Do Topicals Have a Future?
Round 1: The Vaginal Microbicide

The GREAT DEBATE

SYSTEMICS vs TOPICALS?

HEROLD
ONLY SYSTEMICS

BAETEN
TOPICALS STILL MAKE SENSE
Resolved: Systemic products for HIV prevention in women/young girls should be prioritized over vaginal/topical formulations.
Women and girls matter!

- Disproportionately fewer studies focused on women/girls reflecting US versus global epidemic
- Biology of women and HIV is complex
  - Site of acquisition differs
    - Primarily vaginal
  - PK of drugs differs in women
    - Transporters/enzymes
    - Vaginal microbiome
    - Hormones/pregnancy
  - Toxicity profiles may differ
- Factors that impact access and adherence differ
<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Design</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>FHI Savvy Gel</td>
<td>2152 women</td>
<td>1:1 C31G vs Placebo</td>
<td>No protection; trial terminated</td>
</tr>
<tr>
<td>Carraguard</td>
<td>6202 women</td>
<td>1:1 Carageena vs Placebo</td>
<td>No protection</td>
</tr>
<tr>
<td>PRO2000</td>
<td>9385 women</td>
<td>1:1:1 (0.5%, 2%, Placebo)</td>
<td>No protection</td>
</tr>
<tr>
<td>Cellulose sulfate FHI</td>
<td>1700 women</td>
<td>1:1 6% CS vs Placebo</td>
<td>No protection (terminated early)</td>
</tr>
<tr>
<td>Cellulose sulfate (CONRAD)</td>
<td>1398 women</td>
<td>1:1 6% CS vs Placebo</td>
<td>? increased risk of HIV</td>
</tr>
<tr>
<td>VOICE</td>
<td>~1000/arm</td>
<td>TFV vs Placebo Gel</td>
<td>Terminated early futility 39% (6-60)</td>
</tr>
<tr>
<td>FACTS 001</td>
<td>2029</td>
<td>TFV gel vs Placebo</td>
<td>0% protection</td>
</tr>
<tr>
<td>RING study</td>
<td>1959 women</td>
<td>2:1 Dapivirine vs Placebo IVR</td>
<td>31% protection (CI 1-51)</td>
</tr>
<tr>
<td>ASPIRE</td>
<td>2629 women</td>
<td>1:1 Dapivirine vs Placebo IVR</td>
<td>27% protection (CI 1-46)</td>
</tr>
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| Partners PrEP | 1164 women                  | 1:1:1 TDF, TDF-FTC, Placebo   | **TDF 71%** reduction (37-87, p< 0.0001)  
**TDF-FTC 66%** reduction 28-84, p< 0.001) |
| TDF2          | 557 women 1219 total        | 1:1 TDF-FTC vs Placebo        | **49% (22-81)**  
**Overall 62.2% (21.5-83.4, p=0.03)** |
| FemPrEP       | 2120 women                  | 1:1 Daily Truvada vs Placebo  | No protection (attributed to low adherence)                              |
| VOICE         | ~1000/arm                   | TDF, TDF-FTC, Placebo PO      | No protection (terminated early for futility)                           |
|               |                             |                               | (Attributed to low adherence)                                           |
| Bangkok       | 489 women (inject drugs)    | TDF vs placebo                | **79% (17-97)**                                                       |
| HPTN084       | 3200 women                  | Phase 3 LA-Injectable cabotegravir vs Daily Oral TDF-FTC                  |

**OPINION:** No homerun- but if we have limited resources better bet is systemics
Obstacles to developing effective topical PrEP

- **Vaginal microbiome** modulate drug PK multiple mechanisms
  - Dapivirine “sticks” to bacteria rendering it inaccessible to target CD4 T cells
  - Tenofovir uptake by CD4 T cells is blocked by adenine, which is released by *G. vaginalis* and other bacteria; also impacted by local pH
- Vaginal dysbiosis facilitates HIV acquisition
Obstacles to effective topical PrEP

• Sex and semen impact drug PK

Postcoital Bioavailability and Antiviral Activity of 0.5% PRO 2000 Gel: Implications for Future Microbicide Clinical Trials


Impact of Sex on the Pharmacokinetics and Pharmacodynamics of 1% Tenofovir Gel

Betsy C. Herold1, Benntara A. Chen1, Robert A. Salmin2, Mark A. Marcinkev1, Cllton W. Kelli3, Charlotta S. Daccs2, Jon Mccarren2, Beth Galkina2, Lisa Levy3, Jessica M. Piper2, Benjamin Hillier3, and Craig W. Hendrix4, on behalf of the MTN-011 Study Team

Background. Tenofovir (TFV) gel partially protected against human immunodeficiency virus (HIV) in one but not subsequent trials. The disappointing results were attributed largely to poor adherence. However, timing of gel application relative to sex may impact pharmacokinetics and contribute to outcomes. Thus, we conducted a single-dose pharmacokinetic study of TFV gel applied 1 or 24 hours before or 1 hour after and 1 hour after sex and compared results with dosing without sex.

Methods. Twenty-four couples were enrolled; cervical/vaginal lavage (CVL) and tissue were collected 2 hours after sex with matching timed collections at no sex visits and assayed for drug concentrations and CVL anti-HIV activity.

Results. Compared with dosing without sex, median TFV concentrations after sex decreased 72% and 78% (P < 0.001) in CVL, 75% and 71% (P = 0.001) in vaginal tissue, and 75% and 55% (P < 0.001) in cervix tissue with 1 hour and 24 hour dosing, respectively. Median concentration of TFV–diphosphate also decreased significantly in cervical tissue with 1 hour, 24 hour, and 1 hour after dosing. BAT dosing resulted in drug levels at least as great as those in the absence of sex. Percent inhibition of HIV infection by post-coital CVL increased significantly from median (interquartile range) of 55% (51%) in the absence of gel to 99% (76%, 77%, 57%), and 100% (0%) with 1 hour, 24 hour, or BAT dosing, respectively, and correlated significantly with drug concentration.

Conclusions. Timing of TFV gel application relative to sex significantly impacts drug levels. BAT dosing or sustained delivery may be optimal for pre-exposure prophylaxis.

Keywords. MTN-011; tenofovir gel; pharmacokinetics; post-coital; HIV.
Topicals only have one chance to block: the vaginal portal. Systemics cover a larger area, but achieve lower vaginal levels.

Topicals $\gg$ Systemics

Systemics only

Topicals $\cong$ Systemics
Anticipated and not so anticipated safety concerns with topicals

Disruption of epithelium and inflammation with recruitment of immune cells in response to nonoxynol-9 may have explained increased risk for HIV

Disruption of epithelium also observed with cellulose sulfate (and N=9) in murine model, which was associated with increased susceptibility to HSV infections
Unanticipated toxicities with tenofovir-based topicals
High local exposure may be problematic
Early safety concerns for systemic PrEP not supported by experience to date

- **Resistance** has not emerged as significant problem to date
  - M184I/V or K65R resistance mutations documented in subjects with unrecognized acute HIV at time of PrEP initiation (importance of testing)
  - Isolated reports of resistance in subjects seroconverting after starting PrEP (males)
- Small non-progressive decline eGFR not thought to be clinically significant
  - May be mitigated by newer prodrugs (e.g. TAF/FTC)
- Bone mineral density reductions small and CDC does not recommend screening prior to starting PrEP; however data is limited
- Conversely, low systemic levels associated with TOPICAL drugs may translate into greater risk for resistance selection
But women prefer and will adhere better to topicals ....

- Adherence barrier to both topicals and systemics
  - No advantage to topicals observed in any studies
- Knowing that a product protects leads to increased adherence
  - Post-licensure studies
- Integrating PrEP delivery in routine family planning clinics may be effective
- Next generation long acting and MPT products will mitigate some of the problems with adherence
  - Potential for fast-tracking systemic MPT building on already approved products (TDF/FTC/LNG/ethinyl estradiol)
We need MORE STUDIES for Women/Girls
We do not have unlimited resources:
I would bank my $ on systemic PrEP
Vaginal microbicides make sense

Jared Baeten MD PhD
Vice Dean, School of Public Health
Professor, Departments of Global Health, Medicine, and Epidemiology
Director, UW/Fred Hutch Center for AIDS Research (CFAR)
Co-Director, International Clinical Research Center
University of Washington
Affiliate Investigator, Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center
Co-Principal Investigator, Microbicides Trials Network

MTN Annual Meeting, February 2020
PrEP began with microbicides

Commentary

HIV Prevention: The Need for Methods Women Can Use

Zena A. Stein, MA, MB, BCh

“The sole barrier promoted for the prevention of sexual transmission of HIV from men to women is the condom.... The empowerment of women is crucial for the prevention of HIV transmission to women. It follows that prophylaxis must include procedures that ... are under her control.”

(Am J Pub Health, 1990)
Topical PrEP makes sense

You don’t need to get PrEP to your shoulder to not get HIV.

Carias and Hope 2019; Chicago AIDS Foundation
Do topicals have a future for vaginal protection against HIV?

Vaginal microbicides work

Choice matters

Topicals provide unique advantages
Do topicals have a future for vaginal protection against HIV?

Vaginal microbicides work

Choice matters

Topicals provide unique advantages
Vaginal microbicides work

It is a true wonder that topical delivery of an anti-infective agent can prevent a systemic infection like HIV.

(And, notably, with better adherence and HIV protection that in the original trials of oral PrEP in women.)

Baeten et al., Nel et al., NEJM 2016
With high adherence, protection approaches/exceeds 75%

More dapivirine released = more use = more protection

Brown et al., AIDS 2016 & submitted
The ring is workable in open-label settings

- High uptake
- Good adherence (better than phase III)
- Well-tolerated safety profile (consistent with phase III)
- Lower HIV incidence than expected in the absence of ring access

To be clear, in populations at substantial risk for HIV, with high rates of STIs and BV and frequent condomless sex, this microbicide stops HIV. Period.

Nel et al. SA AIDS 2019; Baeten et al. IAS 2019
Do topicals have a future for vaginal protection against HIV?

Vaginal microbicides work

Choice matters

Topicals provide unique advantages
Choice matters

Behavior science testing different placebo topical PrEP products

Preference Varies Geographically and with Experience

“We are not the same. Some they will like the ring. Some they will like the tablet … People are not the same.”

“As people we have different choices … I might not like the pills … and the injections but there’s other people who would.”

(Shapley-Quin et al. Intl J Women’s Health 2019. TRIO study)

* Significantly different, p<0.05

(Montgomery et al. QUATRO study, R4P 2018 & JIAS 2019)
People use prevention when they have choices
Many factors drive choice-making

Effectiveness does not drive all decision-making

Perception of safety is similarly important

Control, privacy, convenience, etc. are important too

Walker et al. J Adolesc Health 2019
More choice = more prevention

Thus, it is **options** that permit **choices** that result in **use**. It is not the **products** themselves, but the **right product** chosen by each person.

**Why would PrEP be different?** 

EACH add'l product option yields 12% increase in contraceptive use

Do topicals have a future for vaginal protection against HIV?

Vaginal microbicides work

Choice matters

Topicals provide unique advantages
A systemic may not be wanted

For some people, a systemic medication, perhaps particularly one they cannot easily stop/restart themselves, might not be right.

Favorable safety profile
Low levels in breastmilk and plasma
Rapidly drug gone from blood within days of ring removal

594 nanograms of dapivirine per day for the rest of your life would still add up to less than one grain of rice.
Systemic PrEP & pregnancy

In other words, systemic PrEP may be less-er, in a population that needs prevention even more.
Unique research at the interface of pregnancy & HIV prevention

Group 1
36+ weeks
150 women
4-6 weeks
6 weeks follow-up
Data review

Group 2
30-35 weeks
150 women
7-12 weeks
6 weeks follow-up
Data review

Group 3
20-29 weeks
150 women
13-22 weeks
6 weeks follow-up
Data review

Group 4
12-19 weeks
300 women
Up to 30 weeks
6 weeks follow-up
Study Complete
It is the whole package

**High potential for safety:**
- Rely on dissolution of drug directly into vaginal/rectal fluid.
- Limited systemic exposure and need for systemic safety monitoring.
- Easy to discontinue if a side effect occurs.

**Ease of use:**
- Can be inserted by user.
- Little or no impact on sexual activity, potentially enhancing sex.

**Low cost:**
- Small amount of active drug = inexpensive to manufacture.

**Privacy:**
- Can be inserted in private and used discreetly.
- Portable.

Baeten, Hendrix, Hillier Ann Rev Med 2020
Options outside of clinic may appeal to many & offer reproductive justice autonomy
Gaps

The science

Johannesburg

Harare

Kampala

Cape Town

The reality

Slide adapted from Thes Palanee-Phillips
Do topicals have a future for vaginal protection against HIV?

Vaginal microbicides work

Choice matters

Topicals provide unique advantages
Options → choices → coverage → impact
In the end, it about use & impact

Commentary

HIV Prevention: The Need for Methods Women Can Use

Zena A. Stein, MA, MB, BCh

“...a less efficacious barrier (one that fails more often than another on each sexual encounter), if frequently used, might serve the public health as well or better than a more efficacious but less frequently used barrier, and could in the end play an important role in preventing transmission at the population level.”

(Am J Pub Health, 1990)
Round 2: The Rectal Microbicide

The GREAT DEBATE

SYSTEMICS vs TOPICALS?

HENDRIX
ONLY SYSTEMICS

LIU
TOPICALS STILL MAKE SENSE
RESOLVED:
Only Systemics Should Move Forward
(With regard to Rectal HIV PrEP)

Craig W. Hendrix, MD
Johns Hopkins University
Why is Systemic PrEP Enough?

- What problems are we trying to solve with rectal microbicides?
- What’s the possible impact of continued rectal microbicide investment?
- Why rectal microbicides may not work?
Why is Systemic PrEP Enough?

- What problems are we trying to solve with rectal microbicides?
- What’s the possible impact of continued rectal microbicide investment?
- Why rectal microbicides may not work?
High Degree of Efficacy in Rectal Protection

- **Ipergay 2+1+1**
  - MSM/TGW
  - Daily oral vs. on demand
  - 86% relative risk reduction

- **Prevenir**
  - MSM/TGW
  - Select desired regimen
  - On demand (54%), Daily (45%)
  - No HIV in 506 (on demand) & 443 (daily) person-years

- Molina NEJM 2015; Molina IAS 2018
Stunning Population Level Impact for Rectal Risk

- Setting: Urban, 80% MSM among HIV+
- Design: Pre/Post Demonstration Project
- Intervention: PrEP a priority in 21 public & private clinics
- Inclusion: High HIV Risk (est. incidence >2%)

Study Participant Outcomes
- Among 3,700 ppts, 2 HIV cases in >4,100 PY
- Incidence 0.05/100 person-years (95% CI 0.01–0.19)

NSW Population Outcomes
- HIV incidence ↓ 25% (95% CI 11%-37%)

Grulich at al. Lancet HIV 2018; UNSW Kirby Institute Annual Surveillance Report 2017
Long-Acting Promise

- Islatravir (MK-8591)
- Antiviral effect NHP & clinical ART
- PrEP efficacy targets postulated
- Implant kinetics possibly one year
- Oral kinetics possibly one month

Matthews R, et al. IAS 2019

...not yet proven effective & adherence not the only problem of uptake & persistence
Why is Systemic PrEP Enough?

- What problems are we trying to solve with rectal microbicides?

- What’s the possible impact of continued rectal microbicide investment?

- Why rectal microbicides may not work?
Choice argument needs better data

- MTN-017 – Only direct oral vs. rectal comparison

Is there enough impact for each niche product to have impact?

<table>
<thead>
<tr>
<th>Theoretical Preferred Formulation</th>
<th>Oral</th>
<th>Lube</th>
<th>Douche bottle</th>
<th>Douche bulb</th>
<th>Duoche hose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral PrEP</td>
<td>14</td>
<td>7</td>
<td>2.24</td>
<td>2.24</td>
<td>2.24</td>
</tr>
<tr>
<td>Daily TFV Gel</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>TFV Gel with RAI</td>
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</table>

Most Preferred 73%
- Oral PrEP 19%
- Daily TFV Gel 8%

Least Preferred 43%
- Oral PrEP 28%
- Daily TFV Gel 28%

Carballo-Diéguez PLOS One 2017; Giguere AIDS Behav 2018
Choice argument lacks key user experience data

- Quatro & DESIRE critically important to understand relative preference for several possible choices based on preference, but...

- Where’s the data proving PrEP choice improves adherence when real oral & rectal product options?

- Phase II Extended Safety Context
  - Oral vs. Rectal Product
  - Required exposure to each product
  - Final user product option period (ala Quatro) with
  - Provides needed safety & preference data to advance to Phase 3
  - May avoid cost of Phase 3 if results unconvincing
Why is Systemic PrEP Enough?

- What problems are we trying to solve with rectal microbicides?
- What’s the possible impact of continued rectal microbicide investment?
- Why rectal microbicides may not work?
Systemic Dosing’s Deeper Defenses

- Vaginal underperforms (60-75% RRR) oral (86-100% RRR) adjusting for adherence

- Rectal dosing heterogeneous & superficial concentrations achieved in rectum

- Rectal dosing does not protect vaginal exposure

- Oral achieves full suppression in explants of colon tissue explants despite lower mucosal concentrations with systemic PrEP vs. topical (TDF & FTC)

- Systemic dosing provides second echelon of defense, if imperfect rectal adherence or heterogeneous drug distribution
Why is Systemic PrEP Enough?

- What problems are we trying to solve with rectal microbicides?
- What’s the possible impact of continued rectal microbicide investment?
- Why rectal microbicides may not work?
"The test of a first-rate intelligence is the ability to hold two opposed ideas in mind at the same time and still retain the ability to function."

– F. Scott Fitzgerald

... and remember me when!
I yield to the gentleman from California
The Rectal Microbicide Debate: Topical Products Still Make Sense

2020 MTN Annual Meeting

Albert Liu, MD, MPH
San Francisco Department of Public Health
University of California, San Francisco
1. Topicals can achieve high tissue concentrations and are highly protective in animal studies

**DREAM Program: Tenofovir Douche**

**Human PK: Colon Cell TFV-DP**

**Macaque PD: SHIV Challenge**

Daily Oral PrEP / Enema 1 hr Exp

- **Douche C**
- **Oral TDF/FTC**
- **Oral TDF**
- **Douche B**

Percent uninfected

Vehicle control

R4P: OA20.03 Weld; P29.13LB Villinger; P24.20 Hoang
2. Choice matters – no one size fits all

- In MTN-017, **27%** preferred either RAI-associated/daily gel vs. daily PrEP

- Dutch MSM preferred a rectal microbicide applied before/after anal sex (**61%**) to daily oral PrEP (**20%**) [fewer adverse events, more user friendly, less stigma]  

- MSM in Vietnam preferred rectal microbicides (**66%**) to injectable PrEP (**17%**) or oral PrEP (**17%**)  

- In an online survey of 1329 sexually active MSM in the US, **17%** ranked a lube containing PrEP as their highest preference (vs. **26%** injection, **43%** daily oral PrEP)  

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**Non-systemic, on-demand products are a critical part of the HIV prevention toolbox to meet the needs of people around the globe**

Carballo-Dieuez A et al, AIDS Behav 2017; Marra E et al, AIDS Care 2015; Oldenburg CE Sex Health 2018; Kahle E et al, AIDS Impact 2019
3. Systemic PrEP will not meet the needs of all people, and will leave vulnerable communities behind

- Concerns raised about systemic side effects, long-term toxicity, fear of needles, not wanting surgical procedures, particularly in communities with significant medical mistrust
- HIV resistance common in animal models – observed in 3/6 macaques that received CAB-LA before seroconversion
- Some people are not sexually active all the time, and don’t want a long-acting product in their body -- prefer an on-demand product

Patel R et al. PLOS ONE 2018; Radzio-Basu, J. Nature Communications 2019
Specific concerns raised by transgender women regarding long-acting prevention

- Transwomen with silicone in buttocks, hips, thighs unable to receive gluteal injections
- Concern regarding scarring from repeated injections
- Dislike of implants that are visible or perceptible
- Transwomen already juggling multiple provider visits – additional medical appointments undesirable
In their own words:

• “I wouldn’t do injection, I guess a lube. Why lube, because I mean you have to have lube for condoms. I think like I could just put it on. I think that would be easier”
  -- 24 year old AA male

• “I would be up for the lube, contrary to my piercing I am not that crazy about needles”
  -- 28 year old AA male

• [regarding implants] “I think this is unpopular, because if you can still see and feel it, people are going to be weird”
  – Trans woman FG participant
4. People want prevention options that fit into their lives

- People who have anal sex already use lube and douche before sex = **behaviorally congruent**

**Grindr Douche Survey (N=4751 MSM and TGW)**

- 78% had RAI last 3 mo
- **80%** douche before RAI
  - To be clean (97%)
  - Enhance sexual pleasure (24%)
- **98%** of douchers and **95%** of non-douchers expressed likelihood of using a rectal douche that could protect against HIV
4. People want prevention options that fit into their lives

**Young MSM Survey (N=180)**

- Mean age 21.7 years
- 61% had RAI last 3 mo
- **48%** had ever doused, **40%** reported frequent douching
- YMSM engaging in RAI more likely to douche
- **Racial/ethnic minorities** more likely douse (AOR 2.24, p=0.02) and reported more frequent douching
- **YMSM who doused had higher rectal microbicide acceptability**

Tingler AIDS and Behavior 2019
“The desirability for an on demand, behaviorally-congruent PrEP product has been voiced loudly by the populations at greatest risk of HIV nationally and internationally, especially young black MSM in the US for more than 10 years... Rectal microbicide products now in clinical development demonstrate the capacity to meet these requirements”

-- US Researcher
5. We need prevention options available **OUTSIDE** medical system

- Vulnerable populations are disproportionately impacted by stigma, medical mistrust in health-care settings – greatly limit access to medical care
5. We need prevention options available **OUTSIDE** medical system

- Systemics will require provider visits for injections, insertion/removal of implants
- Will **overwhelm the medical system at scale**, drive up costs
  - In US 1.1 million adults for whom PrEP is indicated
  - If half are on injectable PrEP (Q2 month visits)
    - 3.3 Million new healthcare visits per year

Smith D et al. Annals of Epidemiology 2018
5. We need prevention options available **OUTSIDE** medical system

Products (e.g. topicals) delivered outside the clinic and within community settings could greatly increase access to HIV prevention, minimize stigma, and avoid overburdening the medical system.
Finale: Let not the Perfect be the Enemy of the Good.

“A highly effective product that stays in the wrapper/in pill bottle/on the shelf/in the syringe will prevent fewer infections than a less effective but more acceptable product that people actually use.

So if people tell us that the currently available products and the current pipeline does not meet their needs, then by all means, bring on imperfect products that will be used more often.”

-- Marc-Andre LeBlanc