spotted Rings

- 27 (39%) of 69 rings recovered from NARI study participants had identifiable dark spots
- 24 (50%) of 48 rings returned to NL had identifiable spots to the naked eye
- Unused rings available from NARI site
- All used U.S. rings available for comparative assessment



Spotted Rings

- MTN NL cut cross-sections of all of the returned rings
- Rings from the US sites were smooth and had no “bubbles” in the interior matrix
- 29 of the 48 rings from NARI had “bubbles” in the silicone elastomer matrix

Spotted Rings

- MTN NL: 100% correlation between “spots” and internal “bubbles”
- Spots or erosions on the ring surface could be replicated by brushing the surface of the rings with internal “bubbles” but not in rings without “bubbles.”
- Conclusion: Silicone elastomer was not homogenous in the NARI rings which led to visual spotting on the ring surface

Adherence Analysis

Country	Evaluable participants enrolled in IVR arm	No. and % of participants with complete adherence
U.S. sites	**67***	**40 (59.7)**
India site	**63**	**35 (55.6)**

*** One participant missed all visits after enrollment and completed no forms regarding ring adherence**

Adherence Analysis – IVR Removal

Country	Evaluable ppts. enrolled IVR arm	Avg. number of removals	Avg. period of time when IVR was outside vagina (days)
U.S. sites	67*	5.56	7.75
India site	63	2.79**	4.46**

*** One participant missed all visits after enrollment and completed no forms regarding ring adherence**

****For the India site, the average number of removals and the average period of time when the IVR was outside the vagina is based on a follow-up time of less than 12 weeks due to product hold. The mean IVR use for this group was ~ 9 weeks.**

The average number of IVR removals per 30 days was similar at the U.S. and India sites (2.12 and 1.56, respectively).

Selected Acceptability Data

Response	U.S. (%) N=66	India (%) N=60
"Week 12" Acceptability Assessment:		
Prefer not to wear everyday	17%	13%
Prefer not to wear during menses	26%	25%
Not acceptable to primary partner	2%	10%
Worry about ring falling out	11%	32%*
Dislike wearing during sex	17%	20%
Would not wear, if partner doesn't like	3%	32%*
Changes the feeling of sex	18%	8%
Ring difficult or very difficult to use	5%	3%

***p < 0.05**

Conclusions

- The unmedicated silicone elastomer IVR is safe in HIV-uninfected women over 12 weeks of use
- The presence of dark spots noted on some NARI rings was secondary to lack of homogeneity in ring manufacturing
  - No adverse events linked to this finding
  - Related to placebo rings only
    - Issue has never occurred with same ring when medicated
  - NARI investigators were diligent and responded promptly

Conclusions (2)

- Full adherence with IVR use was achieved over 12 weeks in over half the evaluable women
  - Mean number of IVR removals per 30 days was similar in India, U.S.
  - Further data mining needed relative to etiology of IVR removals
- IVR was deemed acceptable to the majority of women in India, U.S

Acknowledgements

National AIDS Research Institute, Pune, India
Sanjay Mehendale, MBBS, MD, MPH
Mallika Alexander, MBBS, DGO
Seema Sahay, MSc, PhD

Bronx-Lebanon Health Center
Jessica Justman, MD

Population Council
Barbara S. Mensch, PhD
Pamela Clax
Mohcine Alami, MD
Deborah Tolenaar

SCHARP
Missy Cianciola, MS
James Dai, PhD
Jason Pan, PhD

FHI
Ayana Moore, PhD
Katherine Richards, MPH
Jonathan Paul Lucas, MPH

NIH
Lydia E. Soto-Torres, MD, MPH
Roberta Black, PhD

MTN CORE, Network Lab
Beth Galaska Burzuk, MID
Cindy Jacobson, PharmD
Katherine Bunge, MD
Devika Singh, MD, MPH
Sharon Hilllier, PhD
Lorna Rabe, BS, M (ASCP)

Protocol team wishes to thank all the 005 participants at the 3 sites for their willingness to volunteer for this study