Overview of Microbicide Development

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A microbicide is a product that can be applied to the vaginal or rectal mucosa with the intention of preventing the transmission of sexually transmitted infections including HIV.

Microbicides containing antiretroviral drugs = Topical PrEP (Pre-exposure prophylaxis)
History of microbicide effectiveness trials:
Surfactants

Efficacy of Nonoxynol 9 Contraceptive Sponge Use in Preventing Heterosexual Acquisition of HIV in Nairobi Prostitutes

Phase 1 trial of nonoxynol-9 film among sex workers in South Africa

Effectiveness of COL-1492, a nonoxynol-9 vaginal gel, on HIV-1 transmission in female sex workers: a randomised controlled trial

SAVVY Vaginal Gel (C31G) for Prevention of HIV Infection: A Randomized Controlled Trial in Nigeria

SAVVY® (C31G) Gel for Prevention of HIV infection in Women: A Phase 3, Double-Blind, Randomized, Placebo-Controlled Trial in Ghana

Legend:
- **Safe but not effective**
- **Increased HIV infection**
- **Stopped for futility**
- **Safe and effective**
History of microbicide effectiveness trials: Viral entry blockers and buffers

Effectiveness of Cellulose Sulfate Vaginal Gel for the Prevention of HIV Infection: Results of a Phase III Trial in Nigeria

Lack of Effectiveness of Cellulose Sulfate Gel for the Prevention of Vaginal HIV Transmission

Efficacy of Carraguard for prevention of HIV infection in women in South Africa: a randomised, double-blind, placebo-controlled trial

Safety and effectiveness of BufferGel and 0.5% PRO2000 gel for the prevention of HIV infection in women

PRO2000 vaginal gel for prevention of HIV-1 infection (Microbicides Development Programme 301): a phase 3, randomised, double-blind, parallel-group trial
AIDS 2010: Proof-of-concept that an antiretroviral can prevent HIV infection

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

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<table>
<thead>
<tr>
<th>Months of follow-up</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative HIV endpoints</td>
<td>37</td>
<td>65</td>
<td>88</td>
<td>97</td>
<td>98</td>
</tr>
<tr>
<td>Cumulative women-years</td>
<td>432</td>
<td>833</td>
<td>1143</td>
<td>1305</td>
<td>1341</td>
</tr>
<tr>
<td>HIV incidence rates (Tenofovir vs Placebo)</td>
<td>6.0 vs 11.2</td>
<td>5.2 vs 10.5</td>
<td>5.3 vs 10.2</td>
<td>5.6 vs 9.4</td>
<td>5.6 vs 9.1</td>
</tr>
<tr>
<td>Effectiveness (p-value)</td>
<td>47% (0.069)</td>
<td>50% (0.007)</td>
<td>47% (0.004)</td>
<td>40% (0.013)</td>
<td>39% (0.017)</td>
</tr>
</tbody>
</table>

[Graph showing the probability of HIV infection over time for Tenofovir and Placebo]

[Table summarizing the effectiveness and incidence rates for Tenofovir gel and Placebo]
## Antiretroviral (PrEP) effectiveness microbicide clinical trials

<table>
<thead>
<tr>
<th>Phase</th>
<th>Trial name</th>
<th>Candidate(s)</th>
<th>Countries</th>
<th>Number of women</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Completed Trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIb</td>
<td>CAPRISA 004 (RCT)</td>
<td>Tenofovir gel (coital)</td>
<td>South Africa</td>
<td>1085</td>
<td>AIDS 2010 39% (6; 60)</td>
</tr>
<tr>
<td></td>
<td>MTN 003 VOICE Trial (RCT)</td>
<td>Tenofovir gel (daily) * and daily oral PrEP (tenofovir or Truvada)</td>
<td>South Africa, Uganda, Zimbabwe</td>
<td>5029</td>
<td>CROI 2013 15% (-21; 40)</td>
</tr>
<tr>
<td>III</td>
<td>FACTS 001 (RCT)</td>
<td>Tenofovir gel (coital)</td>
<td>South Africa</td>
<td>2059</td>
<td>CROI 2015 0% (-40, 30)</td>
</tr>
<tr>
<td></td>
<td>MTN 020 ASPIRE Trial (RCT)</td>
<td>Dapivirine vaginal ring (every 4 weeks)</td>
<td>South Africa, Malawi, Uganda, Zimbabwe</td>
<td>2629</td>
<td>CROI 2016 31% (1; 51)</td>
</tr>
<tr>
<td></td>
<td>IPM 027 Ring Study (RCT)</td>
<td>Dapivirine vaginal ring (every 4 weeks)</td>
<td>South Africa, Uganda</td>
<td>1959</td>
<td>CROI 2016 27% (1; 46)</td>
</tr>
</tbody>
</table>
# Antiretroviral (PrEP) open label extension (OLE) microbicide trials

<table>
<thead>
<tr>
<th>Phase</th>
<th>Trial name</th>
<th>Candidate(s)</th>
<th>Countries</th>
<th>Number of women</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td><strong>Completed Trials</strong></td>
</tr>
</tbody>
</table>
| IIIb  | CAPRISA 008 (OLE RCT)    | Tenofovir gel (coital)        | South Africa         | 382             | Adherence was higher (79.9%) in the FP service compared to the trial clinic (73.9%).
|       |                          |                               |                      |                 | Most women (75.3%) expressed a preference for receiving HIV prevention from FP service clinics. |
|       |                          |                               |                      |                 | Integration of PrEP into FP services is feasible, acceptable and can achieve good adherence, similar to those achieved in clinical trial settings. |
|       |                          |                               |                      |                 | This clinical trial evidence may be helpful to policy makers and health care providers planning on implementing oral PrEP scale-up. |
|       |                          |                               |                      |                 | **Ongoing Trials**                           |
| IIIb  | MTN 025 HOPETrial(OLE)   | Offered Dapivirine vaginal ring (every 4 weeks) | South Africa, Malawi, Uganda, Zimbabwe | ± 2000          | Initiated: Q3 2016 |
|       | IPM 032 DREAM Trial (OLE) | Dapivirine vaginal ring (every 4 weeks) | South Africa, Uganda | ± 1400          | Initiated: Q3 2016 |
Microbicide product pipeline

- **Microbicide film formulations:**
  - Multiple ARVs being evaluated in early stage development as vaginal films
    - Dapivirine, tenofovir, maraviroc, IQP-0528, RC-101
  - Phase 1 clinical evaluation of dapivirine film vs dapivirine gel: ongoing

- **Rectal gel formulations:**
  - Multiple ARVs being evaluated in phase I / II trials as rectal gels
    - Tenofovir, maraviroc, dapivirine, UC-781
  - Phase I expanded safety study of 1% rectal tenofovir gel showed product is safe and acceptable. Pericoital use is preferred.

- **Intravaginal ring formulations:**
  - With tenofovir and/or other antiretroviral agents
  - Maraviroc + CMPD 167 silicone matrix IVRs
  - MC1220 (NNRTI) silicone matrix IVR
  - MIV-150 (NNRTI) silicone matrix IVR
  - MIV-160 (NNRTI) EVA matrix IVR
  - Tenofovir 90 day polyurethane IVR
  - Tenofovir silicone “POD” IVR
  - Tenofovir + IQP-0528 polyurethane matrix IVR
  - Tenofovir disoproxyl fumarate polyurethane reservoir IVR
Multi-purpose prevention technologies

- A single product, configured for at least two SRH prevention indications:
  - Contraception
  - Protection against HIV
  - Protection against other STIs e.g. BV, HSV-2
  - Other health benefits

- Greater efficiency in terms of cost, access and delivery of SRH prevention products

- Capitalize on the demand in populations for one product for one indication to achieve uptake and use of a second “product” for a different indication eg. a ring to prevent pregnancy that also prevents HIV
MPT products in development

- **Vaginal Rings**
  - Tenofovir and levonorgestrel (LNG)
  - Dapivirine and levonorgestrel

- **MIV-150 products - Population Council**
  - MIV-150 (NNRTI), zinc acetate, LNG, carrageenan in IVR or gel
  - Combination dependent prevention of HIV, HSV, HPV, pregnancy

- **Barrier microbicides**
  - SILCS diaphragm with microbicide gel
  - SILCS diaphragm releasing a microbicide

- **Other MPT products/technology options**
  - Rectal specific microbicides, implants, lactobacillus GMO,
    - Verselle gel delivery, broad spectrum natural products,
    - non-hormonal contraceptives and vaginal ring/film with monoclonal antibodies.
**HIV prevention with ARVs (since 2010)**

- **Microbicicides for women**
  Abdool Karim Q, Science 2010

- **Oral pre-exposure prophylaxis**
  Grant R, NEJM 2010 (MSM)
  Baeten J, NEJM 2012 (Couples)
  Thigpen M, NEJM 2012 (Heterosexuals)

- **Dapivirine intravaginal ring**
  Baeten J, NEJM 2016

- **Treatment for prevention**
  Cohen M, NEJM 2011

**HIV prevention (before 2010)**

- **Male circumcision**
  Auvert B, PloS Med 2005
  Gray R, Lancet 2007
  Bailey R, Lancet 2007

- **Treatment of STIs**
  Grosskurth H, Lancet 2000

- **Female Condoms**

- **Male Condoms**

- **HIV Counselling & Testing**
  Coates T, Lancet 2000

- **Behavioural Intervention**
  - Abstinence
  - Be Faithful

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*Note: PMTCT, Screening transfusions, Harm reduction, Universal precautions, Vaccines, etc. have not been included*
The world needs a range of options...

- Multipurpose prevention technologies
- Dapivirine ring
- Injectable ARVs: Cabotegravir
- HIV vaccines
- Potential future prevention technologies
- Broadly neutralising antibodies
- CRISPR-CAS9 gene editing
- ARV-based implants
- F/TAF & Truvada
Acknowledgements

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  - US Agency for International Development (USAID) via FHI and CONRAD
  - President’s Emergency fund for AIDS Relief (PEPFAR)
  - US Centers for Disease Control and Prevention (CDC)
  - South African Department of Science and Technology (DST)
  - Fogarty International Center, NIH
  - Howard Hughes Medical Institute (HHMI)
  - Gilead Sciences (Tenofovir API)
  - Royal Netherlands Embassy and MIET
  - MACAIDS Fund (via Tides Foundation)
  - Technology Innovation Agency (LIFELab)

- Past Funders:
Quiz Question 1

1. Name an antiretroviral microbicide product that has shown to prevent HIV infection?

A. Dapivirine intravaginal ring
B. Carraguard vaginal gel
C. Tenofovir vaginal gel
D. Maraviroc vaginal film
E. SAVVY vaginal gel
Quiz Question 2

2. Should a range of HIV prevention options become available, which one method would you choose?

A. Long-acting injectable – received every 2 months
B. Vaginal ring – changed every 30 days
C. Implant – changed every 6 months
D. Vaginal gel – used coitally
E. Oral tablet – taken daily
Overview of HIV Vaccine Development

AWACC

Dr Kathy T Mngadi
CAPRISA,
School of Laboratory Medicine UKZN
Ending AIDS — Is an HIV Vaccine Necessary?

Anthony S. Fauci, M.D., and Hilary D. Marston, M.D., M.P.H.

In the past decade, according to the 2013 Global Report of the Joint United Nations Program on HIV/AIDS (UNAIDS), the numbers of AIDS-related deaths and new human immunodeficiency virus (HIV) infections have fallen by about one third from their peaks — accomplishments made possible by the accelerated implementation of effective prevention and treatment tools.

Of particular note, the scale-up of antiretroviral therapy (ART) averted 5.4 million deaths in low- and middle-income countries between 1995 and 2012. HIV prevention efforts have expanded from a narrow agenda of providing condoms and clean needles to use of a comprehensive toolkit of preventive interventions that have had a profoundly positive effect on the pandemic. For example, improved approaches to the prevention of mother-to-child transmission have averted the deaths of more than 1 million children worldwide. The rate of male acquisition of HIV can be diminished by two thirds through voluntary medical male circumcision. Preexposure prophylaxis with antiretroviral medication, when adhered to, significantly reduces the risk of HIV infection. Finally,

“Ultimately, we believe, the only guarantee of a sustained end of the AIDS pandemic lies in a combination of non-vaccine prevention methods and the development and deployment of a safe and effective HIV vaccine.”
The Space for HIV Vaccines

Innovations in the management of HIV that will impact on community viral load and infectiousness: prevention of secondary transmission

Innovations in the Prevention of Sexual Acquisition that will be required when secondary transmission is not averted

HIV Cure: the ultimate control of the HIV epidemic will be in the elimination of viremia in those infected

Gray, G et al Plos Biol, 2016
Quick Quiz

• How many HIV vaccines have been tested for efficacy in South Africa?

A. One  
B. Two  
C. Five  
D. More than 5
## Recent History of HIV Vaccine Development

<table>
<thead>
<tr>
<th>Study/Location</th>
<th>Vaccine/s</th>
<th>Risk Group/HIV Incidence</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vax003 Thailand</td>
<td>AIDSVAX B/E gp120 in alum</td>
<td>IDUs 3.4%</td>
<td>No VE</td>
</tr>
<tr>
<td>Vax004 US/Europe</td>
<td>AIDSVAX B/B gp120 in alum</td>
<td>MSM/high risk women 2.6%</td>
<td>No VE</td>
</tr>
<tr>
<td>HVTN 502 Americas</td>
<td>MRKAd5 HIV-1 gag/pol/nef</td>
<td>MSM/high risk women 3%</td>
<td>Halted for futility; early transient increased infection in vaccinees</td>
</tr>
<tr>
<td>HVTN 503</td>
<td>MRKAd5 HIV-1 gag/pol/nef</td>
<td>Heterosexual men &amp; women 3.7%</td>
<td>No VE; late increased HIV infection in unblended male vaccinees</td>
</tr>
<tr>
<td>RV144 Thailand</td>
<td>ALVAC-HIV vCP1521, AIDSVAX B/E rgp120 in alum</td>
<td>Heterosexual men and women with variable risk 0.28%</td>
<td>31.2% VE at 42/12; 60% VE @ 12/12</td>
</tr>
<tr>
<td>HVTN 505</td>
<td>DNA, rAD5 (A,B,C)</td>
<td>Circumcised MSM Ad5 neg 1.8%</td>
<td>Halted at interim analysis for futility</td>
</tr>
</tbody>
</table>
Potential Impact of a Vaccine

Even a vaccine with low efficacy and limited coverage can impact the epidemic and play a role in preventing future infections.

Formation of the P5 Partnership

**Purpose:**
To build on RV144 data and ultimately license a pox-protein based HIV vaccine with the potential for broad and timely public health impact.

**Strategy:**
Continue to build public-private partnerships critical for success.
1. Work with host countries to support a flexible regulatory strategy in target populations and regions.
2. Generate and incorporate knowledge from the assessment of next-generation vaccine concepts.
Current Vaccine Development in HVTN

**HVTN 097**
Designed to evaluate RV144 vaccine regimen in RSA and compare immunogenicity to that in Thailand

**HVTN 100**
A standard phase 1 trial of the clade C products to decide whether to proceed to phase 3

**HVTN 702**
A Classic phase 3 RCT assessing efficacy and safety aimed at licensure
Mosaic Vaccine Development

Different HIV-1 clades dominate in different geographic regions:

- Adolescents (11-17 years) / Adults (18-65 years) in endemic countries and populations at risk in Western world.

1. Vectors that elicit optimal immune responses:
   - Low seroprevalent Ad26
   - Ad26.HIV-Gag-Pol
   - Ad26.HIV-Env (MVA.HIV-Gag-Pol-Env)

2. Mosaic inserts for global coverage

3. Trimeric env protein for improved humoral immunity

Reference:
High Level Clinical Development Plan

Phase 1/2a (2014-2016)
- USA, Africa, Asia
  - Safety
  - Regimen selection
  - Dose confirmation

Phase 2b/3 (2017-2021)
- Africa and Asia
  - Efficacy in high risk population

Phase 3/4 (2021+)
- Long term efficacy
  - Persistence of Immunity
- Additional trials
  - ≠populations
  - ≠countries

Ancillary studies
- Evaluation of alternative schedules
- Evaluation of Mosaic trimer
- Evaluation of tetravalent Ad26

Additional trials
- Lot to lot, bridging

BLA-MAA submissions?
Janssen and Collaborators

Phase 1
Approach

Phase 2b
Traverse

Phase 3
Ascent

IAVI
Ragon
NIAID/HVTN

BIDMC
Harvard
MHRP
Passive Immunisation

- VRC01 and 3BNC117 in trials
- CAP 256 in clinical trials in 2017/18
Quick quiz

• How long did it take to develop a licenced Influenza vaccine?

A. 10 years
B. 20 years
C. 50 years
D. 90 years
## Vaccine Research in Perspective

<table>
<thead>
<tr>
<th>VACCINE</th>
<th>DISCOVERY OF VIRUS</th>
<th>VACCINE DEVELOPED FOR HUMAN USE</th>
<th>YEARS TO VACCINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. Influenza-B</td>
<td>1892</td>
<td>1985</td>
<td>93</td>
</tr>
<tr>
<td>Herpes (HSV-1)</td>
<td>1919</td>
<td>Not available</td>
<td>&gt;90</td>
</tr>
<tr>
<td>Pertussis</td>
<td>1906</td>
<td>1926</td>
<td>20</td>
</tr>
<tr>
<td>Polio</td>
<td>1909</td>
<td>1954</td>
<td>47</td>
</tr>
<tr>
<td>Yellow Fever</td>
<td>1900</td>
<td>1935</td>
<td>35</td>
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<tr>
<td>Influenza</td>
<td>1933</td>
<td>1945</td>
<td>12</td>
</tr>
<tr>
<td>Measles</td>
<td>1911</td>
<td>1957</td>
<td>46</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>1973</td>
<td>1995</td>
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<tr>
<td>Hepatitis B</td>
<td>1967</td>
<td>1984</td>
<td>17</td>
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<tr>
<td>HPV</td>
<td>1974</td>
<td>2007</td>
<td>33</td>
</tr>
<tr>
<td>HIV</td>
<td>1983</td>
<td>Not available</td>
<td>&gt;30</td>
</tr>
</tbody>
</table>
Acknowledgements

Prof. Glenda Gray
Collaborators: HVTN and Janssen
Communities and Participants
Vaccine team at ECRS
HIV VACCINES: THE WORLD’S BEST HOPE TO END AIDS

Questions??