INTERNATIONAL PARTNERSHIP FOR MICROBICIDES

Microbicides: Where are we today?

Session 6: Multipurpose Prevention Technologies for Girls and Women

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Developing HIV Prevention Products for Women worldwide

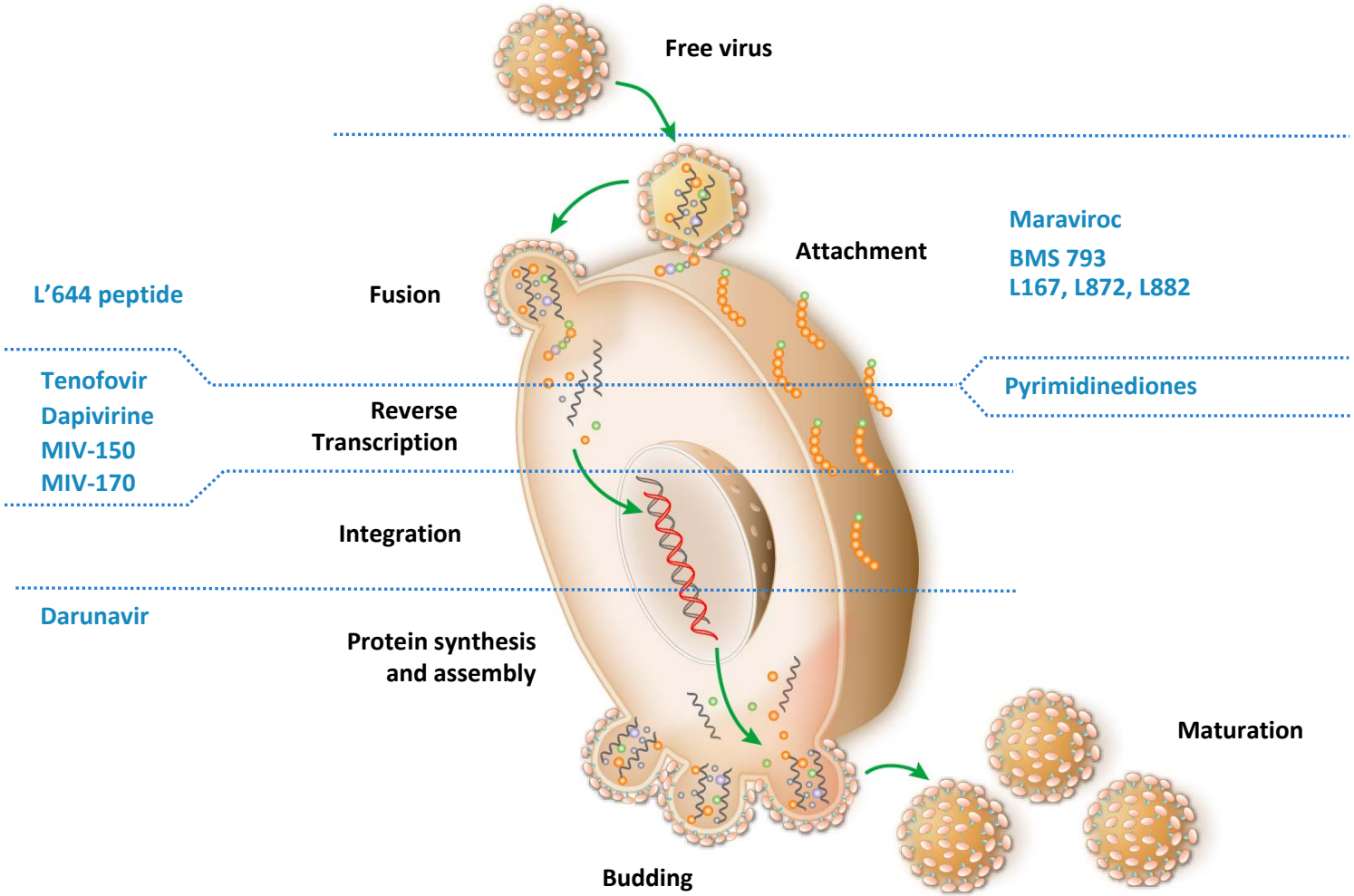
Landscape of HIV Prevention Options

- Male and female condoms
- Behavior change
- Prevention of mother-to-child transmission
- Male circumcision (protection for men)
- Post-exposure ARV drugs (healthcare workers)
- Treatment as prevention
- Pre-exposure Prophylaxis (PrEP)
- Microbicide gels and rings
- HIV vaccines

Male condoms

Female condom

ARV Microbicides in Development



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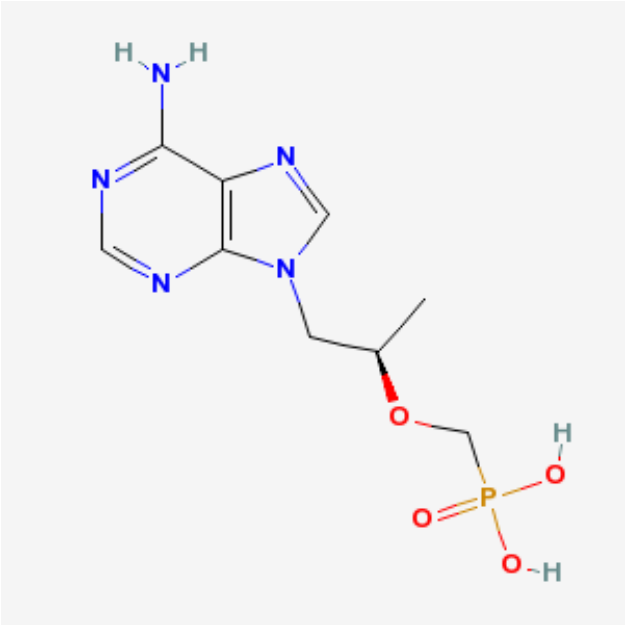
Tenofovir (Tenofovir Disoproxil Fumarate)

- Nucleotide reverse transcriptase inhibitor (NRTI)
  - Stops HIV from copying its genetic material inside human cells
  - Marketed as oral therapeutic Viread®
- Tenofovir vaginal gel: *most clinically advanced* ARV-based microbicide
  - Gilead license to CONRAD & IPM (2006)
  - **Proof-of-concept:** CAPRISA 004 trial
  - Combination and re-formulated rectal products also in development

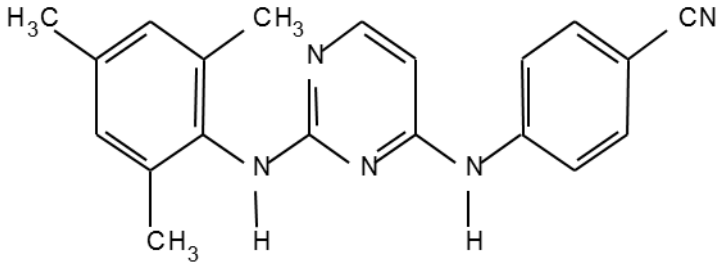


CAPRISA 004 Study

- First *efficacy* trial of an *ARV-based* microbicide
  - Tenofovir gel (results July 2010)
- First microbicide trial to show "proof of concept"
  - 889 women in South Africa
  - Gel used twice, within 12 hours before and after sex (BAT24)
  - 39% protection against HIV
  - 51% protection against HSV-2
  - Gel safe as tested and no drug resistance detected
- Additional efficacy trials
  - VOICE – Tenofovir gel arm (daily dosing) stopped for futility
  - FACTS 001- Confirmatory trial ongoing in South Africa (BAT24 dosing)
    - Results expected in 2015

Dapivirine (TMC120)

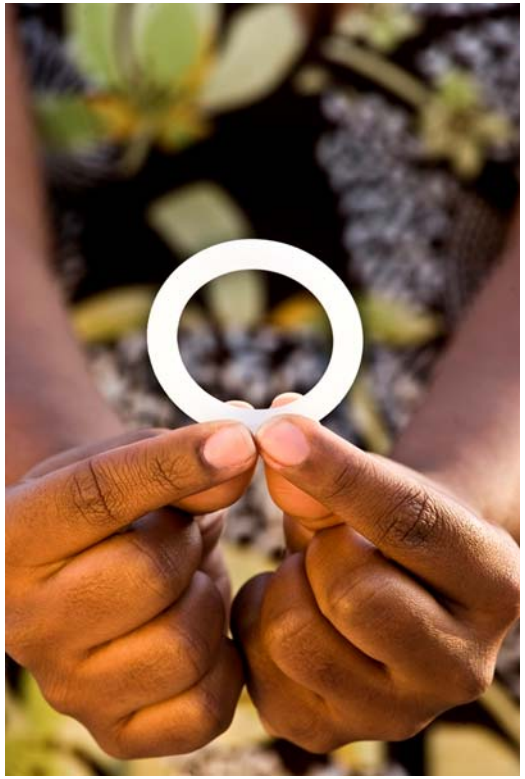
- Highly potent ARV: non-nucleoside reverse transcriptase inhibitor (NNRTI)
- Developed by Janssen R&D Ireland
  - Originally tested as oral therapeutic in 11 clinical studies



- Licensed to IPM in 2004
  - Development as topical microbicide for HIV prevention in developing countries
- 15 Phase I/II safety studies (dapivirine ring or gel)
  - Good safety profile in all studies to date
  - Data on more than 700 study participants before efficacy studies
- Dapivirine Ring Licensure Program started in 2012

Microbicide Vaginal Rings

- **Long-acting: monthly or longer**
  - Could potentially improve adherence
  - Better adherence → better effectiveness
- **Easy to use, comfortable**
  - Flexible ring, can be self-inserted
  - Rarely felt by women or male partners
  - Little or no impact on sexual activity
- **Suitable for developing world**
  - Relatively low manufacturing cost
  - Good safety and acceptability data
- **Potential for drug combinations**



Dapivirine Ring Licensure Program

IPM 027 *The Ring Study*	• **Long-term safety and efficacy** study • 1650 participants, ongoing (2012-2015) in Africa
MTN-020 *ASPIRE*	• **Safety and efficacy** study • 3476 participants, ongoing (2012-2014) in Africa
Additional safety studies	• Drug-drug interactions – ongoing • Male condom functionality – ongoing • Female condom functionality • Safety in adolescents & women >45

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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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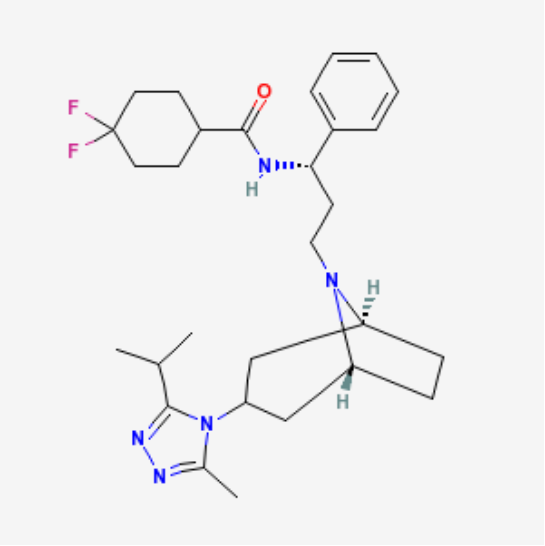
Maraviroc

- CCR5 blocker with established safety profile as marketed oral therapeutic (Selzentry™)
- Developed by Pfizer
- Licensed to IPM in 2008 for microbicide indication in developing world
- Clinical development:
  - Maraviroc rings alone and in combination with dapivirine
- Preclinical development:
  - Maraviroc gel (rectal use)- Magee Women's Research Institute
  - Maraviroc/tenofovir combination in early preclinical development



Dapivirine/Maraviroc Ring Trial

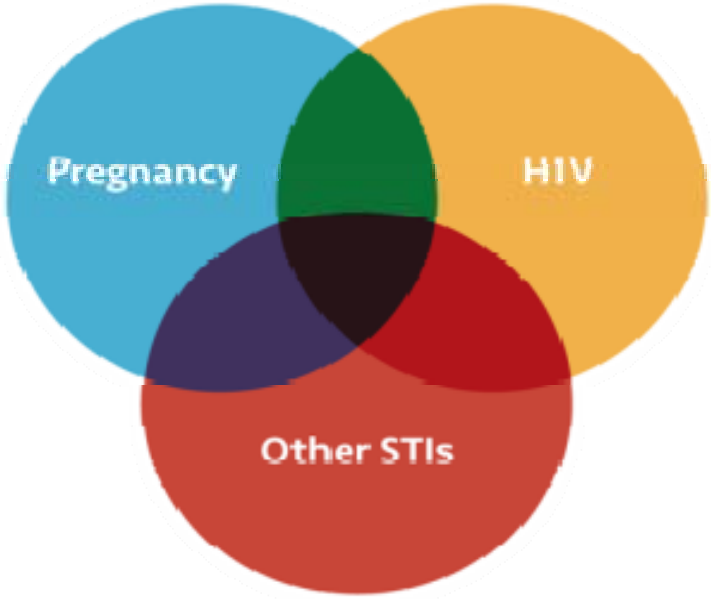
- **MTN-013 / IPM 026: Phase 1 PK & safety vaginal ring**
  - 3 research centers in the United States
- **Study design:**
  - 4 arms: dapivirine-maraviroc ring, dapivirine ring, maraviroc ring, placebo ring
  - N = 48 women
  - 28 days on product + 24 days of follow-up
  - Participant follow-up completed
  - Results expected Q2 2013

First clinical trial of a combination microbicide & first clinical trial of maraviroc for HIV prevention

10

Multipurpose Prevention Technologies (MPTs)

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



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

Microbicides: One Step to MPTs

- *Leverage existing technologies*
  - Data from microbicide field can be used to develop and expand combined HIV prevention and contraceptive options
- *Streamlining regulatory pathways*
  - Regulatory achievements for microbicide products can be built upon and combined with current data on contraceptives
  - Possible options to expedite product approval (i.e. bridging studies)

MPT Development Considerations

Indication	Mechanism of Action	Dosage	Delivery

• Pregnancy
• HIV
• HSV
• HPV
• Syphilis,
• Chlamydia
• Bacterial vaginosis
• Candida
• Trichomoniasis
	• Antiviral
	• Antimicrobial
	• Antifungal
	• Hormonal
	• Non-hormonal
	• Barrier device
	• Probiotic
		• Daily
		• Peri-coital
		• Sustained release
			• *Topical (Vaginal)*
			  • Ring
			  • Gel
			  • Tablet
			  • Film/Mesh
			• *Systemic*
			  • Oral pill
			  • Implant
			  • Injection

Adapted from: J. Romano/NWJ Group, 2012. *High-impact MPT products: Necessary attributes, development prospects, and challenges.* Available at CAMI-health.org

MPTs in the Pipeline

- ***"On-demand" products***
  - Gels
  - Barrier devices
- ***Sustained release products***
  - Vaginal rings
  - Long-acting injectables
- ***Other options***
  - Implants, films, nanofibers, vaccines, non-hormonal contraceptives

"On-demand" MPTs

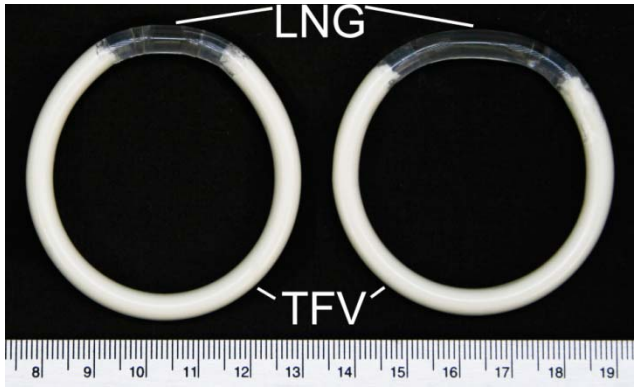
- ***Tenofovir gel***
  - CONRAD
  - Building upon CAPRISA 004 results confirmation from FACTS 001)
  - Targeted protection: HIV + HSV-2

- ***SILCS diaphragm with tenofovir gel***
  - PATH/CONRAD/NICHD
  - *Non-hormonal,* barrier method of contraception + HIV + HSV-2
  - Aims to provide protection for 24 hours

Source: J. Manning, AIDS 2012. *From Ideal to Real: What's in the MPT Pipeline.* Available at CAMI-health.org

MPT Rings in Development

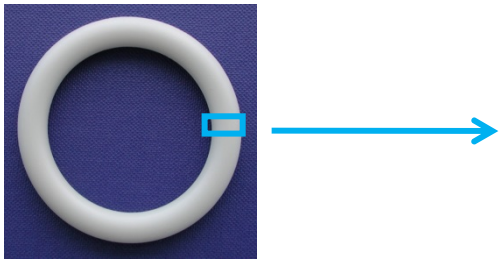
- ***90-day tenofovir-levonorgestrel (LNG) ring***
  - CONRAD
  - HIV + HSV-2 + pregnancy
  - 90 day sheep study complete
  - Phase 1 planned Q3-2013



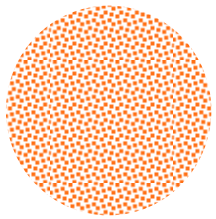
- ***90-day "MZCL" ring***
  - Population Council
  - Contains the ARV drug MIV-150 along with zinc acetate, carrageenan and LNG
  - HIV + HSV-2 + HPV + pregnancy
  - Prototype development and preclinical evaluation ongoing
  - Additional formulations planned: 30-day & on-demand nanofibers

MPT Rings in Development (cont'd)

- ***60-day dapivirine-LNG ring***
  - IPM
  - HIV + pregnancy
  - Silicone matrix ring identified as lead formulation for 60-day use
  - Phase I clinical study planned in Q3-2014
  - Focus on low-cost formulations, accelerated dev. timeline
  - Will guide design of more complex, longer-acting rings



Courtesy of Karl Malcolm, QUB



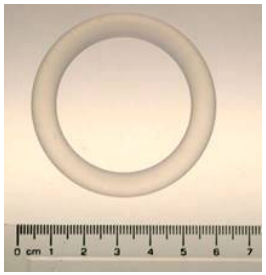
Matrix ring

Need for Multiple Drugs & Formulations

- More drug choices, more options for protection
- Different women, different preferences
- Vaginal gels, rings, films, tablets, soft gel capsules – all found to be acceptable in studies in Africa

Vaginal gel applicator

Vaginal tablet, soft gel capsule, film



Vaginal ring

MPTs: Addressing Women's Health Needs in Tandem

- Protection against HIV, unintended pregnancy and/or STIs
- On-demand and long-acting options could help ensure women have products that fit their unique lifestyle
- Potential to be more cost-effective, convenient
- Combining indications in one product may make protection more appealing and/or acceptable to women

Acknowledgements

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Thank you.