The Beginning

- 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.

Stein Z. Am J Pub Health 1990
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

Microbicidess

Microbicidess 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 reverse transcriptase
- Inhibition of HIV uptake by dendritic cells (e.g., anti-DC-SIGN)
- Fusion/absorption inhibition (e.g., polyanions, co-receptor antagonists)
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 Partners PrEP
- 2011 TDF2
- 2013 MTN-003 VOICE
- 2015 FACTS-001
Antiretroviral Microbicides

Concentration of ARV

Vaginal Exposure to ART

CAPRISA 004

- 889 South African women randomized to receive tenofovir 1% gel or placebo with BAT regimen

<table>
<thead>
<tr>
<th>HIV EP</th>
<th>%</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Tenofovir</td>
<td>38</td>
<td>39</td>
</tr>
</tbody>
</table>

- Protection significantly higher with concentrations of TFV in cervical fluid
  - (> 1,000 ng/mL)
- Reduction in HSV-2 acquisition by 51%

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

Malcolm RK et al. Antiviral Research 2010
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

Ex vivo IC₅₀ = 0.49 ng/mL in cervical explant tissue
Ex vivo IC₉₉ = 3.3 ng/mL in cervical explant tissue
Rectal Microbicides

Rationale for RM

- Unprotected receptive anal intercourse (RAI) is the highest risk sexual activity for HIV transmission
- Men and women in the developed and developing world practice RAI
- Murine and non human primate studies have shown proof of concept that rectal application of ARV microbicides can prevent SIV/HIV infection
- Use of lubricants common in MSM
Phase 1 Rectal Microbicide Studies

- UC781 (RMP-01 study)
  - Anton PA et al., *PLOS ONE*, 2011
- Tenofovir (original formulation) (RMP-02/MTN-006 study)
- Tenofovir (reduced glycerin formulation) MTN-007
  - McGowan I et al. *PLOS ONE*, 2013
Rectal Microbicide Distribution


### Phase 1 GI Adverse Events

<table>
<thead>
<tr>
<th>GI Adverse Events in the Tenofovir Arm</th>
<th>MTN-007 (N = 16)</th>
<th>RMP-02/MTN-006 (N = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>6/16</td>
<td>6/12</td>
</tr>
<tr>
<td>Rectal urgency</td>
<td>5/25%</td>
<td>5/42%</td>
</tr>
<tr>
<td>Bloating</td>
<td>5/42%</td>
<td>5/42%</td>
</tr>
<tr>
<td>Nausea</td>
<td>4/33%</td>
<td>4/33%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7/58%</td>
<td>7/58%</td>
</tr>
<tr>
<td>Flatulence</td>
<td>3/25%</td>
<td>3/25%</td>
</tr>
<tr>
<td>Proctalgia</td>
<td>0/0%</td>
<td>0/0%</td>
</tr>
<tr>
<td>Other</td>
<td>5/42%</td>
<td>5/42%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>12/100%</strong></td>
<td><strong>12/100%</strong></td>
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<tbody>
<tr>
<td>Abdominal pain</td>
<td>3  16%</td>
<td>6  50%</td>
</tr>
<tr>
<td>Rectal urgency</td>
<td>0  0%</td>
<td>5  42%</td>
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<td>Bloating</td>
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<td>Diarrhea</td>
<td>1  6%</td>
<td>7  58%</td>
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<tr>
<td>Flatulence</td>
<td>6  38%</td>
<td>3  25%</td>
</tr>
<tr>
<td>Proctalgia</td>
<td>1  6%</td>
<td>0  0%</td>
</tr>
<tr>
<td>Other</td>
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<td>5  42%</td>
</tr>
<tr>
<td>Total</td>
<td>9  56%</td>
<td>12 100%</td>
</tr>
</tbody>
</table>
MTN-007: Transcriptome

Gene expression 9 cm rectum following 7 days of product application

Summary of Microarray Data

Gene expression 9 cm rectum following 7 days of product application
MTN-017

- Phase 2 rectal safety study of tenofovir gel in MSM and transgender women
- N = 186
- Domestic and International sites
- Starting Q3 2013

Endpoints
- Safety
- Adherence
  - Self report
- Real time PK
- Acceptability
- PK/PD

MTN-017 Sites
### MTN-017

<table>
<thead>
<tr>
<th></th>
<th>8 weeks</th>
<th>8 weeks</th>
<th>8 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BL</strong></td>
<td>TFV Gel</td>
<td>TFV Gel</td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td>Daily</td>
<td>With sex</td>
<td>Truvada</td>
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</table>

Mucosal PK/PD subset (N = 36)

### Challenges in Microbicide Development
Challenges

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

Product Adherence

- Self Report
- Drug level monitoring
- Wisebag
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

Colorectal Explant Infection

McGowan I, Unpublished data
PK/PD in RMP-02/MTN-006

Graph showing cumulative p24 levels against Log$_{10}$[Tissue TFV-DP]fmol/mg, with points for Oral Dose, Single Rectal Dose, and Multiple Rectal Dose, and a regression line with $r^2 = 0.33$ and $P = 0.0011$.

Anton P et al. AIDS & Human Retroviruses 2012

Combination HIV Prevention

Conventional HIV Prevention Package + PrEP

SC ± Oral ± Rectal ± Vaginal ± HIV Vaccine
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
The Microbicide Trials Network

The MTN Recompetition

- Safe and effective vaginal microbicides
- Safe and effective rectal microbicides
- Combination hormonal contraceptive and antiretroviral vaginal ring
- Special populations
  - Pregnancy
  - Adolescence
  - Post menopausal women
  - MSM and transgender women
**Behavioral Research Agenda**

- Maximizing adherence to study products
- Understanding differential adherence
- Determining product preferences
- Investigating changes in risk behavior during trials
- Identifying the most reliable and informative measures of acceptability and adherence
- Understanding motivations and characteristics of trial participants
- Examining participant comprehension of partial efficacy

**Biomedical Research Agenda**

- To test and evaluate novel biomarkers within MTN protocols:
  - Efficacy
  - Safety
  - Adherence
  - HIV risk

- Determine impact of microbicides on:
  - Host microbiome
  - Host mucosal immune response

- Impact of mucosa on antiretrovirals:
  - Transporters, metabolism, and dNTP pools
New Products & Formulations

- Candidates
  - Griffithsin
  - 5P12-RANTES
  - MIV-150
  - IQP-0528

- Formulations
  - Intravaginal rings
    - Combination antiretroviral and contraceptive
  - Vaginal films
  - Suppositories
  - Rectal-specific formulations

The MTN Portfolio
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