Transforming a Molecule to a New Prevention Product: the Journey Toward an Extended Release Film

Sharon Hillier, PhD
Richard Sweet Professor of Reproductive Infectious Disease
Departments of Obstetrics, Gynecology and Reproductive Sciences and Microbiology and Molecular Genetics
Overview of the Presentation

• Do we need more HIV prevention options for young women?
• Fast dissolving films
  – Can they deliver ARVs to genital tissues?
  – What do films and gels do to the vaginal microenvironment?
  – What does the microbiota do to the drugs?
• Building a film for extended release of ARVs
• Conclusions
Our world is home to 1.8 billion young people between the ages of 10 and 24, and the youth population is growing fastest in AFRICA nearly 2% every year. If adolescents were a country they would be the most populous country. Within this generation are 600 million adolescent girls with specific needs, challenges and aspirations for the future.
Since the Start of PEPFAR, New HIV Infections Have Declined 51-76%

Reduction in rate of new HIV infections (incidence rate) during 12 years of PEPFAR implementation

- **Zimbabwe**: 67% decline
- **Malawi**: 76% decline
- **Zambia**: 51% decline

Source: UNAIDS & PHIA IMPACT Studies, 2016
Disproportionate Success in Epidemic Control by Age Group

New HIV Infections by Population and Year

<table>
<thead>
<tr>
<th>Year</th>
<th>Pediatric (0-14 yrs)</th>
<th>15 - 24 yrs</th>
<th>25 yrs +</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000*</td>
<td><img src="purple" alt="" /></td>
<td><img src="red" alt="" /></td>
<td><img src="yellow" alt="" /></td>
</tr>
<tr>
<td>2015*</td>
<td><img src="purple" alt="" /></td>
<td><img src="red" alt="" /></td>
<td><img src="yellow" alt="" /></td>
</tr>
<tr>
<td>2020**</td>
<td><img src="purple" alt="" /></td>
<td><img src="red" alt="" /></td>
<td><img src="yellow" alt="" /></td>
</tr>
<tr>
<td>Projected</td>
<td><img src="purple" alt="" /></td>
<td><img src="red" alt="" /></td>
<td><img src="yellow" alt="" /></td>
</tr>
</tbody>
</table>

Sources: * UNAIDS AIDS info Online Database, 2016; ** 15-24 yrs age group projected based on Africa Development Forum / World Bank 2015, “Africa’s Demographic Transition: Dividend or Disaster?”
Why?

• Increasing population of youth in Africa (youth bulge)
• Rollout of circumcision and treatment as prevention has much less impact on reducing incidence in young women than older women and men
Medicalization of Sex

• To a large extent, HIV medicalized sexuality for many people
  – In HIV endemic areas, to be young and to have sex is be at “high risk”
  – For MSM, to be young and sexually active is to be a “high risk” person

• Some HIV prevention options are nonmedicalized (condoms) while others are very medicalized (oral PrEP)
What Do Young Women Want?

• To be healthy, but not to be reminded every day that they are “at risk” just because they have sex
• Not to be stigmatized by their families and communities for using prevention products
• To be able to access products in less medicalized settings like pharmacies
• To have products that do not require monitoring for toxicity and that look like reproductive health products rather than drugs
• To use single products for family planning and HIV
Won’t the Tools We Have Be Enough?

• Young people less than 25 years of age have been the least “adherent” to oral treatment and prevention regimens
  – Neither of the studies of oral PrEP conducted in younger women demonstrated PrEP efficacy
  – In iPrEX, MSM <25 years had lower PrEP efficacy than older people

• Injectable ARVs will not require daily adherence but they will require returning for injections every 2 months
### “Scorecard” for HIV prevention modalities for women

<table>
<thead>
<tr>
<th>Modality</th>
<th>Efficacy</th>
<th>Low user burden</th>
<th>Low Cost</th>
<th>Low systemic side effects</th>
<th>Reversibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily oral PrEP</td>
<td><img src="emoji" alt="Score" /></td>
<td><img src="emoji" alt="Score" /></td>
<td><img src="emoji" alt="Score" /></td>
<td><img src="emoji" alt="Score" /></td>
<td><img src="emoji" alt="Score" /></td>
</tr>
<tr>
<td>On demand PrEP</td>
<td><img src="emoji" alt="Score" /></td>
<td><img src="emoji" alt="Score" /></td>
<td><img src="emoji" alt="Score" /></td>
<td><img src="emoji" alt="Score" /></td>
<td><img src="emoji" alt="Score" /></td>
</tr>
<tr>
<td>Injectable Cabotegravir</td>
<td><img src="emoji" alt="Score" /></td>
<td><img src="emoji" alt="Score" /></td>
<td><img src="emoji" alt="Score" /></td>
<td><img src="emoji" alt="Score" /></td>
<td><img src="emoji" alt="Score" /></td>
</tr>
<tr>
<td>PrEP implant</td>
<td><img src="emoji" alt="Score" /></td>
<td><img src="emoji" alt="Score" /></td>
<td><img src="emoji" alt="Score" /></td>
<td><img src="emoji" alt="Score" /></td>
<td><img src="emoji" alt="Score" /></td>
</tr>
<tr>
<td>Vaginal ring</td>
<td><img src="emoji" alt="Score" /></td>
<td><img src="emoji" alt="Score" /></td>
<td><img src="emoji" alt="Score" /></td>
<td><img src="emoji" alt="Score" /></td>
<td><img src="emoji" alt="Score" /></td>
</tr>
</tbody>
</table>
Promise of multi-purpose technologies (MPTs)

Illustrative challenges (III): MPT pipeline and investment

What would women pick if all 4 MPTs were available to them today?

- 93% of women want an MPT
- 4% HIV only
- 2% Pregnancy only

All Women
n=1722
Preferences for prevention products among women in VOICE-D: Luecke, JIAS 2016

### Percent of products selected*

<table>
<thead>
<tr>
<th>Product Type</th>
<th>Percentage Selected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injectables</td>
<td>25%</td>
</tr>
<tr>
<td>Implants</td>
<td>20%</td>
</tr>
<tr>
<td>Ring</td>
<td>15%</td>
</tr>
<tr>
<td>Oral tablet</td>
<td>10%</td>
</tr>
<tr>
<td>Suppository</td>
<td>5%</td>
</tr>
<tr>
<td>Film</td>
<td>5%</td>
</tr>
<tr>
<td>Gel</td>
<td>5%</td>
</tr>
<tr>
<td>CB</td>
<td>0%</td>
</tr>
</tbody>
</table>

* Multiple selections allowed (median 2, range 0-6)

Young age associated with implant, film or tablet preference. Gel not selected by any young person.

***p ≤ 0.001, using Fisher’s exact p value

![Graph showing preferences for prevention products among women in VOICE-D: Luecke, JIAS 2016](image-url)
Creating Options

Drug Options

Dosage Form Options

Drug Discovery  Preformulation  Formulation  Formulation Assessment  Scale up  First in Human Studies
Thin Polymeric Films offer several advantages

- Vaginal films rely on dissolution of drug directly into vaginal fluid, thus decreasing the dilution of endogenous antiviral properties of vaginal fluid
- Because of lower volume, there is reduced sensation of vaginal discharge and less impact on innate protective factors
- For vaginal delivery, films are discreet, portable, inexpensive and easier to store than gel
Development of Coitally Dependent “Quick Dissolve” Thin Films for HIV Prevention

Dapivirine

NNRTI

Tenofovir

NtRTI

Developed at MWRI

IND Submitted to FDA

1st in human clinical studies completed

Results:

• Safe
• Acceptable
• Showed Ex Vivo Antiviral Activity

Novel Application of Manufacturing Technologies

Hot Melt Extrusion

3D Printing
• Fast dissolving films
  1. Can they deliver ARVs to genital tissues?
  2. What do films and gels do to the vaginal microenvironment?
  3. What does the microbiota do to the drugs?
Can Films Deliver ARVs as Well As Gels?

Dapivirine
FAME-01

Tenofovir
FAME-02
Tenofovir Vaginal Film Development

- Chemical and Physical Characterization
  - Weight, thickness, & appearance
  - Residual Water Content
  - Drug Content Uniformity
  - Dissolution
  - Disintegration
  - Mechanical Strength
- In vitro Safety and Bioactivity
  - *Lactobacillus* compatibility
  - Cell based Toxicity & Bioactivity
  - Ex vivo permeability
  - Ex vivo toxicity
  - Ex vivo HIV challenge study
- R&D Stability Study
Animal Toxicity Testing

Study Design:

- Animals: Sexually mature female *Macaca nemestrina*
- Design: Two arm (Six macaques) crossover study comparing tenofovir film to placebo film
- Dosing: one 1”x2” film (40 mg tenofovir) once daily for five days one week, followed by four days the next week
- Endpoints: Colposcopy, microflora, vaginal pH, vaginal PMNs

NO SAFETY ISSUES FOUND
Scale up Manufacture

- No significant scale-up issues
- Only small formulation changes required at scale-up
FAME-04 Protocol Summary

- Double blinded, randomized, placebo-controlled phase 1 study
- 75 HIV uninfected women, 18-45 years old
- 7 daily doses
  - Tenofovir gel
  - Placebo gel
  - Tenofovir film (10mg)
  - Tenofovir film (40mg)
  - Placebo film

Concentration of Tenofovir

Plasma | Vaginal epithelium | Vaginal fluid


Topical administration of tenofovir
Study Design

Day 1:
- Collect:
  - Vaginal swabs for qPCR for microbiota
  - Tenofovir applied in clinic

Day 2:
- Tenofovir applied daily at home

Day 3 to Day 6:
- Collect plasma, CVL and vaginal fluid for tenofovir levels

Day 7:
- Collect:
  - Plasma
  - Cervical biopsy

### Tenofovir Levels: 40 mg in Gel vs Film

<table>
<thead>
<tr>
<th>Tenofovir (ng/mL)</th>
<th>1% TFV Gel (n=13)</th>
<th>40 mg Film (n=15)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma TFV trough after 6 doses</td>
<td>0.86 (0.40, 1.72)</td>
<td>1.84 (0.46, 2.81)</td>
<td>0.17</td>
</tr>
<tr>
<td>Plasma TFV 2 hrs after 7th dose</td>
<td>2.34 (1.38, 4.75)</td>
<td>2.74 (0.85, 5.31)</td>
<td>0.96</td>
</tr>
<tr>
<td>Cervicovaginal lavage 2 hour post-dose</td>
<td>$193 \times 10^3$ (138 $\times 10^3$, 608 $\times 10^3$)</td>
<td>$181 \times 10^3$ (114 $\times 10^3$, 320 $\times 10^3$)</td>
<td>0.39</td>
</tr>
</tbody>
</table>


**FIG A NTIRETROVIRAL M ICROBICIDE E VALUATION**
## Tenofovir Levels: 40 mg in Gel vs Film

<table>
<thead>
<tr>
<th>Tenofovir (ng/mg)</th>
<th>1% TFV Gel (n=13)</th>
<th>40 mg Film (n=15)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervicovaginal fluid trough after 6 doses</td>
<td>532 (311, 622)</td>
<td>1044 (447, 2171)</td>
<td>0.052</td>
</tr>
<tr>
<td>Cervicovaginal fluid 2 hrs after 7th dose</td>
<td>2850 (2070, 3571)</td>
<td>8340 (4000, 11,540)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rectal fluid TFV 2 hrs after 7th dose</td>
<td>33.7 (3.2, 832.2)</td>
<td>34.0 (15.0, 228.3)</td>
<td>0.75</td>
</tr>
</tbody>
</table>

## Tenofovir Diphosphosphate Levels: 40 mg in Gel vs Film

<table>
<thead>
<tr>
<th>TFV-DP levels (fmol/mg)</th>
<th>1% TFV Gel (n=13)</th>
<th>40 mg Film (n=15)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical tissue 2h post dose 7</td>
<td>222 (71, 556)</td>
<td>937 (56, 1457)</td>
<td>0.27</td>
</tr>
<tr>
<td>Vaginal tissue 2h post dose 7</td>
<td>296 (150, 917)</td>
<td>241 (113, 546)</td>
<td>0.44</td>
</tr>
</tbody>
</table>

FAME-04

• Films delivered tenofovir as well or better than gel in the following compartments following vaginal administration:
  – Plasma
  – Cervicovaginal lavage
  – Rectal fluid
  – Undiluted cervicovaginal fluid
  – Cervical and vaginal tissues

# FAME-04: User preferences

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Gel</th>
<th>Film</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not difficult to insert</td>
<td>94%</td>
<td>51%</td>
<td>0.002</td>
</tr>
<tr>
<td>Comfortable</td>
<td>52%</td>
<td>81%</td>
<td>0.25</td>
</tr>
<tr>
<td>No Leakage</td>
<td>0%</td>
<td>34%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Likely to use</td>
<td>77%</td>
<td>72%</td>
<td>0.14</td>
</tr>
</tbody>
</table>
What do films and gels do to the vaginal microenvironment?

• Vaginal microbiota as assessed by qPCR and deep cultivation
• Innate antiviral activity
• Glycomic studies
## FAME-04: Impact of Gel and Film Polymers on Innate Antiviral Activity

<table>
<thead>
<tr>
<th>Product</th>
<th>Innate anti-HIV-1 activity (% control)</th>
<th>2 hours after 7th dose</th>
<th>3 weeks later</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo Film</td>
<td>70.2 (43.4, 87.4)</td>
<td>85.8 (66.4, 90.8)</td>
<td>69.1 (50.0, 80.8)</td>
</tr>
<tr>
<td>(n=14)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value*</td>
<td>0.013</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td>Placebo Gel</td>
<td>77.7 (41.9, 89.6)</td>
<td>34.8 (12.9, 64.3)</td>
<td>59.8 (-8.3, 77.3)</td>
</tr>
<tr>
<td>(n=15)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value*</td>
<td>0.003</td>
<td>0.036</td>
<td></td>
</tr>
</tbody>
</table>
Glycomic Studies

- Drugs or formulations that affect the mucus may alter its functions
- Polymers present in the films or gels could plausibly impact innate immunity.
- Glycomic studies compare impacts of products on the glycome using two methods in separate laboratories
  - Impact on mucin proteins and lectins binding in CVL using ELLA assays before and after product use
  - Lectin microarray
FAME-04 Mucins and Lectin Binding

Butch Moncla, PhD
FAME-04 Analyses

• In CVL obtained at the screening visit, 2 hours post product placement and at 4 weeks evaluated the following:
  – Protein content
  – MUCs:
    • Membrane bound mucin proteins: MUC 1 and 16
    • Secreted mucins: MUC 5ac and 7
  – Lectin binding: SNA, GRFT, Jacalin, RCA, ECA
FAME-04: Summary of Mucin and Lectin Binding

• Film
  – Decreased protein
  – Decreased MUC 1 and 7
  – No effect on MUC 5ac or 16
  – Decreased lectin binding to GRFT and ECA

• Gel
  – Decreased protein
  – Decreased MUC1
  – No effect on MUC5ac, 7 or 16
  – No change in lectin binding
Glycomic Analysis of FAME: Sweet Surprises

Lara K. Mahal
New York University
Dual-Color Comparison of FAME

Linlin Wang
Gel but not Film alters the CVL glycome

Linlin Wang
Gel alters the CVL glycome

This is the same change observed when women have BV
Mapping the Glycome onto Innate Immunity: HIV-1 Assay

CVL + TZM-bl cells

HIV-1 inhibition percentage
Active/Inactive anti-HIV-1 activities

ANOVA

Control

Performed by Dr. Charlene Dezzuti, Magee-Womens Research Institute
Innate Immunity Against HIV-1 has a Glycomic Signature

High mannose signature associated with higher innate anti-HIV activity
Glycome Conclusions

- Drug delivery in gel lowers the level of high mannose glycoproteins, directly impacting innate immunity against HIV-1
- Film does not have this impact.
- The impact of gel on the glycome (an by extension innate anti-viral activity) is not mediated by changes in the microbiome.

Future Work

- Identification of high mannose glycoproteins involved in anti-viral activity.
What does the microbiota do to the drugs?
Tenofivir gel effective against HIV with Lactobacillus dominance

**A. Lactobacillus dominant**

- Efficacy, 61% 95% CI, 11 to 84%
- HR = 0.39 (95% CI: 0.20; 0.83)

**B. Non-Lactobacillus dominant**

- Efficacy, 18% 95% CI, -77 to 63%
- HR = 0.82 (95% CI: 0.40; 1.65)

**Placebo**

- 202 (0) 196 (4) 173 (12) 123 (19) 51 (22)
- Placebo 141 (0) 137 (4) 116 (12) 97 (17) 0 (17)

**Tenofivir**

- 205 (0) 204 (1) 183 (3) 129 (7) 46 (9)
- Placebo 141 (0) 137 (4) 116 (12) 97 (17) 0 (17)

<table>
<thead>
<tr>
<th># HIV-1 infections</th>
<th>Tenofivir</th>
<th>Placebo</th>
<th>Tenofivir</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 incidence per 100 person-years</td>
<td>9</td>
<td>22</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>HIV-1 protection effectiveness</td>
<td>2.7</td>
<td>6.9</td>
<td>6.4</td>
<td>7.8</td>
</tr>
<tr>
<td>95% CI, P-value</td>
<td>61% (-11, 84), p=0.013</td>
<td>18% (-77, 63), p=0.644</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Klatt/Burgener et al., submitted
Limitations

- Women having greater numbers of partners and more frequent sexual activity at greater risk of BV and HIV
- Relationship between BV-type microbiota and decreased effectiveness of tenofovir could be attributed to unmeasured differences in behavior
Hypothesis

• Women having microbiota associated with bacterial vaginosis will have decreased levels of tenofovir in genital tissue
• Women having beneficial lactobacilli associated with LB dominant microbiota will have higher levels of tissue tenofovir

Hillier et al, CROI 2017
Methods

• qPCR performed from vaginal swab samples collected at baseline
  – *Gardnerella vaginalis*
  – *Atopobium vaginae*
  – *Lactobacillus crispatus, L jensenii, L gasseri, L iners*
• Bacterial vaginosis detected using Nugent criteria from a Gram stained vaginal smear collected at baseline
• Statistics:
  – Relationship between vaginal microbiota and TFV concentrations was assessed using linear regression models
  – A quadratic term was included in the models with *G. vaginalis* to improve model fit.
  – Reported P-values are from the global F-test.

Hillier et al, CROI 2017
Impact of *G. vaginalis* on Tenofovir Levels in Plasma and Vaginal Fluid After 6 Doses

Hillier et al, CROI 2017
Impact of *L. crispatus*, *L. jensenii* and *L. gasseri* on Tenofovir Levels in Plasma and Vaginal Fluid After 6 Doses

Hillier et al, CROI 2017
G vaginalis vs Tenofovir diphosphate in Cervical Biopsy Tissue and Tenofovir in Plasma

Hillier et al, CROI 2017

FILM ANTIRETROVIRAL MICROBICIDE EVALUATION
Atopobium vaginae and Tenofovir diphosphate in Cervical Tissue and Tenofovir in Plasma

Hillier et al, CROI 2017
Nugent Score and Tenofovir diphosphate in Cervical Tissue and Tenofovir in Plasma

Hillier et al, CROI 2017
*Lactobacillus crispatus, jensenii and gasseri vs Tenofovir diphosphate in the Cervix and Tenofovir in the Plasma*
*Lactobacillus iners* vs Tenofovir diphosphosphate in the Cervical Tissue and Tenofovir in the Plasma
Summary and Conclusions

• Women having vaginal microbiota associated with bacterial vaginosis have significantly lower levels of tenofovir in plasma and vaginal fluid after 6 daily doses, and less tenofovir in plasma and cervical tissues 2 hours after application of tenofovir to the vagina.

• Higher density of *L. crispatus, jensenii and gasseri*, but not *L. iners*, was associated with higher systemic and tissue concentrations of tenofovir.

• These data are supportive of the secondary analyses from the CAPRISA study reporting lower effectiveness of tenofovir gel among women having *Lactobacillus*-deficient microbiota.  

Hillier et al, CROI 2017
Fast dissolving films

1. Can deliver ARVs to genital tissues as efficiently as gels

2. Neither films nor gels were disruptive to the vaginal microbiota but both caused some changes in mucin expression and glycosylation patterns in the vaginal microenvironment.
   - Gel polymers decreased innate antiviral activity while films did not
   - Lectin micro arrays showed that after gel use, there were changes in the glycome that mapped to anti-HIV activity

3. BV microbiota metabolized tenofovir (but not dapivirine)
Building a film for extended release of ARVs

- Need a different drug with extended residence in tissues (not dapivrine) and which is not metabolized by vaginal microbiota (not tenofovir)
- Different film polymers that release drug slowly
- Film polymers that do not disrupt innate immunity, vaginal microbiota or glycome
RAISING THE BAR

Produce a safe, acceptable, efficacious extended release (7 day protection) vaginal film containing the HIV strand integrase inhibitor MK-2048.
Optimization of MK-2048 Film

• Film Composition
  – Base- Create a film base so that regardless of excipient combinations/ratios we can still get a film
    • HPMC E5
    • HEC
    • Plasticizers (PEG 400, Propylene glycol)
  – Extended Release Components
    • HPMC K4M (↑ Molecular Weight)
    • HPC (hydrophobic)
    • Eudragit RS 30D (Extended Release)

• Size
  • 2x2 cm

• Drug loading
  • 10 mg/film
Visual Dissolution/Drug Delivery: Placebo & MK-2048 ER Films

**Purpose:** Document dissolution time for extended release (ER) film platform (placebo) **AND** collect MK-2048 PK data to document drug delivery.

<table>
<thead>
<tr>
<th></th>
<th>D0</th>
<th>D3</th>
<th>D7</th>
<th>D10</th>
<th>D14</th>
<th>D17</th>
<th>D21</th>
<th>D24</th>
<th>D27</th>
<th>D30</th>
<th>D34</th>
<th>D36</th>
<th>D41</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Visualize Colpo-Photo n=6</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>MK-2048 PK (Vaginal swab) n=3</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Film Dose n=3+3</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

*Day 0: menstruating; D3 No Film Residual; D7 Apply 2nd Film; D10 Film Present; D14 No Film Residual*
NHP Study Results: **FILM DISSOLUTION**

- **MK-2048 Film**
  - L03367
  - A10013
  - A10026
  - K02267
  - K05166
  - R06303

- **Placebo Film**
  - M
  - M
  - M
  - M
  - M
  - M

**FILM ANTIRETROVIRAL MICROBICIDE EVALUATION**
NHP Study Results
MK-2048 Extended Release Film

MK-2048 Swab Concentration vs. Time

<table>
<thead>
<tr>
<th>Sample</th>
<th>AUC (0-36) (ng/mL)</th>
<th>Css (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R06303</td>
<td>2,079</td>
<td>58</td>
</tr>
<tr>
<td>K02267</td>
<td>1,257,476</td>
<td>34,930</td>
</tr>
<tr>
<td>K05166</td>
<td>868,866</td>
<td>24,135</td>
</tr>
</tbody>
</table>

IC_{50} = 0.924 ng/mL

*No visual evidence of film
Progress Toward an ER Film

• Proof of principle established in the pig-tailed macaque model that after a single film application drug levels 10,000X the inhibitory dose for 21 days
  – This persisted through menses and sex (data not shown)
  – No safety concerns; no impact on microbiota

• Film polymers used for ER film have been used orally but never vaginally, so doing a safety study of the ER placebo film later this year

• Will do the first in human study of the ER film next year
### “Scorecard” for HIV prevention modalities for women

<table>
<thead>
<tr>
<th>Modality</th>
<th>Efficacy</th>
<th>Low user burden</th>
<th>Low Cost</th>
<th>Low systemic side effects</th>
<th>Reversibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily oral PrEP</td>
<td>😊</td>
<td>⚠️</td>
<td>⚠️</td>
<td>⚠️</td>
<td>😊</td>
</tr>
<tr>
<td>On demand PrEP</td>
<td>⚠️ ?</td>
<td>😊</td>
<td>⚠️</td>
<td></td>
<td>😊</td>
</tr>
<tr>
<td>Injectable Cabotegravir</td>
<td>?</td>
<td>😊</td>
<td>😊</td>
<td>❔</td>
<td>❔</td>
</tr>
<tr>
<td>PrEP implant</td>
<td>?</td>
<td>😊</td>
<td>⚠️</td>
<td>❔</td>
<td>❔</td>
</tr>
<tr>
<td>Vaginal ring</td>
<td>😊 😊 😊</td>
<td>😊</td>
<td>😊 😊 😊</td>
<td></td>
<td>😊 😊 😊 😊</td>
</tr>
<tr>
<td>Vaginal film On demand</td>
<td>?</td>
<td>❔</td>
<td>❔</td>
<td></td>
<td>☑️ ☑️ ☑️ ☑️</td>
</tr>
</tbody>
</table>

---

**Film Antiretroviral Microbicide Evaluation**
Conclusions

- Vaginal Films
- Women Controlled
- Portable
- Discreet
- Minimal impact on innate immunity
- Inexpensive

Non Medicalized
Conclusions

• Developing interdisciplinary teams to attack challenges in HIV prevention is super fun!

• We need to focus on end users more as we develop products.

• Films are an attractive dosing option for “on demand” HIV prevention in women
University of Pittsburgh