

HIV PrEP Products Pipeline

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Disclosures

Research grants managed by Johns Hopkins

- Gates Foundation
- ViiV/GSK
- Gilead
- Merck

Scientific Advisory Board (*ad hoc*) managed by Johns Hopkins

- Population Council
- ViiV/GSK
- Gilead
- Merck

Consultant managed by Johns Hopkins

- RTI
- Orion Biotechnology

US Patent managed by Johns Hopkins

- #10,092,509 hypotonic microbicide formulations & methods of use

Objectives

- ▶ Describe the impact of CHOICE in PrEP Effectiveness
- ▶ Discuss long-acting PrEP pipeline
- ▶ Discuss on demand topical microbicide pipeline

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METHOD EXPLORER /

★
most effective

Y
party ready

🛡️
STI prevention

🚫
hormone free

🔍
easy to hide

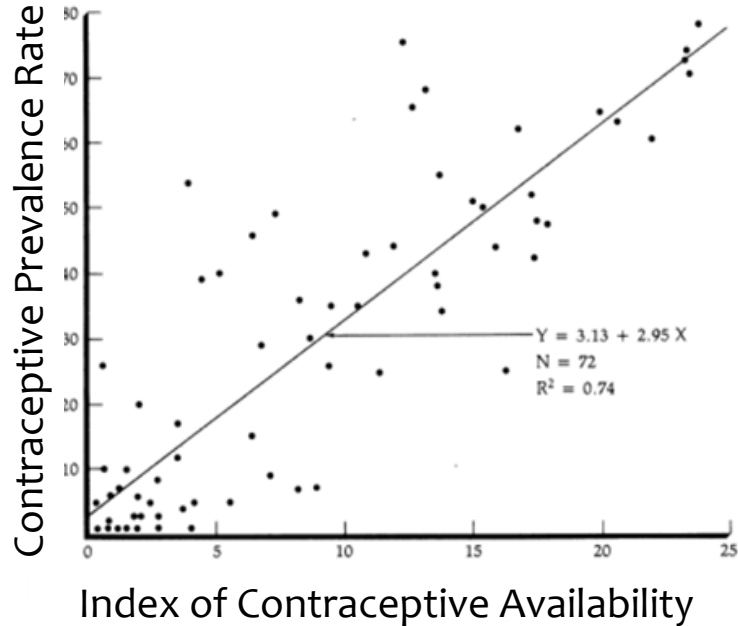
♥️
do me now



share this /



CHOICE: Proven Benefit in Contraception



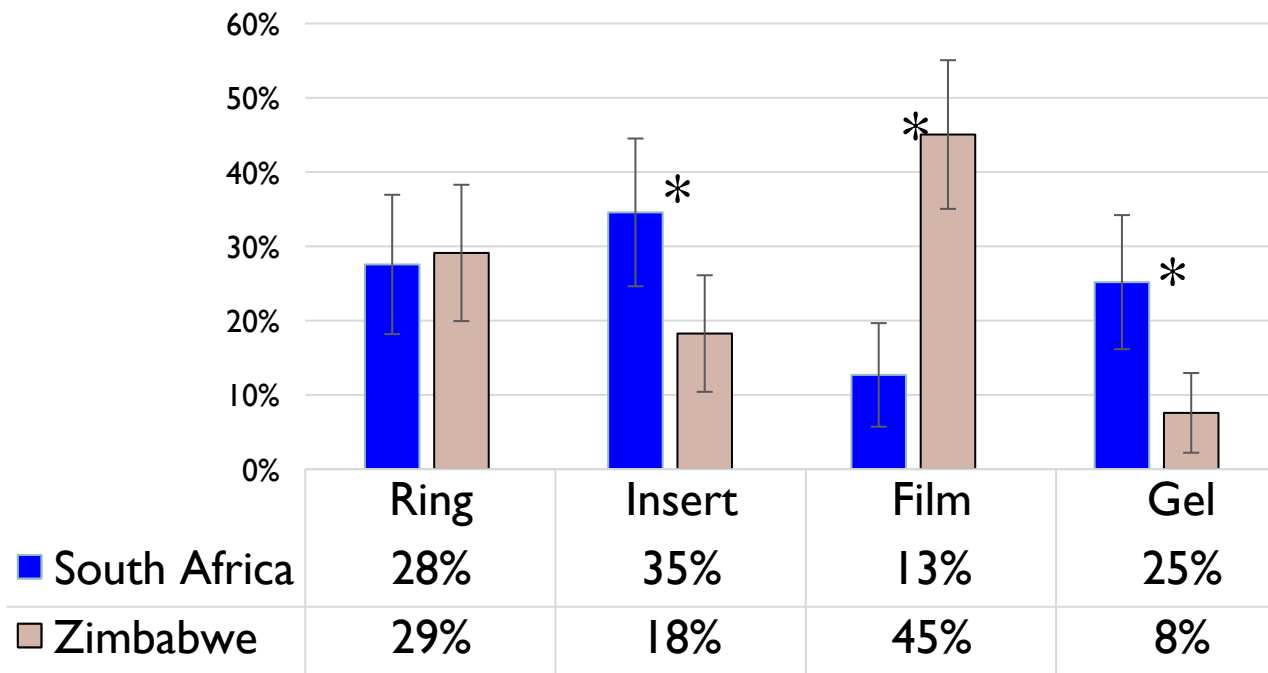
- Each added option yields 12% increase in contraceptive use
- **How steep for PrEP?**

- ▶ 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

- **How will PrEP differ?**

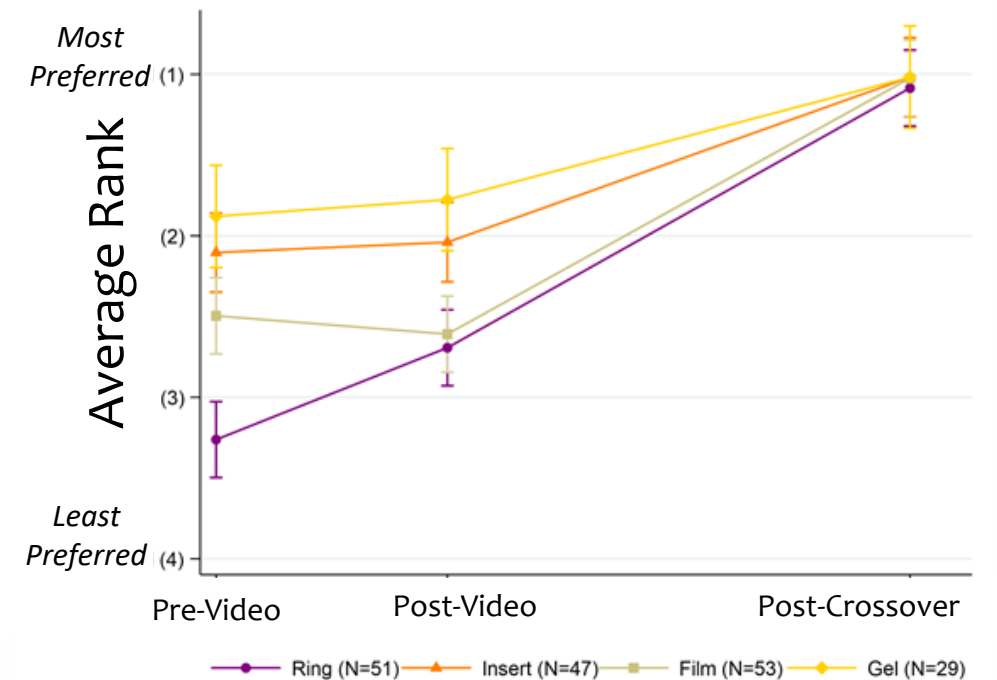
CHOICE: Diverse Vaginal Product Preference

Preference Varies Geographically



* Significantly different, $p < 0.05$

... and with Experience



Groups defined by final "Most Preferred" selection

Dapivirine Intravaginal ring (IVR) RCTs

▶ ASPIRE (Baeten NEJM 2016)

- ▶ 2,629, 18-45 yo women
- ▶ S. Africa, Uganda, Zimbabwe, Malawi
- ▶ RRR 27% (95% CI: 1-46; $p=0.05$)
- ▶ No efficacy in women <21 yo
- ▶ Increased efficacy ≥ 25 (61%)
- ▶ RRR 56% with high adherence

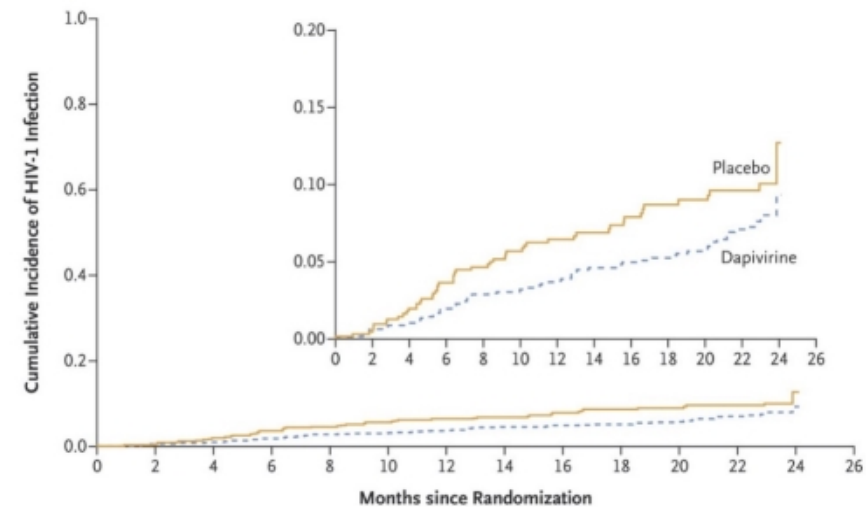
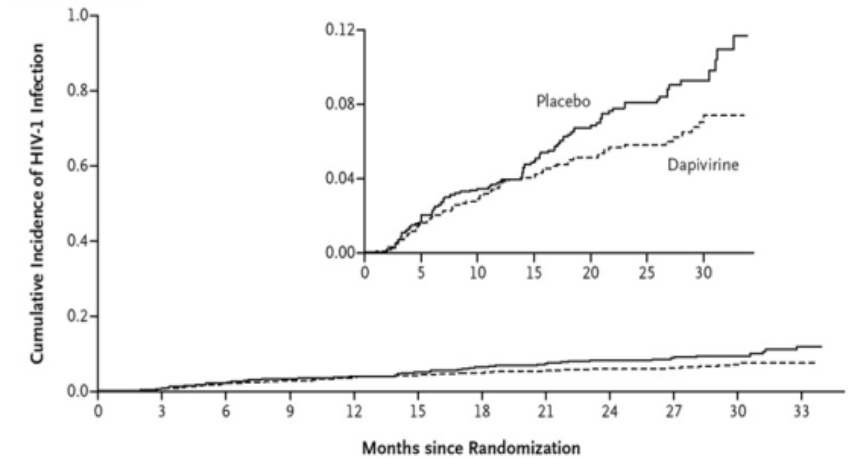


▶ The Ring Study (Nel NEJM 2016)

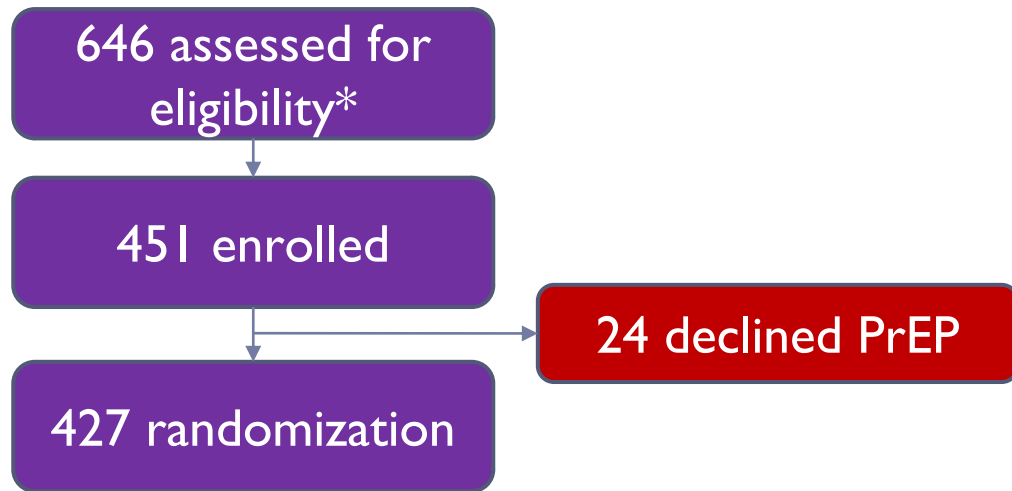
- ▶ 1,259, 18-45 yo women
- ▶ S. Africa, Uganda
- ▶ RRR 31% (95% CI: 1-52%; $p=0.04$)
- ▶ No efficacy in women <21 yo
- ▶ Increased efficacy >21 y.o. (38%)
- ▶ RRR ~56% with high adherence



Primary 15-Site Analysis



PrEP Uptake



94% PrEP Uptake

*16-25 yo, Uninfected women Ages 16-25 yrs
Johannesburg & Cape Town, South Africa Harare, Zimbabwe
Sexually active past month; VOICE risk score >5
PrEP interest; mobile phone; HepB neg.

Adherence Persistence

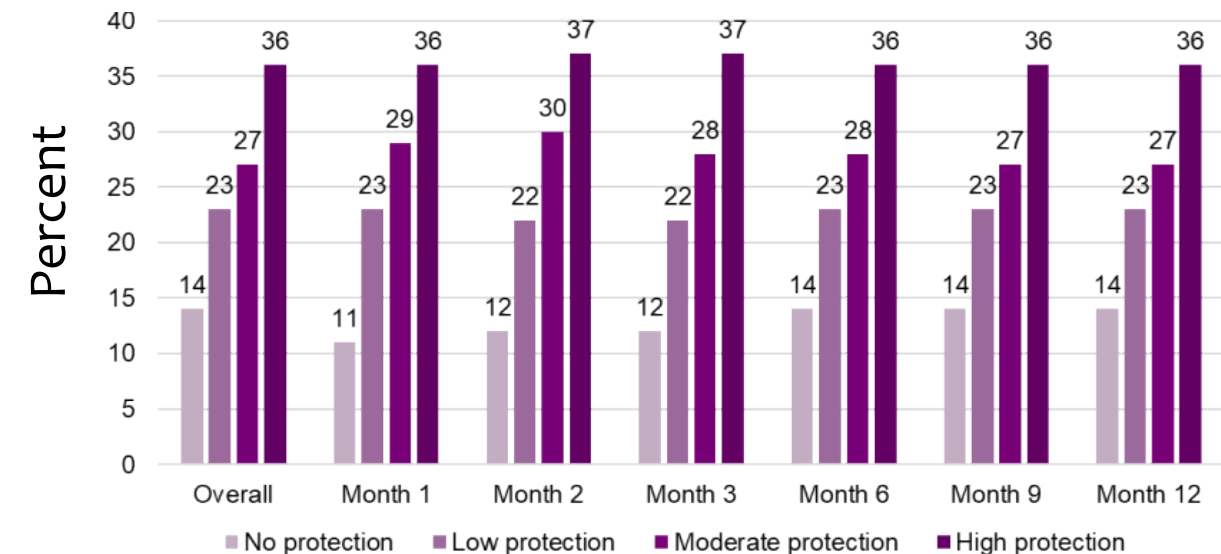
	3 mos.	6 mos.	12 mos.
DBS any drug detected	84%	57%	31%
DBS Protective*	25%	21%	9%

*Dried blood spot TFV-DP ≥ 700 fmol/punch a/w 100% efficacy among MSM in iPrEx OLE & 25th %ile of 4 doses /wk (Grant Lancet HIV 2014)

HOPE: Dapivirine IVR OLE

- Adherence strata remained constant
- Persistence remained high > 79% over 12 mos.

Persistence 92% 90% 89% 87% 83% 79%



Adherence & Protection

Relative HIV Protection	Dapivirine released/month	Estimated HIV protection*
No	≤1.4 mg	11-20%
Low	1.4 - 3 mg	29-47%
Moderate	3 - 3.9 mg	58-75%
High	≥3.9 mg	47-92%

*MTN-020/ASPIRE, Brown, AIDS 2016

Commentary

HIV Prevention: The Need for Methods Women Can Use

ZENA A. STEIN, MA, MB, BCh

“...a **less efficacious [method], frequently used**, might serve the public health as well or better than a **more efficacious, but less frequently used [method]**, and ...**play an important role in preventing transmission at the population level.**”

(Am J Pub Health, 1990)

Impact of Adherence

Variable	Study Method Author	iPrEx F/T Oral mITT Log Reg Grant Anderson	Partners F/T Oral mITT TMLE Baeten Ruberman	CAPRISA TFV Gel mITT Log Reg Karim Kashuba	VOICE TFV Gel mITT Poisson TMLE Marrazzo Dai Ruberman	ASPIRE DPV Ring mITT Cox Baeten Brown
Point estimate		44 → 95	75 → 83	39 → 73	15 → 60 → 89	27 → 85

All formulations studied - high efficacy when used

Product options increase possibility for alignment with personal preferences to enhance uptake, persistence, and adherence

Maximizing population level PrEP effectiveness

Partners PrEP use knowledge						
Partner #		x				x
Contraceptive use						x

Choices Maximize PrEP Uptake & Persistence

Formulations



Active Ingredients

Luminally-active

ARVs

bnMabs

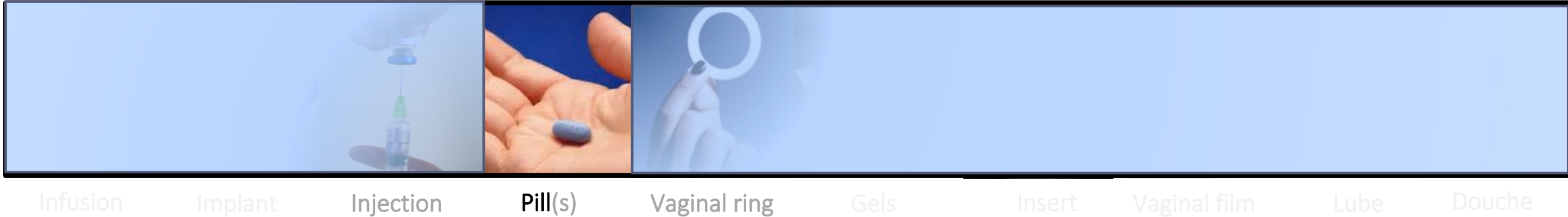
STI

Contraception

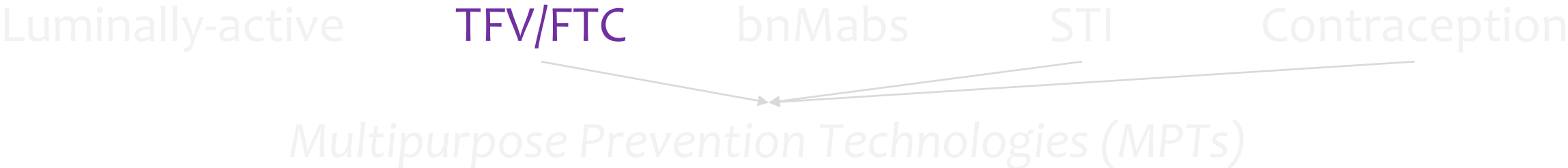
Multipurpose Prevention Technologies (MPTs)

Today's Choice

Formulations



Active Ingredients



More Formulations, More CHOICE, Better Adherence

Adherence Challenges Motivate Alternative Formulation Development



Long-Acting Formulations

- Parenteral
- Oral
- Topical

*Infrequent dosing to minimize need for adherence
Trade-off increased exposure for improved adherence*

On Demand

± Behaviorally Congruent

- Oral
- Topical

*Infrequent dosing to minimize need for adherence
Reduced systemic exposure
Trivial behavior change*

Objectives

- ▶ Describe the value of CHOICE of PrEP Effectiveness
- ▶ **Discuss long-acting PrEP pipeline**
- ▶ Discuss on demand topical microbicide pipeline

Long-Acting Products

- ▶ **Injectable – irreversible**

- ▶ Intramuscular – e.g., Cabotegravir-LA
- ▶ Subcutaneous – e.g., bnMabs (possibly if increased breadth, potency, half-life)
- ▶ Intradermal – e.g., microneedles

- ▶ **Implantable**

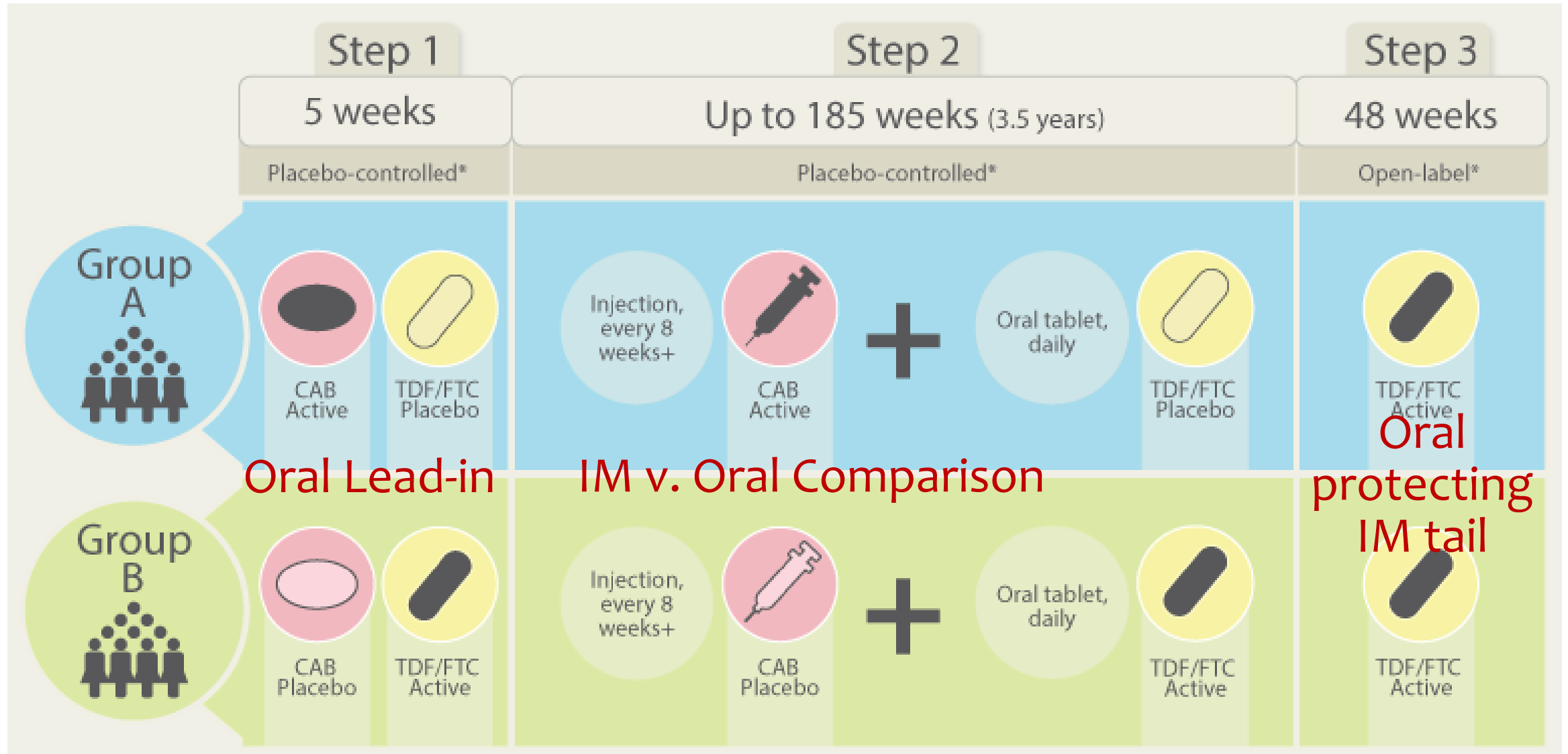
- ▶ Removable - e.g., Merck (islatravir), Oak Crest (TAF)
- ▶ Biodegradable – e.g., RTI (TAF)
- ▶ Refillable reservoir - e.g., Houston Methodist (TAF, FTC)

- ▶ **Oral - irreversible**

- ▶ Potent, long half-life – e.g., islatravir



Phase 3 CAB-LA RCT: HPTN 083/084



Phase 3 CAB-LA RCT: HPTN 083/084

Step 1

5 weeks

Step 2

Up to 185 weeks (3.5 years)

Step 3

48 weeks

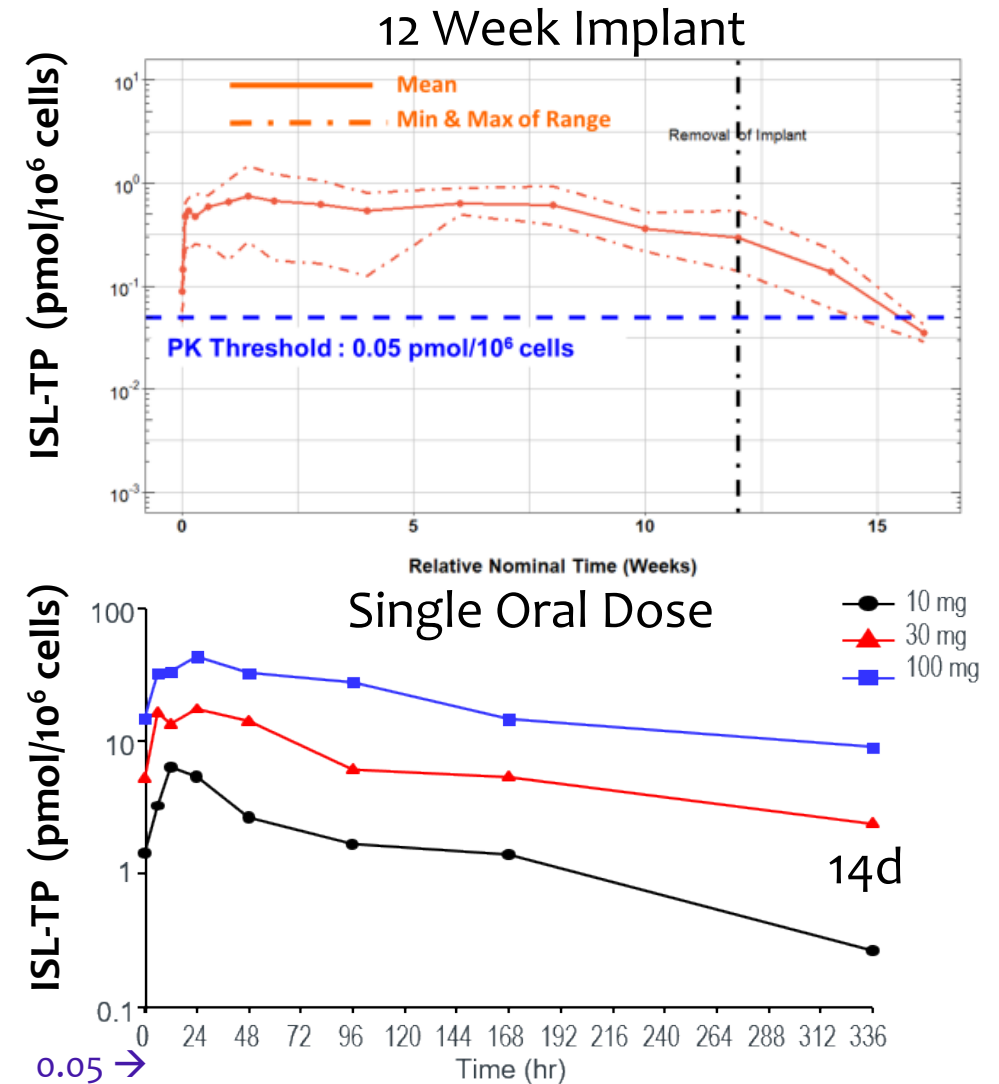
Key Questions:

- Does CAB alone protect despite
 - Monotherapy? (unlike TFV+FTC combination)
 - Systemic > Tissue concentration? (unlike TDF)
- Is ISR as acceptable in PrEP and in Rx?
- Is safety good enough to drop oral lead-in?
- Is resistance in long PK tail rare enough to drop oral coverage?

Islatravir (MK-8591):

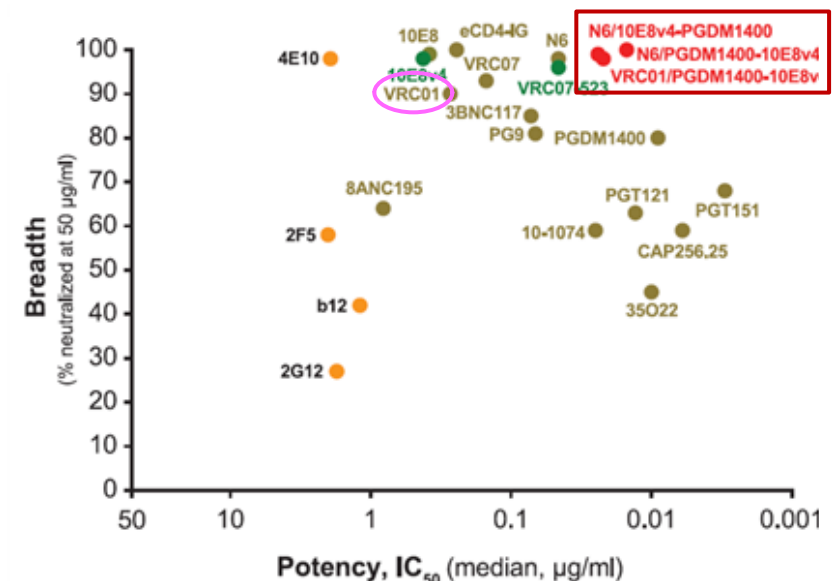
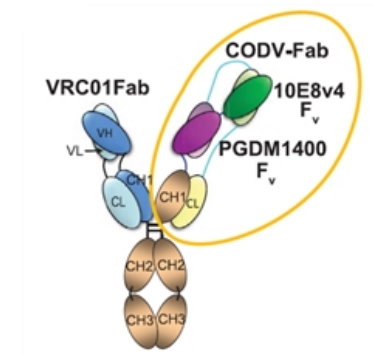
Nucleoside Reverse Transcriptase/Translocation Inhib.

- ▶ Multiple mechanisms of action
- ▶ Good safety profile oral & implantable
- ▶ Pharmacokinetics
 - ▶ Plasma ISL (parent) $t_{1/2}$ 50-60 hr
 - ▶ PBMC ISL-TP $t_{1/2}$ 120-177 hr
 - ▶ ISL-TP rectal & vaginal tissue similar to PBMC
- ▶ Pharmacodynamics
 - ▶ Monotherapy antiviral effect NHP & clinical
 - ▶ Target 0.05 pmol/10⁶ cells (NHP & clinical Rx)
 - ▶ In vitro WT IC₅₀ ~0.01 pmol/10⁶ cells
 - ▶ 0.05 pmol/10⁶ cells > in vitro IC₅₀ M184I/V
- *Likely yearly implantable & monthly oral dosing*



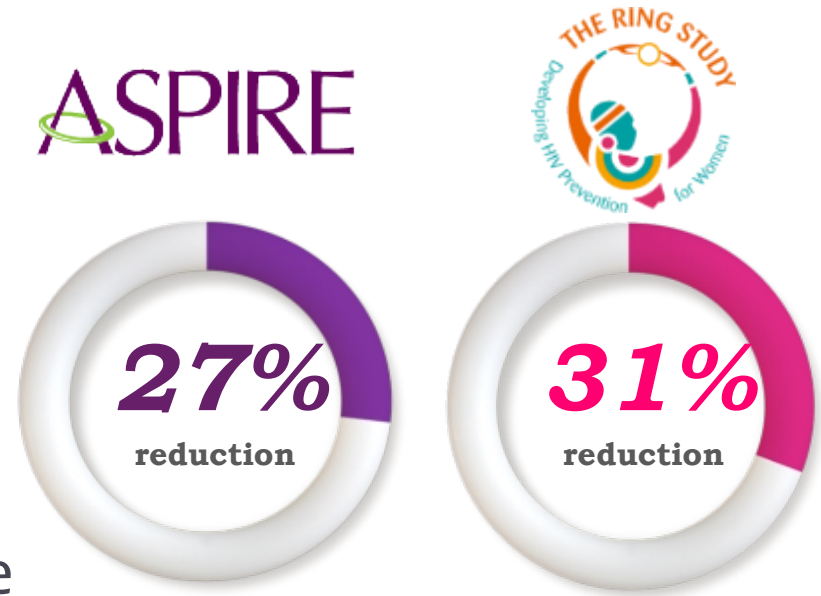
Broadly Neutralizing Monoclonal Antibodies

- ▶ Rare “elite” neutralizers: evolve nAbs which neutralize within & across clades
- ▶ Selection & molecular engineering to
 - ▶ Increase potency (*move right*)
 - ▶ Broaden coverage (mixtures & multi-specific [figure]) (move up)
 - ▶ Increase half-life (FcRn substitution)
- ▶ Treatment
 - ▶ Transiently reduces viral load (VRC01)
- ▶ Prevention
 - ▶ High level SHIV vaginal/rectal protection macaques
 - ▶ 2 RCTs underway with VRC01 infusion



Long-Acting Dapivirine Intravaginal Ring

- ▶ IVR Design
 - ▶ Silicone matrix ring, 25 mg of dapivirine (NNRTI)
 - ▶ Monthly replacement, trivial systemic exposure
- ▶ Two phase III placebo-controlled trials
 - ▶ Well tolerated
 - ▶ Reduced HIV incidence ~30%
 - ▶ Greater protection (up to 85%) with high adherence
- ▶ OLEs High uptake, better adherence
- ▶ 90-day Ring in Development
- ▶ EMA review ongoing



HOPE
HIV Open-label Prevention Extension
Out of ASPIRE, there is HOPE

DREAM
Dapivirine Ring Extended Access and Monitoring

Multipurpose Prevention Technologies (MPT)

- **Concept:**

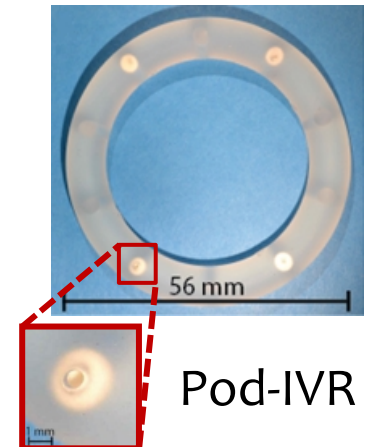
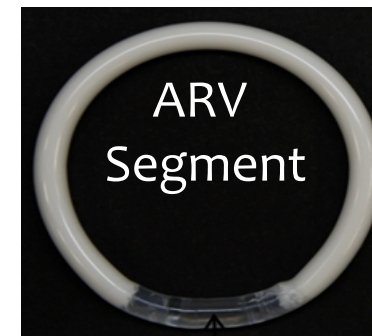
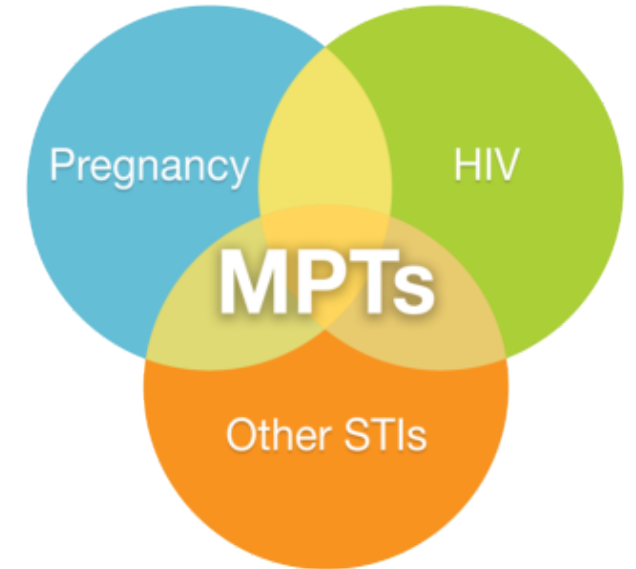
- Many women at risk of HIV also want family planning
- Why not combine HIV prevention with contraception?
- Improve adherence with single product
- Greater capacity for combination than implantable

- **MPT IVRs – phase I / early phase II**

- Tenofovir / levonorgestrol ring (CONRAD)
- Dapivirine / levonorgestrol ring (IPM, MTN044/IPM-053/CCN019)
- Pod-IVRs ARVs / contraceptive / α -STI (Oak Crest Institute of Science)

- **Development trade-offs:**

- Combination requires compromise, e.g., duration

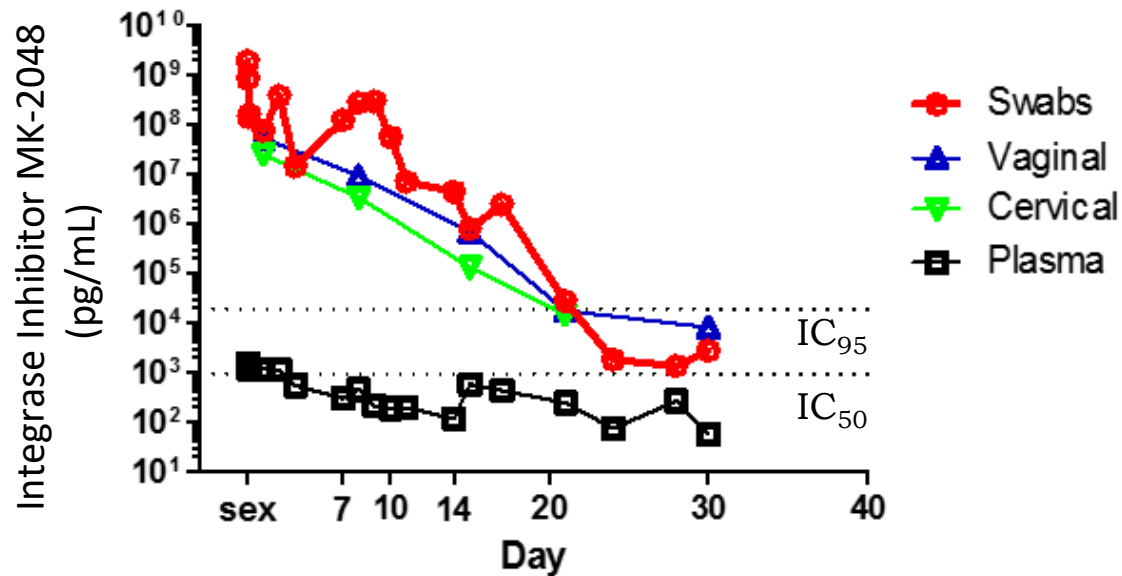


Objectives

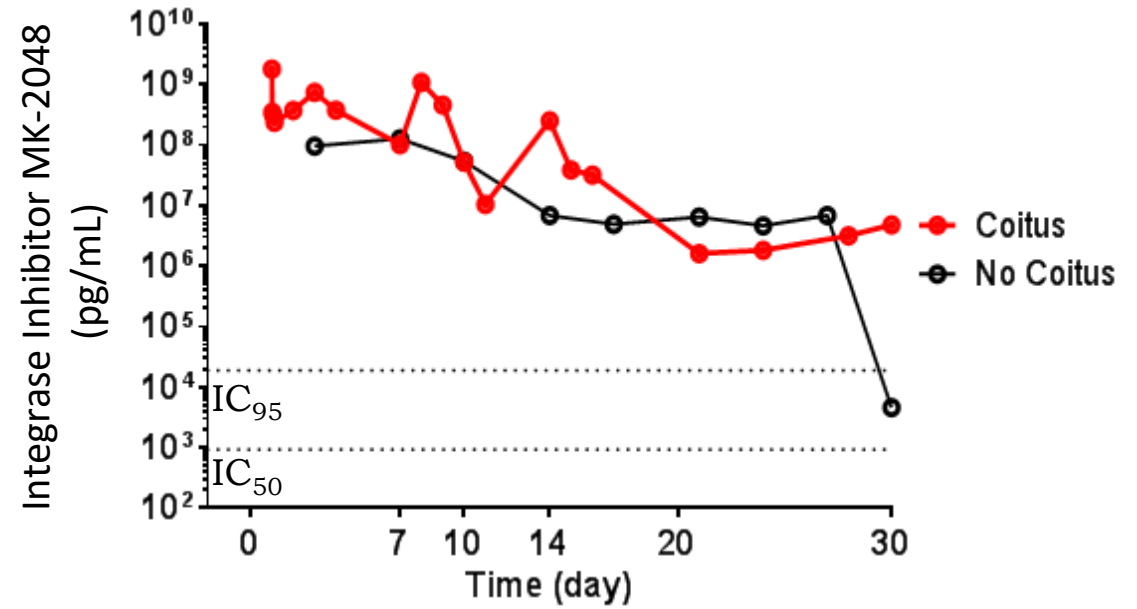
- ▶ Describe the value of CHOICE of PrEP Effectiveness
- ▶ Discuss ongoing development of long-acting PrEP
- ▶ **Discuss on demand topical microbicides**

On Demand & Extended Release Film (NHP)

- Rapid release
- Extended release: 14 Days $> 10^2$ IC₉₀
- Low systemic exposure



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



On Demand Fast-Dissolving Inserts - Vaginal & Rectal

▶ Characteristics

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

▶ 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 (> bnMAbs), protective in macaques & mice



-
- ▶ R4P P05.08 Friend, P21.02 Nuttall; OA15 Dobard; OA20.04 Zydowsky, P05.19LB Friedland, P16.16LB Sze

On Demand & Behaviorally-Congruent PrEP

- ▶ **Common health fortification of existing products**
 - ▶ Fluoridated drinking water & toothpaste
 - ▶ Calcium & vitamin fortified bread
 - ▶ Vitamin A & D fortified 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 well studied among women, but modest to high among FSW (22-56%)

Anal Lube as Microbicide

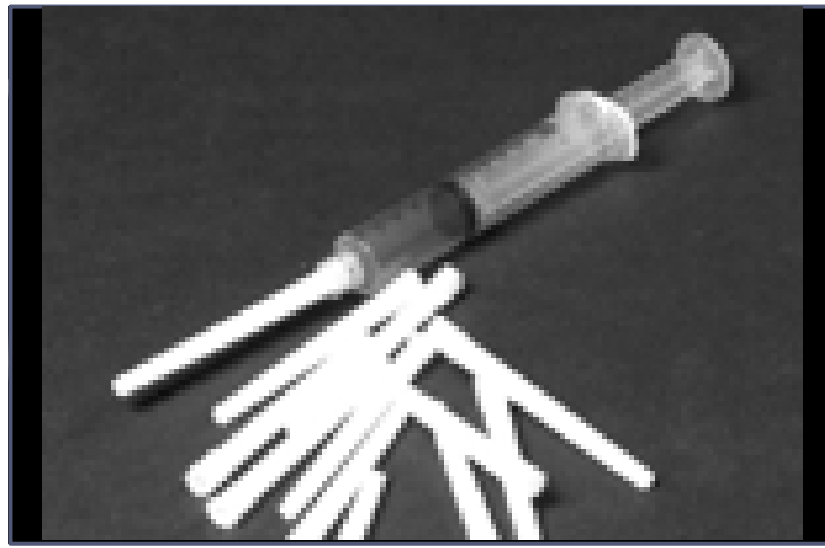
Douche

Saline-like 125 mL



Applicator Gel

HEC 10 mL



Manual Lube Application

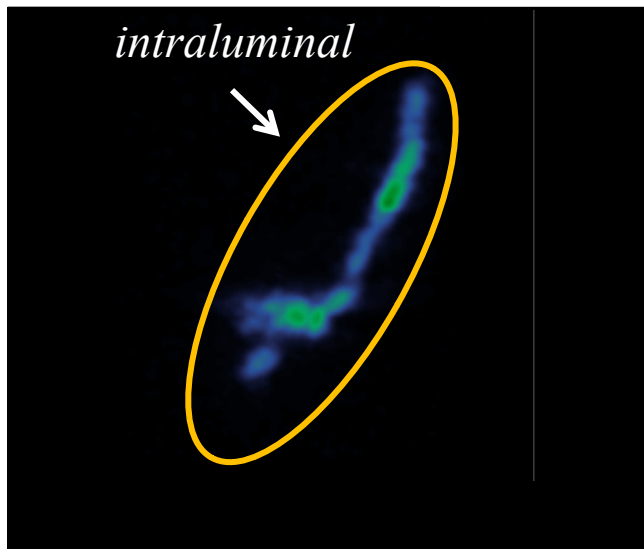
Wet™ 10 mL



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

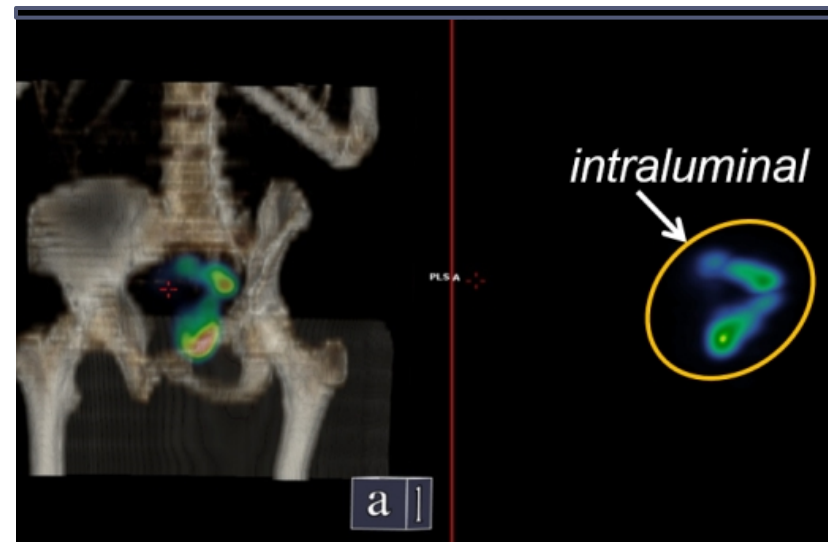
Anal Lube as Microbicide

Douche
Saline-like 125 mL



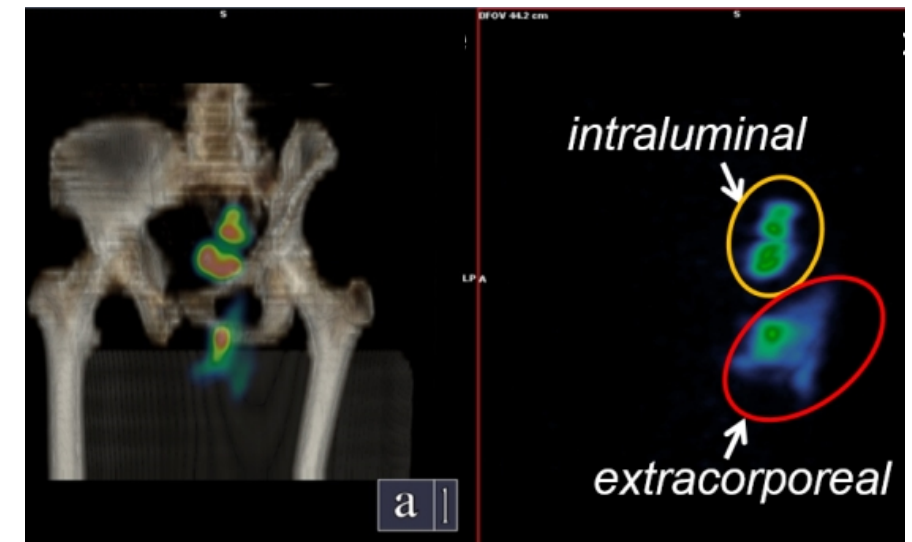
- Retention: 60%
- Distribution: 60 cm

Applicator Gel
HEC 10 mL



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

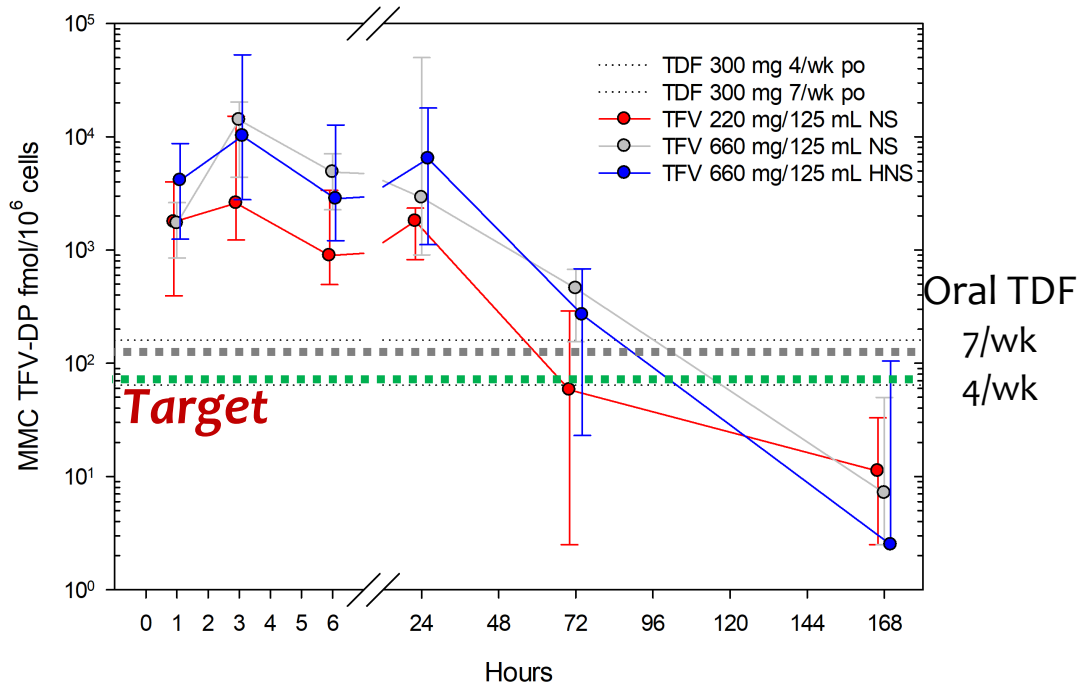
Manual Lube Application
Wet™ 10 mL



- Retention: 10% (3.5 mL gel)
- Distribution: 4.4–15.3 cm
(requires 10x [API] increase)

Rectal Douche as Microbicide

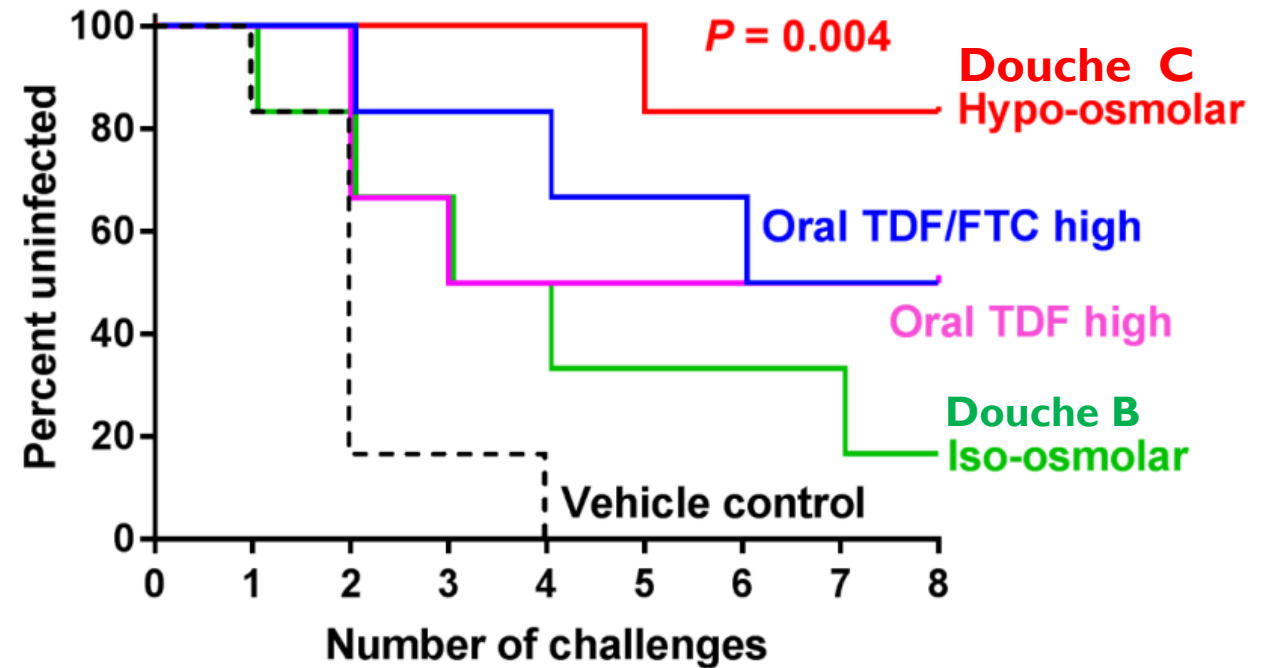
Colon Cell TFV-DP



- High dose exceeds **Target** >30x @ 1h, >100x @ 3h
- High dose exceeds target x 4 days (~1pergay)
- Plasma C_{max} 5x < daily oral C_{tau}

Macaque: Rectal SHIV Challenge

Daily Oral F/TDF vs. Single Douche 1 hr before SHIV



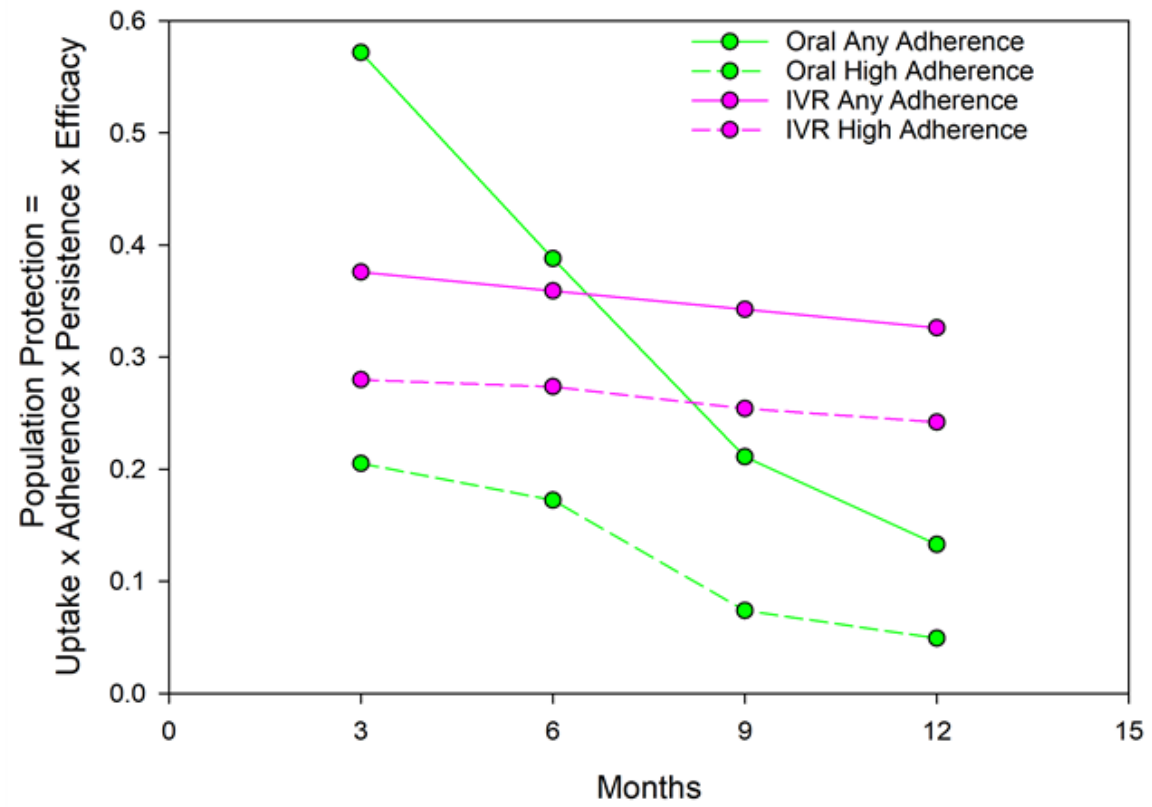
- High dose douche superior to daily oral F/TDF

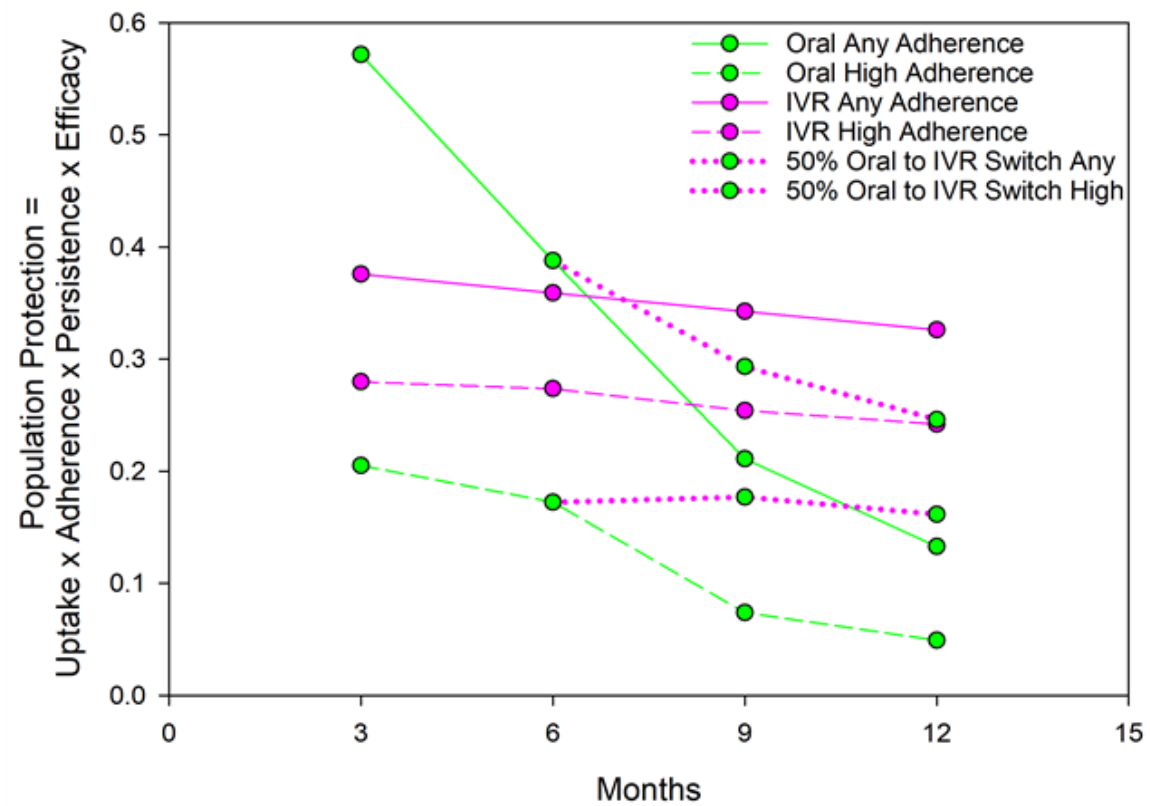
Summary

- ▶ **CHOICE of PrEP options – *Essential for broad inclusion***
 - ▶ Options increase population level contraceptive effectiveness (possibly PrEP also)
 - ▶ Less efficacy with better adherence increases options & may increase effectiveness
- ▶ **Long-acting PrEP – *Adherence busters***
 - ▶ Injectables so far require oral lead-in & tail
 - ▶ Removable implantables avoid pre/post oral dosing, reduce dosing interval
 - ▶ Oral formulation potentially monthly dosing, also on demand?
 - ▶ Vaginal ring nearest new option
- ▶ **On Demand Topical Microbicide – *Lower exposure, Adherence friendly***
 - ▶ Vaginal TFV proven effective, but adherence challenges
 - ▶ New form's - on demand, behaviorally-congruent protection without systemic exposure

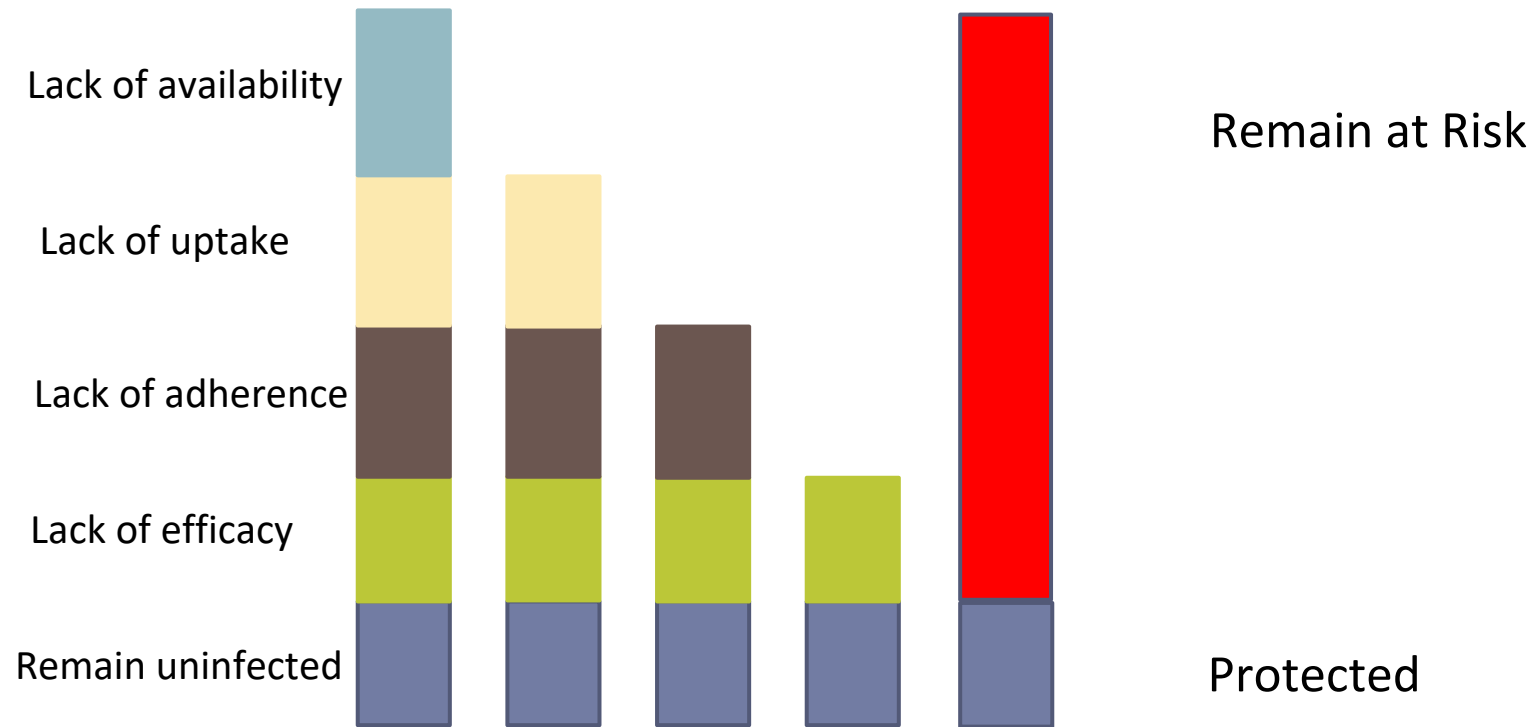
Thank You!

- ▶ Meeting Organizers
- ▶ Meeting Attendees
- ▶ My teachers, esp. Paul Lietman
- ▶ My students, who teach me every day
- ▶ Study Participants, our partners in discovery
- ▶ Key Collaborators
 - ▶ Ed Fuchs, Johns Hopkins
 - ▶ Mark Marzinke, Johns Hopkins
 - ▶ Peter Anton, UCLA
 - ▶ Alex Carballo-Dieguez, Columbia
 - ▶ Ian McGowan, Orion Technologies
 - ▶ Lisa Rohan, University of Pittsburgh/MWRI
 - ▶ Sharon Hillier, University of Pittsburgh/MWRI
 - ▶ Marc Baum, Oak Crest Institute of Science
 - ▶ John Moss, Oak Crest Institute of Science
 - ▶ Jim Pickett, iRMA
- ▶ Collaborating Organizations - CONRAD
 - ▶ Population Council, International Partnership for Microbicides
- ▶ Funders - CDC, NIH/DAIDS, Gates Foundation, Gilead, ViiV/GSK, Merck

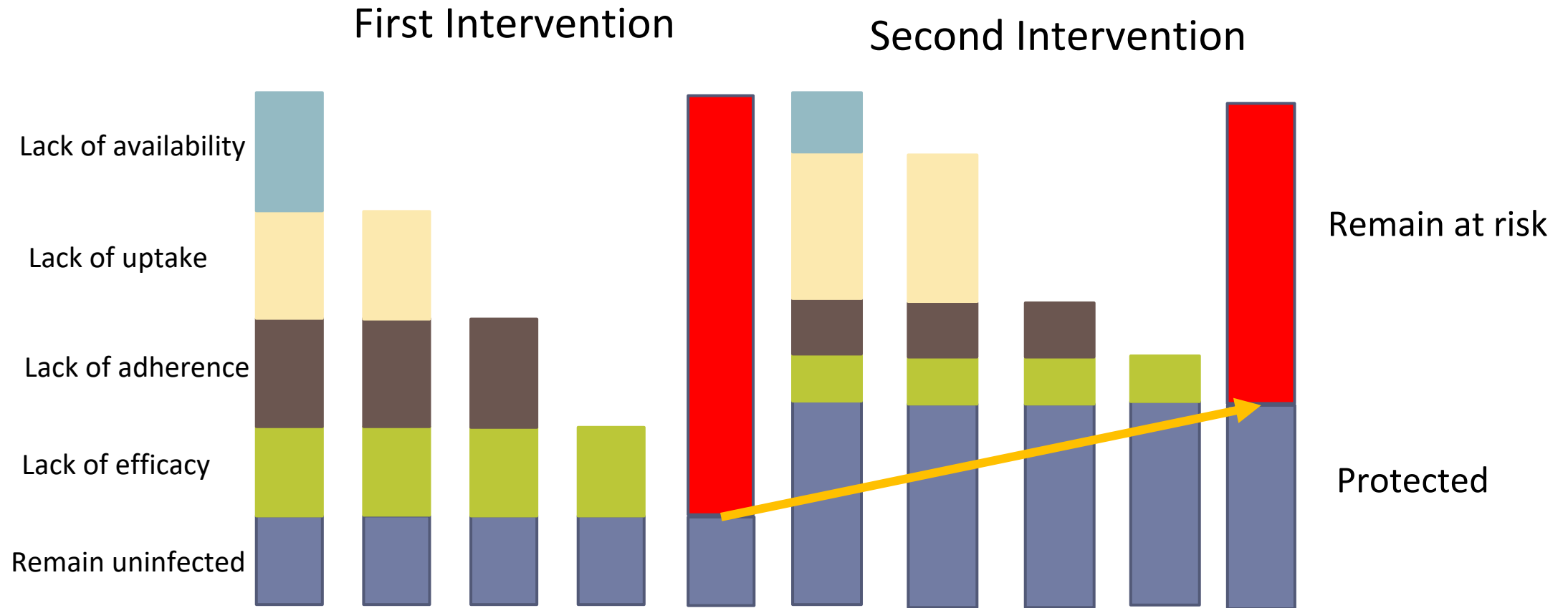




HIV Prevention Cascade



HIV Prevention Cascade



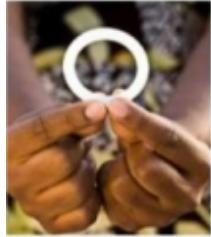
Womens' PrEP Desires



Injectables



Implants



Vaginal Ring



Oral Tablets



Vaginal Film



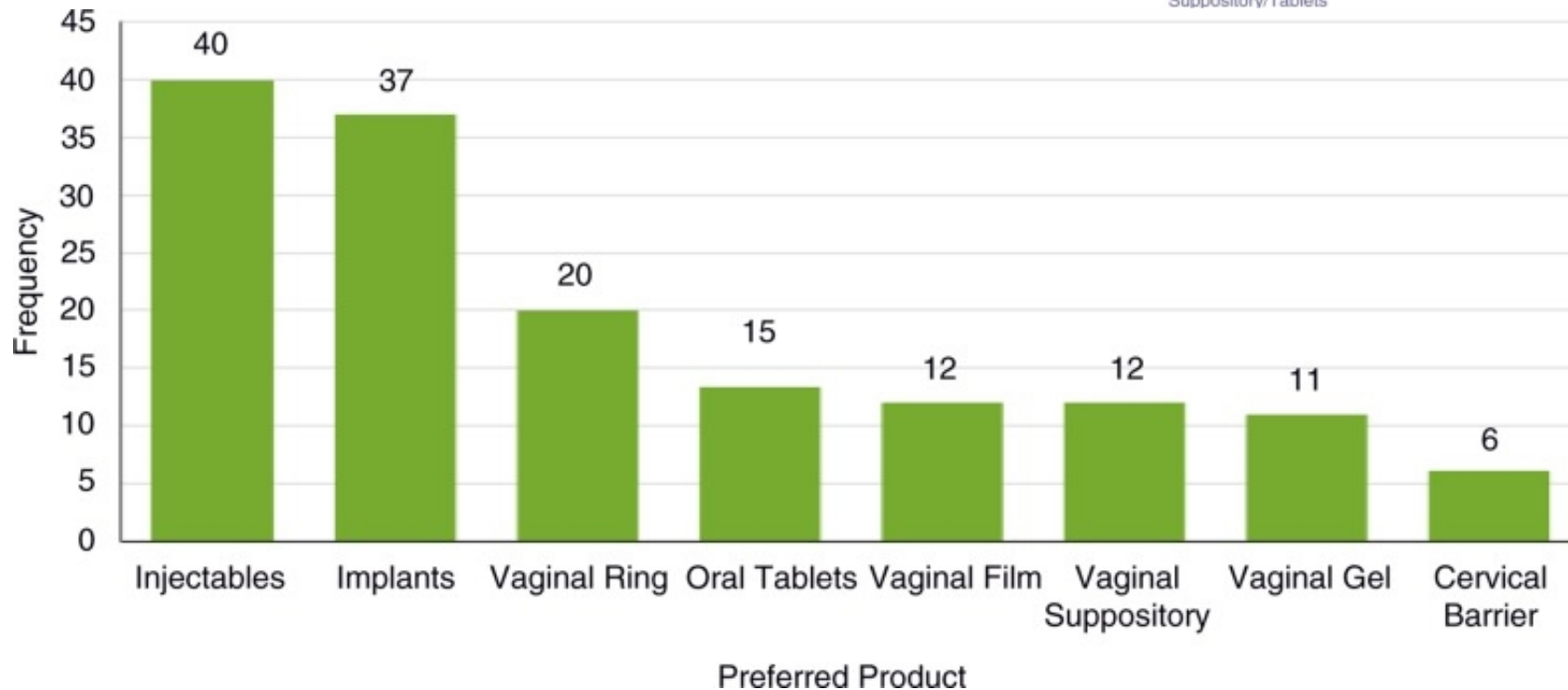
Vaginal
Suppository/Tablets



Vaginal Gel

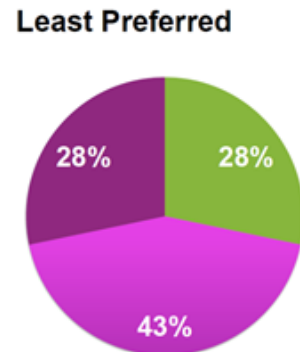
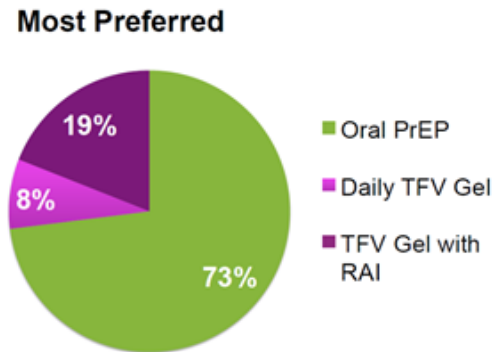


Barrier Methods

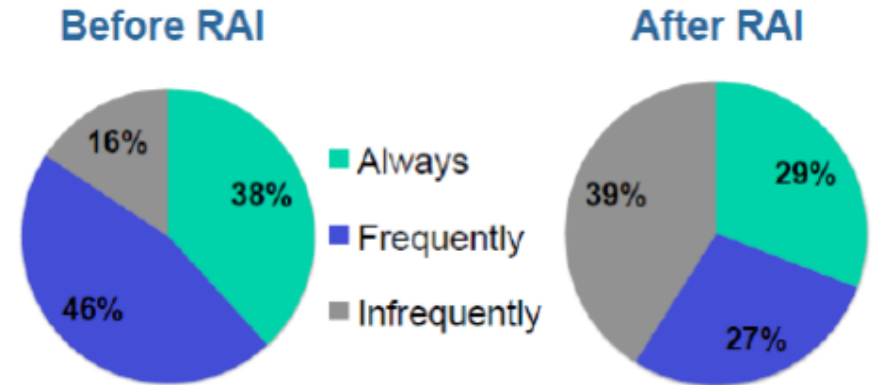


MSM's PrEP Desires

▶ MTN-017: Gel vs. Oral



▶ YMSM Survey: Douching



▶ Online Survey: 4,638 at-risk MSM in US (March 2016)

- ▶ 78% heard of PrEP, 15% taken PrEP, 44% side effects

