Advances in Topical Protection Against HIV-1 Infection

Ross D. Cranston MB ChB MD FRCP
Fundació Lluita contra la SIDA
Barcelona
Summary

- Microbicide background
- The concept and potential acceptability
- Vaginal gel, rings, and films
- Rectal gel, and inserts
- Topical protection in the PrEP era
Microbicides
The Rationale for Topical Prevention Products

- **Females**
  - Familiar with intravaginal product insertion
    - Sanitary products (tampons)
    - Contraceptive Rings
    - Candida treatment (applicators/tablet)
    - Sexual lubricants

- **Males (men who have sex with men)**
  - Lubricant frequently used to facilitate anal intercourse
## Rectal Microbicide ‘Acceptability’

<table>
<thead>
<tr>
<th>Country</th>
<th>Population</th>
<th>‘Acceptability’</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peru</td>
<td>MSM</td>
<td>92%</td>
<td>Peinado J et al</td>
</tr>
<tr>
<td>US</td>
<td>MSM</td>
<td>75%</td>
<td>Anton et al</td>
</tr>
<tr>
<td>US</td>
<td>MSM</td>
<td>75%</td>
<td>Carball-Diéguez et al</td>
</tr>
<tr>
<td>US</td>
<td>MSM</td>
<td>87%</td>
<td>McGowan et al</td>
</tr>
<tr>
<td>China</td>
<td>MSM and TW</td>
<td>73%</td>
<td>Zhang et al</td>
</tr>
<tr>
<td>US</td>
<td>MSM</td>
<td>56%</td>
<td>Ventuneac et al</td>
</tr>
</tbody>
</table>
Heterosexual Anal Intercourse in South Africa

![Graph showing prevalence of anal intercourse among sexually active general population in South Africa.](image-url)

- **Recall Period, partner type**
  - **Lifetime, any**
    - Nel, 2011
    - Gutley, 2014
    - Gutley, 2014
  - **12 months, any**
    - Lane, 2006
    - Lane, 2006
  - **6 months, steady**
    - Anderson, 2009
  - **6 months, casual**
    - Anderson, 2009
  - **3 months, any**
    - Kalichman & Simbaya, 2004
    - Skoller-Karpoff, 2008
    - Jemmott, 2014
  - **1 month, any**
    - Abdool Karim, 2010
    - Kalichman, 2011
    - Cain, 2012
    - Cain, 2012
    - Cain, 2012
- **General, steady**
  - Smith, 1998
  - Smith, 1998
- **General, casual**
  - Smith, 1998
  - Smith, 1998

**Prevalence of Anal Intercourse among Sexually Active General Population (%)**

**Estimate (95% CI) Sex Location**
- 1.7 (1.1 - 2.5) F Multiple
- 4.1 (2.8 - 6.0) F Durban
- 0.3 (0.0 - 1.9) F Hlabisa
- **2.0 (0.3 - 3.8) F 99%**
- 5.3 (4.6 - 6.0) F National
- 5.5 (4.8 - 6.3) M National
- **5.4 (4.9 - 5.9) M 90%**
- 6.3 (4.1 - 9.5) Mix Soweto
- 9.7 (5.5 - 16.3) Mix Soweto
- 10.2 (6.8 - 15.0) F W. Cape
- 2.3 (1.9 - 2.7) F Multiple
- 13.4 (11.4 - 15.8) M E. Cape
- 13.6 (11.0 - 16.7) M E. Cape
- 0.7 (0.2 - 2.0) F KZNatal
- 13.6 (11.8 - 15.6) F Cape Town
- 17.2 (15.9 - 18.6) M Cape Town
- 12.9 (8.8 - 18.4) F Cape Town
- 7.9 (3.5 - 16.1) F Cape Town
- 16.6 (13.7 - 19.9) M Cape Town
- 15.8 (8.6 - 31.9) M Cape Town
- **10.4 (2.5 - 18.5) F 99%**
- 4.1 (1.3 - 10.7) M Cape Town
- 12.0 (5.0 - 25.0) M Pretoria
- **8.0 (3.1 - 13.0) M 1%**
- 27.4 (17.9 - 39.3) F NS
- 27.8 (16.9 - 41.9) M NS
- **27.6 (19.7 - 35.5) M 90%**
- 33.3 (21.1 - 48.0) F NS
- 32.4 (18.0 - 50.6) M NS
- 32.8 (22.7 - 43.0) M NS

![Image of graph showing prevalence of anal intercourse among sexually active general population in South Africa.](image-url)
Sexual Lubricants

$219 million annual market in the US - Forbes
# Sexual Lubricant Use During Intercourse

<table>
<thead>
<tr>
<th>Country</th>
<th>Population</th>
<th>Use</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>MSM</td>
<td>87%</td>
<td>Butler et al</td>
</tr>
<tr>
<td>US</td>
<td>Black MSM</td>
<td>33-43%</td>
<td>Calabrese et al</td>
</tr>
<tr>
<td>US</td>
<td>WSW</td>
<td>60%</td>
<td>Hensel et al</td>
</tr>
<tr>
<td>US</td>
<td>WSM</td>
<td>43%</td>
<td>Brown et al</td>
</tr>
<tr>
<td>Australia</td>
<td>MSM</td>
<td>68%</td>
<td>Chow et al</td>
</tr>
<tr>
<td>Peru</td>
<td>MSM</td>
<td>50%</td>
<td>Clark et al</td>
</tr>
<tr>
<td>India</td>
<td>MSM</td>
<td>64%</td>
<td>Ramanathan et al</td>
</tr>
<tr>
<td>Tanzania</td>
<td>MSM</td>
<td>66%</td>
<td>Romijnders et al</td>
</tr>
</tbody>
</table>
Vaginal Gel
# Non-ARV Vaginal Microbicide

<table>
<thead>
<tr>
<th>Microbicide Candidate</th>
<th>Clinical Trial Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>N9 surfactant</td>
<td>No reduction in HIV</td>
<td>Kreiss et al</td>
</tr>
<tr>
<td></td>
<td>No reduction in HIV/GC/CT</td>
<td>Roddy et al</td>
</tr>
<tr>
<td></td>
<td>Enhances HIV acquisition</td>
<td>Van Damme et al</td>
</tr>
<tr>
<td>SAVVY surfactant</td>
<td>No reduction in HIV</td>
<td>Feldblum et al</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Guffey et al</td>
</tr>
<tr>
<td>Carraguard</td>
<td>No reduction in HIV</td>
<td>Skoler-Karpoff et al</td>
</tr>
<tr>
<td>Buffer-Gel</td>
<td>Did not prevent STIs</td>
<td>Guffey et al</td>
</tr>
<tr>
<td>Pro-2000</td>
<td>No reduction in HIV</td>
<td>McCormack et al</td>
</tr>
<tr>
<td>Cellulose Sulphate</td>
<td>Enhances HIV acquisition</td>
<td>Ramjee et al</td>
</tr>
<tr>
<td>VivaGel</td>
<td>Altered genital flora</td>
<td>Carballo-Dieguez et al</td>
</tr>
<tr>
<td>ACIDFORM</td>
<td>Genital irritation</td>
<td>Keller et al</td>
</tr>
</tbody>
</table>

**No Efficacy**
Vaginal Tenofovir Gel

- CAPRISA 004
  - 39% reduction in HIV (CI 6-60%)
  - Protection significantly higher with concentrations of TNF in cervical fluid (> 1,000 ng/mL)
- MTN-003 (VOICE)
  - No significant reduction in HIV infections
- FACTS-001
  - No significant reduction in HIV infections
Adherence to Product (VOICE)

Marrazzo NEJM 2015
Vaginal Rings
Dapivirine Ring Effectiveness Studies

- IPM-027 (RING study)
  - 37% (95% CI, 12 to 56; P = 0.007)

- MTN-020 (ASPIRE study)
  - 31% (95% CI, 0.49 to 0.99; P = 0.04)

Nel NEJM 2016, Baeten NEJM 2016
Follow-Up Studies

- MTN-025 (HOPE)
  - A Phase 3B Open-Label Follow-on Trial to Assess the Continued Safety of and Adherence to a Vaginal Ring Containing Dapivirine in Women

- IPM 032
  - A Follow-on Open-Label Trial to Assess Continued Safety of and Adherence to the Dapivirine (25mg) Vaginal Ring-004 in Healthy, HIV-Negative Women
Future Developments in Vaginal Rings

- Combination antiretroviral rings
  - Maraviroc/dapivirine
  - MK 2048/vicriviroc
- Antiretroviral/contraceptive rings
  - Dapivirine/levonorgestrel
  - Tenofovir/levonorgestrel
- Three month rings
- Additional safety data in:
  - Pregnant, lactating, adolescent, and post-menopausal women
Vaginal Film
Vaginal Film

- **FAME study:**
  - Open label comparative crossover study design of tenofovir gel and film pharmacokinetics in blood, cervical tissue, and cervicovaginal fluid

- **BnAb film:**
  - A Phase 1, single center study to assess the safety of MB66, a combined anti-HIV (VRC01-N) and anti-HSV (HSV8-N) monoclonal antibody film for vaginal application as microbicide

PIs: Sharon Hillier, University of Pittsburgh; Deborah Anderson, Boston University
Rectal Gel
Would this Approach Work?

“HIV” \((^{99}\text{Tc-SC})\) in Ejaculate

“Microbicide”\((^{111}\text{In-DTPA})\)
Pivotal Rectal Microbicide Studies

- RMP-02/MTN-006
  - A two-site, Phase 1, partially-blinded, placebo-controlled safety, acceptability and pharmacokinetic trial of topical, vaginally-formulated tenofovir 1% gel applied rectally compared with oral 300 mg tenofovir disoproxil fumarate in HIV-1 seronegative adults
Cervical/Rectal Explant Challenge

Tissue biopsies

Gelatin sponge

Abner JID 2005, Fletcher AIDS 2006
Pivotal Rectal Microbicide Studies

- **RMP-02/MTN-006**
  - A two-site, Phase 1, partially-blinded, placebo-controlled safety, acceptability and pharmacokinetic trial of topical, vaginally-formulated tenofovir 1% gel applied rectally compared with oral 300 mg tenofovir disoproxil fumarate in HIV-1 seronegative adults

- **MTN-007**
  - A Phase 1 Randomized, Double-Blinded, Placebo-Controlled Rectal Safety and Acceptability Study of Tenofovir 1% Gel
MTN-017 Study Design

- Open label crossover design
- Each participant was randomized to follow all study regimens for eight weeks, with a one-week wash-out period between regimens
- Study regimens
  - Rectal RG 1% TFV gel used daily
  - Rectal RG 1% TFV gel used before and after receptive anal intercourse (RAI)
  - FTC/TDF tablet taken daily
Key Findings from MTN-017

- Rectal tenofovir gel was safe and acceptable compared to oral TDF/FTC
- Participants preferred using gel before and after sex rather than on a daily base
- Participants did not like using the vaginal applicator to insert the gel
MTN-026

- Phase 1 rectal safety study
  - Dapivirine 0.05% gel
  - HEC placebo
- Safety, acceptability, PK, PD
- Three sites N = 27
  - Pittsburgh, Birmingham, Bangkok
MTN-033

- Phase 1 evaluation of dapivirine gel to determine whether digital / phallic insertion equivalent to applicator insertion of microbicide
- University of Pittsburgh

PI: Ken Ho, University of Pittsburgh
MTN-039 (In development)

- Phase 1 rectal safety, acceptability, and PK/PD assessment of a combination fast dissolving tablet (rectal insert)
- Tenofovir rectal insert
- Collaboration with CONRAD
- Men and women (N = 30)
- Single dose study

PI: Sharon Riddler, University of Pittsburgh
Population Council Program

- MIV-150/Carageenan/Zinc gel
  - Preclinical activity against HIV, HSV, and HPV
- A Phase 1 Safety and Pharmacokinetic Study of PC-1005 (MIV-150/Zinc Acetate/Carrageenan Gel) Administered Rectally Using a Sequential Dose/Volume Escalation Method to HIV-1 Seronegative Sexually Abstinent Adults
- Phase 1 rectal safety study (MTN-037)

PI: Craig Hendrix, Johns Hopkins Medical School
PREVENT Program

- Development of GRFT rectal microbicide
  - GRFT has activity against HIV, HSV, and HCV
- Preclinical program
  - NHP studies ongoing
- Phase 1 study
  - University of Pittsburgh
  - Scheduled for Q2 2018

PI: Kenneth Palmer, University of Louisville
DREAM Program

- Development of enemas as delivery vehicle for TFV prodrugs
- Preclinical program
  - Mice & non-human primate studies
- Clinical program
  - DREAM-01
    - Comparison of iso-osmolar and hypo-osmolar formulations of TFV
  - UCLA, University of Pittsburgh, and JHU

PI: Craig Hendrix, Johns Hopkins Medical School
What Can Rectal Microbicides Offer?

- Pericoital
- Potential for limited behavioural change (gel)
- ARV or BnAb or other
- Gel or enema or rectal insert
- Lower systemic exposure
Oral PrEP Trials in MSM

Effect Size

44%

86%

86%

TDF/FTC PrEP

1. Approved for off-label use.
2. The European Commission granted Gilead marketing authorization for Truvada as PrEP in Q3 2016. This should encourage countries within the EU to make PrEP available within their national health systems, based on cost factors and individual country regulatory requirements.

Updated August 2016
HIV Prevention Pipeline Summary
The Future

- Dapivirine vaginal ring – towards licensure
- Topical rectal products:
  - Uncertainty
    - What product?
    - How to insert?
    - What regime?
  - Cost of research leading to licensure studies
  - NIH agenda focus on multicompartment products
  - How to conduct an efficacy study in the context of highly efficacious oral PrEP
Acknowledgements

- **MTN:**
  - Ian McGowan
  - Jeanne Marrazzo
  - Peter Anton
  - Ken Ho
  - Jared Baeten
  - Sharon Riddler

- **IPM:**
  - Analene Nel

- **FACTS-001:**
  - Helen Rees

- **PREVENT:**
  - Kenneth Palmer

- **DREAM:**
  - Craig Hendrix

- **Funders/collaborators:**

![Logos of collaborating organizations]