Microbicides: Where are we today?

Session 6: Multipurpose Prevention Technologies for Girls and Women

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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
ARV Microbicides in Development

- Free virus
- Attachment
- Fusion
- Reverse Transcription
- Integration
- Protein synthesis and assembly
- Budding
- Maturation

**L’644 peptide**

**Tenofovir**
**Dapivirine**
**MIV-150**
**MIV-170**

**Maraviroc**
**BMS 793**
**L167, L872, L882**

**Pyrimidinediones**

**Darunavir**

**Maturation**
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
  o Tenofovir gel (results July 2010)

• First microbicide trial to show “proof of concept”
  o 889 women in South Africa
  o Gel used twice, within 12 hours before and after sex (BAT24)
  o 39% protection against HIV
  o 51% protection against HSV-2
  o Gel safe as tested and no drug resistance detected

• Additional efficacy trials
  o VOICE – Tenofovir gel arm (daily dosing) stopped for futility
  o FACTS 001- Confirmatory trial ongoing in South Africa (BAT24 dosing)
    o 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
  o Could potentially improve adherence
  o Better adherence $\rightarrow$ better effectiveness

• Easy to use, comfortable
  o Flexible ring, can be self-inserted
  o Rarely felt by women or male partners
  o Little or no impact on sexual activity

• Suitable for developing world
  o Relatively low manufacturing cost
  o 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

International Partnership for Microbicides

National Institute of Allergy and Infectious Diseases

Leading research to understand, treat, and prevent infectious, immunologic, and allergic diseases.
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*
Multipurpose Prevention Technologies (MPTs)

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

Graphic from: CAMI/PATH, Saving Lives with Multipurpose Prevention Technologies, 2010
Microbicides: One Step to MPTs

• *Leverage existing technologies*
  o Data from microbicide field can be used to develop and expand combined HIV prevention and contraceptive options

• *Streamlining regulatory pathways*
  o Regulatory achievements for microbicide products can be built upon and combined with current data on contraceptives
  o Possible options to expedite product approval (i.e. bridging studies)
# MPT Development Considerations

<table>
<thead>
<tr>
<th>Indication</th>
<th>Mechanism of Action</th>
<th>Dosage</th>
<th>Delivery</th>
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</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>Antiviral</td>
<td>Daily</td>
<td>Topical (Vaginal)</td>
</tr>
<tr>
<td>HIV</td>
<td>Antimicrobial</td>
<td>Peri-coital</td>
<td>Ring</td>
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<tr>
<td>HSV</td>
<td>Antifungal</td>
<td>Sustained release</td>
<td>Gel</td>
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<tr>
<td>HPV</td>
<td>Hormonal</td>
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<td>Tablet</td>
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<td>Syphilis,</td>
<td>Non-hormonal</td>
<td></td>
<td>Film/Mesh</td>
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<tr>
<td>Chlamydia</td>
<td>Barrier device</td>
<td></td>
<td>Systemic</td>
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<tr>
<td>Bacterial vaginosis</td>
<td>Probiotic</td>
<td></td>
<td>Oral pill</td>
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<td>Candida</td>
<td></td>
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<td>Implant</td>
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<td>Trichomoniasis</td>
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<td></td>
<td>Injection</td>
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MPTs in the Pipeline

• “On-demand” products
  o Gels
  o Barrier devices

• Sustained release products
  o Vaginal rings
  o Long-acting injectables

• Other options
  o 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
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