An Update on Topical Microbicide Development

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Greater emphasis is urged for research on preventive methods women could use, including the possibility of a topical virucide that might block transmission through the vaginal route.
Overview

- The biology of HIV infection
- Microbicide development
  - Vaginal microbicides
  - Intravaginal rings
  - Multipurpose technology
  - Rectal microbicides
- Challenges in microbicide development
The Biology of HIV Infection

Haase A. Nature 2010
Recruitment of Target Cells

Haase A. Nature 2010
Microbicides

Microbicides are products that can be applied to the vaginal or rectal mucosa with the intent of preventing or significantly reducing the risk of acquiring STIs including HIV.
Microbicides
Mechanism of Action

- Viral disruption
- Prevention of STDs
- Maintenance of normal microflora

**Gel/cream:**
- Physical barrier
- Lubrication

- Inhibition of HIV uptake by dendritic cells (e.g. anti-DC-SIGN)
- Inhibition of reverse transcriptase
- Fusion/absorption inhibition (e.g. polyanions, co-receptor antagonists)

McGowan I. Biologicals, 2006
Non-Antiretroviral Microbicides

- Nonoxynol-9
- Savvy®
- Carraguard®
- Cellulose sulfate®
- PRO 2000
- BufferGel™
Antiretroviral PrEP

1995
PMPA effective in macaque model

2005
HPTN-050 Phase 1

2006
HPTN-059 Phase 2

2007
TDF PrEP Study

2010
iPrEX

2010
CAPRISA 004 Phase 2B

2011
FEM-PrEP

2011
HPTN-052

2011
Partners PrEP

2011
TDF2

2013
MTN-003 VOICE

2015
FACTS-001
Antiretroviral Microbicides

Oral

Topical

Blood

Mucosa

Concentration of ARV
Vaginal Exposure to ART

CAPRISA 004

- 889 women randomized to receive tenofovir 1% gel or placebo with BAT regimen
- South Africa
- Protection significantly higher with concentrations of TFV in cervical fluid (> 1,000 ng/mL)

<table>
<thead>
<tr>
<th></th>
<th>HIV EP</th>
<th>%</th>
<th>CI</th>
</tr>
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<tbody>
<tr>
<td>Placebo</td>
<td>60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir</td>
<td>38</td>
<td>39</td>
<td>6-60</td>
</tr>
</tbody>
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Abdool Karim Q et al. Science 2010
Karim SS et al. Lancet 2011
The VOICE Study

5,029 HIV- women

Vaginal sex in prior 3 months
Not pregnant or breastfeeding
Willing to use effective contraception

Randomized to once daily use

Oral TDF  Oral FTC/TDF  Oral Placebo  Vaginal TFV  Vaginal placebo

Monthly visits

Comprehensive HIV prevention counseling, condoms, contraception, STI evaluation & treatment, provision of study product

1° endpoints: HIV infection, safety
## Primary Efficacy Results (mITT)

<table>
<thead>
<tr>
<th></th>
<th>TDF*</th>
<th>FTC/TDF</th>
<th>TFV Gel</th>
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<tbody>
<tr>
<td><strong>HIV protection efficacy versus placebo</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>HR</strong></td>
<td>1.49</td>
<td>1.04</td>
<td>0.85</td>
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<tr>
<td><strong>95% CI</strong></td>
<td>(0.97, 2.3)</td>
<td>(0.7, 1.5)</td>
<td>(0.6, 1.2)</td>
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<tr>
<td><strong>P-value</strong></td>
<td>0.07</td>
<td>&gt;0.2</td>
<td>&gt;0.2</td>
</tr>
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</table>

*Censored on date when sites were informed to take women off of TDF and TDF placebo pills*
Plasma Tenofovir Detection in Random Cohort Sample

Level of TFV detection ≥ 0.3 ng / ml
Conclusions from VOICE

- Adherence to study products was low, especially among younger, unmarried women
- No study drug significantly reduced risk of HIV acquisition
- Results consistent with FEM-PrEP
- Incidence of HIV infection substantially higher than anticipated
- A better understanding HIV risk perception and biomedical, social and cultural determinants of adherence in this high-risk population is urgently needed
FACTS-001

- Phase 3 safety and effectiveness study of 1% tenofovir versus placebo gel (1:1) in preventing HIV/HSV-2 infection
- BAT dosing regimen
- N = 2,900
  - 2,600 18-30 year old women
  - 300 > 30 year old women
- Current status
  - Approximately 1,900 of 2,600 enrolled
Intravaginal Rings
Intravaginal Rings

- Sustained release platform
- Ring replaced monthly
- Potential for combination ARV ± contraception
- Dapivirine is the current lead candidate
Dapivirine Vaginal Ring: Vaginal Fluids

Ex vivo $IC_{50} = 0.49$ ng/mL in cervical explant tissue

Ex vivo $IC_{99} = 3.3$ ng/mL in cervical explant tissue
Intravaginal Ring Development

- **Phase 3 Dapivirine program**
  - IPM-027 (RING study)
  - Residual drug levels being monitored
  - MTN-020 (ASPIRE study)
  - Real time PK being introduced to monitor adherence at a site level

- **Combination rings**
  - MTN-013
  - Antiretroviral/ contraceptive rings
Rectal Microbicides
Rectal Microbicides

- RAI associated with significant risk of HIV acquisition
- HIV infections in MSM stable or increasing
- Proof of concept protection in non-human primate studies
- Phase 1 rectal PK/PD studies completed for tenofovir and UC781
- Phase 2 study of tenofovir starting in Q3 2013
Challenges in Microbicide Development
Challenges

- Product adherence
- Need for biomarkers of
  - Sexual behavior
  - Sexual risk
  - Product adherence
  - Mucosal safety
- Surrogates for product efficacy
  - Explant model
- Creating desire / social marketing
Product Adherence

Self Report

Drug level monitoring

Dye Test

Wisebag
Mucosal Safety

N=60

2% N-9 (N=15)

1% Tenofovir (N=15)

HEC (N=15)

No Treatment (N=15)

Baseline Evaluation

Single dose

7 day daily doses

7-14 day interval

Endoscopy Safety/behavioral assessment

McGowan I et al. PLoS ONE 2013
Microarray Data from MTN-007

No Treatment

HEC gel

N-9 gel

Tenofovir gel

Hladik F et al. Unpublished data
Summary of Microarray Data

Gene expression 9 cm rectum following 7 days of product application
Surrogates of Product Efficacy
Explant Challenge Model

Endoscopic biopsies + Absorbable gelatin sponge

Abner SR et al. JID 2005
Fletcher P et al. AIDS 2006
Maraviroc *In Vitro* Colorectal Explant Efficacy Data

Dezzutti C et al. Unpublished data
PK/PD in RMP-02/MTN-006

Oral Dose  Single Rectal Dose  Multiple Rectal Dose

Cumulative p24 (pg/mL)

\( r^2 = 0.33 \)
\( P = 0.0011 \)

Anton P et al. AIDS & Human Retroviruses 2012
Creating Desire
Next Steps

- Critically dependent on the results of:
  - FACTS-001
    - Vaginal tenofovir gel
  - ASPIRE and RING studies
    - Intravaginal dapivirine ring
  - MTN-017
    - Rectal tenofovir gel
- Combination products
  - Antiretroviral + hormonal contraceptive
- Rectal microbicide effectiveness study
Summary

- Completed studies have suggested that oral antiretroviral PrEP is both safe and effective in MSM, serodiscordant couples, and IDU.
- Data for antiretroviral vaginal microbicides are more limited and divergent
- Complex Phase 1 PK/PD studies may help optimize the product pipeline
- Product adherence is a significant challenge and sustained delivery platforms may be needed to improve PrEP effectiveness
Acknowledgements