INTERNATIONAL PARTNERSHIP FOR MICROBICIDES

Preventing HIV in Women:
Current Status of Microbicide Efficacy Trials

Zeda Rosenberg, Sc.D.
European AIDS Treatment Group (EATG)
Brussels, January 23, 2015

Developing HIV Prevention *Products for* **Women** *worldwide*

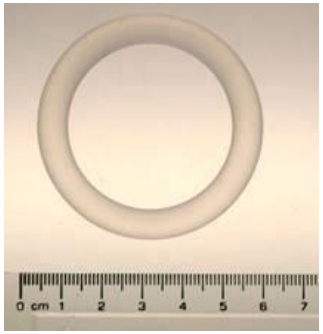
The Face of HIV/AIDS in Africa

- **Female**
  - HIV/AIDS leading cause of death globally among women 15-44
  - Nearly 60% of adults living with HIV in sub-Saharan Africa are women
- **Young**
  - Young women are *at least* as twice as likely to be infected than young men
- **Married or living with a partner**
  - Stable relationships not a haven
- **A mother**
  - 12-18% of pregnancy-related deaths due to HIV/AIDS

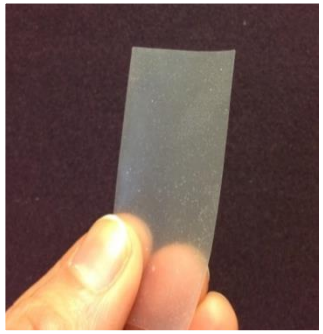
What Are Microbicides?

- Products being developed to help prevent HIV during sex
- Most contain ARVs, already used successfully to *treat* HIV
- Microbicides for women could offer convenience, more options
  - Use around the time of sex; monthly or longer
  - Option to combine ARVs, contraceptives and other drugs

Vaginal gel applicator



Long-acting vaginal ring



Vaginal film tablet, soft gel, capsule

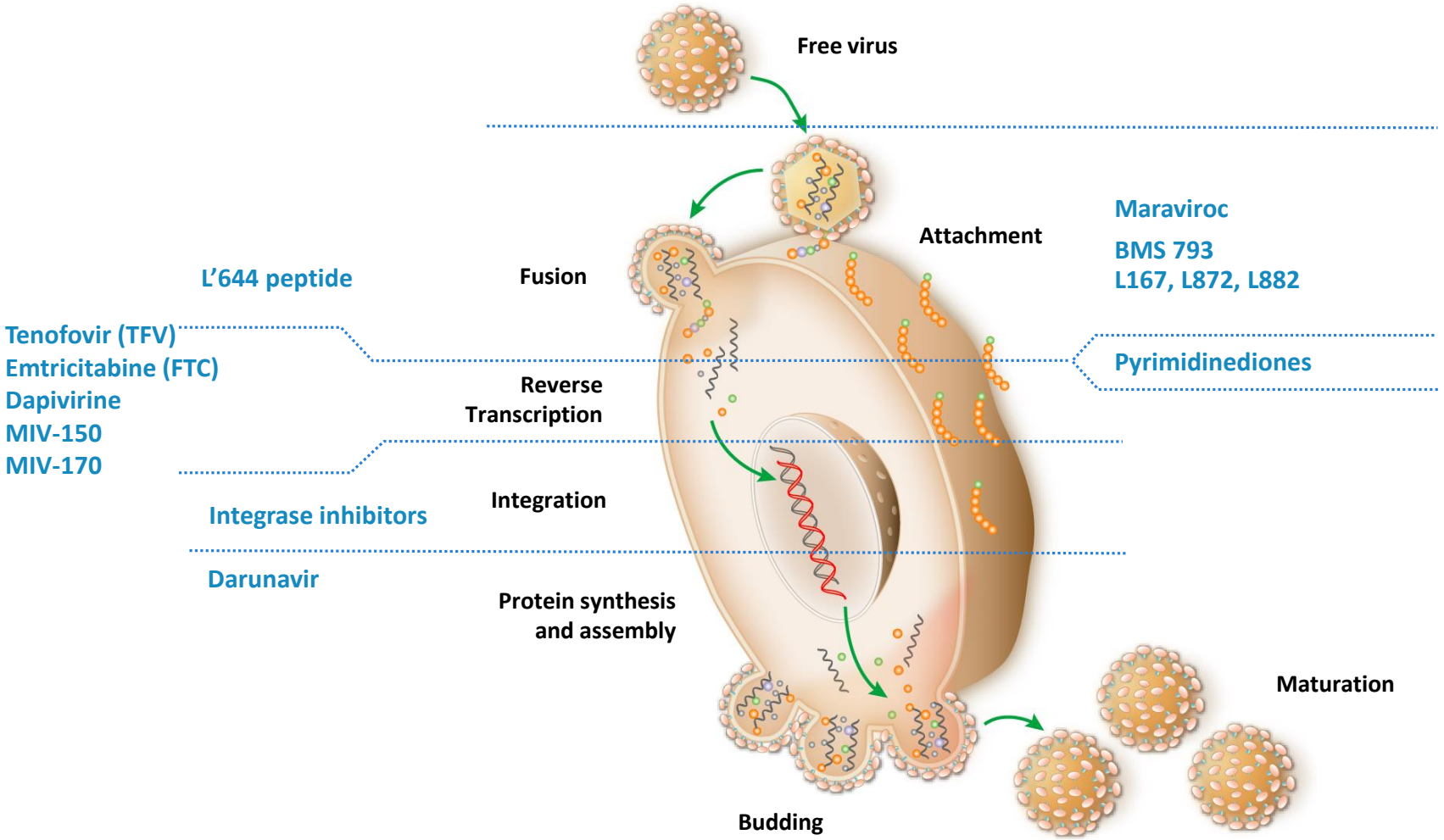
- Ideally safe, effective, low cost, user-friendly

Evidence of ARVs for HIV Prevention

- Prevention of mother-to-child transmission (PMTCT)
- Early ARV treatment as prevention (TasP)
- Oral Truvada approved by FDA (PrEP)
- Tenofovir gel proof-of-concept (microbicide)
- Work is under way to identify the most promising ARV drugs, combinations and delivery mechanisms that would be acceptable for use in multiple populations

There will be no silver bullet for HIV prevention – women need multiple choices

ARV Microbicides in Development



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Microbicides in Efficacy Trials

Tenofovir gel

- FACTS 001
- Results Q1 2015

Source: FACTS 001

Dapivirine ring

- The Ring Study and ASPIRE
- Results by 2016

Source: IPM

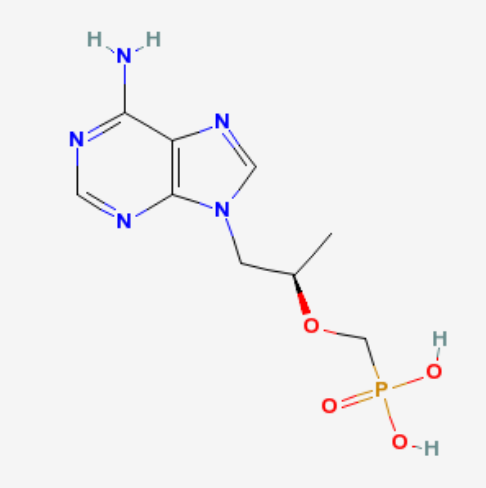
Tenofovir Gel

Source: Mapping Pathways

Tenofovir Gel

- **Tenofovir:** Nucleotide reverse transcriptase inhibitor (NRTI)
  - Stops HIV from copying its genetic material inside human cells
  - Marketed as oral therapeutic Viread®
  - Gilead license to CONRAD & IPM (2006) for HIV prevention

- **Tenofovir gel:** most clinically advanced ARV-based microbicide
  - **Proof-of-concept:** CAPRISA 004 trial showed 39% efficacy against HIV
    - VOICE trial stopped for futility (once-daily dosing)
  - Efficacy against HSV-2: CAPRISA 004 (51%) and VOICE (46%) trials
  - FACTS 001 confirmatory study



FACTS 001: at-a-glance

FACTS
Follow-on African Consortium for Tenofovir Studies

- **FACTS:** Follow-on African Consortium for Tenofovir Studies
- **FACTS 001**
  - Phase III tenofovir gel safety and effectiveness trial
    - To confirm whether before and after sex dosing (BAT24) regimen is effective for HIV and HSV-2 prevention
    - To provide additional safety and efficacy data for product registration

FACTS 001: at-a-glance

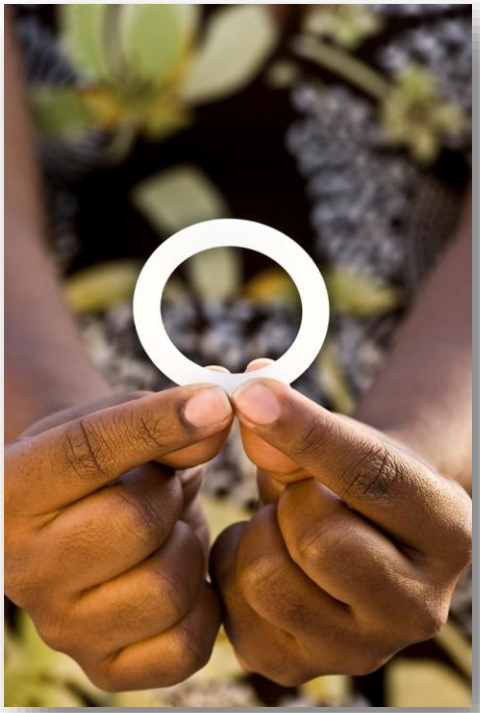
FACTS
Follow-on African Consortium for Tenofovir Studies

- Randomized, double-blind
- Endpoint driven
- Population: 2,900 women 18-30 years at nine sites in South Africa
  - Includes subset of 300 women over age 30
- Screening began Oct. 2011
- ***Results expected early 2015***

Tenofovir Gel: Next Steps

- Follow-up studies
  - CAPRISA 008: Ongoing, HIV-negative participants
  - CAPRISA 009: Ongoing, HIV-positive participants
  - Studies in adolescents, post-menopausal women, drug-drug interactions
- Approvals and access
  - Possible regulatory approvals in 2016/17

Dapivirine Ring

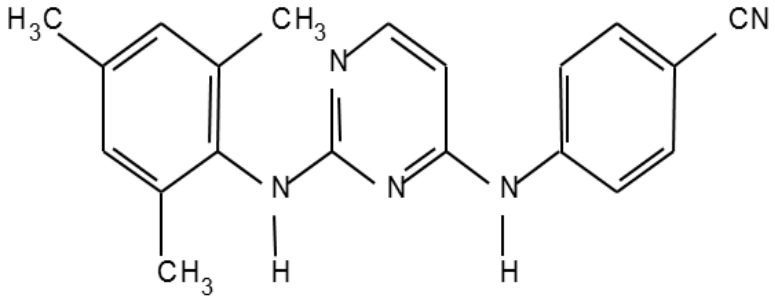


Source: IPM

Dapivirine Ring

Dapivirine: Non-nucleoside reverse transcriptase inhibitor (NNRTI)

- Acts inside cells in the vagina to block the ability of HIV to multiply
- Originally tested by Janssen as therapeutic in 11 studies
- Licensed to IPM in 2004, expansion to exclusive worldwide rights in 2014



Dapivirine vaginal ring

- Off-white flexible ring
- Self-inserted every 4 weeks
- Slowly releases drug into vaginal tissue
- Good safety profile in 17 Phase I/II studies (dapivirine ring or gel)
- Dapivirine Ring Licensure Program launched in 2012

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Dapivirine Ring Licensure Program

IPM 027 *The Ring Study*	**Long-term safety and efficacy** study • 1959 participants, ongoing (2012-2016) in Africa
MTN-020 *ASPIRE*	**Safety and efficacy** study • 2629 participants, ongoing (2012-2015) in Africa
Additional safety studies	• Drug-drug interaction (completed) • Male condom functionality (data analysis) • Female condom functionality (data analysis) • Extended use PK (data analysis) • Safety in women >45 (ongoing) • Safety in adolescents (ongoing)

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MTN microbicide trials network

National Institute of Allergy and Infectious Diseases
Leading research to understand, treat, and prevent infectious, immunologic, and allergic diseases.

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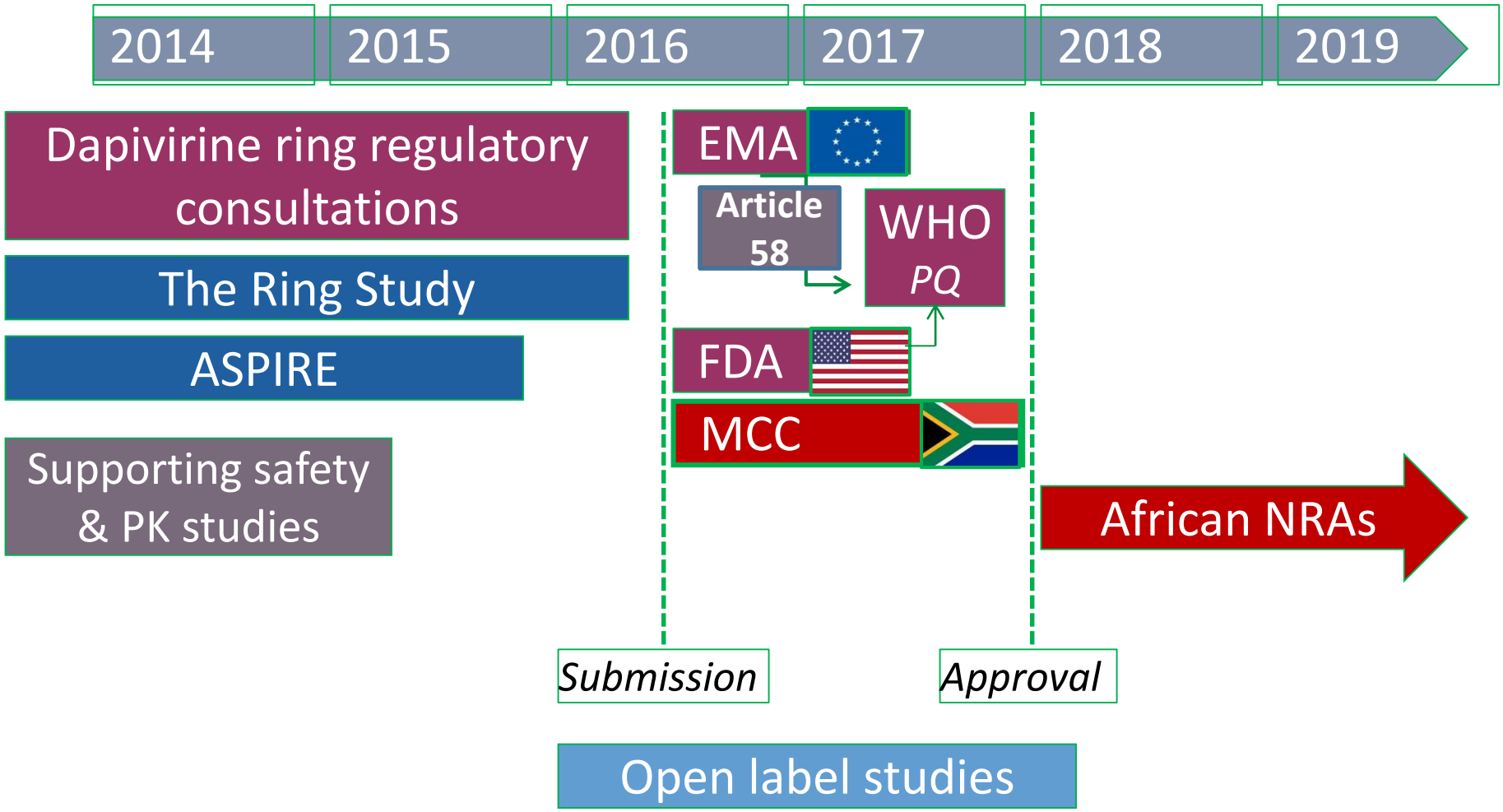
Dapivirine Ring Phase III Studies

	The Ring Study (IPM 027)	ASPIRE (MTN-020)
Objectives	Long-term safety and efficacy	Safety and effectiveness
Study design	Double-blind, randomized (2:1), placebo-controlled	Double-blind, randomized (1:1), placebo-controlled
Endpoints	96 endpoints, 2 year on IP	Endpoint driven: 120 endpoints
Power	81% power to detect 50% treatment effect	90% power to detect 60% treatment effect
Enrollment	1959 women, ages 18-45 (completed enrollment)	2629 women, ages 18-45 (completed enrollment)
Sites in Africa	7 IPM research center partners (South Africa and Uganda)	15 MTN research centers in 4 countries (NIH CTUs)
Participant follow-up	2 years + 6 weeks following ring discontinuation	Approx 1-2 years + 4 weeks following ring discontinuation
Initiation	Q1-2012	Q2-2012

Dapivirine Ring Phase IIIb Open-Label Trials

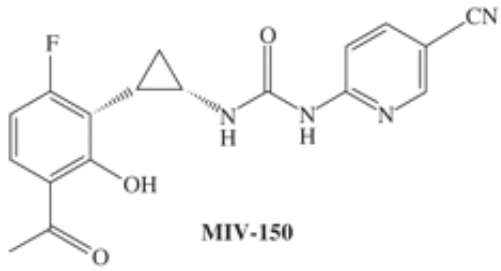
	IPM 032	MTN-025
Study design	Open-label; monthly visits for first 3 months, then quarterly	Open-label; monthly visits for first 3 months, then quarterly
Population	HIV-negative women, ages 18-45, priority to those who participated in IPM 027	HIV-negative women, ages 18-45, who participated in MTN-020
Countries	South Africa and Uganda	Malawi, South Africa, Uganda, Zimbabwe
Participant follow-up	12 months	12 months
Study period	Between determination of efficacy and regulatory approval	12 months starting from determination of efficacy

Dapivirine Ring Licensure Program



Additional Products in Phase I/II Trials

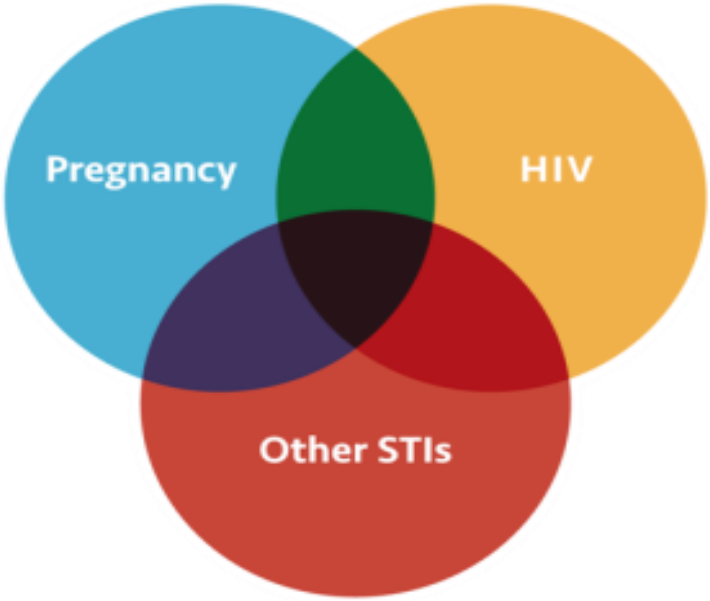
- **Tenofovir (TFV)**
  - Reformulated TFV gel for rectal use (MTN)
    - Phase I study ongoing
  - TFV-only and TFV/FTC rapid disintegrating tablet (CONRAD)
    - Phase I study ongoing
  - TFV ring (CONRAD)
    - Phase I planned in 2015
- **MIV-150**
  - NNRTI developed by Medivir AB
  - Licensed to Population Council in 2003
  - PC-1005 vaginal gel: MIV-150/zinc acetate/carrageenan
    - Phase I study launched in 2014



MIV-150

Multipurpose Prevention Technologies

- An MPT is a single product with at least two SRH prevention indications
  - Contraception
  - HIV prevention
  - STI prevention (e.g., HSV)
  - Other health benefits



Graphic from: CAMI/PATH, *Saving Lives with Multipurpose Prevention Technologies, 2010*

“On-demand” MPTs

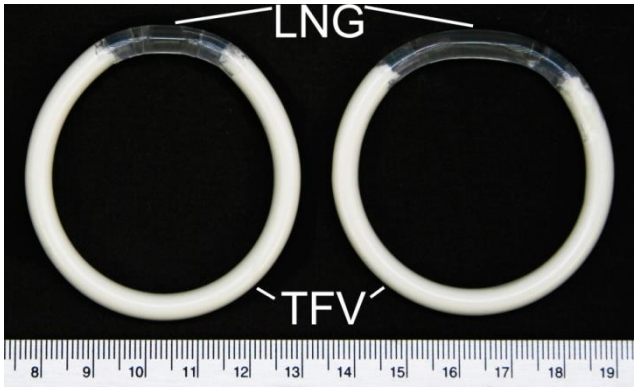
- ***Tenofovir gel***
  - CONRAD
  - Building on CAPRISA 004, FACTS 001
  - HIV + HSV-2

- ***Caya (SILCS) diaphragm with tenofovir gel***
  - PATH/CONRAD/NICHD
  - Non-hormonal barrier method with 24-hour effectiveness
  - Pregnancy + HIV + HSV-2
  - Phase I study planned Q1 2015

- ***PC-1005 vaginal gel with MIV-150***
  - Population Council
  - MIV-150 (an ARV), zinc acetate, carrageenan
  - HIV + HSV-2
  - Phase I study launched in 2014

MPT Rings

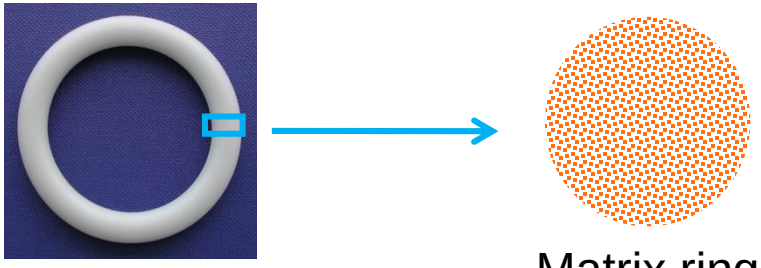
- ***90-day tenofovir-levonorgestrel (LNG) ring***
  - CONRAD
  - HIV + HSV-2 + pregnancy
  - 90-day sheep study complete
  - Phase 1 trial launched in late 2014



- ***90-day MZCL ring***
  - Population Council
  - Contains the ARV drug MIV-150 along with zinc acetate, carrageenan and LNG
  - HIV + HSV-2 + HPV + pregnancy
  - Prototype development and preclinical evaluation ongoing
  - Additional formulations planned: 30-day & on-demand nanofibers

MPT Rings (cont'd)

- ***90-day dapivirine-LNG ring***
  - IPM
  - HIV + pregnancy
  - Silicone matrix ring
  - Phase I clinical study planned in 2015
  - Focus on low-cost formulations, accelerated development timeline
  - Will guide design of more complex, longer-acting rings



Courtesy of Karl Malcolm, QUB

Summary

- **Proof-of-concept established for ARV prevention products in adults**
  - ARVs can reduce risk of infection in certain populations
- **Adherence matters; consistent use leads to greater protection**
  - Longer-acting products such as monthly vaginal rings or injectable PrEP could increase adherence, effectiveness
- **Resistance not a concern in trials to date; research continues**
  - Evaluated in all efficacy trials and follow-up studies
- **Multiple prevention tools needed**
  - No one prevention option will satisfy all