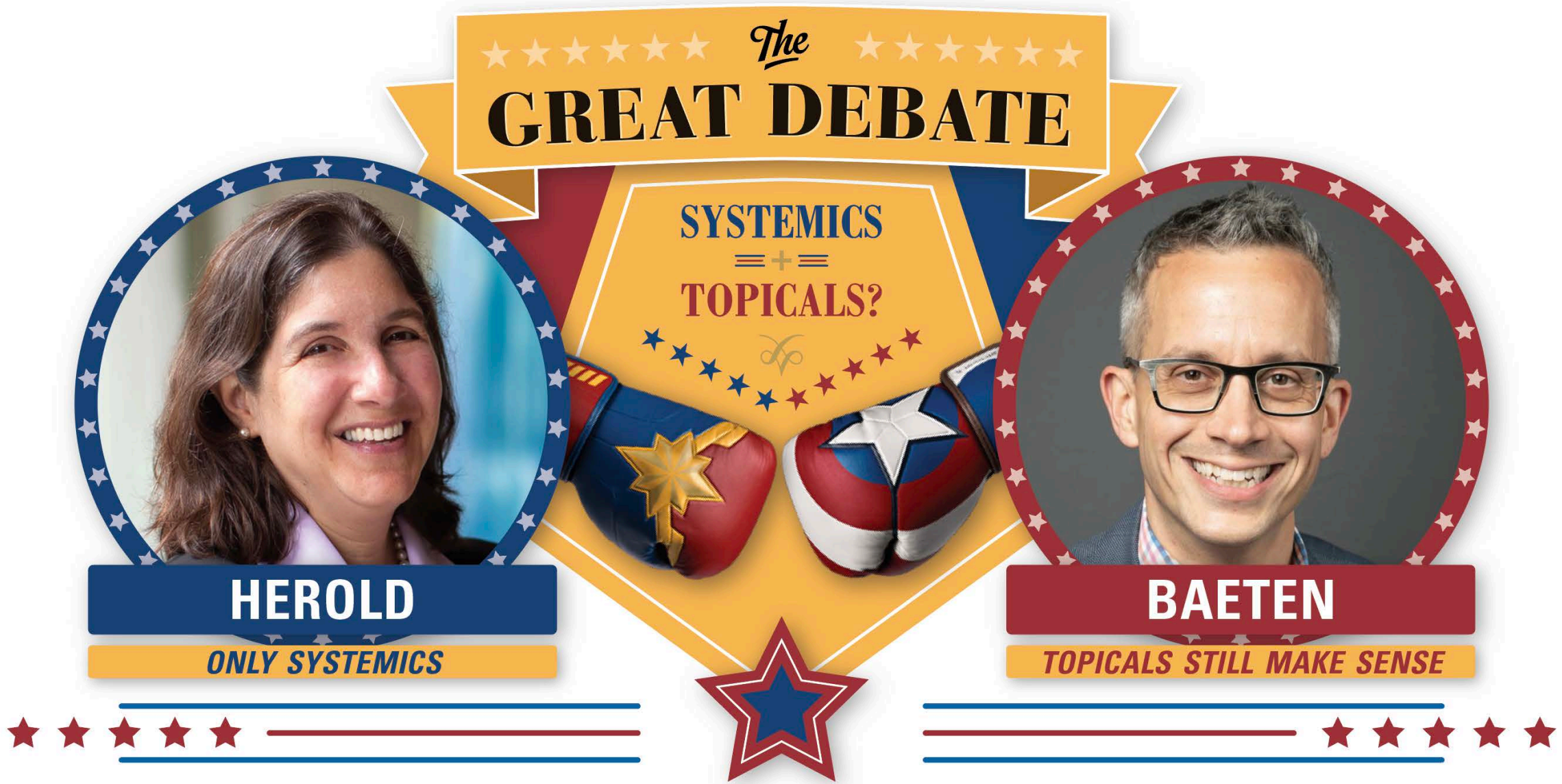
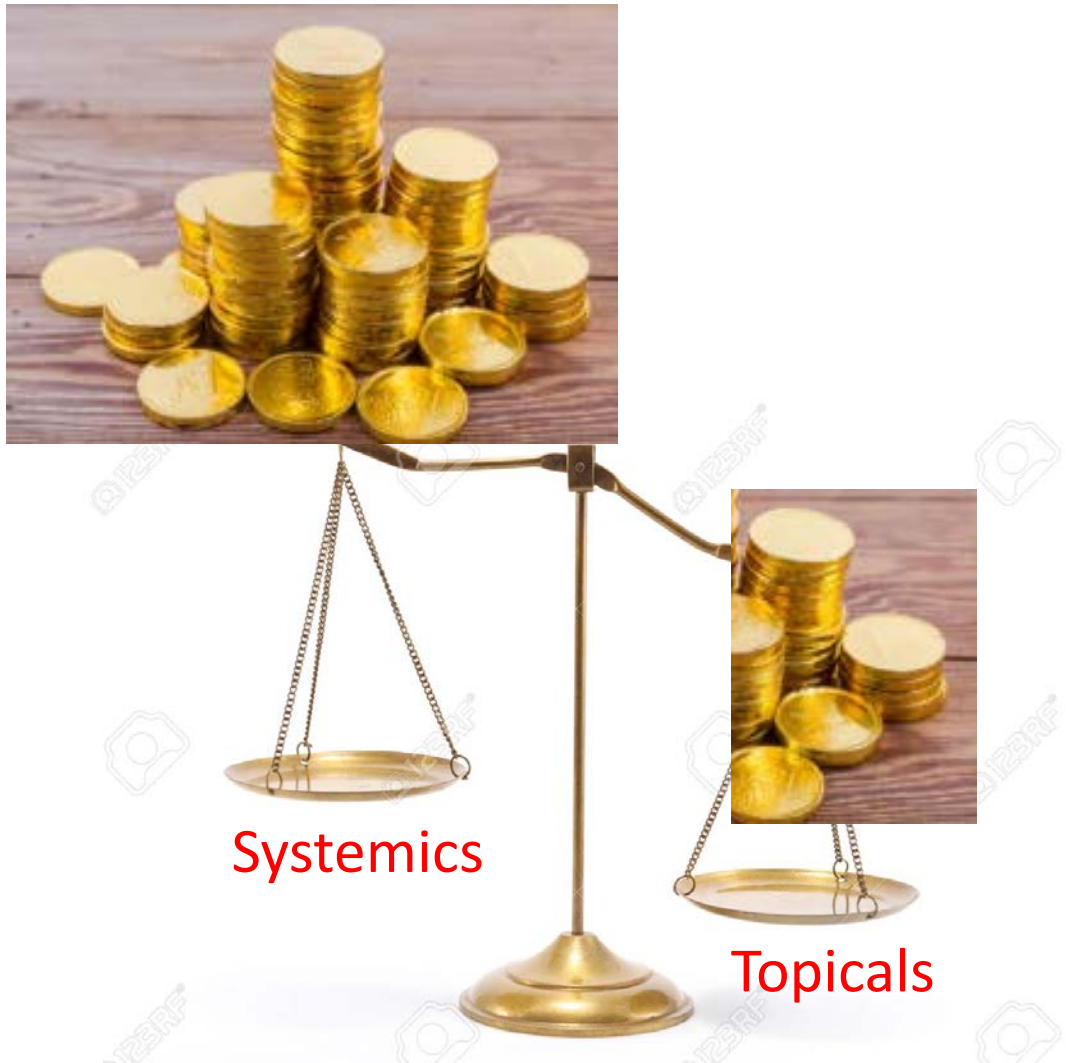
Do Topicals Have a Future?

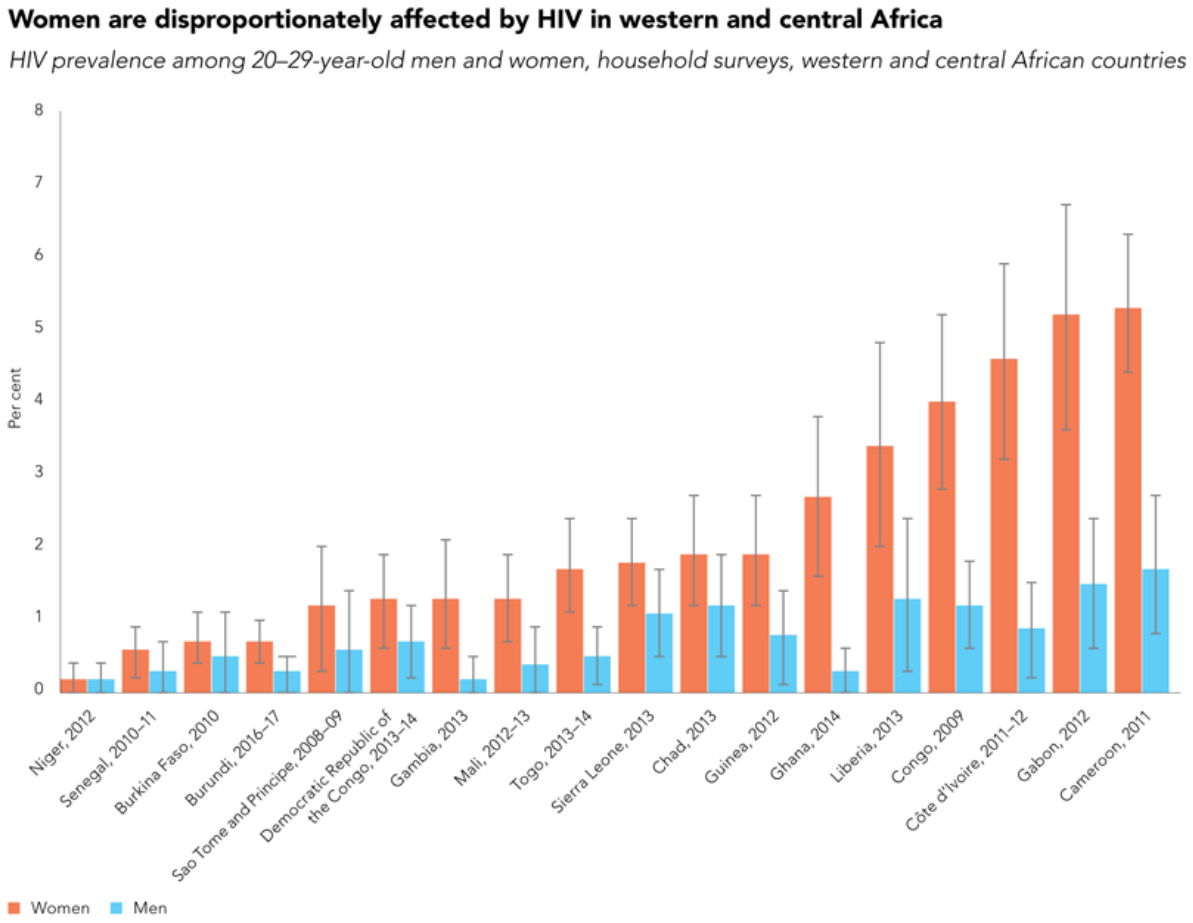
Round 1: The Vaginal Microbicide



Resolved: Systemic products for HIV prevention in women/young girls should be prioritized over vaginal/topical formulations

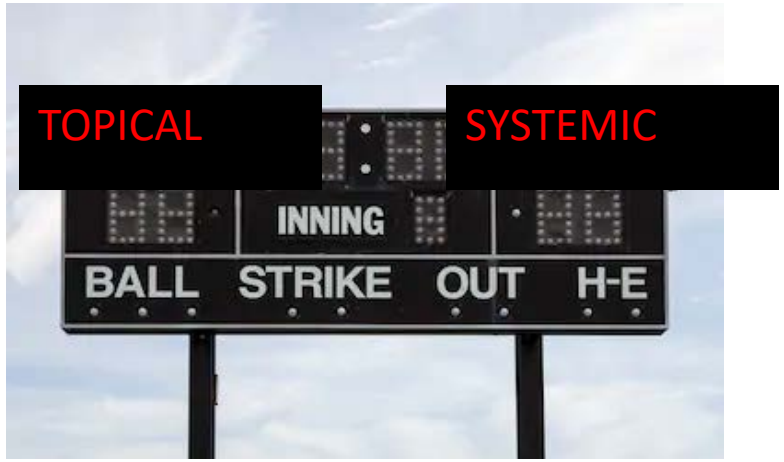


Women and girls matter!



- 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

Study	Population	Design	Outcome
FHI Savvy Gel	2152 women	1:1 C31G vs Placebo	No protection; trial terminated
Carraguard	6202 women	1:1 Carageena vs Placebo	No protection
PRO2000	9385 women	1:1:1 (0.5%, 2%, Placebo)	No protection
Cellulose sulfate FHI	1700 women	1:1 6% CS vs Placebo	No protection (terminated early)
Cellulose sulfate (CONRAD)	1398 women	1:1 6% CS vs Placebo	? increased risk of HIV **25 HIV cases vs 16 in placebo, p=0.13**
VOICE	~1000/arm	TFV vs Placebo Gel	Terminated early futility **39% (6-60)**
FACTS 001	2029	TFV gel vs Placebo	0% protection
RING study	1959 women	2:1 Dapivirine vs Placebo IVR	**31% protection (CI 1-51)**
ASPIRE	2629 women	1:1 Dapivirine vs Placebo IVR	**27% protection (CI 1-46)**

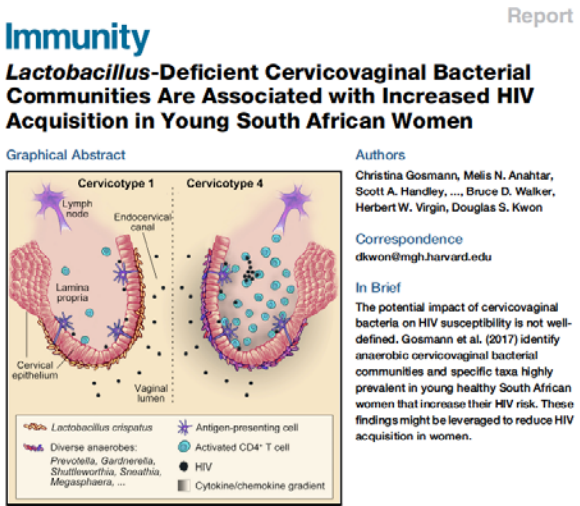


Study	Population	Design	Outcome
Partners PrEP	1164 women	1:1:1 TDF, TDF-FTC, Placebo	**TDF 71%** reduction (37-87, p< 0.0001) **TDF-FTC 66%** reduction 28-84, p< 0.001)
TDF2	557 women 1219 total	1:1 TDF-FTC vs Placebo	**49% (22-81)** Overall 62.2% (21.5-83.4, p=0.03)
FemPrEP	2120 women	1:1 Daily Truvada 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



JCI insight

Vaginal microbiome modulates topical antiretroviral drug pharmacokinetics

Ekaterina Taneva, … , Marla J. Keller, Betsy C. Herold

JCI Insight. 2018;3(13):e99545. https://doi.org/10.1172/jci.insight.99545.

Research Article AIDS/HIV

Tenofovir gel and dapivirine ring provided variable HIV protection in clinical trials, reflecting poor adherence and possibly biological factors. We hypothesized that vaginal microbiota modulates pharmacokinetics and tested the effects of pH, individual bacteria, and vaginal swabs from women on pharmacokinetics and antiviral activity. Tenofovir, but not dapivirine, uptake by human cells was reduced as pH increased. *Lactobacillus crispatus* actively transported tenofovir leading to a loss in drug bioavailability and culture supernatants from *Gardnerella vaginalis*, but not *Atopobium vaginae*, blocked tenofovir endocytosis. The inhibition of endocytosis mapped to adenine. Adenine increased from 65.5 µM in broth to 246 µM in *Gardnerella*, but decreased to 9.5 µM in *Atopobium* supernatants. This translated into a decrease in anti-HIV activity when *Gardnerella* supernatants or adenine were added to cultures. Dapivirine was also impacted by microbiota, as drug bound irreversibly to bacteria, resulting in decreased antiviral activity. When drugs were incubated with vaginal swabs, 30.7% ± 5.7% of dapivirine and 63.9% ± 8.8% of tenofovir were recovered in supernatants after centrifugation of the bacterial cell pellet. In contrast, no impact of microbiota on the pharmacokinetics of the prodrugs, tenofovir disoproxil fumarate or tenofovir alafenamide, was observed. Together, these results demonstrate that microbiota may impact pharmacokinetics and contribute to inconsistent efficacy.

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

Marla J. Keller[1,2], Pedro M. M. Mesquita[3], N. Merna Torres[3], Sylvia Cho[3], Gail Shust[3], Rebecca P. Madan[3], Hillel W. Cohen[4], Julie Petrie[1], Tara Ford[1], Lydia Soto-Torres[6], Albert T. Profy[7], Betsy C. Herold[2,3,5]*

Clinical Infectious Diseases

MAJOR ARTICLE

HIV/AIDS

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

Betsy C. Herold,[1] Beatrice A. Chen,[2] Robert A. Salata,[3] Mark A. Marzinke,[4] Clifton W. Kelly,[5] Charlene S. Dezzutti,[2] Ian McGowan,[2] Beth Galaska,[2] Lisa Levy,[6] Jeanna M. Piper,[7] Sharon Hillier,[2] and Craig W. Hendrix[4]; for the MTN-011 Study Team

[1]Departments of Pediatrics and Microbiology-Immunology, Albert Einstein College of Medicine, Bronx, New York; [2]Department of Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh, School of Medicine, Pennsylvania; [3]Department of Medicine, Case Western Reserve, Cleveland, Ohio; [4]Department of Medicine (Clinical Pharmacology), Johns Hopkins University School of Medicine, Baltimore, Maryland; [5]Statistical Center for HIV/AIDS Research & Prevention, Fred Hutchinson Cancer Research Center, Seattle, Washington; [6]Family Health International 360, Durham, North Carolina; and [7]Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland

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 before and 1 hour after (BAT) sex and compared results with dosing without sex.

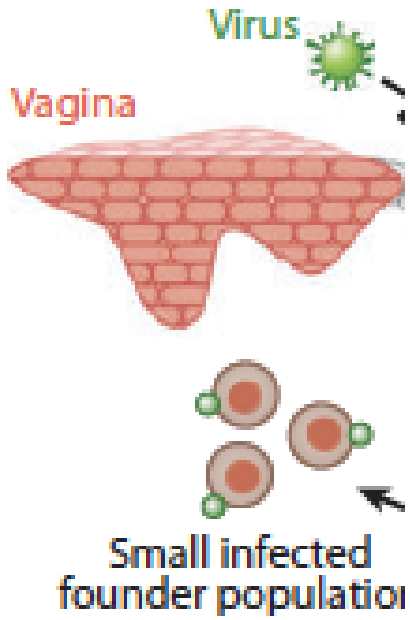
Methods. Twenty-four couples were enrolled; cervicovaginal lavage (CVL) and tissue were collected 2 hours after sex with matching timed collections at no sex visits and assayed for drug concentrations and CVL anti-HIV activity.

Results. Compared with dosing without sex, median TFV concentrations after sex decreased 72% and 78% ($P < .001$) in CVL, 75% and 71% ($P < .001$) in vaginal tissue, and 75% ($P = .06$) and 55% ($P < .001$) in cervical tissue with −1 hour and −24 hour dosing, respectively. Median concentration of TFV–diphosphate also decreased significantly in cervical tissue with −1 hour, 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% (54%) in the absence of gel to 99% (7%), 77% (57%), and 100% (0.4%) with −1 hour, −24 hour, or BAT dosing, respectively, and correlated significantly with drug concentration.

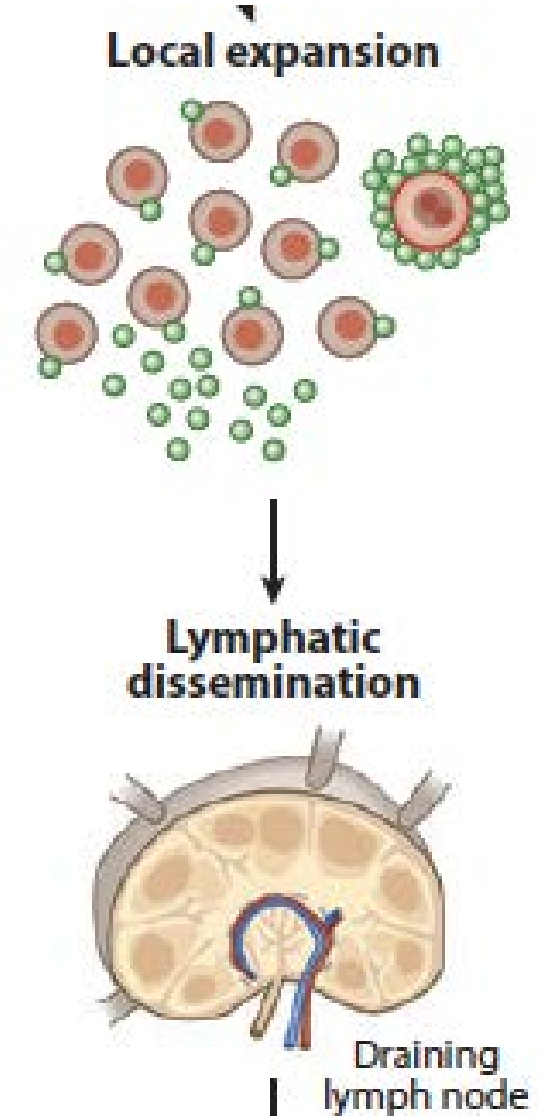
Conclusions. Timing of TFV gel application relative to sex significantly impacts drug levels. BAT dosing or sustained delivery may be optimal for preexposure prophylaxis.

Keywords. MTN-011; tenofovir gel; pharmacokinetics; post-coital; HIV.

Topicals only have one chance to block: the vaginal portal
Systemics cover larger area, but achieve lower vaginal levels



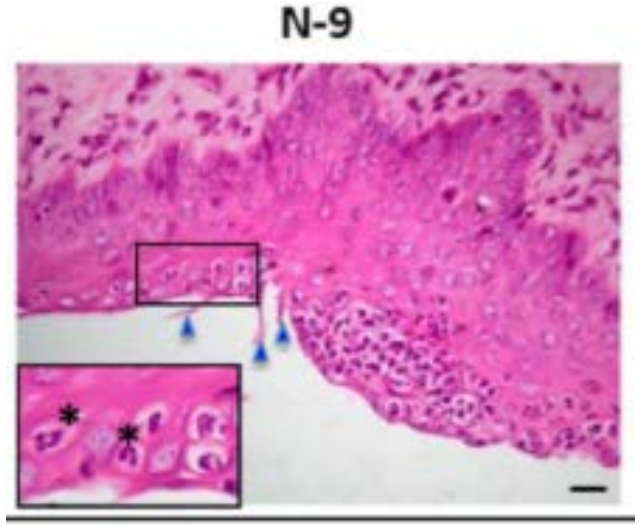
Topicals>> systemics



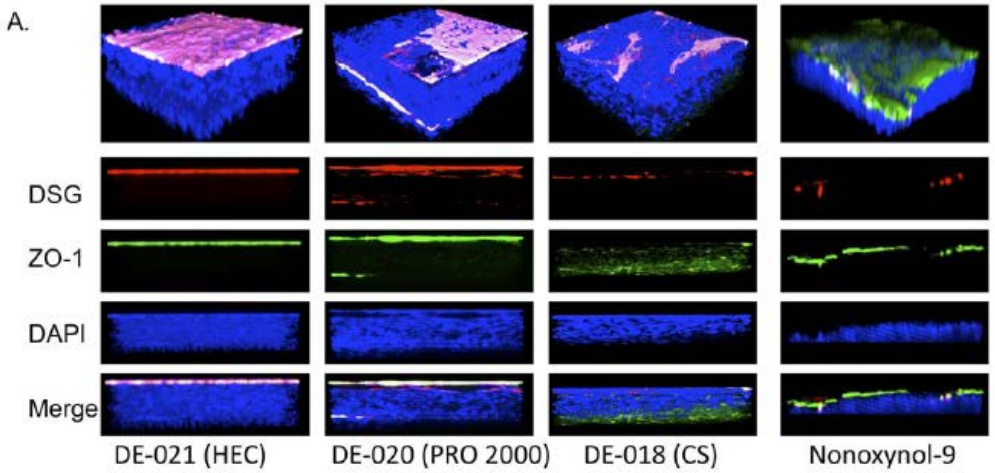
Topicals ≅ Systemics

Systemics only

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



Bridging the Gap between Preclinical and Clinical Microbicide Trials: Blind Evaluation of Candidate Gels in Murine Models of Efficacy and Safety

Theodore J. Segarra[1], Esra Fakioglu[1], Natalia Cheshenko[1], Sarah S. Wilson[1¤], Pedro M. M. Mesquita[1], Gustavo F. Doncel[2], Betsy C. Herold[1*]

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

eLIFE elifesciences.org

RESEARCH ARTICLE

Mucosal effects of tenofovir 1% gel

Florian Hladik[1,2,3*], Adam Burgener[4,5†], Lamar Ballweber[3†], Raphael Gottardo[3,6,7], Lucia Vojtech[1], Slim Fourati[8], James Y Dai[6,7], Mark J Cameron[8], Johanna Strobl[3], Sean M Hughes[1], Craig Hoesley[9], Philip Andrew[10], Sherri Johnson[10], Jeanna Piper[11], David R Friend[12], T Blake Ball[4,5], Ross D Cranston[13,14], Kenneth H Mayer[15], M Juliana McElrath[2,3,16], Ian McGowan[13,14*]

SCIENTIFIC REPORTS

OPEN

Tenofovir Inhibits Wound Healing of Epithelial Cells and Fibroblasts from the Upper and Lower Human Female Reproductive Tract

Received: 14 September 2016
Accepted: 06 March 2017
Published: 03 April 2017

Marta Rodriguez-Garcia, Mickey V. Patel, Zheng Shen, Jack Bodwell, Richard M. Rossoll & Charles R. Wira

Tenofovir disoproxil fumarate intravaginal ring for HIV pre-exposure prophylaxis in sexually active women: a phase 1, single-blind, randomised, controlled trial

Marla J Keller, Lianna Wood, James M Billingsley, Laurie L Ray, Jessica Goymer, Shada Sinclair, Aileen P McGinn, Mark A Marzinke, Bruce Frank, Sujatha Srinivasan, Congzhou Liu, Jessica M Atrio, Lilia Espinoza, Nelly Mugo, Hans M L Spiegel, Peter L Anderson, David N Fredricks, Craig W Hendrix, Jeanne Marrazzo, Steven E Bosinger, Betsy C Herold

Interpretation Future studies are needed to establish whether the unanticipated finding of ulcerations is specific to this tenofovir disoproxil fumarate ring or generalisable to other sustained topical release formulations of tenofovir or its prodrugs.

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

Antiviral Agents

A Subcutaneous Implant of Tenofovir Alafenamide Fumarate Causes Local Inflammation and Tissue Necrosis in Rabbits and Macaques

Jonathan T. Su, Solange M Simpson, Samuel Sung, Ewa Bryndza Tfaily, Ronald Veazey, Mark Marzinke, Jiang Qiu, David Watrous, Lakmini Widanapathirana, Elizabeth Pearson, M. Melissa Peet, Dipu Karunakaran, Brooke Grasperge, Georgina Dobek, Charlette M. Cain, Thomas Hope, Patrick F. Kiser

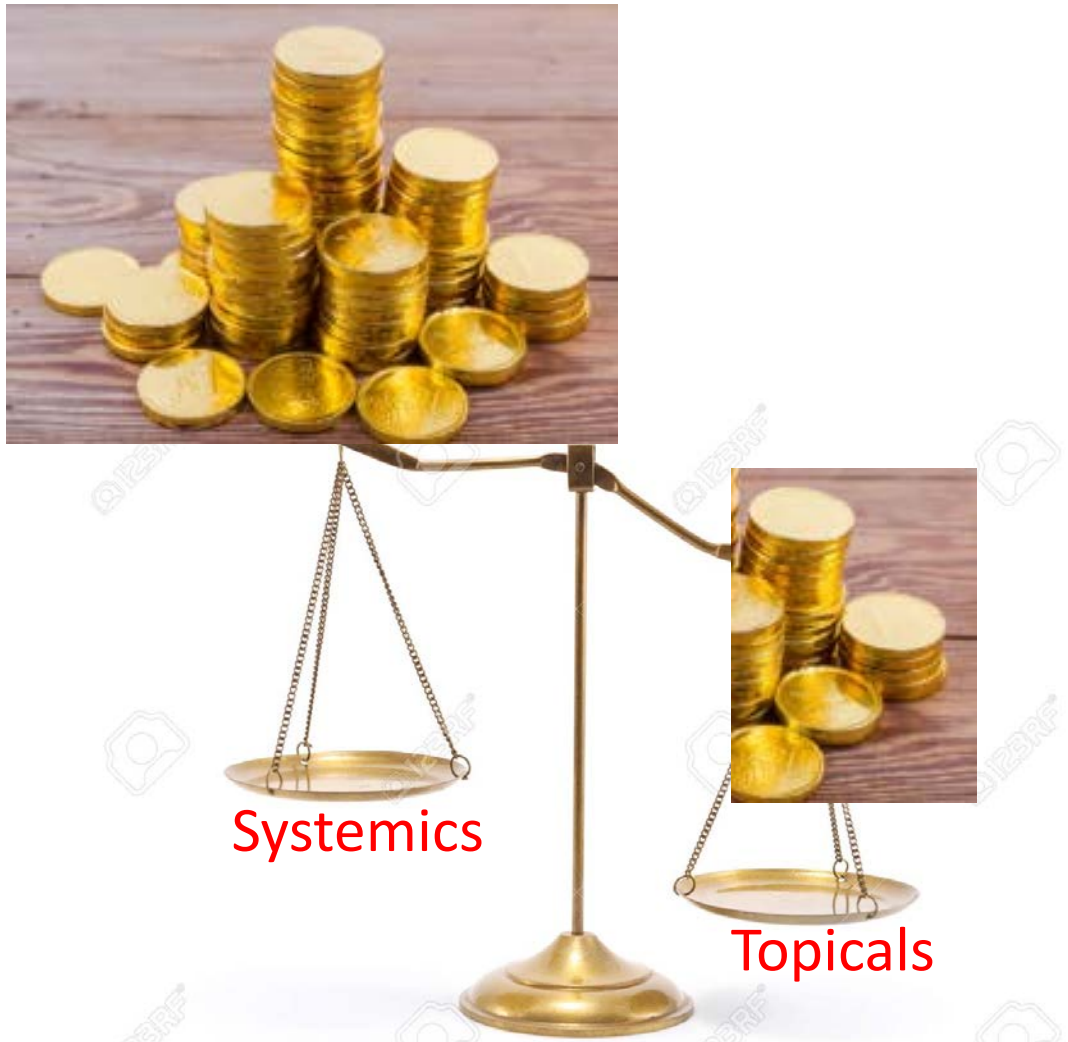
Early safety concerns for systemic PrEP not supported by experience to date

- **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 <u>both</u> 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

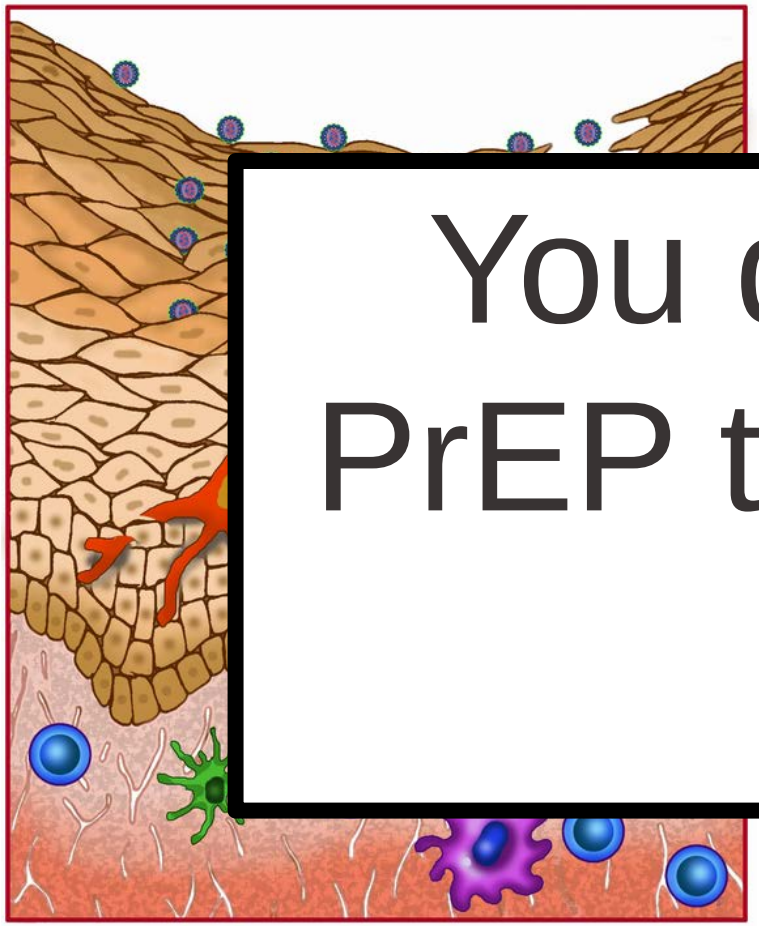
"The sole barrier promoted for the prevention of sexual transmission of HIV from men to women is the condom....

The empowerment *of* women is crucial for the prevention of HIV transmission *to* women.

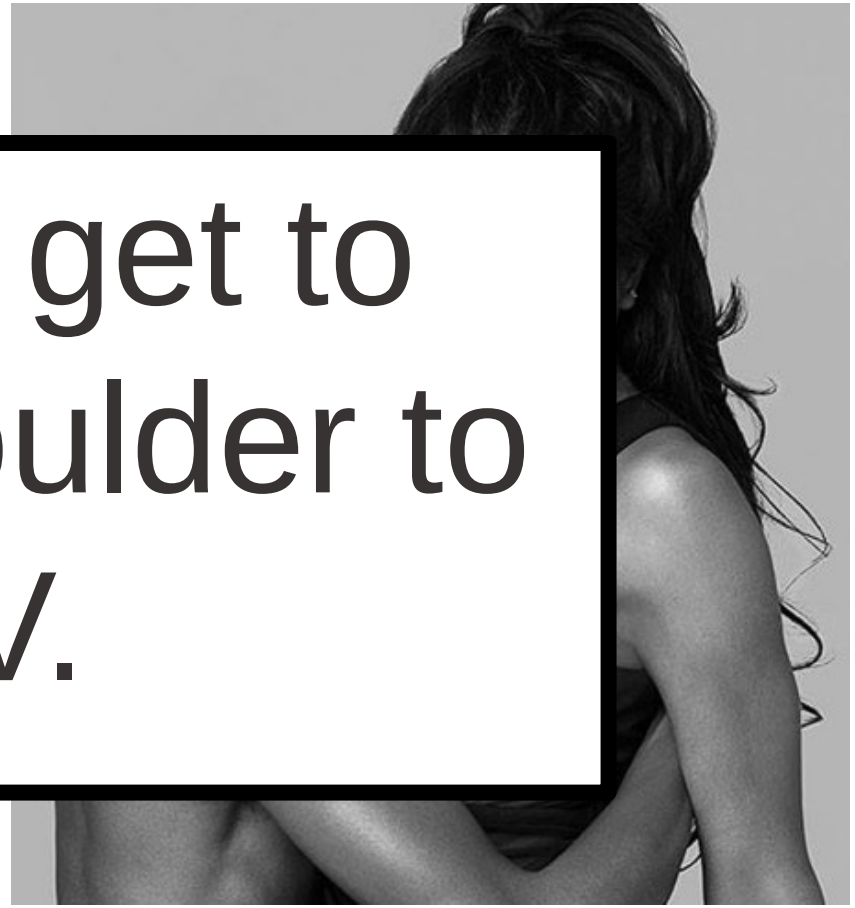
It follows that prophylaxis must include procedures that ... are under her control."

(Am J Pub Health, 1990)

Topical PrEP makes sense



You don’t need get to 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

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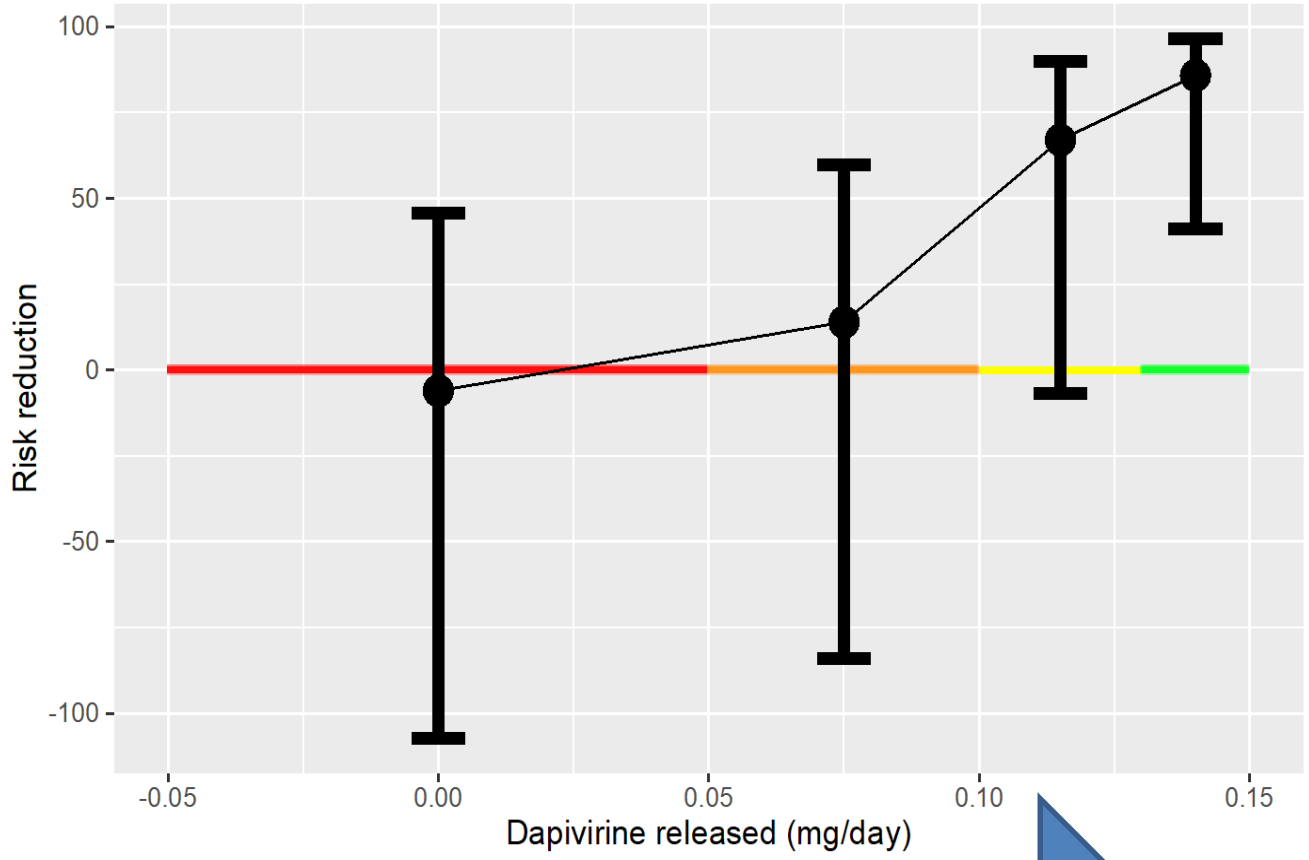
ASPIRE

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%

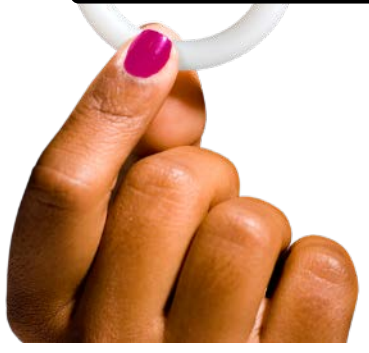


More dapivirine released = more use = more protection

Brown et al., AIDS 2016 & submitted

The ring is workable in open-label settings

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.



Lower HIV incidence than expected in the absence of ring access

DREAM
Dapivirine Ring Extended Access and Monitoring

Nel et al. SA AIDS 2019; Baeten et al. IAS 2019

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Choice matters

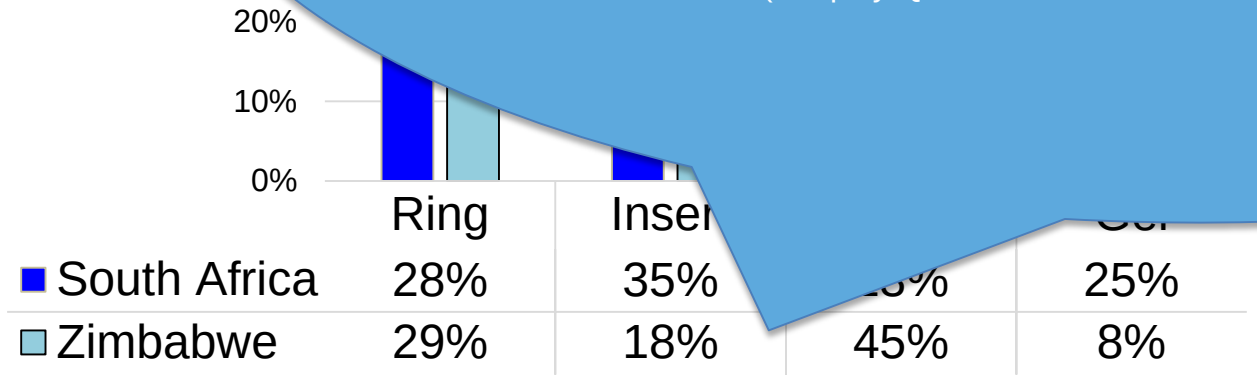
Behavior science … products

P… rience

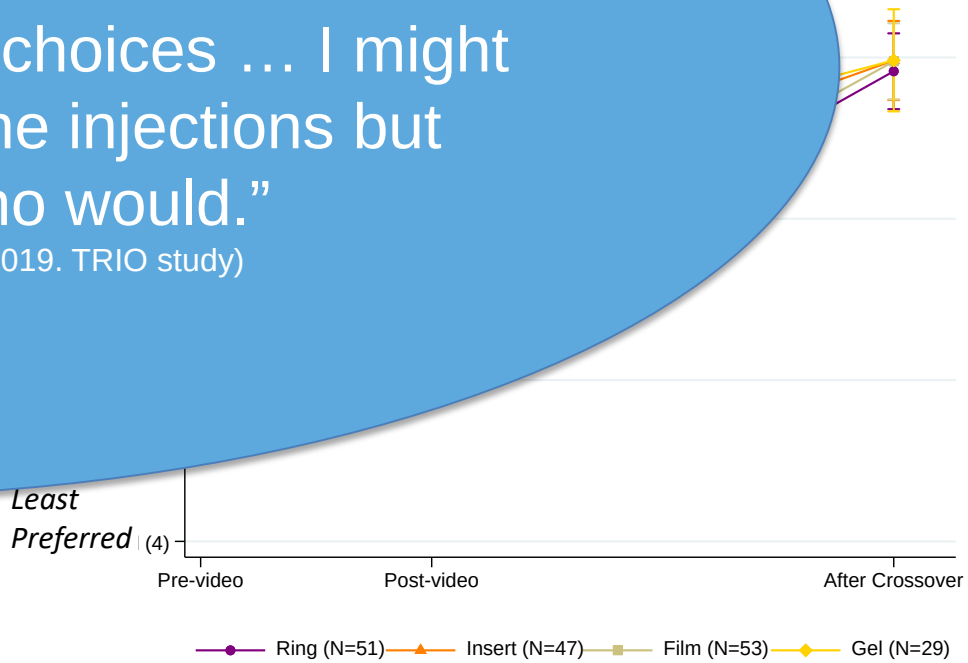
"We are not the same. Some they will like the ring. Some they will like the tablet … People are not the same."

"…As people we have different choices … I might not like the, the pills … and the injections but there's other people who would."

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

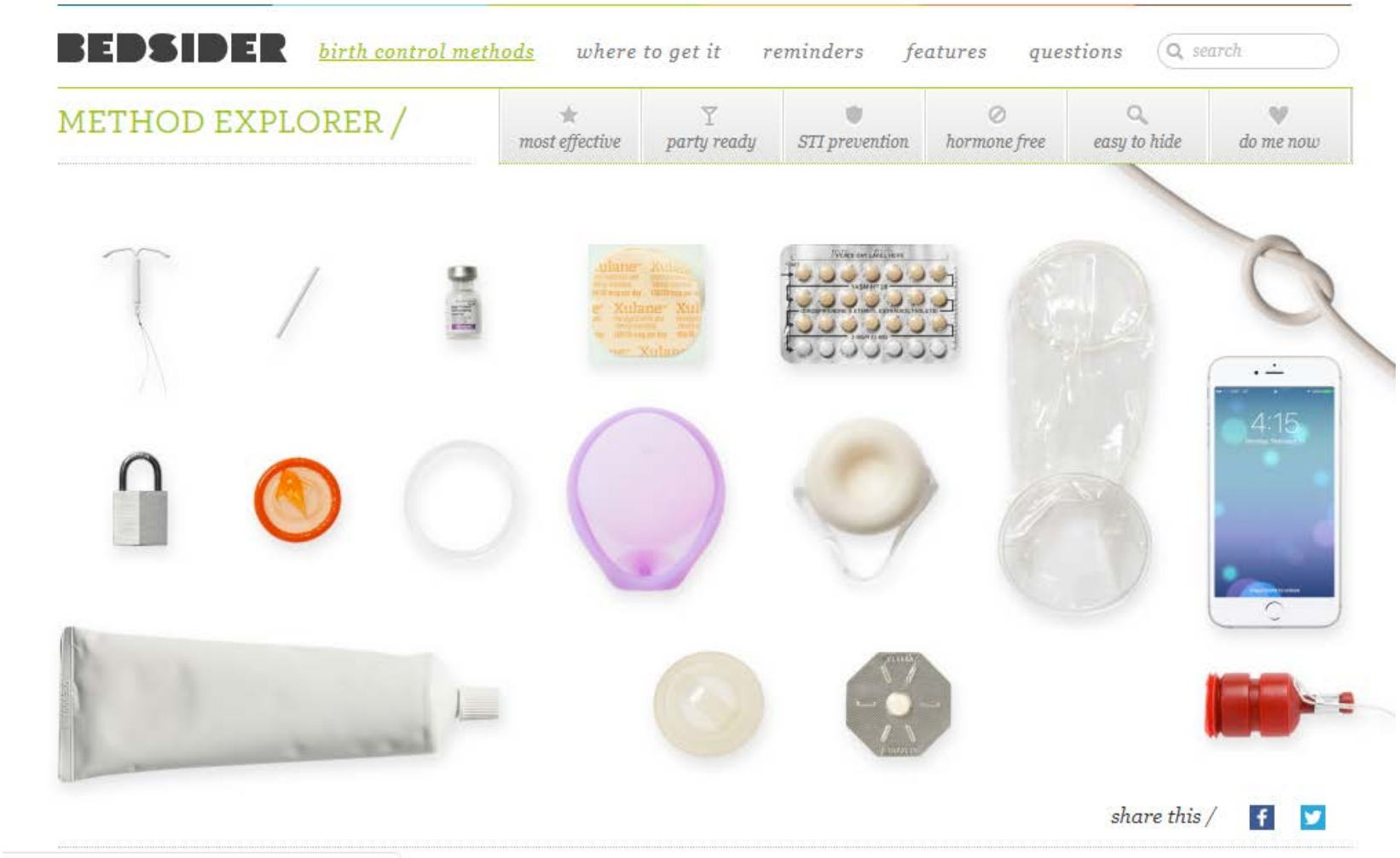


* Significantly different, p<0.05



(Montgomery et al. QUATRO study, R4P 2018 & JIAS 2019)

People use prevention when they have choices

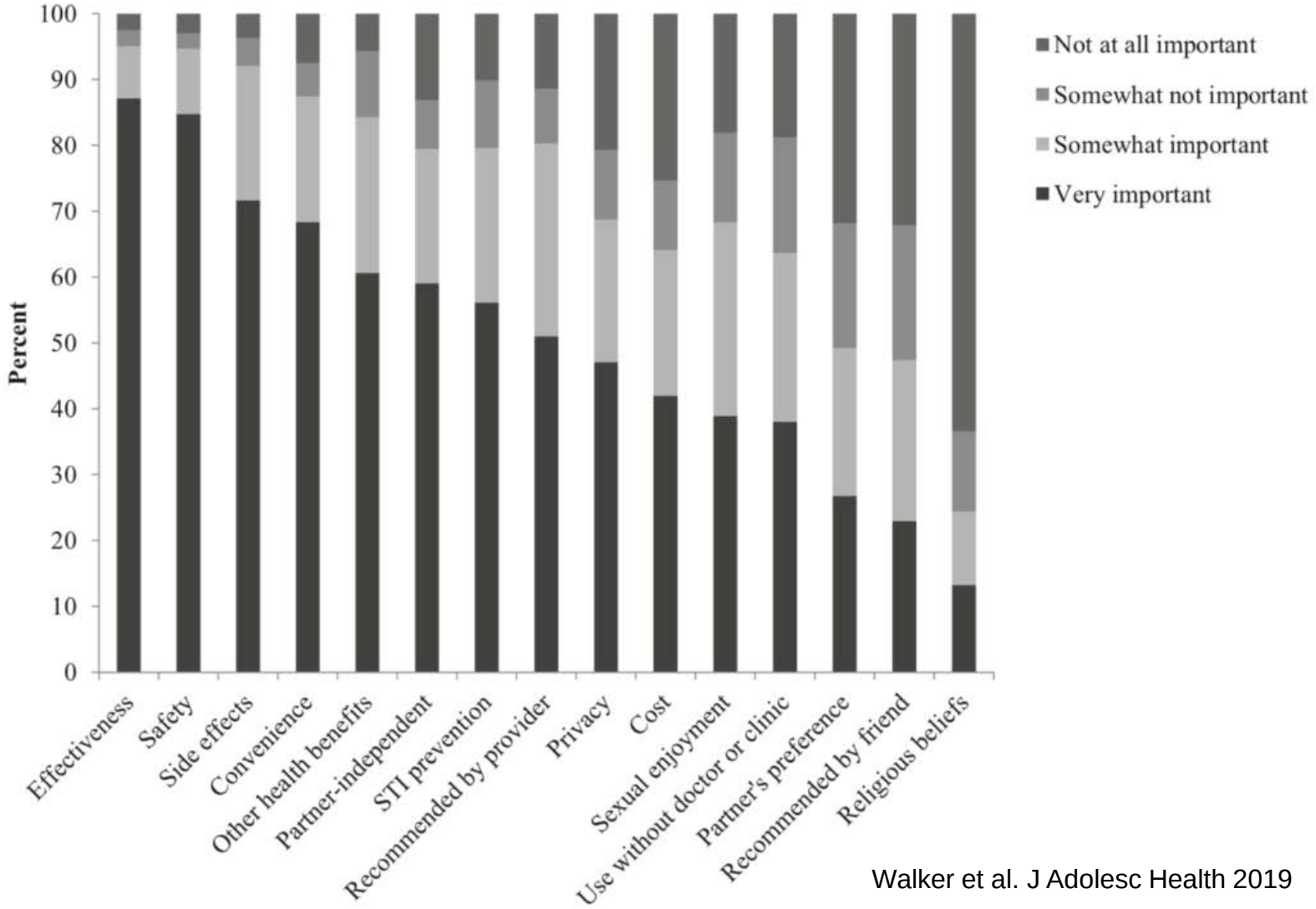


Many factors drive choice-making

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

WHO Systematic Review (231 articles)

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

Gray et al. WHO RHRU 2006 & Jain et al. Stud Fam Plan 1989

Do topicals have a future for vaginal protection against HIV?

Vaginal microbicides work

Choice matters

Topicals provide unique advantages

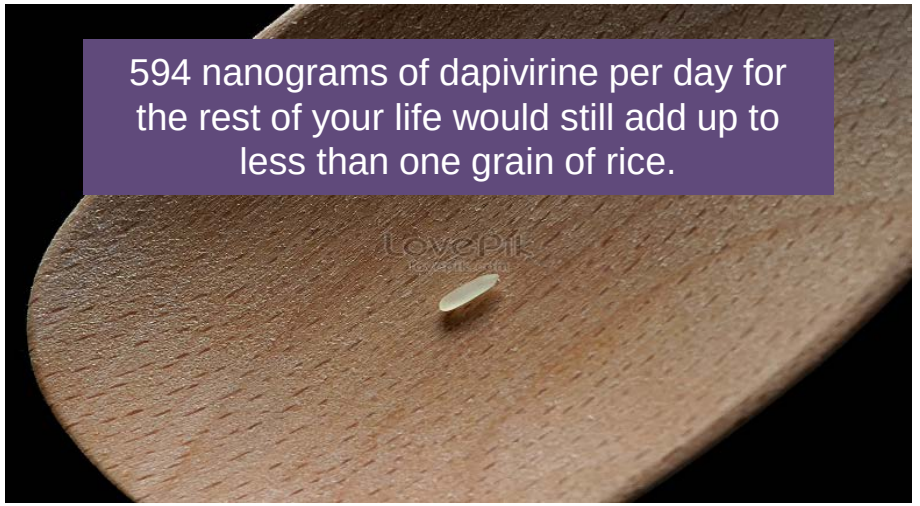
A systemic may not be wanted

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



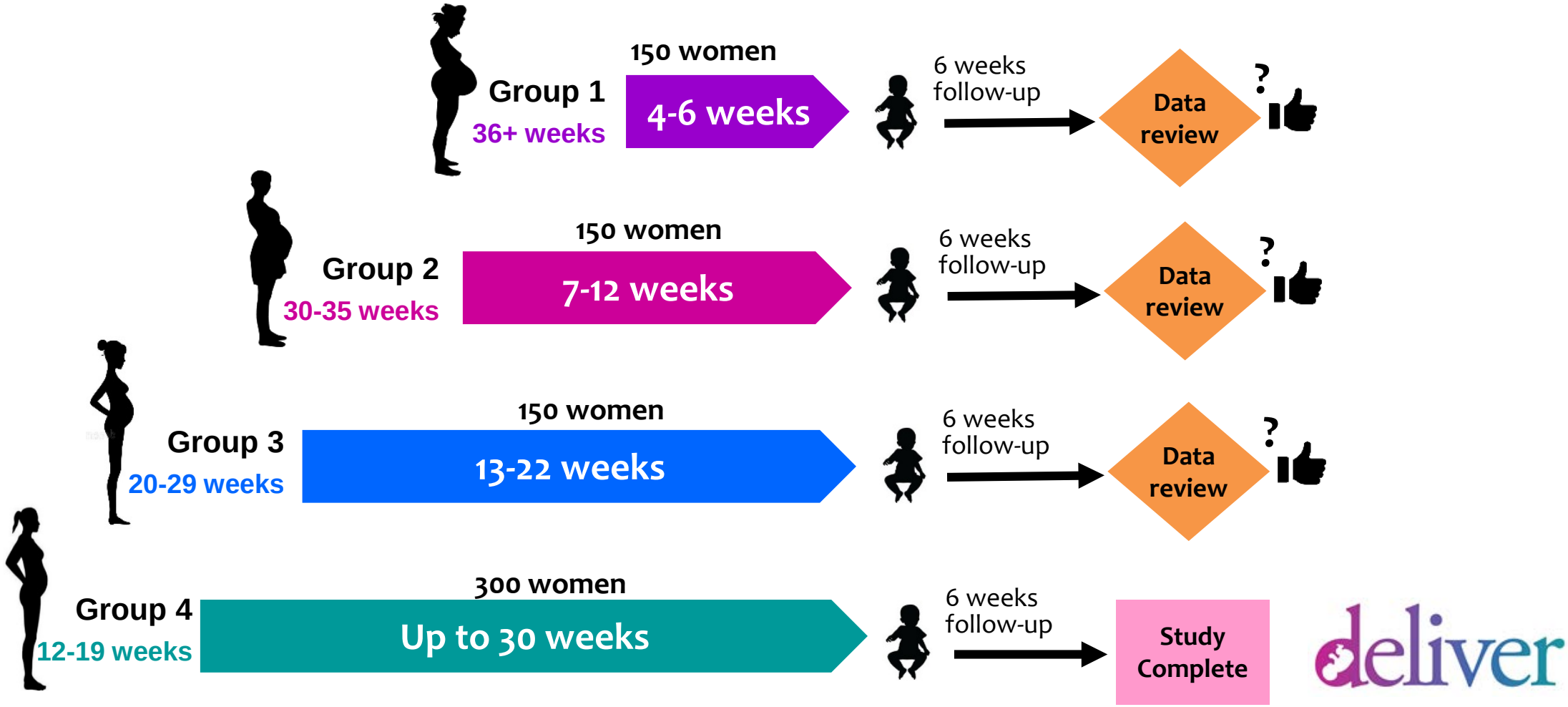
Systemic PrEP & pregnancy

In other words, systemic PrEP may be less-er, in a population that needs prevention even more.

volume & clearance.

Pyra et al. AIDS 2018

Unique research at the interface of pregnancy & HIV prevention



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

Opinion

The Dangerous Rise of the IUD as Poverty Cure

The notion that limiting women's reproduction can cure societal ills has a long, shameful history.

Dehlendorf & Holt NYTimes 2019

Gaps

The science

The reality

Slide adapted from Thes Palanee-Phillips

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More options

Infusion | Implant | Injection | Pill | Vaginal ring | Gels | Insert | Vaginal film | Lube | Douche

Options → choices → coverage → impact

In the end, it about use & impact

Commentary

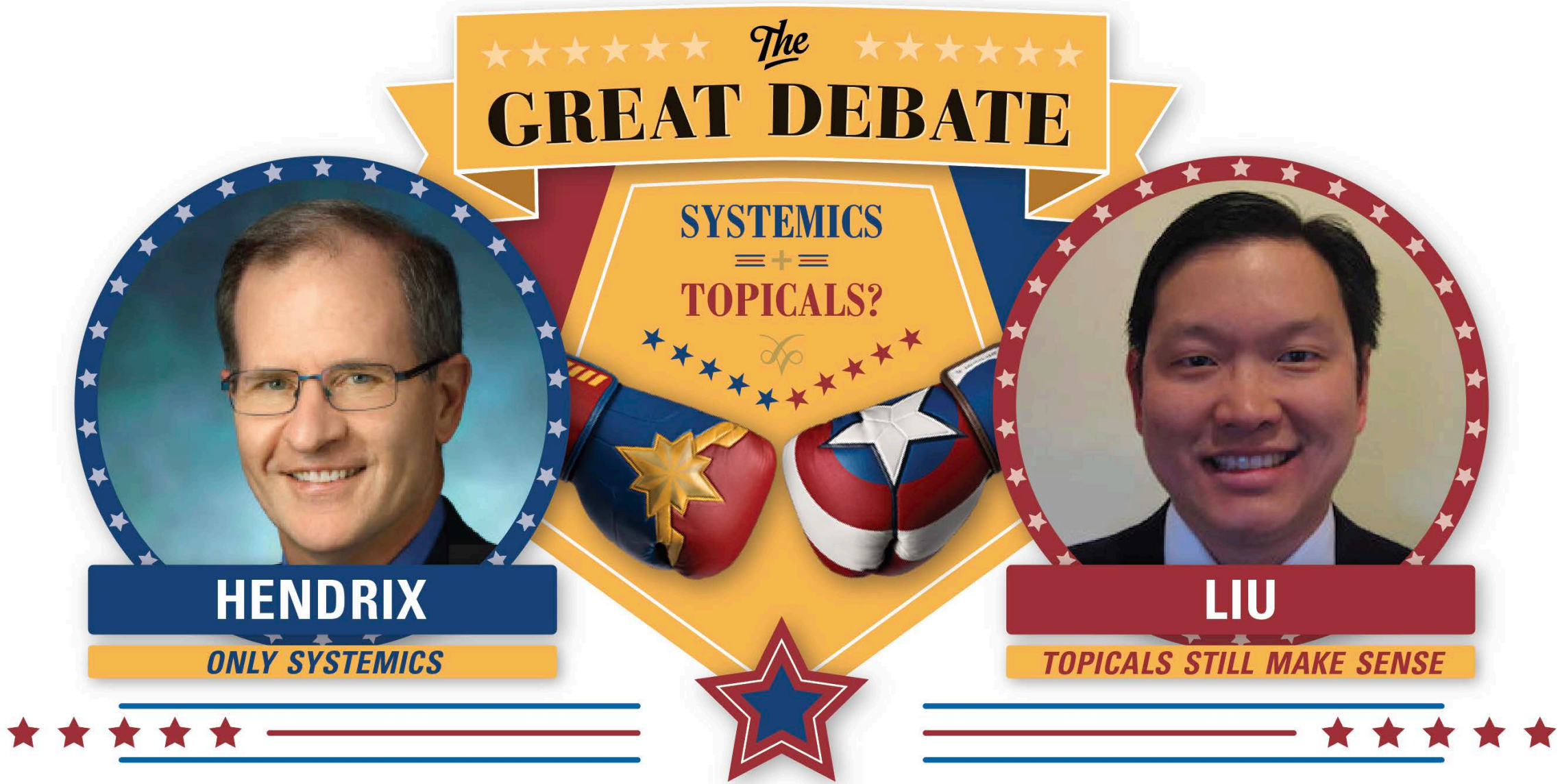
HIV Prevention: The Need for Methods Women Can Use

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



RESOLVED:

Only Systemics Should Move Forward

(With regard to Rectal HIV PrEP)

Craig W. Hendrix, MD
Johns Hopkins University

Why is Systemic PrEP Enough?

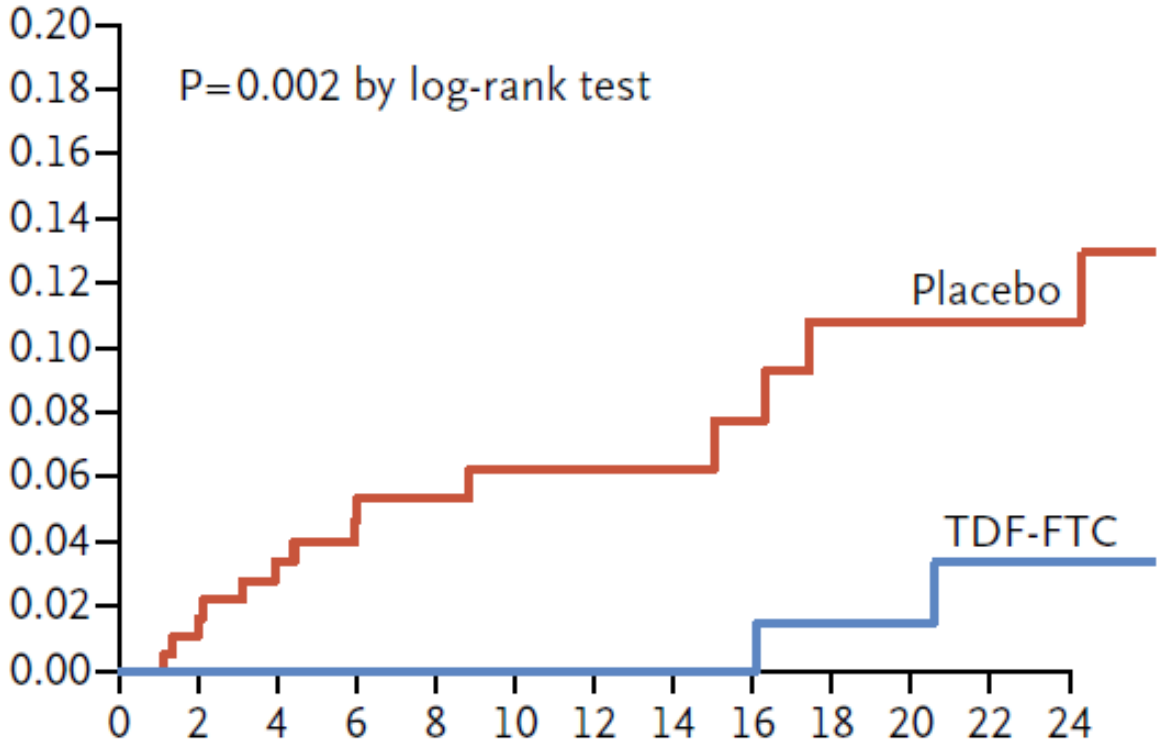
- What problems are we trying to solve with rectal microbicides?
- What's the possible impact of continued rectal microbicide investment?
- Why rectal microbicides may not work?

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

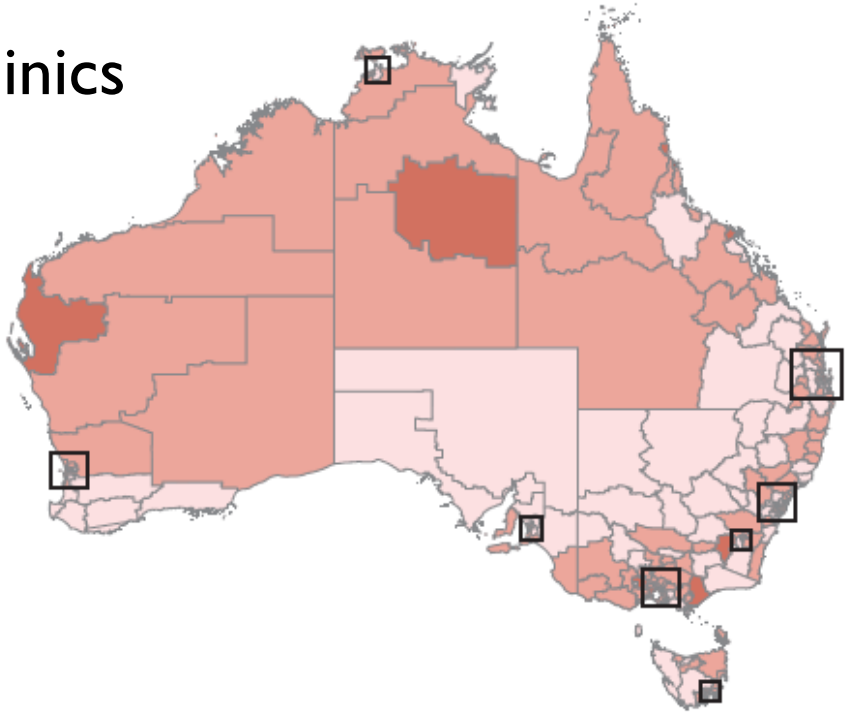
- Ipergay 2+1+1
  - MSM/TGW
  - Daily oral vs. on demand
  - 86% relative risk reduction
- Prevenir
  - MSM/TGW
  - Select desired regimen
  - On demand (54%), Daily (45%)
  - No HIV in 506 (on demand) & 443 (daily) person-years



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%)

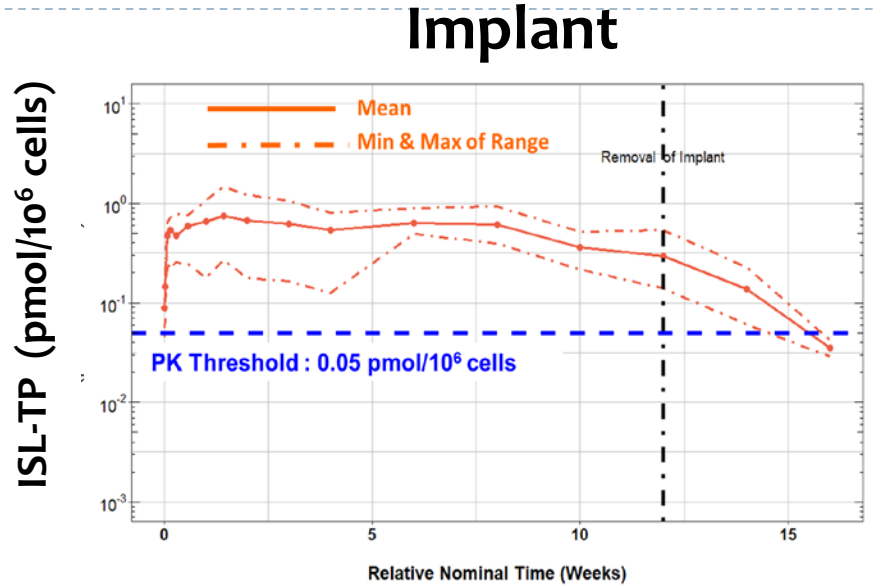


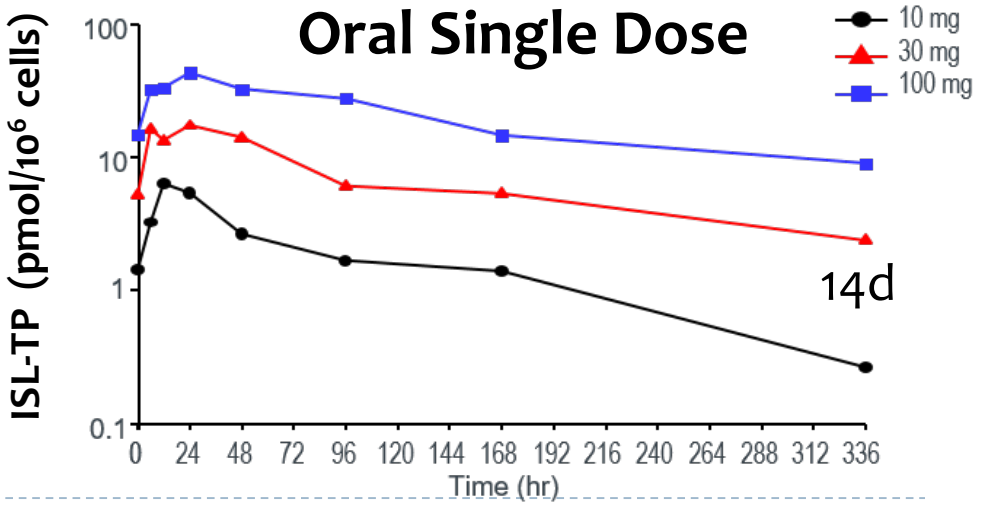
- Grulich at al. Lancet HIV 2018; UNSW Kirby Institute Annual Surveillance Report 2017

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

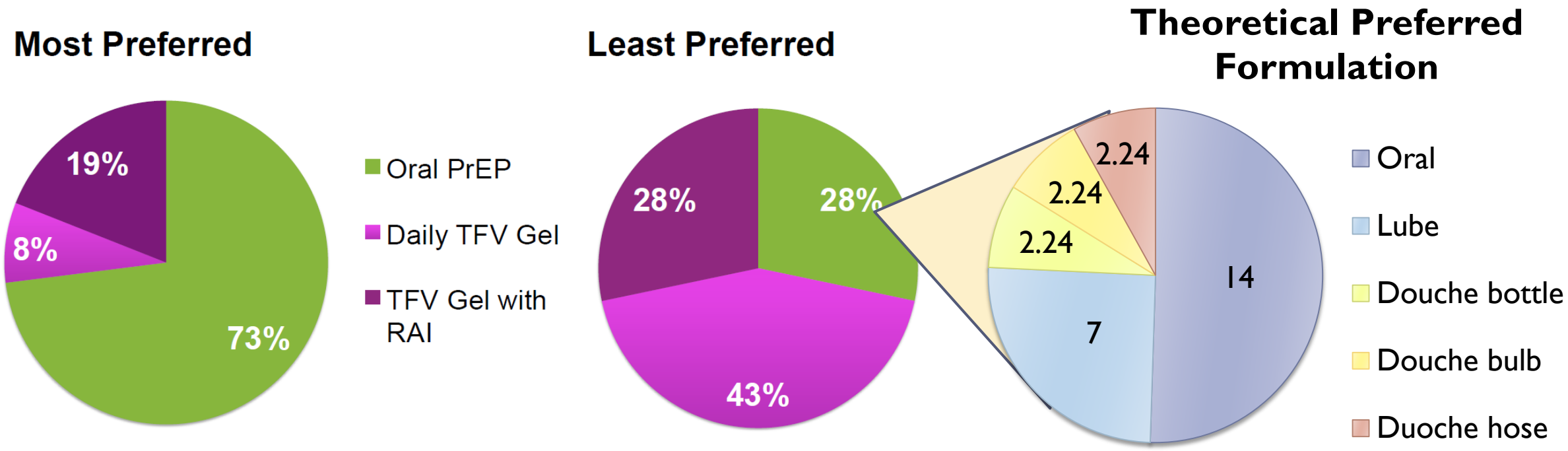
Why is Systemic PrEP Enough?

- 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?*



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?

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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?

Remember, this is an academic exercise …

"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

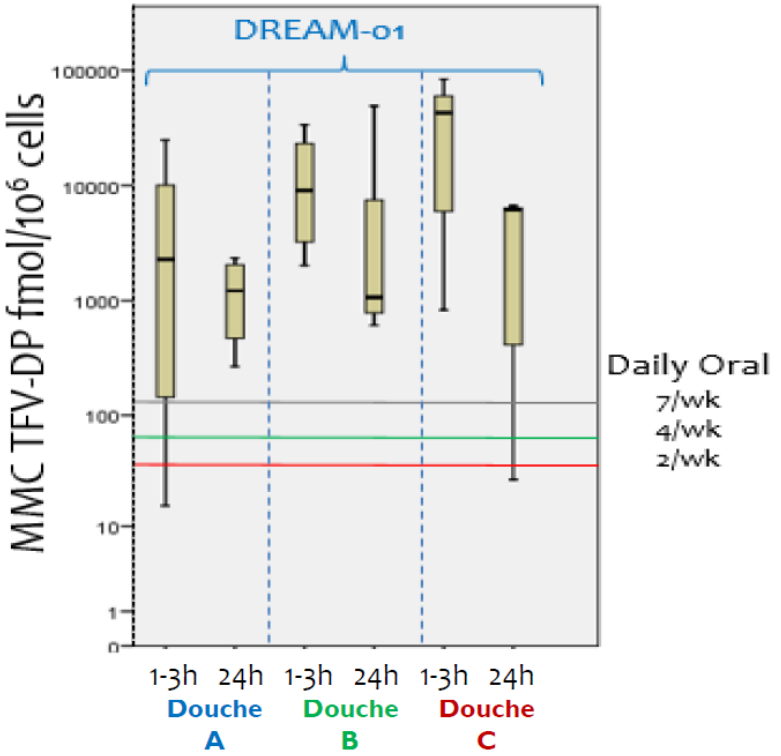
Albert Liu, MD, MPH
San Francisco Department of Public Health
University of California, San Francisco


ALTERNATIVE FACTS
FAKE NEWS

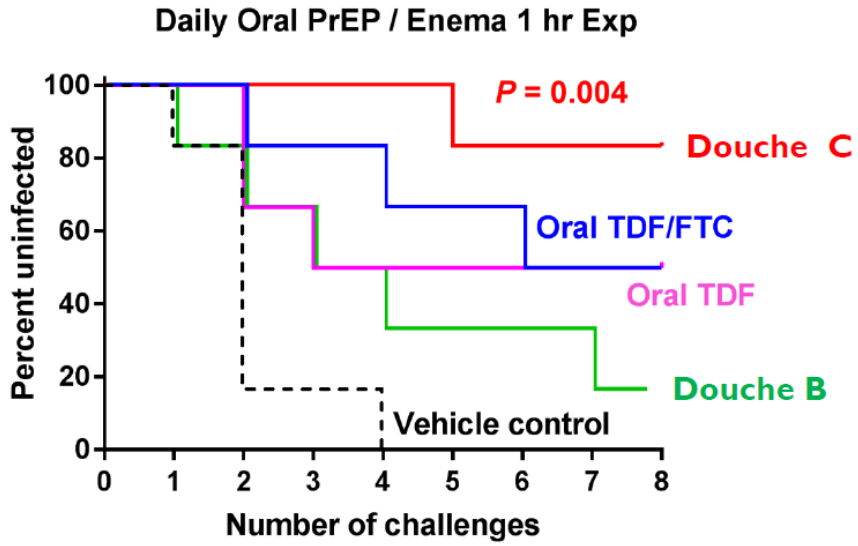
1. Topicals can achieve high tissue concentrations and are highly protective in animal studies

DREAM Program: Tenofovir Douche

Human PK: Colon Cell TFV-DP



Macaque PD: SHIV Challenge



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)

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

Carballo-Dieguez 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

Rael CT et al. AIDS and Behavior. 2019

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

Patel R et al. PLOS ONE 2018; Rael CT et al. AIDS and Behavior. 2019

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

Carballo-Dieguez AIDS and Behavior 2019

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 douched, **40%** reported frequent douching
- YMSM engaging in RAI more likely to douche
- **Racial/ethnic minorities** more likely douche (AOR 2.24, p=0.02) and reported more frequent douching
- **YMSM who douched had higher rectal microbicide acceptability**

Tingler AIDS and Behavior 2019

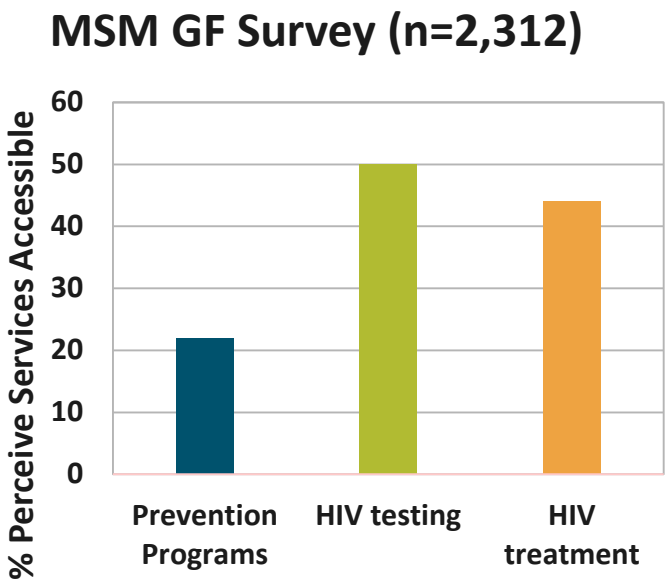
"The desirability for an **on demand, behaviorally-congruent** PrEP product has been voiced loudly by the populations at greatest risk of HIV nationally and internationally, especially young black MSM in the US for more than 10 years… Rectal microbicide products now in clinical development demonstrate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

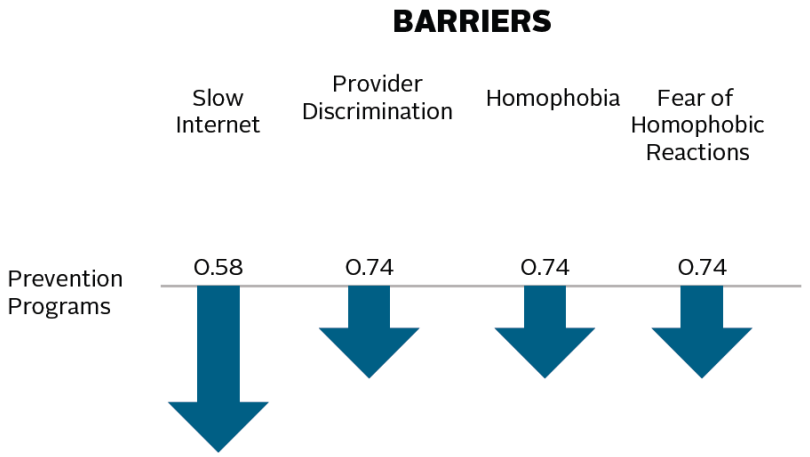
-- **US Researcher**

International Rectal Microbicide Advocates. Whose Choice is it Anyway? Tinyurl.com/whosechoiceanyway

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





MSM Global Forum. Rights in Action. Access to HIV Services among Men Who Have Sex with Men.

5. We need prevention options available <u>OUTSIDE</u> medical system

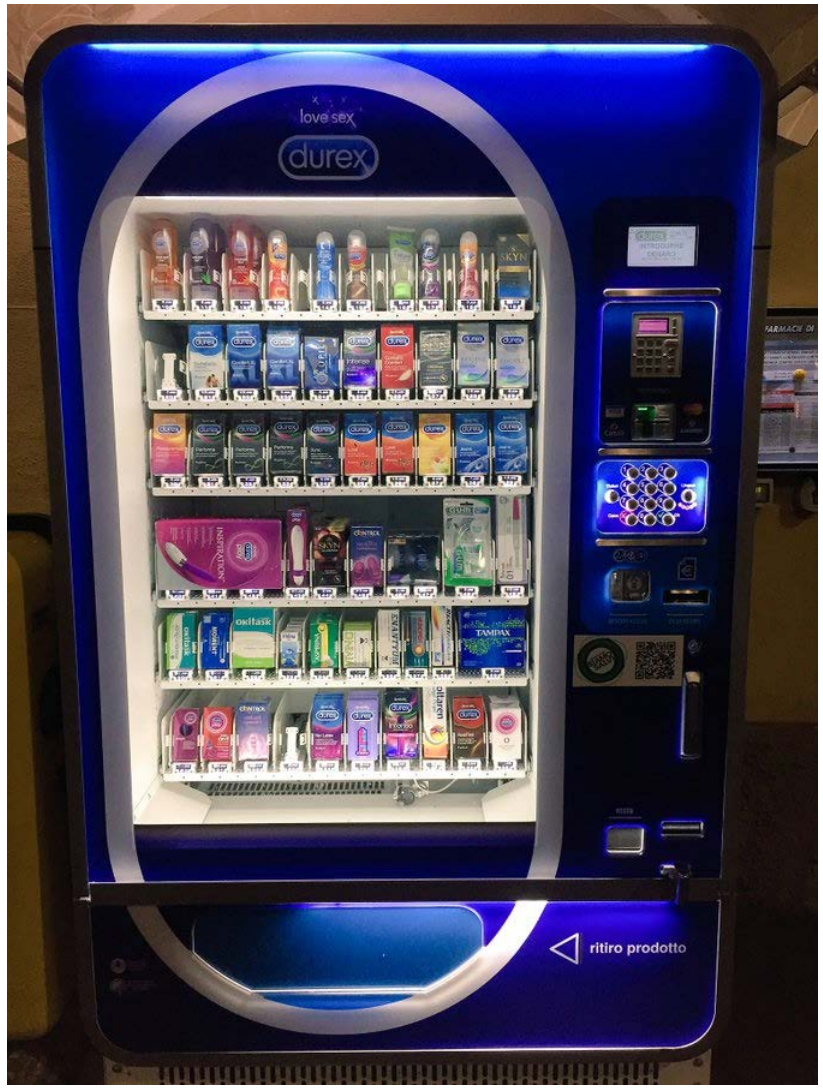
- Systemics will require provider visits for injections, insertion/removal of implants
- **Will overwhelm the medical system at scale, drive up costs**
  - In US 1.1 million adults for whom PrEP is indicated
  - If half are on injectable PrEP (Q2 month visits)

  ➡ **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