



# *The Case for On Demand Topical PrEP: Maintaining Options to Optimize CHOICE*

Craig W. Hendrix  
MTN Annual Meeting 2019

# Disclosures

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- **Research grants** from Gates Foundation, ViiV/GSK, & Gilead managed through Johns Hopkins
- **US Patent** 10,092,509 (October 9, 2018) for hypotonic microbicidal formulations and methods of use



# What Does Promise\* Look Like?

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*\*promise, not perfect - product worthy of continued product improvements within a prevention strategy*

- ▶ Decade(s) of product failures
- ▶ First success ~30% protection
- ▶ What is the product development decision?
  - ▶ Abandon the strategy
  - ▶ Build on modest success by
    - ▶ Understanding failure
    - ▶ Re-engineer a better product
    - ▶ Improve implementation

# Converting Promise into Protection

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<b>Prevention Strategy</b>	<b>Challenge</b>	<b>Proposed Solution</b>
<b><i>Vaccine</i></b>	Narrow nAB breadth	Heterologous isolates; clade mosaic vector inserts
	Narrow T-cell breadth	More immunogenic vector platforms for priming
<b><i>Passive Immunization</i></b>	Low neutralizing potency	Larger, more efficient screens
	Narrow coverage	Multiple bNAB combinations
	Short half-life	Fc-receptor modification
<b><i>Vaginal Microbicide</i></b>	Poor adherence	Develop CHOICE of product formulations
	Microbiome	Improved treatment; selective trial enrollment
	Poor rectal penetration	Develop product that protects +/- or dosed rectally

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... this healthy competition of possibilities raises the issues of CHOICES

*A Thought Experiment ...  
of toolboxes & bedside stands*

*Which option do you choose to do the task?*

# When you want to build something ...

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*... what's in YOUR toolbox?*





**When you want to build something ...**

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***... what's in YOUR  
toolbox?***



**When you want to build something ...**

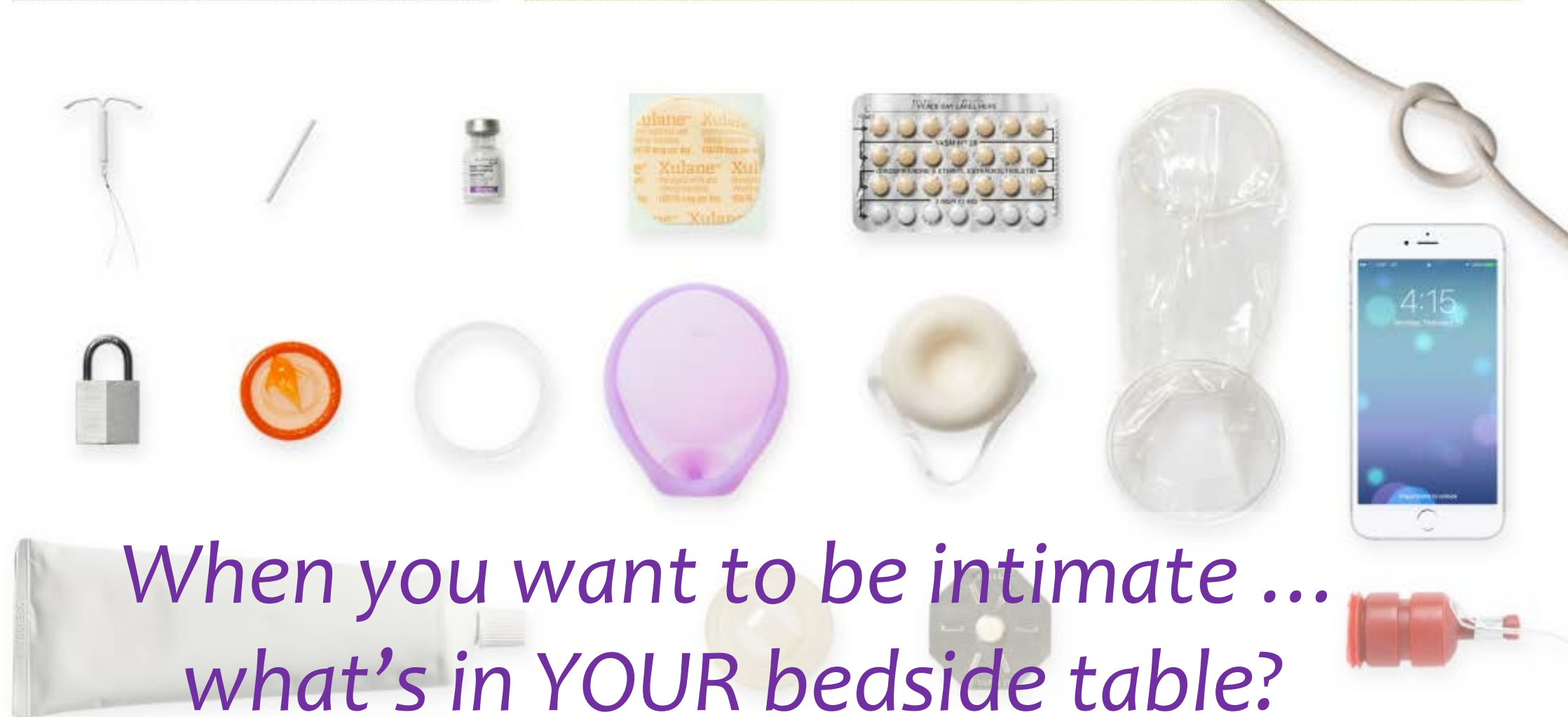
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***... what's in YOUR  
toolbox? (when all the world is not a nail)***



METHOD EXPLORER /

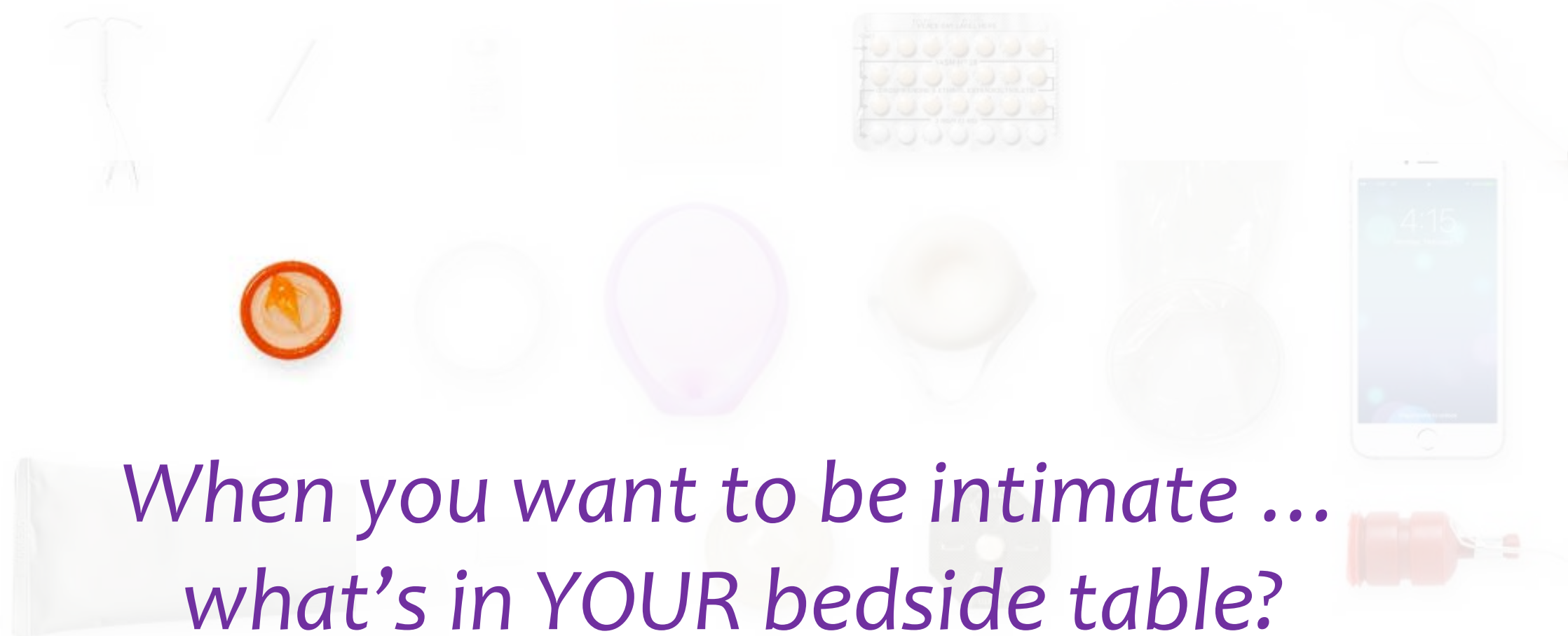
most effective party ready STI prevention hormone free easy to hide do me now



When you want to be intimate ...  
what's in YOUR bedside table?

METHOD EXPLORER /

★ most effective	Y party ready	🛡️ STI prevention	🚫 hormone free	🔍 easy to hide	❤️ do me now
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When you want to be intimate ...  
what's in YOUR bedside table?

# When *building* a program for safe *intimacy*... ... what are **YOUR PrEP CHOICES?**

## Formulations



Infusion

Implant

Injection

Pill

Vaginal ring

Gels

Insert

Vaginal film

Lube

Douche

## Active Ingredients

ARV

bNAbs

Luminal

+Contraception

+STIs

# When *building* a program for safe *intimacy*...

## ... what are YOUR PrEP CHOICES?

### Formulations



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

### Active Ingredients

TDF/FTC	bNAbs	Luminal	+Contraception	+STIs
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# On Demand HIV Prevention

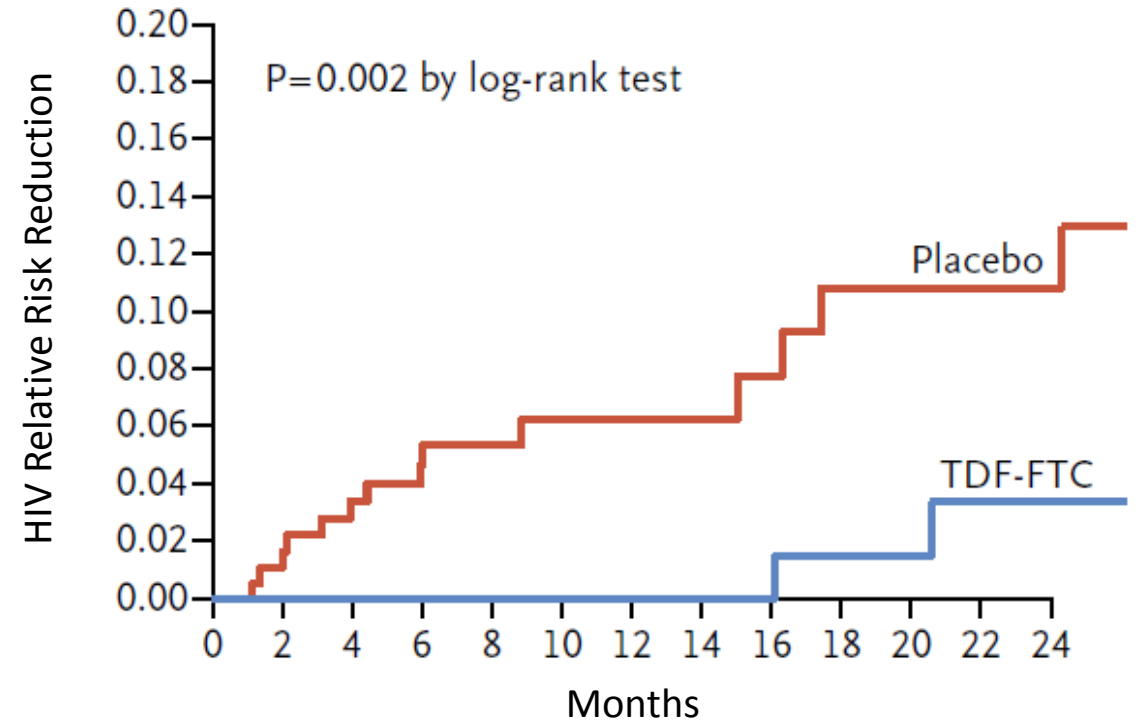
# Does On Demand Protect?

## ▶ Ipergay – Yes!

- ▶ RCT Oral TDF/FTC
- ▶ On demand 2/1/1 regimen
- ▶ 86% Relative risk reduction

## ▶ Prevenir – Yes!

- ▶ Open label, oral TDF/FTC
- ▶ Participant CHOOSES: on demand (54%) or daily (45%)
- ▶ Acquisition Risk 0 (0.0, 0.7) & 0 (0.0, 0.8);
- ▶ No infections in 506 & 443 PY, respectively

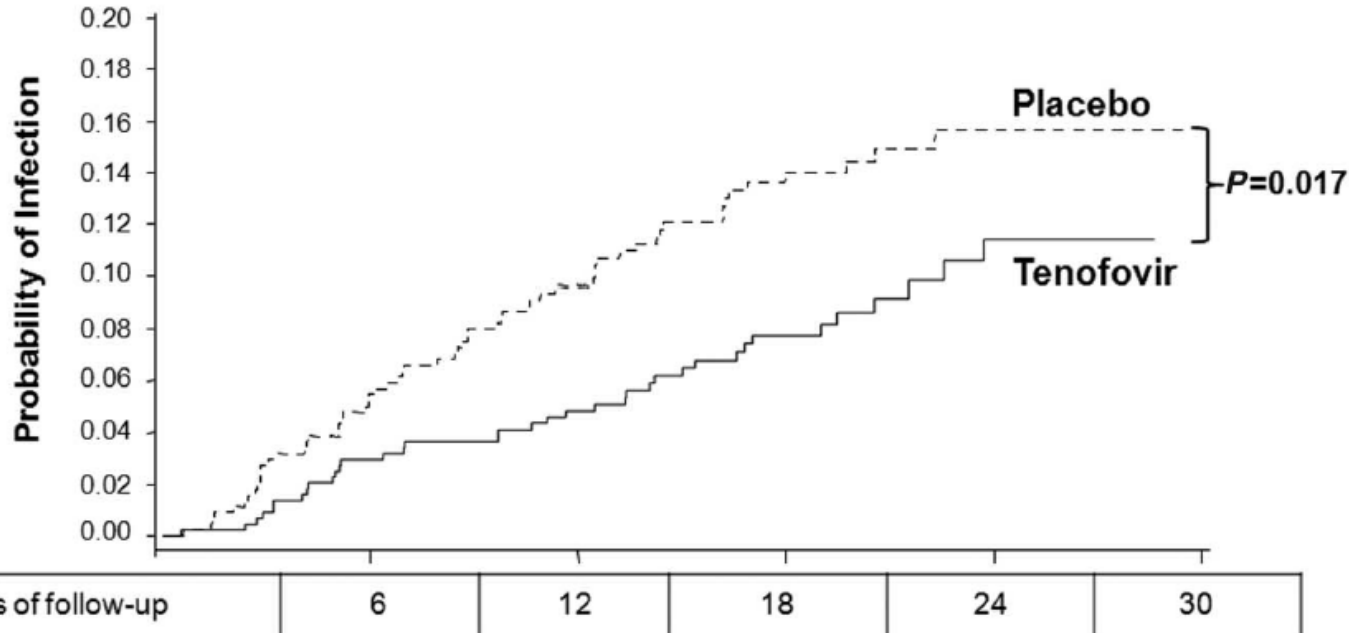




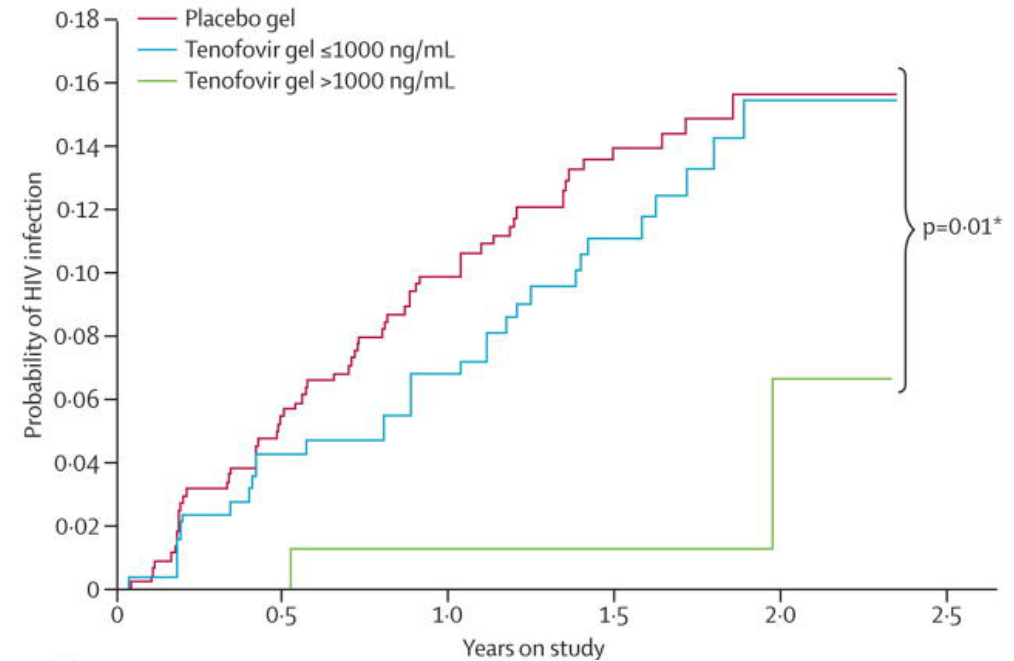
# Does On Demand, Topical Protect?

- ▶ CAPRISA 004 – YES! ...*esp. adjusting for Adherence & Microbiome*

mITT Analysis – 39% RRR



PK-Adjusted Log Reg – 73% RRR



- ▶ Karim *Lancet* 2010; Karim *Lancet* 2011; Klatt *Science* 2017; Taneva *JCI Insight*. 2018



# A Closer Look at Promise

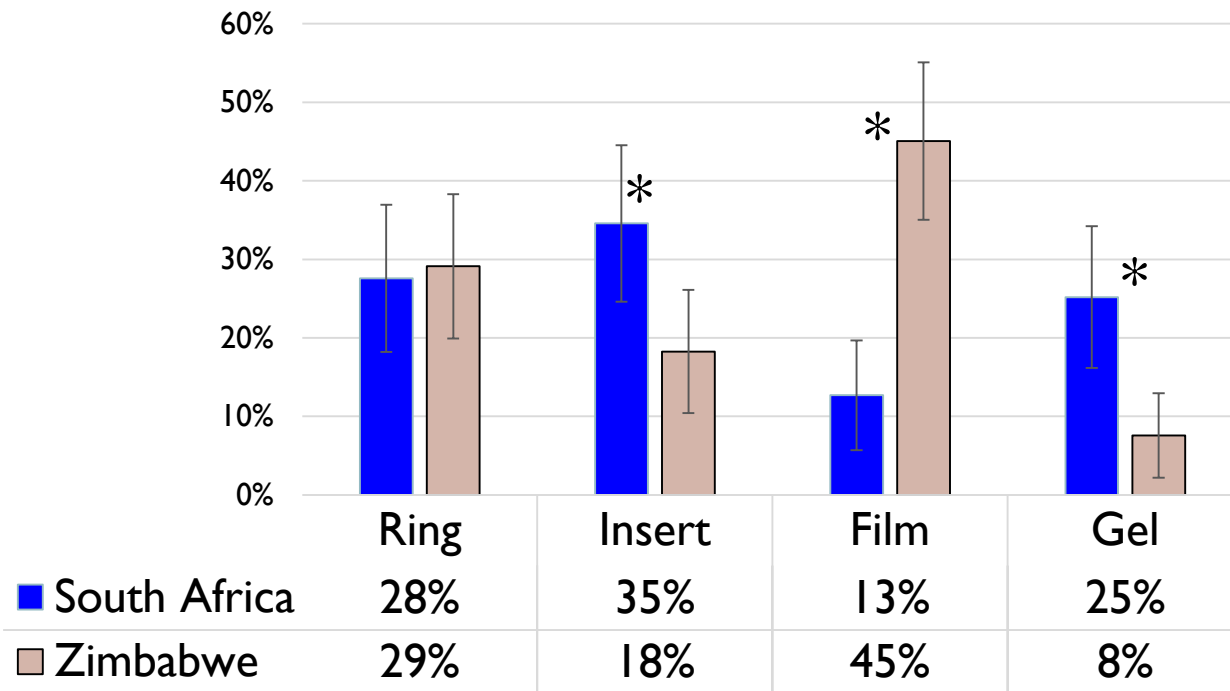
Variable	Study	RV144	iPrEx F/T Oral		Partners F/T Oral		CAPRISA TFV Gel		VOICE TFV Gel			ASPIRE DPV Ring	
	Method	mITT	mITT	Log Reg	mITT	TMLE	mITT	Log Reg	mITT	Poisson	TMLE	mITT	Cox
Author	Kim	Grant	Anderson	Baeten	Ruberman	Karim	Kashuba	Marrazzo	Dai	Ruberman	Baeten	Brown	
Point estimate	31	44	95	75	83	39	73	15	60	85	27	85	
Lower 95%	1	15	70	55	64	6	8	29	2	44	1	51	
Upper 95%	52	63	99	87	94	60	92	-31	84	100	46	96	
High Adherence													Residual
Age													x
Education													x
Site													x
HSV-2 sero													
CrCL													
Gender													
Unprotected													x
Married													x
Partner risk									x				x
STI, BV, HSV-2			x		x				x	x			x
Alcohol									x				x
Sex frequency													x
Partners IVR use knowledge													x
Partner #			x										x
Contraceptive use													x

How do we avoid post hoc adjustments

Solutions lie at the intersection of adherence, product preference, & CHOICE!

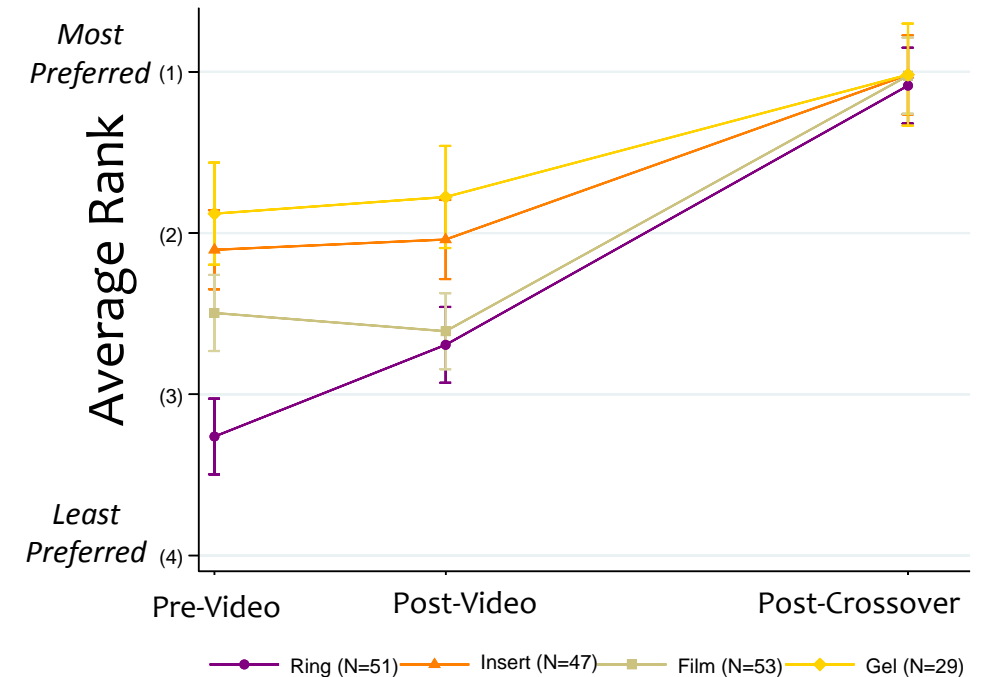
# CHOICE: Experiential Vaginal Product Preference

Preference Varies Geographically



\* Significantly different,  $p < 0.05$

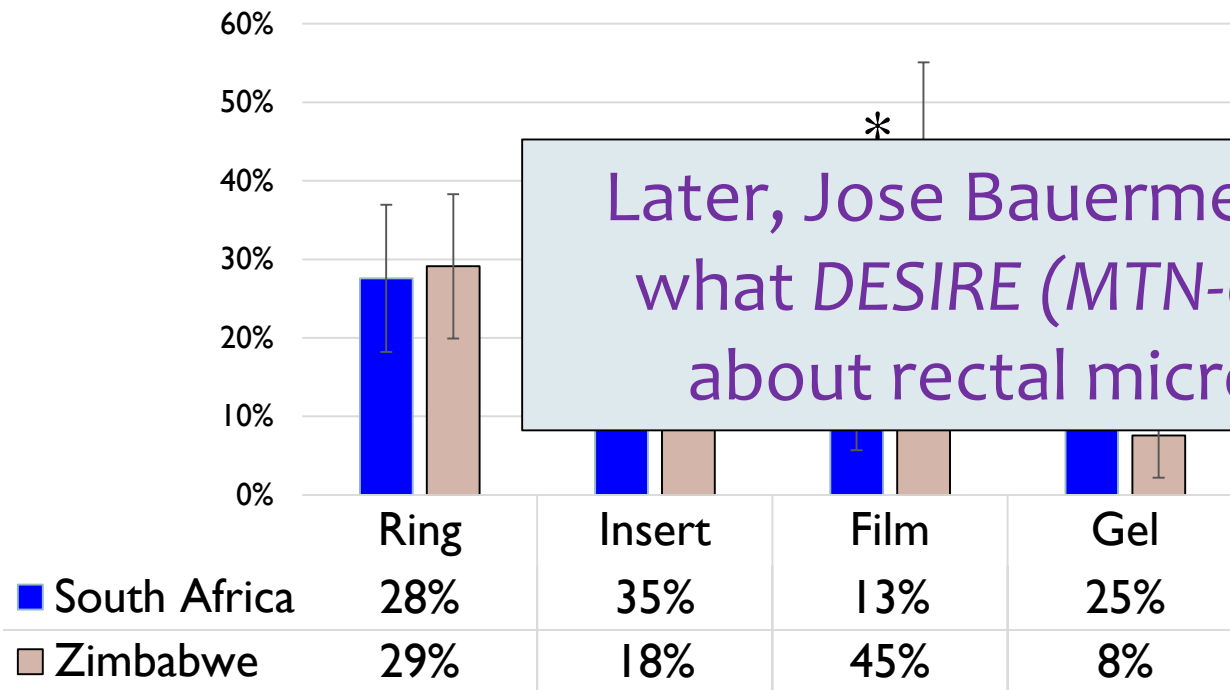
... and Experience



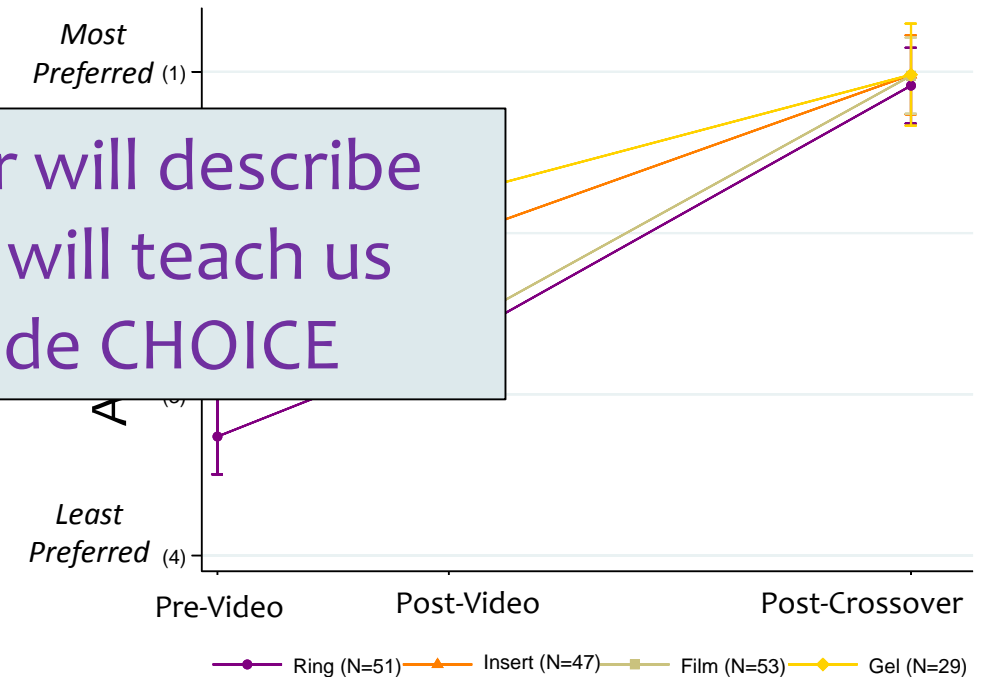
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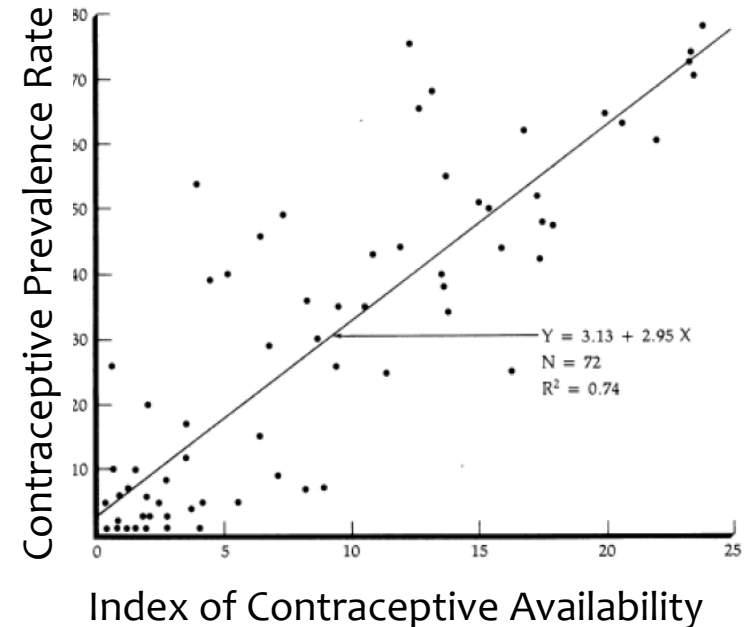
Later, Jose Bauermeister will describe what *DESIRE* (MTN-035) will teach us about rectal microbicide CHOICE



\* Significantly different,  $p < 0.05$

# CHOICE: Proven Benefit in Contraception

- ▶ WHO Systematic Review (231 articles)
- ▶ CHOICE associated with better:
  - ▶ Contraceptive Uptake
  - ▶ Contraceptive Persistence
  - ▶ Health outcomes (↓ pregnancies, ↓ STIs)
- ▶ CHOICE, as with needs, vary over a lifetime
- ▶ **Why would PrEP be different?**

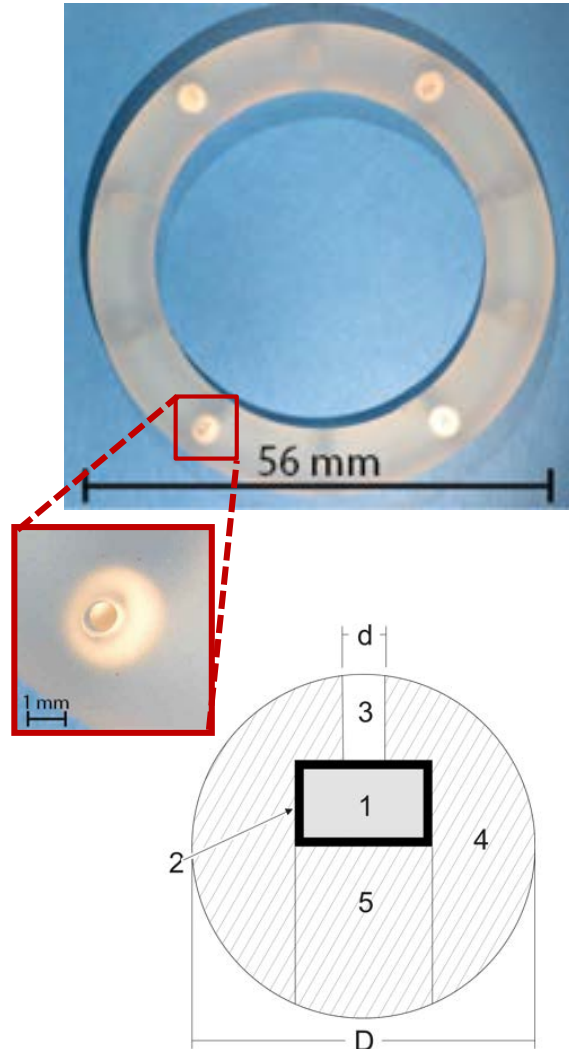


- EACH add'l product option yields 12% increase in contraceptive use
- **How much will it be for PrEP?**



# Vaginal Microbicide Solutions

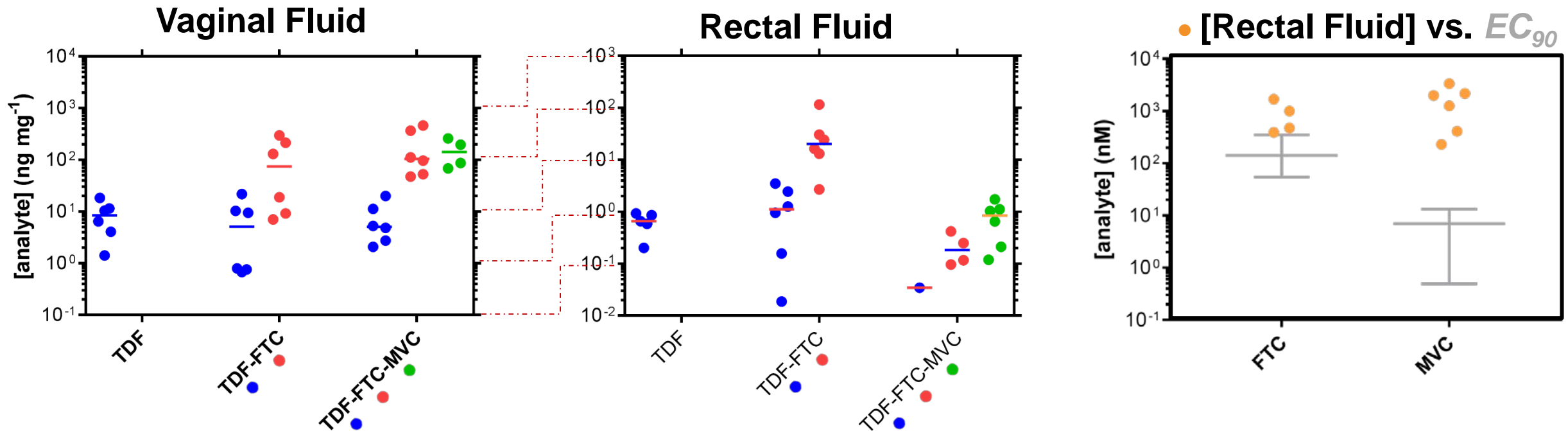
# Pod-IVR : Flexible MPT Capability



- ▶ Up to 10 drug “pods”
- ▶ Drug release rate controlled by channel size
- ▶ Flexible drug combinations
  - ▶ Multiple ARVs (clinical)
  - ▶ Contraceptives (pre-clinical)
  - ▶ STIs (theoretical)
- ▶ One month Pod-IVR ARV clinical study ongoing



# Not all Vaginal ARVs have “poor” Rectal Penetration



- [Vaginal] > [Rectal] for all ARVs tested (10-100-fold)
- [Rectal] after vaginal dose > *in vitro* EC<sub>90</sub> for FTC & MVC
- Vaginal → Rectal penetration varies with drug & drug combination
- Could non-ARVs enhance specific ARV Vaginal → Rectal penetration?

# Quick-Dissolve Vaginal Films



PASII  
526 women



Project MIST  
24 couples



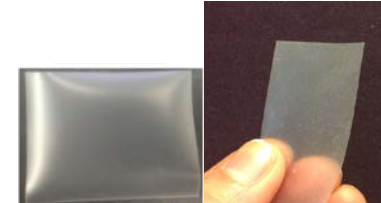
FAME-02/02B  
70 women



FAME-04/05  
85 women



FACE  
80 women



FLAG  
32 women

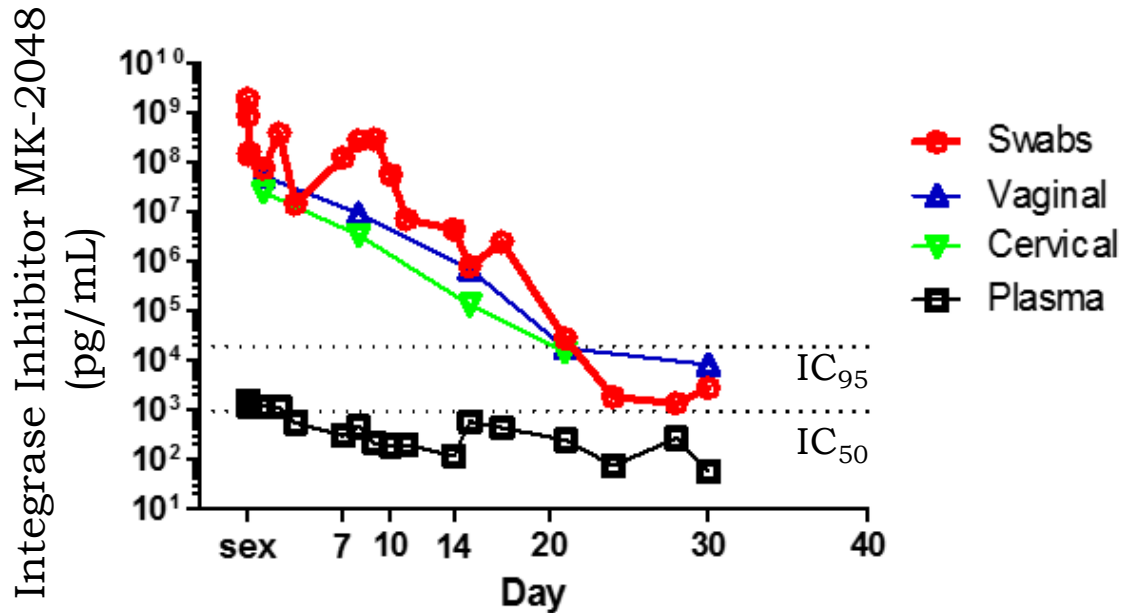
Films are acceptable among African & US Women

*“... as simple as getting out the shower, putting it in, and then moving on.  
Almost like brushing your teeth.”*

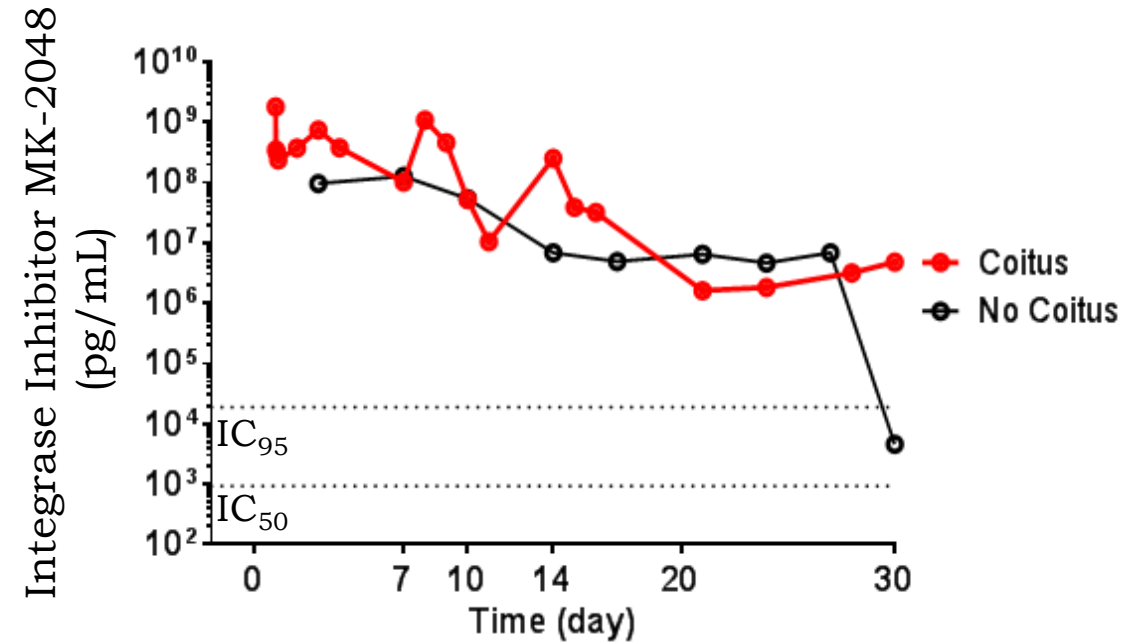
Great example of rigorous, iterative assessment of biomedical & behavioral soundness!

# On Demand & Extended Release Film (NHP)

- Rapid release
- Extended release: 14 Days  $> 10^3 \times IC_{50}$
- Low systemic exposure



- No impact of sex
- No impact of menses
- No impact on microbiome



# Fast-Dissolving Inserts - Vaginal & Rectal

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## ▶ Characteristics

- ▶ CHOICE studies - high level end-user interest
- ▶ Small, easy to store, inexpensive

## ▶ DS003 (IPM)

- ▶ Gp120 blocker, phase I safety/PK completed, ex vivo protection

## ▶ TAF/elvitegravir (CONRAD/MTN)

- ▶ NHP PK & Safety favorable; protects from SHIV challenge
- ▶ Clinical vaginal study enrolling & rectal study begins later this year

## ▶ Griffithsin (Pop Council)

- ▶ Luminally active HIV binding (> bNAbs), protective in macaques & mice





# Rectal Microbicide Solutions

# Tenofovir Vaginal Microbicide Development

## Methods Toolbox

- “HIV” surrogate distribution?
- Tissue pharmacology?
- Luminal distribution?
- Pre-clinical Challenge Models?
- Vaginal product optimization?
- End-User Product Experience?

## Drug Product Development

Vaginal Formulation (VF)  
3,111 mOsm/kg  
TFV 1%

## Phase I

HPTN 050  
PK blood  
AEs, culposcopy

## Phase II

HPTN 059  
PK blood  
AEs

## Phase III

CAPRISA 004 BAT 24  
VOICE QD  
FACTS 001 BAT 24

No NDA

- TFV Gel rapidly advanced to 3 disappointing trials
- Many development & implementation tools now considered essential, were only developed in parallel with these RCTs
- Past few years, a different landscape with a far richer set of tools to inform product development.
- Fast-dissolve film development a good example

# Tenofovir Rectal Microbicide Development

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## Methods Toolbox

**JHU**  
"HIV" surrogate distribution

**JHU**  
Tissue pharmacology

**CDC/NIH**  
Luminal PK-D imaging

**NIH**  
PD Surrogates: Explant, BLT, NHP

**MDP 2/2b**  
RF vehicle development

**MDP 1**  
Enema vehicle development

**JHU**  
Lube dosing feasibility

## Drug Product Development

Phase I

Phase II

Phase III

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## Phase I

RMP-02/MTN-006

## Phase II

No Phase II  
•Safety/AEs

## Phase III





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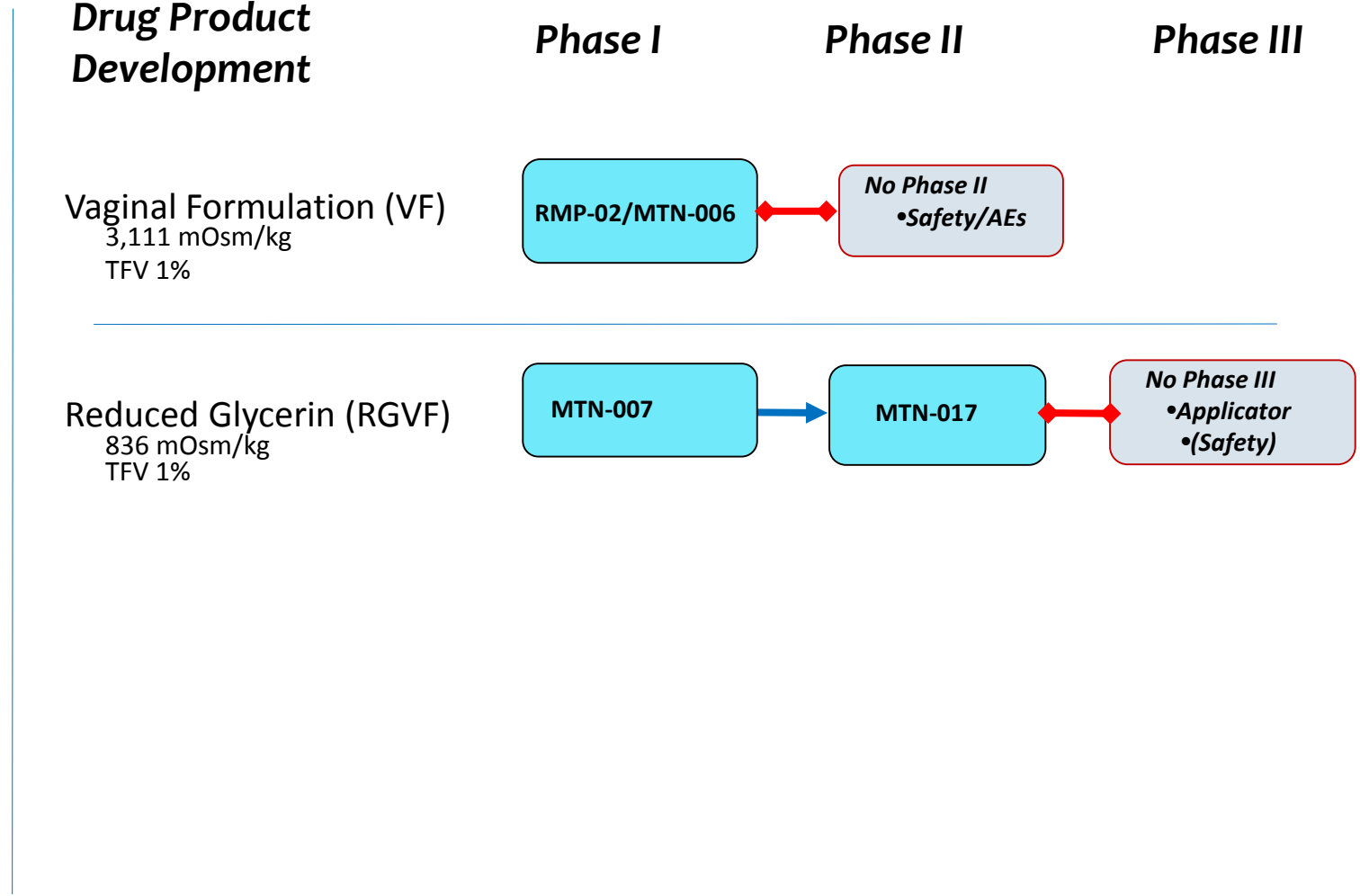
### Phase III

Reduced Glycerin (RGVF)  
836 mOsm/kg  
TFV 1%

MTN-007

MTN-017

No Phase III  
•Applicator  
•(Safety)



# Tenofovir Rectal Microbicide Development

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•Applicator  
•(Safety)

Rectal Formulation (RF)  
479 mOsm/kg  
TFV 1%

CHARM 01/02

No Phase III  
•Applicator

... so, now what?

# Why not combine Protection & Desire?

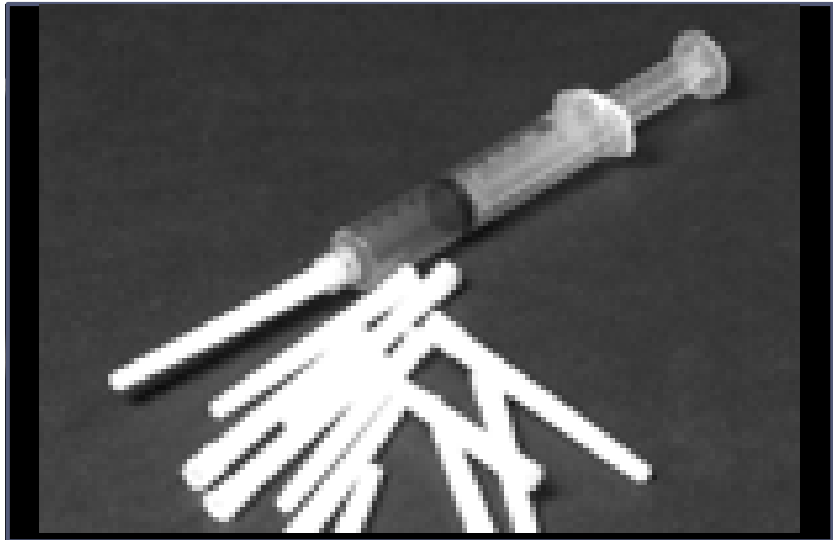
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- ▶ **Behaviorally-Congruent**
  - ▶ PrEP active ingredient added to a product commonly part of one's sexual routine
  - ▶ No to minimal requirement for behavior change (e.g., lubes, douches)
- ▶ **Common in other health settings**
  - ▶ Fluoridated drinking water & toothpaste
  - ▶ Vitamin & mineral fortified bread & milk
- ▶ **PrEP-medicated Sexual Lubricants**
  - ▶ Very high levels (>85%) of lube use among MSM
  - ▶ Modest levels among women, but higher among FSW (>40%)
- ▶ **PrEP-medicated Douches**
  - ▶ High levels of douching among MSM (>75%)
  - ▶ Not as well studied among women, but modest to high among FSW (22-56%)

# Is Lube or Douche Feasible as Rectal Microbicide?

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Applicator Gel  
HEC 10 mL



Douche  
Saline-like 125 mL



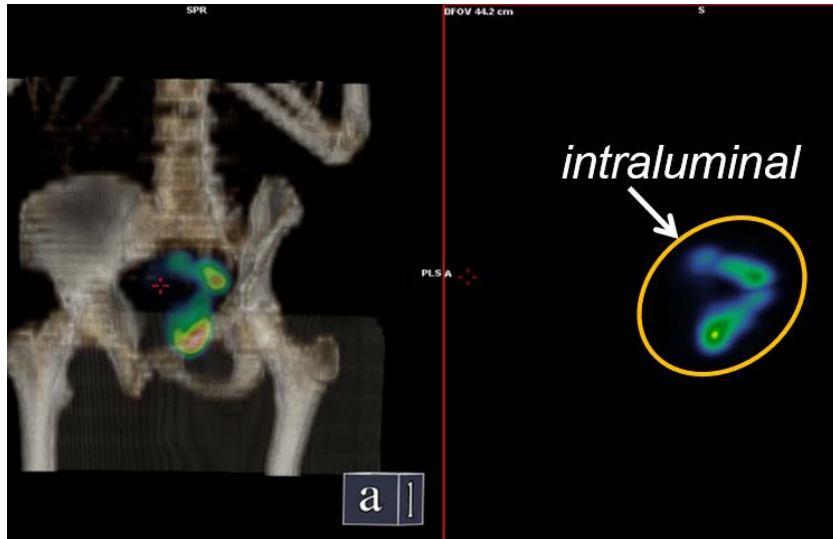
Manual Lube Application  
Wet™ 10 mL



- Where is the gel distributed?
- How much product is delivered?

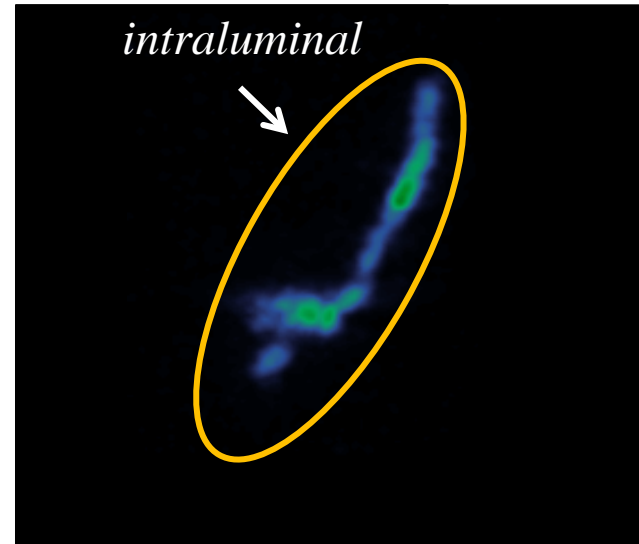
# Is Lube or Douche Feasible as Rectal Microbicide?

Applicator Gel  
HEC 10 mL



- Distribution: 5.9–7.4 cm
- Dose Retention: 95%

Douche  
Saline-like 125 mL



- Distribution: 0-60 cm
- Dose Retention: 60%

Manual Lube Application  
Wet™ 10 mL



- Distribution: 4.4–15.3 cm (*just right*)  
(consistent with “HIV” distribution)
- Dose Retention: 10% (*too low*)  
(requires 10x [API] increase v. applicator)

# Tenofovir Rectal Microbicide Development

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**MDP 1**  
Enema vehicle development

**JHU**  
Lube dosing feasibility

## Drug Product Development

### Phase I

### Phase II

### Phase III

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3,111 mOsm/kg  
TFV 1%

RMP-02/MTN-006

No Phase II  
•Safety/AEs

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MTN-007

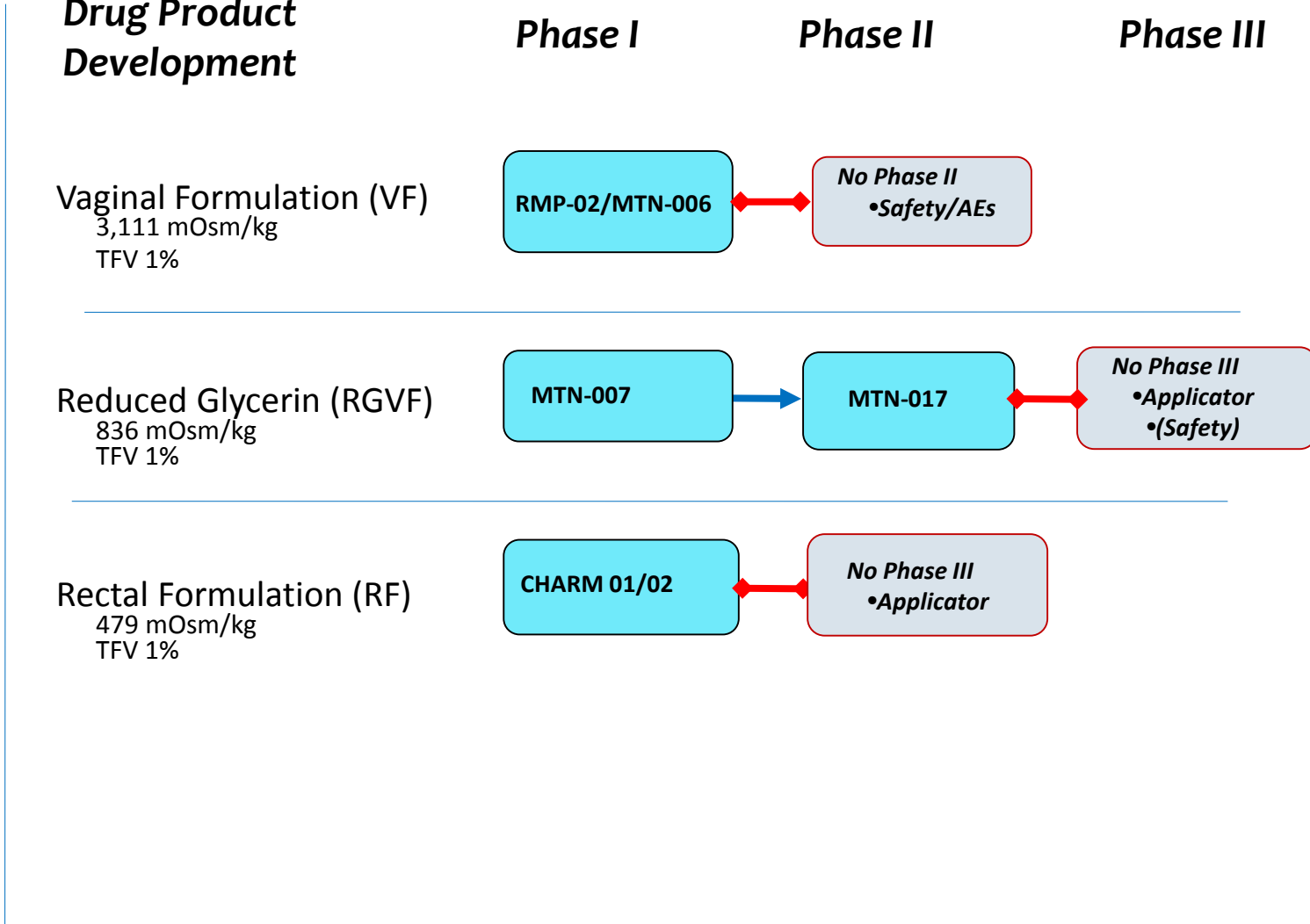
MTN-017

No Phase III  
•Applicator  
•(Safety)

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CHARM 01/02

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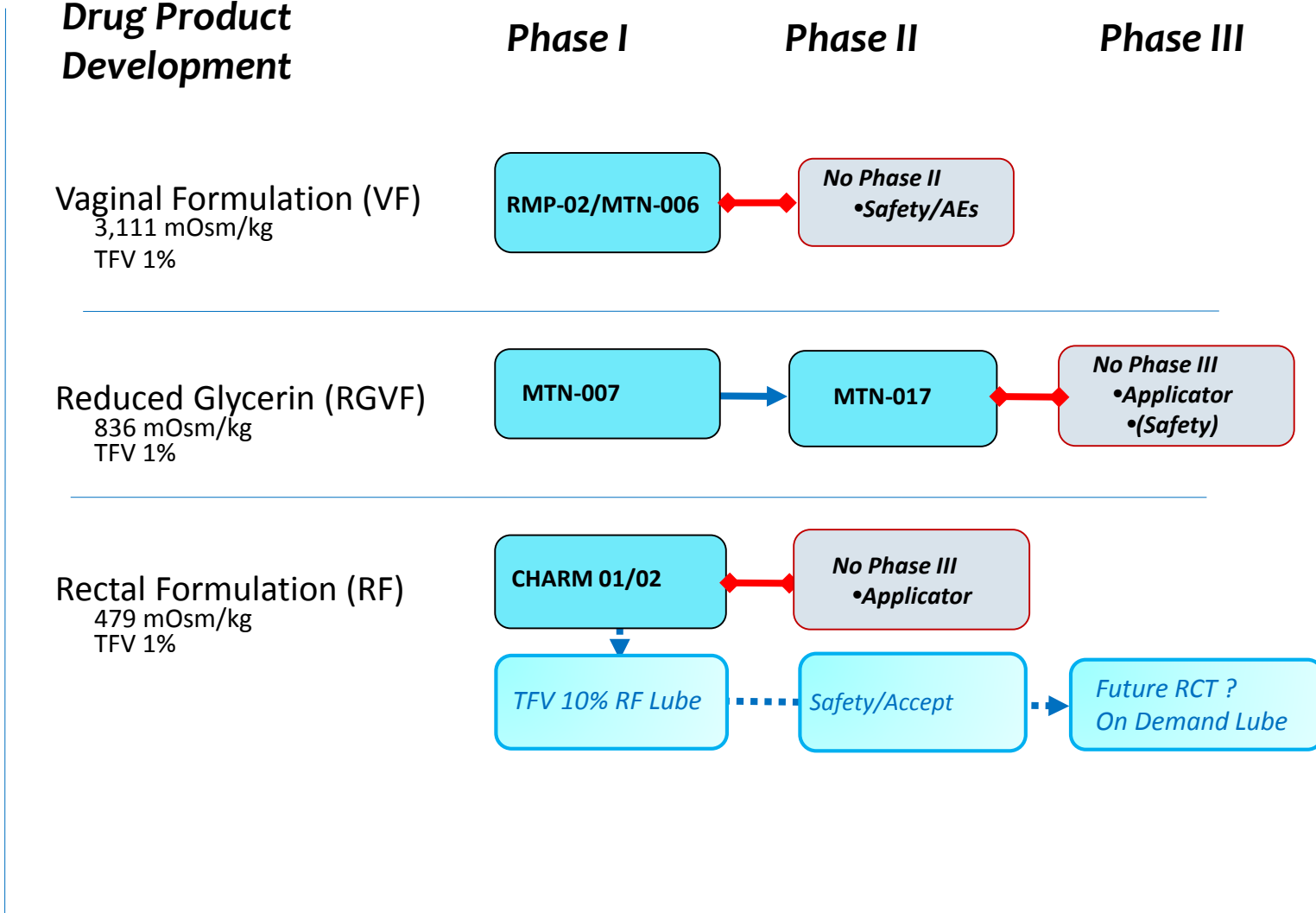
CHARM 01/02

No Phase III  
•Applicator

TFV 10% RF Lube

Safety/Accept

Future RCT ?  
On Demand Lube

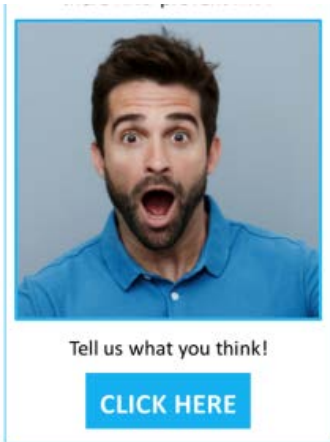


# Is Douche Feasible as Rectal Microbicide?

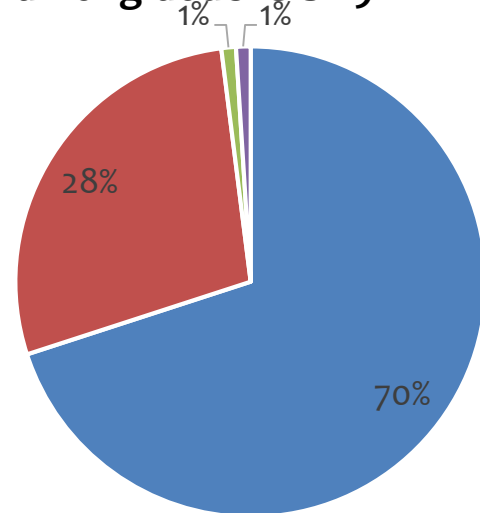
*Especially with sex products, Essential to build around user experience*

## Grindr Douche Survey

- 4,751 Took Online Survey
  - 78% RAI last 3 months
    - 80% douche before RAI
    - 27% douche after RAI

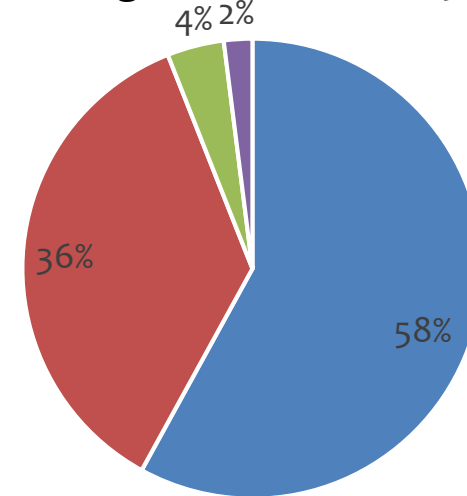


Likelihood of using ...  
among douchers - 98%

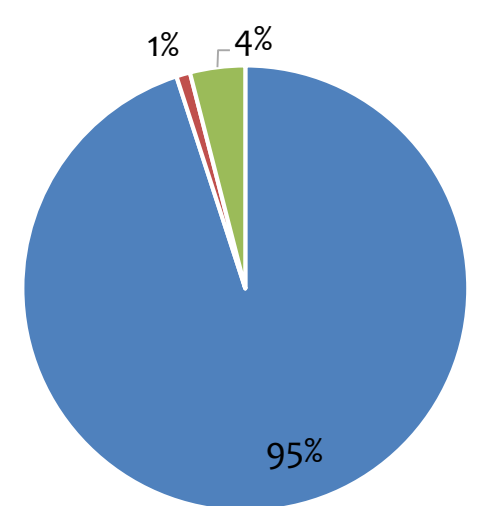


■ Definitely Yes ■ Probably Yes ■ Probably Not ■ Definitely Not

Likelihood of using ...  
among non-douchers - 94%



Insertive partner supportive  
of RM douching partner 96%

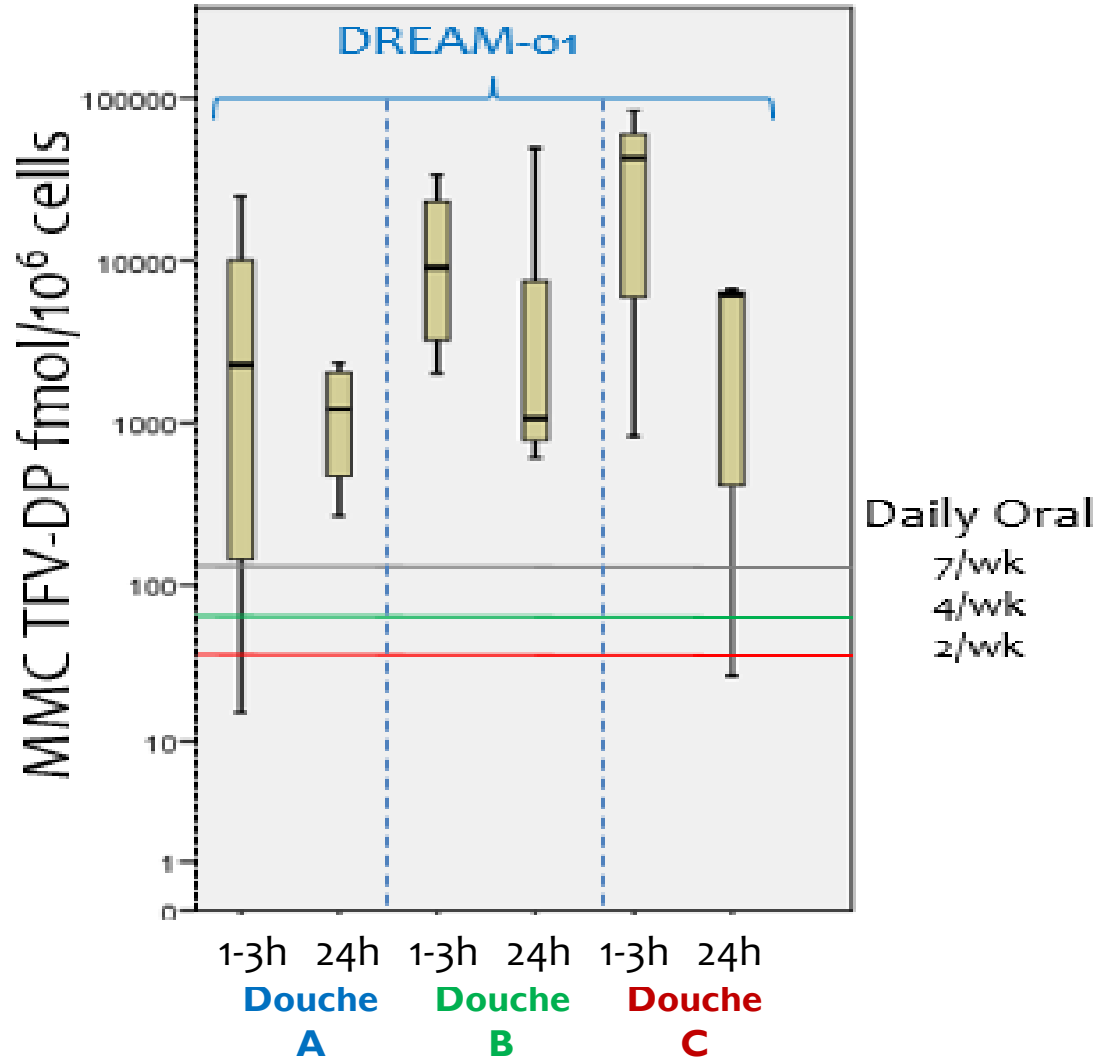


■ Supportive ■ Opposed ■ Neither

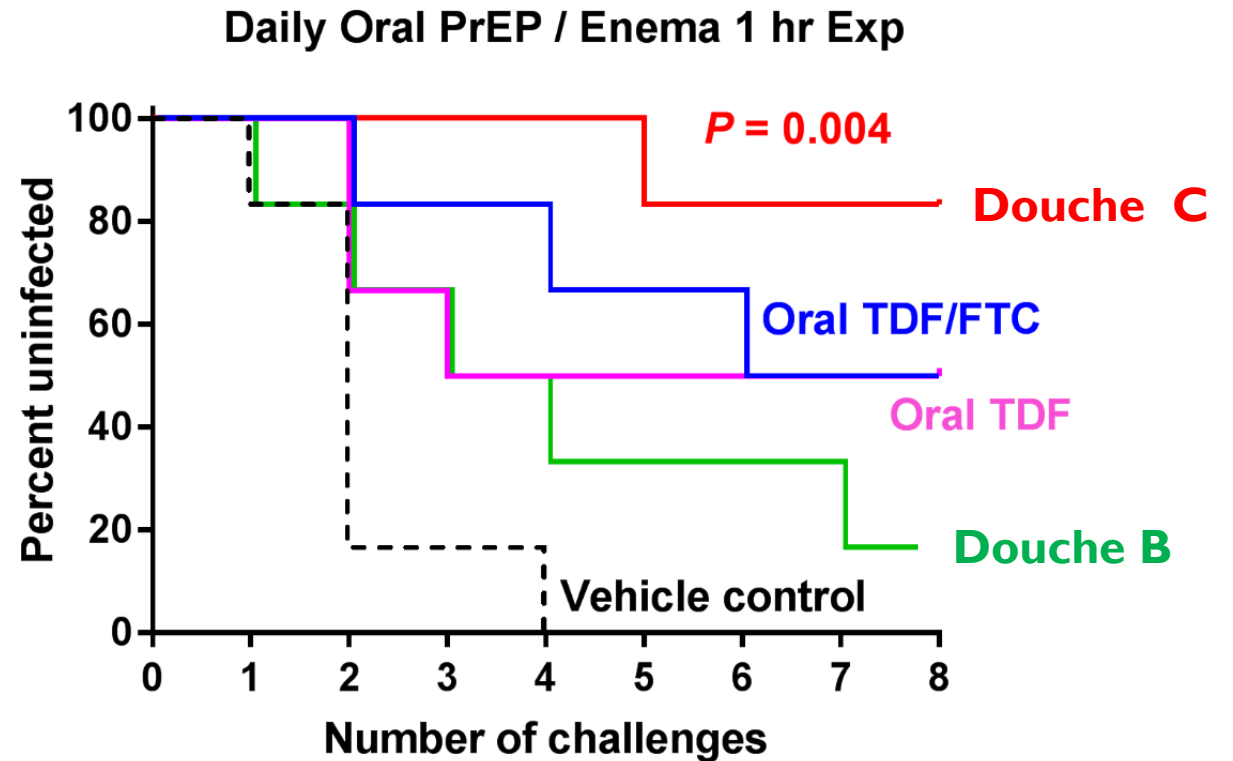


# DREAM Program: Tenofovir Douche

## Human PK: Colon Cell TFV-DP



## Macaque PD: SHIV Challenge



R4P: OA20.03 Weld; P29.13LB Villinger; P24.20 Hoang

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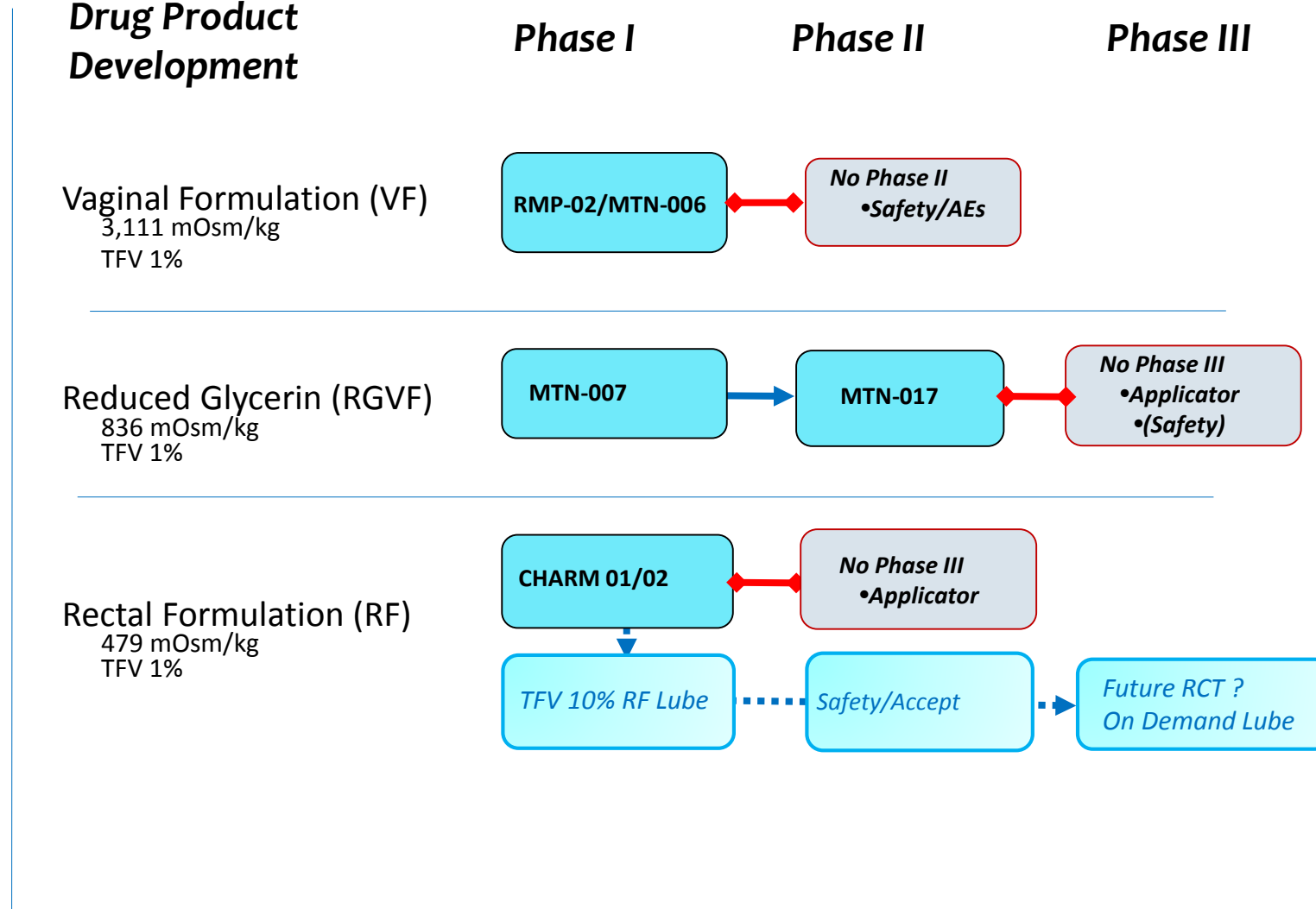
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TFV 10% RF Lube

Safety/Accept

Future RCT ?  
On Demand Lube



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### Phase II

No Phase II  
•Safety/AEs

### Phase III

Reduced Glycerin (RGVF)  
836 mOsm/kg  
TFV 1%

MTN-007

MTN-017

No Phase III  
•Applicator  
•(Safety)

Rectal Formulation (RF)  
479 mOsm/kg  
TFV 1%

CHARM 01/02

No Phase III  
•Applicator

TFV 10% RF Lube

Safety/Accept

Future RCT ?  
On Demand Lube

Enema Formulation (EF)  
Dose escalation  
Iso- or hypo-osmolar

DREAM 01-05

Safety/Accept  
HPTN Concept

Future RCT ?  
On Demand Douche

# Pipeline is Pregnant with Promise for CHOICE

Formulations – fit to purpose & suited to varying personal CHOICE



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

ARV

bNAbs

Luminal

+Contraception

+STIs

**Anti-HIV**

**Other Targets**

**Combinations provide breadth for health**

# ...but who will assure microbicides are part of CHOICE?

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## ▶ MTN & IP/CP-HTM Program

- ▶ Advanced science & successfully executed pre-clinical & full range of clinical studies; many candidates
- ▶ Bring your best intellect, heart, and talents to our common mission to maximize HPTNs future success and to collaborate creatively to find new sources of support to convert promise to prevention choices

## ▶ HPTN

- ▶ Publically embrace microbicides as a viable prevention choice, among others, worth continued investment
- ▶ Generously & inclusively engage MTN topical experience to make good on the investment to date

## ▶ NIH

- ▶ Credit for de-risking oral, injectable, & topical PrEP for industry to more fully engage
- ▶ Thanks for not excluding microbicides in the FOA & keeping the door open
- ▶ Actively solicit biomedically sound & behaviorally sound prevention ideas whatever the platform
- ▶ “Exemplify & promote ... *public accountability, and social responsibility* in the conduct of science”

## ▶ Pharmaceutical Industry

- ▶ Continue to increase your active & financially engaged partnership with NIH thru microbicides
- ▶ Creatively provide academy & NIH “in kind” product development & regulatory expertise

# The Case for On Demand Topical PrEP

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- ▶ On demand protects
- ▶ On demand topical protects
- ▶ Behaviorally-congruent strategies may mitigate the adherence challenges
- ▶ Vaginal microbicides
  - ▶ Numerous formulations & APIs in clinical testing
  - ▶ Challenges are real, but they're methodically being overcome
  - ▶ CHOICE is needed for greatest impact
- ▶ Rectal Microbicides
  - ▶ Benefitted greatly from vaginal development program
  - ▶ Behaviorally-congruent douche or lube has potential for both rectal and vaginal protection
- ▶ Critical investments in MTN & IP/CP expertise must be carried into HPTN to support the unique skills needed to support a topical microbicide program

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The image features two horizontal bars at the bottom. The top bar is white with a thin blue border and a dark blue vertical bar on its left side. The bottom bar is also white with a thin blue border and a light blue vertical bar on its left side. The text "Thank You!" is centered within the top bar.

Thank You!