Biomedical Interventions for HIV Prevention in Women: Past, Present and Future

Nyaradzo M Mgodi (MBChB, MMed)
Project Director – UZ-UCSF
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nmmgodi@uz-ucsf.co.zw
HIV Prevention For Women

• Sub-Saharan Africa (2013) - 24.7 million people HIV infected (>50% were women)

• Unprotected heterosexual intercourse - leading mode of HIV-1 transmission

• Young women twice as likely to be infected as young men – physiology, gender/social imbalances

• HIV-1 prevention interventions demonstrated to be effective in reducing HIV-1 risk
  – Require participation/consent of male partner
  – Inadequate prevention options for women unable to negotiate HIV-1/STI testing/treatment or condom use with partners

• Developing HIV-1 prevention options that women can use remains a global concern
The Past: Before 2010

“The Past is Experience”

1st generation: Surfactants &
2nd generation: Polymers
Where we came from

1st Generation: Surfactants
- N-9 Gel - Trial stopped, evidence of harm
- N-9 Film - Trial completed, no evidence of harm or benefit
- Savvy (C31G) - Trial stopped due to futility, no evidence of harm

2nd Generation: Polymers
- Cellulose Sulfate
  - CONRAD Trial stopped, trend toward evidence of harm
  - FHI Trial stopped, no harm
- Carraguard – 1st phase 3 RCT to go to completion
- PRO 2000
- BufferGel
The Present: 2010 - 2015

“The Present is an Experiment”

3rd generation: ARVs

4th generation: Co-receptor blockers
Proof of Concept: 2010

Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women

Quarraisha Abdool Karim,1,2,4† Salim S. Abdool Karim,3,2,3† Janet A. Frohlich,3 Anneke C. Grobler,3 Cheryl Baxter,1 Leila E. Mansoor,1 Ayesha B. M. Kharsany,1 Senguzwe Sibeko,3 Koleka P. Miliana,1 Zaheen Omar,1 Tanuja N. Gengiah,1 Silvia Maarschalk,1 Natasha Arulappan,1 Mukelisiwe Mlotshwa,1 Lynn Morris,1 Douglas Taylor,2 on behalf of the CAPRISA 004 Trial Group
# Outcomes of Recent HIV Prevention Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>N</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPRISA 004</td>
<td>Women</td>
<td>889</td>
<td>39% [CI = 6-60] efficacy coitally-dependent vaginal TFV gel</td>
</tr>
<tr>
<td>South Africa</td>
<td></td>
<td></td>
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<tr>
<td>(Tenofovir Gel)</td>
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<td></td>
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<tr>
<td>VOICE</td>
<td>Women</td>
<td>5,029</td>
<td>Futility of daily oral truvada, oral tenofovir and vaginal tenofovir</td>
</tr>
<tr>
<td>Zim, S Africa, Uganda</td>
<td></td>
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<td></td>
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<tr>
<td>(Oral Truvada, oral tenofovir, tenofovir gel)</td>
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<tr>
<td>FEM-PrEP</td>
<td>Women</td>
<td>1,950</td>
<td>Futility of daily oral FTC/TDF 6% [CI = -52-41]</td>
</tr>
<tr>
<td>Kenya, S Africa, Tanzania</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Oral Truvada)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FACTS 001</td>
<td>Women</td>
<td>2,059</td>
<td>No effect - coitally-dependent vaginal TFV gel</td>
</tr>
<tr>
<td>South Africa</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Tenofovir Gel)</td>
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</tbody>
</table>
Where we are today

• Demonstrated in recent years that PrEP can help prevent HIV-1 infection

• Randomized trials of the antiretroviral agent tenofovir, formulated as oral pills or a topical vaginal gel, demonstrated efficacy in diverse at-risk populations worldwide.

• However, in two trials among young women at risk for HIV-1 (VOICE and FEM-PrEP), adherence to daily tenofovir-containing pills or vaginal gels was very low and HIV-1 prevention efficacy could not be assessed.

• Data suggest these young women wanted a product they could use to reduce their risk, but that these particular products did not fit into the realities of their daily lives.

• Highlights the need for a product toolkit that fits different needs and preferences
Microbicide Intravaginal Rings

- Long-acting: monthly or longer
  - Could potentially improve adherence
  - Better adherence → better effectiveness

- Sustained Release

- User-initiated, does not require daily action

- 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 contraceptive/ARV combinations
Dapivirine IVR

- **Dapivirine - NNRTI**
- Flexible ring made of an elastic silicone material
- Measures 56 mm (about 2 ½”) in diameter and 7.7 mm (3/4”) thick
- Designed for 28-day use
- **Development Stage:** Clinical – Phase III Trials

- **Description:** monthly IVR, IPM 027 (The Ring Study) and ASPIRE (MTN 020) since 2012, planned to be completed by 2015/2016
- **IPM** providing both the placebo ring and the dapivirine ring for the studies
IPM 027 and MTN-020: Study Locations

IPM 027:
- 7 research centres
  - South Africa: KZN (3), Limpopo, North-West, Western Cape
  - Uganda: Masaka

MTN-020:
- 15 research centres
  - South Africa: Cape Town, Durban (7), Johannesburg
  - Uganda: Kampala
  - Zimbabwe: Harare (3)
  - Malawi: Blantyre, Lilongwe
MTN-020 / ASPIRE

A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Phase III Safety and Effectiveness Trial of a Vaginal Matrix Ring Containing Dapivirine for the prevention of HIV-1 Infection in Women

A Study to Prevent Infection with a Ring for Extended Use
MTN-020 Objectives

• Primary Objective
  – To determine the **effectiveness** and **safety** of dapivirine (25 mg) administered in a silicone elastomer vaginal matrix ring, when inserted once every 4 weeks, in preventing HIV-1 infection among healthy sexually active HIV-1 uninfected women

• Secondary Objectives
  – To assess the **acceptability** of and **adherence** to the dapivirine vaginal ring, the frequency of **drug resistance**, and the **relationship between drug concentrations and HIV-1 seroconversion**
MTN-020 Design

- Randomized, placebo-controlled, double-blind, phase III trial
- Sexually active HIV-1 uninfected women who are non-pregnant, contracepting, and between 18-45 years of age
- HIV-1 testing, risk reduction, contraceptive provision, safety monitoring, pregnancy testing, product provision, adherence counseling
- Ring worn for 4 weeks, replaced every 28-35 days
- All participants receive a comprehensive HIV-1 prevention package including risk-reduction, condoms, treatment of STIs, and partner testing and referral services
ASPIRE: 2,629 women, 15 sites, 4 countries

- **Malawi** (272 women) – 10%
  - Blantyre
  - Lilongwe
- **South Africa** (1,426 women) – 54%
  - Cape Town
  - Durban (7 sites)
  - Johannesburg
- **Uganda** (253 women) – 10%
  - Kampala
- **Zimbabwe** (678 women) – 26%
  - Harare/Chitungwiza (3 sites)
## ASPIRE Participant Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Malawi</th>
<th>South Africa</th>
<th>Uganda</th>
<th>Zimbabwe</th>
<th>All Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants enrolled, N</strong></td>
<td>272 (10%)</td>
<td>1426 (54%)</td>
<td>253 (10%)</td>
<td>678 (26%)</td>
<td>2629/5516</td>
</tr>
<tr>
<td><strong>Age, years (median, IQR)</strong></td>
<td>28 (24, 33)</td>
<td>24 (21, 29)</td>
<td>28 (24, 33)</td>
<td>28 (25, 33)</td>
<td>26 (22, 31)</td>
</tr>
<tr>
<td><strong>Currently unmarried</strong></td>
<td>41 (15%)</td>
<td>1313 (92%)</td>
<td>87 (34%)</td>
<td>112 (17%)</td>
<td>1553 (59%)</td>
</tr>
<tr>
<td><strong>Highest level of education</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No schooling</td>
<td>9 (3%)</td>
<td>3 (0.2%)</td>
<td>9 (4%)</td>
<td>2 (0.3%)</td>
<td>23 (1%)</td>
</tr>
<tr>
<td>Primary school (partial and complete)</td>
<td>140 (51%)</td>
<td>46 (3%)</td>
<td>117 (46%)</td>
<td>78 (12%)</td>
<td>381 (14%)</td>
</tr>
<tr>
<td>Secondary school (partial and complete)</td>
<td>121 (44%)</td>
<td>1245 (87%)</td>
<td>112 (44%)</td>
<td>592 (87%)</td>
<td>2070 (79%)</td>
</tr>
<tr>
<td>Attended college or university</td>
<td>2 (1%)</td>
<td>132 (9%)</td>
<td>15 (6%)</td>
<td>6 (1%)</td>
<td>155 (6%)</td>
</tr>
</tbody>
</table>
## ASPIRE Participant Baseline Contraceptive Use

<table>
<thead>
<tr>
<th>Current method of contraception</th>
<th>Malawi</th>
<th>South Africa</th>
<th>Uganda</th>
<th>Zimbabwe</th>
<th>All Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrauterine device</td>
<td>6 (2%)</td>
<td>79 (6%)</td>
<td>71 (28%)</td>
<td>169 (25%)</td>
<td>325 (12%)</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>6 (2%)</td>
<td>242 (17%)</td>
<td>14 (6%)</td>
<td>18 (3%)</td>
<td>280 (11%)</td>
</tr>
<tr>
<td>Injectable contraceptives</td>
<td>115 (42%)</td>
<td>1046 (73%)</td>
<td>112 (44%)</td>
<td>179 (26%)</td>
<td>1452 (55%)</td>
</tr>
<tr>
<td>Hormonal implant</td>
<td>120 (44%)</td>
<td>21 (1%)</td>
<td>49 (19%)</td>
<td>311 (46%)</td>
<td>501 (19%)</td>
</tr>
<tr>
<td>Sterilization</td>
<td>25 (9%)</td>
<td>42 (3%)</td>
<td>7 (3%)</td>
<td>3 (0.4%)</td>
<td>77 (3%)</td>
</tr>
</tbody>
</table>
## STIs Detected at Screening

<table>
<thead>
<tr>
<th>STIs detected at the screening visit</th>
<th>Malawi</th>
<th>South Africa</th>
<th>Uganda</th>
<th>Zimbabwe</th>
<th>All Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Trichomonas vaginalis</em></td>
<td>28 (10%)</td>
<td>88 (6%)</td>
<td>13 (5%)</td>
<td>51 (8%)</td>
<td>180 (7%)</td>
</tr>
<tr>
<td><em>Neisseria gonorrhoeae</em></td>
<td>13 (5%)</td>
<td>55 (4%)</td>
<td>15 (6%)</td>
<td>26 (4%)</td>
<td>109 (4%)</td>
</tr>
<tr>
<td><em>Chlamydia trachomatis</em></td>
<td>6 (2%)</td>
<td>237 (17%)</td>
<td>25 (10%)</td>
<td>48 (7%)</td>
<td>316 (12%)</td>
</tr>
<tr>
<td><em>Syphilis</em></td>
<td>11 (4%)</td>
<td>7 (0.5%)</td>
<td>6 (2%)</td>
<td>15 (2%)</td>
<td>39 (1%)</td>
</tr>
<tr>
<td></td>
<td>MTN-020</td>
<td>IPM 027</td>
<td></td>
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<td>--------------------------------</td>
<td>----------------------------------------------</td>
<td>----------------------------------------------</td>
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</tr>
<tr>
<td><strong>Design</strong></td>
<td>endpoint driven</td>
<td>fixed time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>No. of participants</strong></td>
<td>2,629</td>
<td>1,650</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Randomization</strong></td>
<td>1:1</td>
<td>2:1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>18-45 yrs</td>
<td>18-45 yrs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Product use period</strong></td>
<td>Until end of study (12-24 months)</td>
<td>24 months fixed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Person-years follow-up</strong></td>
<td>4,396 / 2,198</td>
<td>3,150 / 2,100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(all / Dapivirine Vaginal Ring)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HIV-1 seroconversions</strong></td>
<td>120</td>
<td>80</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Power for 50% effect</strong></td>
<td>97%</td>
<td>83%</td>
<td></td>
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</tbody>
</table>
Dapivirine Ring-004 Program Timeline

Ongoing DPV Ring Regulatory consultations and preparation

2012

2013

2014

2015

2016

Regulatory submission preparation for product approval

The Ring Study

ASPIRE

Drug-drug interaction (IPM 028)

Male condom compatibility (IPM 029)

Female condom compatibility (IPM 033)

2nd DDI (IPM 036)

Post menopausal Women: Safety (MTN-024)

Adolescent: Safety (MTN-023)

PK: Open label Extended use (IPM 034)

PK: Menses (IPM 035)

2016/17: Open-label Compassionate use

International Partnership for Microbicides
The Future: Beyond the Present

“The Future is an Expectation”

Promising Combinations
Multipurpose Prevention Technologies

- A single product, configured for at least 2 SRH prevention indications e.g., Pregnancy, STI, and/or HIV
- Could be different combinations:
  - Drug:Drug       Drug:Device
  - Vaccine
- Greater efficiency in terms of cost, access and delivery of Sexual and Reproductive Health (SRH) products
- Capitalize on demand in populations using one product type to achieve uptake and use of a second “product”

http://www.cami-health.org
Multiple-purpose Prevention Technologies

- New research efforts underway to develop MPT’s designed to prevent unplanned pregnancies and prevent STI’s including HIV
  - **Tenofovir – LNG IVR**: 90-day (CONRAD)
  - **Dapivirine – LNG IVR**: provides HIV-prevention and contraception for a minimum of 60 days (IPM)
  - **Dapivirine – Darunavir**: Gel and Ring (CHAARM)
  - **SILCS – TFV gel**: PrEP + non hormonal contraceptive
  - **DS003 (BMS 793)**: Potent gp120 binding entry inhibitor of HIV-1 infection, in combination with other ARVs
  - **Maraviroc**: CCR5 blocker, established safety profile - Maraviroc VRs, alone or with dapivirine (MTN-013/IPM 026), Maraviroc/Tenofovir
  - **MZC Gel**: MIV-150 (M) NNRTI, zinc acetate (Z) RTI, Carrageenan (C)
**Tenofovir–LNG IVR**

- **CONRAD** - On going Study - First multipurpose ring in clinical trials: Phase I One-Month Safety, PK, PD and Acceptability Study of IVRs Releasing Tenofovir and LNG or Tenofovir Alone *(Protocol A13-128)*
  - 100 women - 50 across 2 sites: US and Dominican Republic
  - 3 arms, randomized 2:2:1 TFV-only ring, TFV/LNG ring and Placebo ring
  - 8 or 9 visits and follow-up contact

**Dapivirine–LNG IVR**

- **IPM 041/MTN-030** – planned
  - 2 LNG Doses
  - Randomized, double-blind, placebo-controlled study
  - 32 healthy HIV-negative women, aged 18-45 years with demonstrated ovulation
  - Randomized in 1:1:1:1 ratio, to use a vaginal ring for 90 days: Placebo, Dapivirine (200mg) + 64mg LNG, Dapivirine (200mg) + 150mg LNG, Dapivirine 200mg only
Conclusion

• “The Past is experience, the Present is an experiment and the Future is an expectation.”
  Adapted, Anon

• Female-initiated HIV prevention product development is an iterative and challenging process,
• Continuously informed and driven by new findings
• We continue to use past experience in our experiments (trials) to achieve our expectations of developing:
• Safe and effective products that would allow women to protect themselves from HIV, STIs, and unintended pregnancy
Thank you!

• All the women who have taken part in microbicide/PrEP studies
• Research Communities
• Advisory Boards
• Sponsors
• All study teams
• Thes Palanee-Philips
• Jared Baeten
• Z. Mike Chirenje
• And you all for listening.