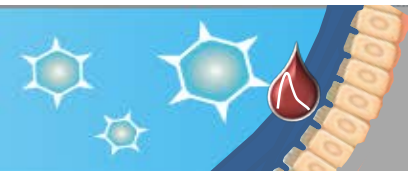


# On Demand, Behaviorally-Congruent Rectal Microbicide Douche

*Craig W. Hendrix, MD  
Johns Hopkins University*

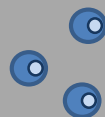
*MTN Annual Meeting 2018*



# Outline

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- Describe need for rectal microbicides
  - Limitations to daily oral PrEP
  - Limitations to on demand rectal gel applicator
- Discuss microbicide douche development
  - Community demand/readiness (next up - Alex!)
  - Vehicle development
  - Clinical Development
  - NHP SHIV challenge proof-of-concept



# Rectal Microbicide Feasibility

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- Oral PrEP *not* for everyone
- Product *options* improve adherence
- *On demand* oral TDF/FTC & vaginal PrEP efficacious; rectal gel high adherence
- *Behaviorally-congruent* ARV formulations “*piggy-back*” onto commonly used sex products



# Rectal Microbicide Development

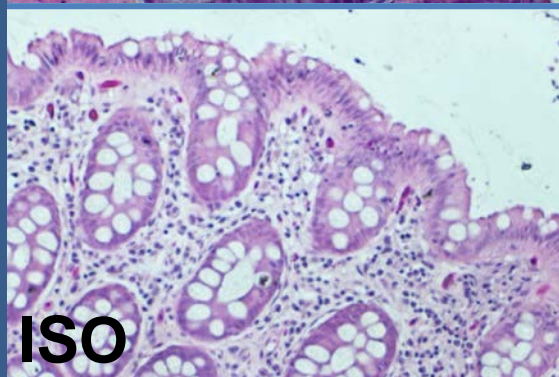
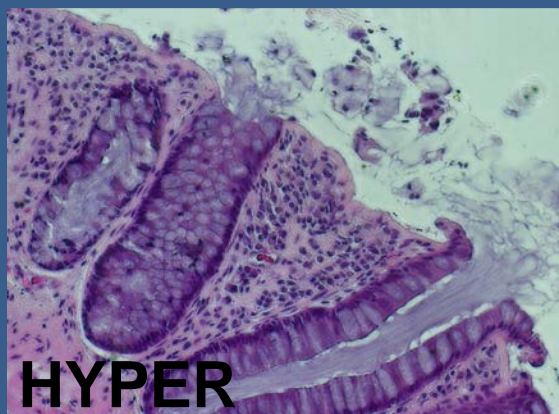
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- Are rectal douches acceptable to those at risk?
- Can ARVs be delivered safely by rectal douche?
- Can douches provide protective concentrations?
- Can a rectal douche prevent HIV?



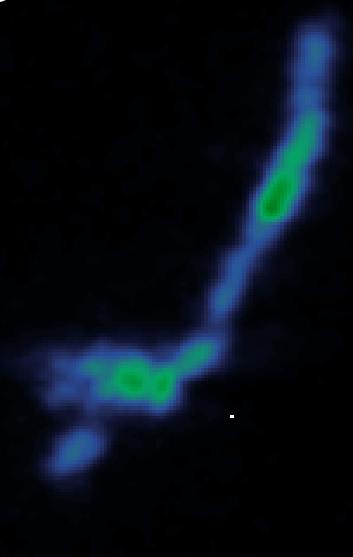
# Enema Vehicle Selection

## Toxicity



## Distribution

ISO



MIP Coronal  
SPECT/CT

## Acceptability

Sexual satisfaction (% of occasions)	Hyper-osmolar		Hypo-osmolar		Iso-osmolar	
	M (SD)	Range	M (SD)	Range	M (SD)	Range
decreased	11.1		11.1		0	
no effect	37.0		29.6		37.5	
increased	51.9		59.3		62.5	
Acceptability rating	3.33 (.68)	2 – 4	3.26 (.94)	1 – 4	3.33 (1.01)	1 – 4

	Hyper-osmolar		Hypo-osmolar		Iso-osmolar	
	M (SD)	range	M (SD)	range	M (SD)	range
Liked douche overall	7.75(2.44)	2 – 10	7.67(2.83)	2 – 10	7.56(2.60)	2 – 10
Sexual enjoyment after product use	7.67(2.35)	3 – 10	8.22(1.79)	5 – 10	8.78(1.30)*	6 – 10
Reports of RAI being worse after douching (n)	1		2		0	
Liked application process	6.89(2.47)	3 – 10	7.78(2.95)	1 – 10	8.33(1.58)*	5 – 10
Likelihood of future use	8.56(1.24)	7 – 10	8.78(1.48)	6 – 10	9.33(1.00)	7 – 10
Likelihood of use without condoms	9.86 (.38)	9 – 10	9.75 (.46)	9 – 10	9.57 (.53)	9 – 10
Likelihood of use if a 30-minute wait is required	8.11(1.76)	4 – 10	8.00(2.96)	1 – 10	8.44(2.83)	1 – 10

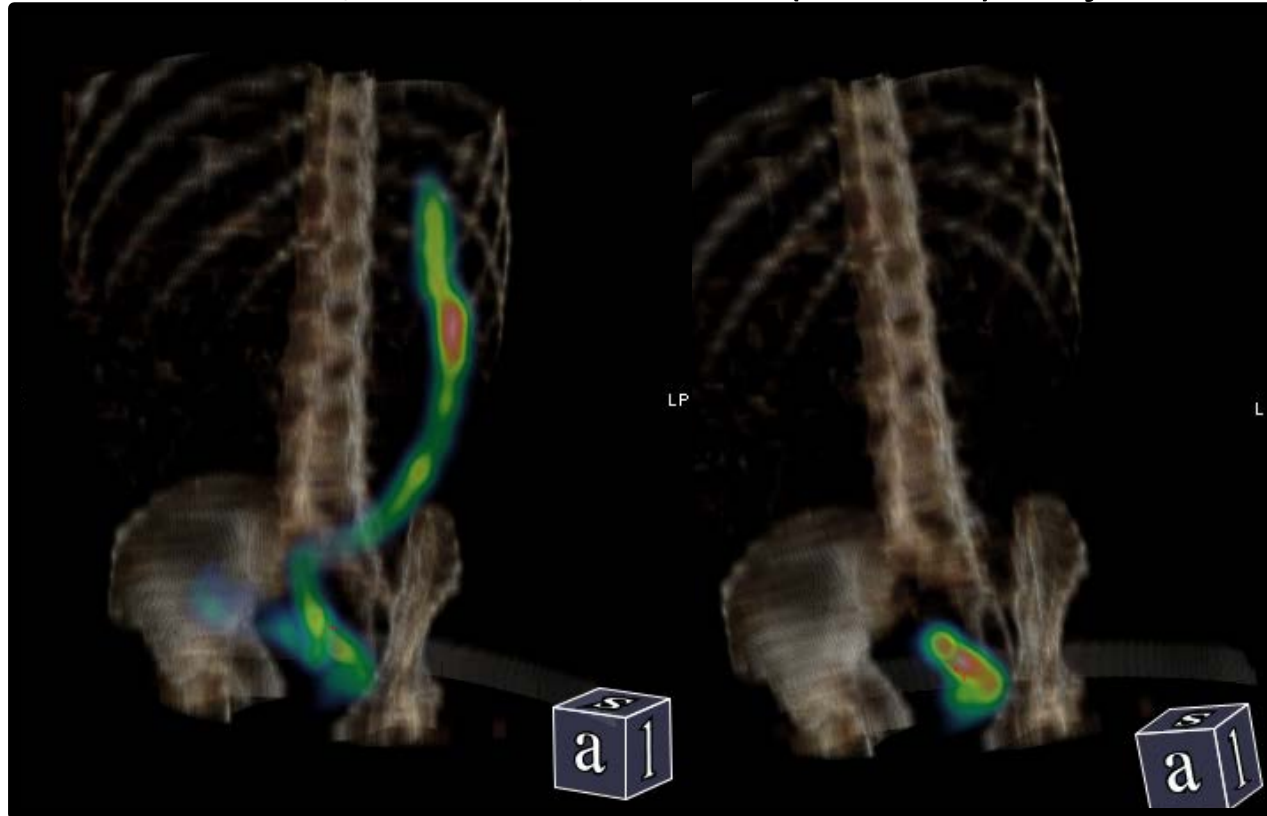
- 9 men, single dose cross-over
- Hyper-, iso-, hypo-osmolar enema
- Luminal PK, histology, acceptability favor iso-osmolar

Leyva, et al. ARHR 2013



# Rectal Distribution: Microbicide & “HIV”

“Microbicide” ( $^{111}\text{In-DTPA}$ )    “HIV” ( $^{99\text{m}}\text{Tc-SC}$ ) in Ejaculate



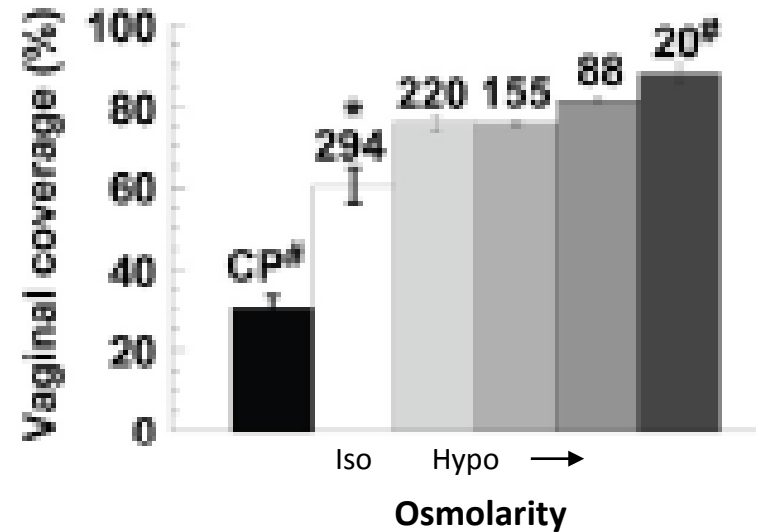
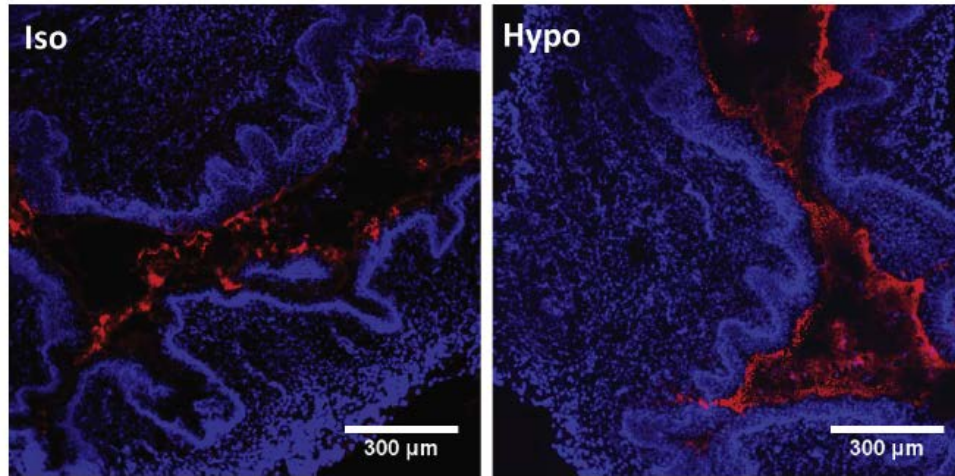
Rectal TFV gel (0h), simulated sex/ejaculation (1h), SPECT/CT (2h)

*Hiruy, et al. ARHR 2015*





# Speeding Tissue Absorption



- Administered in isotonic (iso) or hypotonic (hypo) solution
- Fluorescent particle distribution mouse vagina 10' post-dose
- Vaginal mucosal surface coverage varies with osmolality

Ensign, *et al.*, Biomaterials 2013 & Sci Trans Med 2012



# DREAM Program

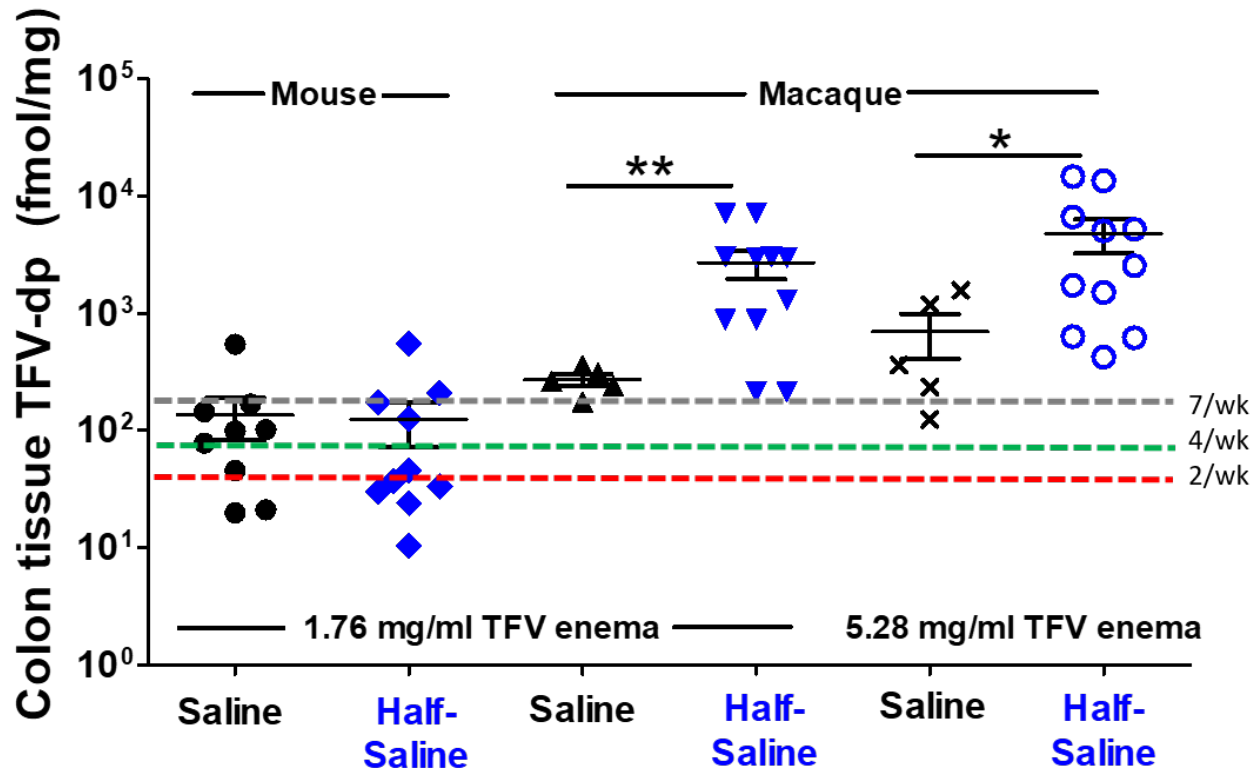
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- Background
  - Adherence & choice greatest PrEP needs
  - On demand, behaviorally congruent widely desired
  - Enema behaviorally-congruent (67-75% RAI MSM)
- Objectives
  - Single dose TFV (prodrug) enema, 1 week protection
- Process
  - Sequential mice, macaque, human
  - Select best of TFV, TDF, TAF, CMX-157
  - Optimize formulation, osmolality, nano, gelling





# Interspecies TFV-DP Comparisons



- Hypo-osmolar >5x increases in tissue TFV-DP in macaques
- Significant variability (1log<sub>10</sub> range common)
- Target concentrations achieved by median low, exceeded by high doses

*Xiao et al AAC 2017*



# Macaque Explant Protection

Time

**Product B**

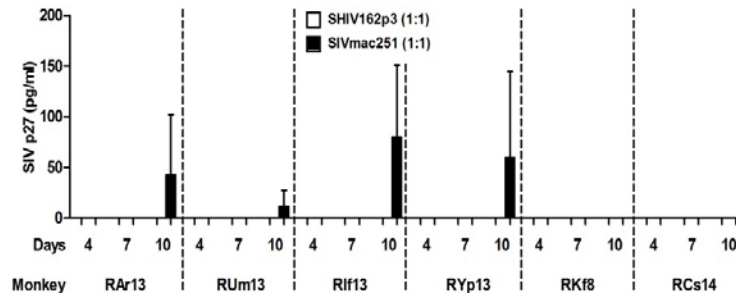
**TFV 5.28 mg/mL Iso-osmolar**

**Product C**

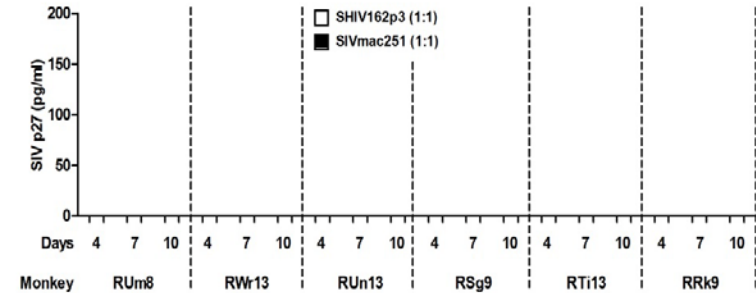
**TFV 5.28 mg/mL Hypo-osmolar**

1 hr

Rectal explant culture: post-1 hr of DREAM product B

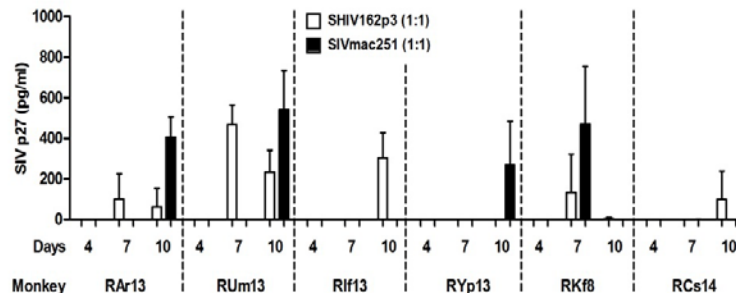


Rectal explant culture: post-1 hr of DREAM product C

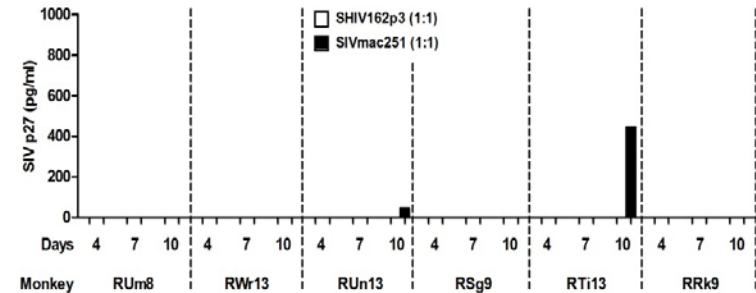


24 hrs

Rectal explant culture: post-24 hr of DREAM product B

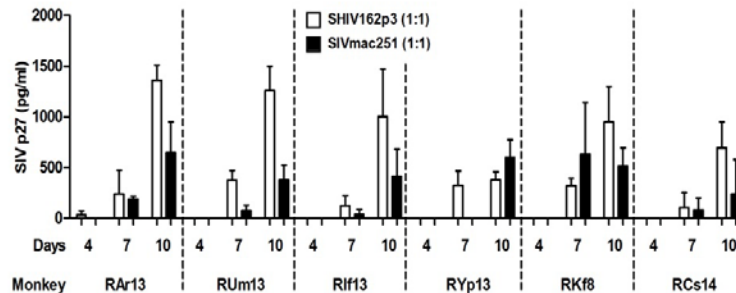


Rectal explant culture: post-24 hr of DREAM product C

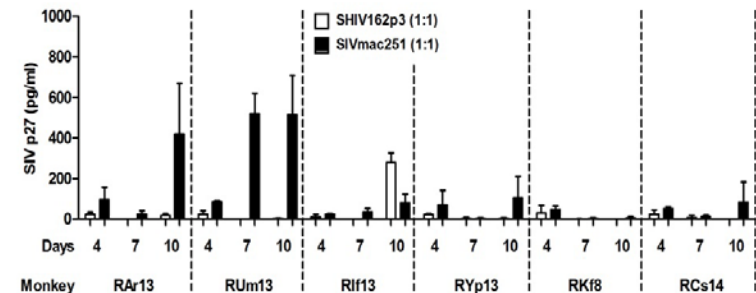


72 hrs

Rectal explant culture: post-72 hr of DREAM product B



Rectal explant culture: post-72 hr of DREAM repeat product C



# DREAM-01 FIH Study

- Design: Phase I, single ascending dose study
- Goal: Identify dose achieving colon cell [TFV-DP] target
- Objectives: Safety, PK, PD (explant), & Acceptability
- Products (125 mL):
  - A: TFV 1.76 mg/mL (normal saline)
  - B: TFV 5.28 mg/mL (normal saline)
  - C: TFV 5.28 mg/mL (half-normal saline)
- Subjects: 18 MSM receive all 3 products sequentially
- Outcomes:
  - Safety: AEs, histology
  - PK: (intense) blood, (sparse), colorectal tissue, rectal fluid
  - Explore: colon proteomics & metabolomics, microbiome



# Safety

AE: None > Grade 2

	Total	Product A	Product B
Participants who experienced an AE			
Grade 1	3	3	1
Grade 2	3	2	1
<b>Total</b>	6	5	2
Total # of AE's Reported			
Grade 1	9	8	1
Grade 2	3	2	1
<b>Total</b>	12	10	2

Histology: No Change from Baseline

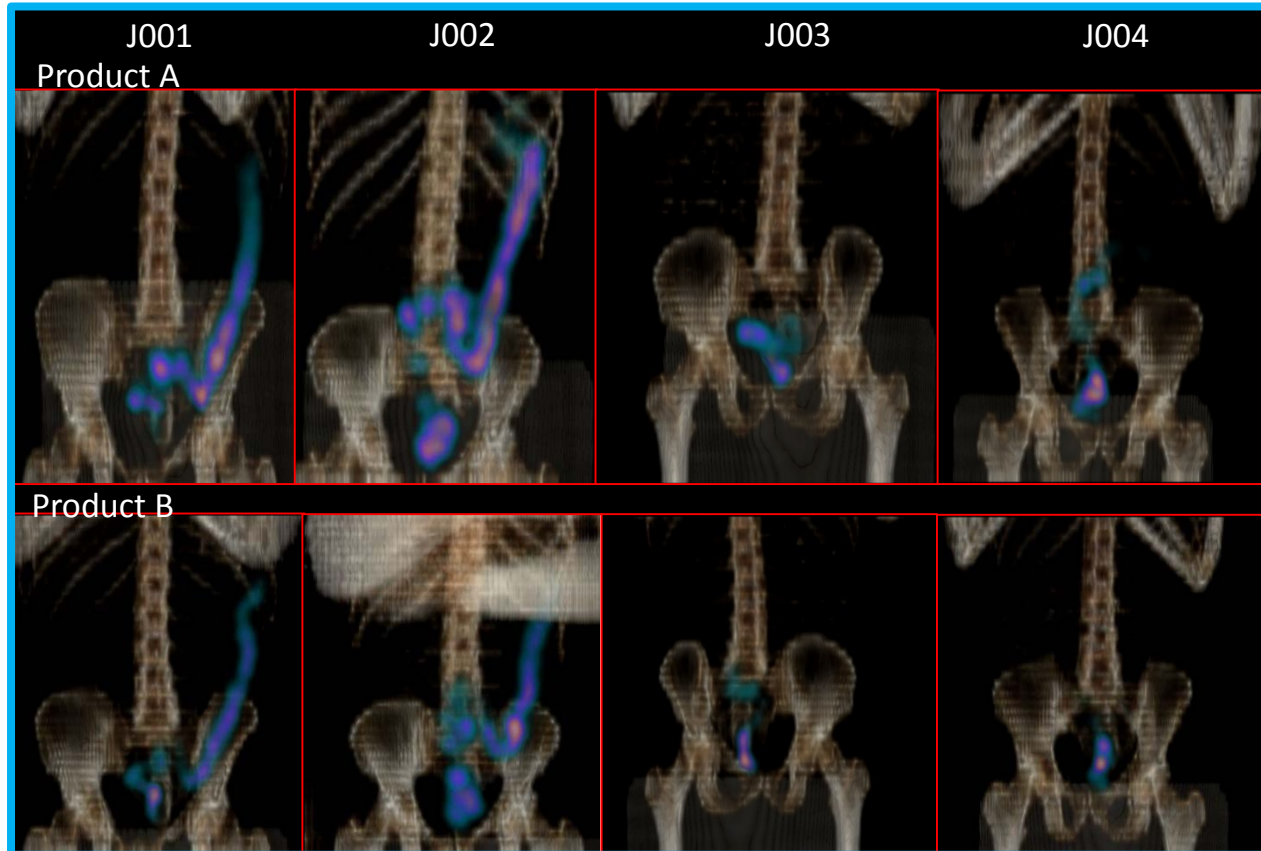
Product	Time	Overall Grade (0-5)	Epithelial Denudation (0-3)	Lamina propria Hemorrhage (0-3)
Baseline	Pre-Dose	0.5	1.0	0.0
Product A	1 or 3 hrs	1.0	1.0	0.5
	24 hrs	0.5	3.0	1.0
	72 hrs	0.5	0.0	0.5
Product B	1 or 3 hrs	1.0	1.0	1.0
	24 hrs	1.0	1.0	1.0
	72 hrs	1.0	0.0	0.0

Product C not shown – No AE > Grade 2 product related, histology no change from baseline



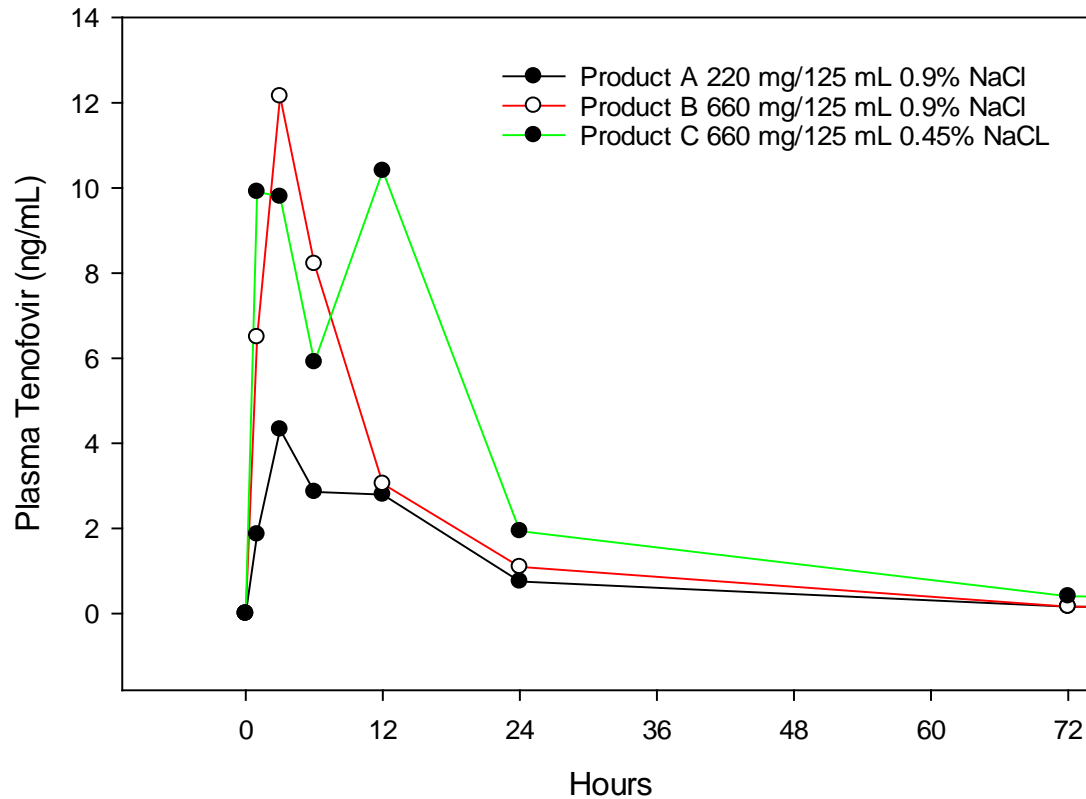
# Colonic Luminal Distribution

## Desired Colon Luminal Coverage



# Plasma TFV & PBMC TFV-DP PK

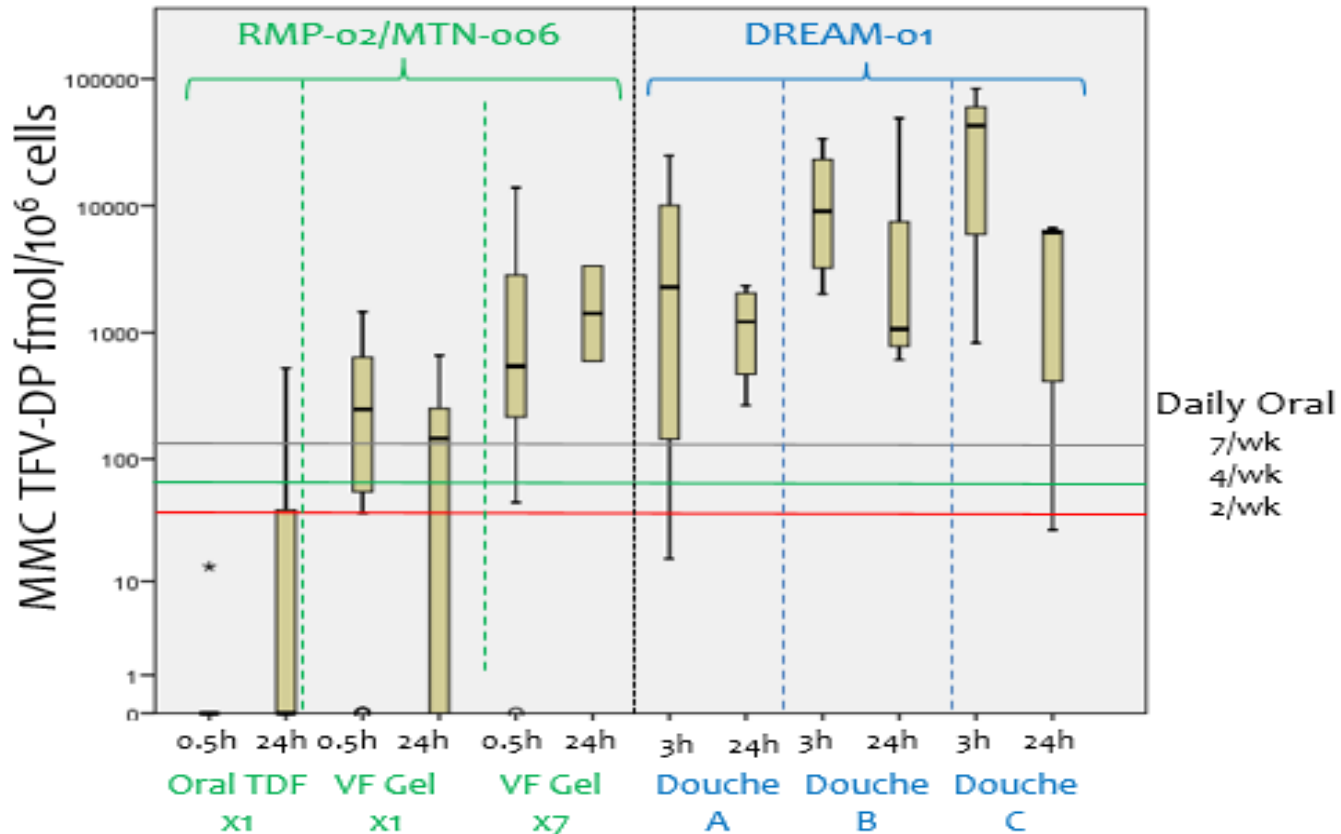
## Low Systemic Exposure



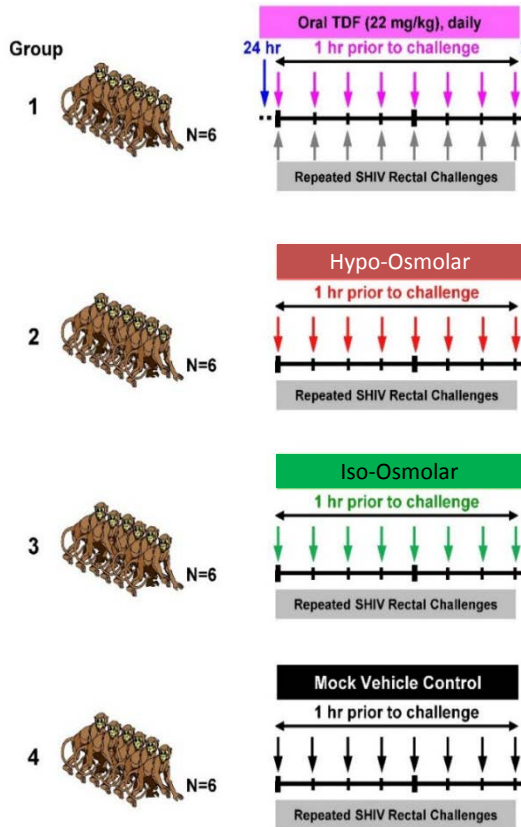


# DREAM-01 Colorectal Tissue PK

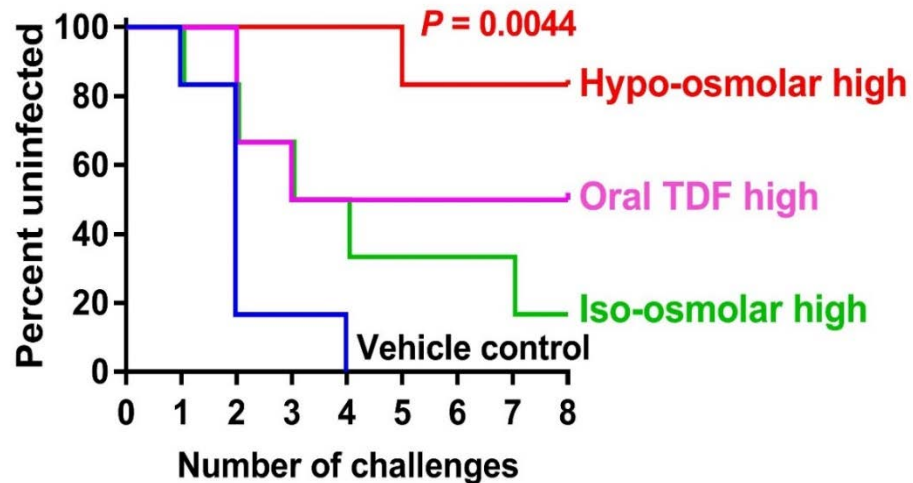
Very High Colon Tissue Cell TFV-DP



# NHP Oral TDF v. TFV Douche PD



- Weekly intrarectal  $10^3$  TCID<sub>50</sub> R5 SHIV
- Weekly plasma viral RNA by qPCR
- 2 vRNA values > 250/mL x 2 wks = infected

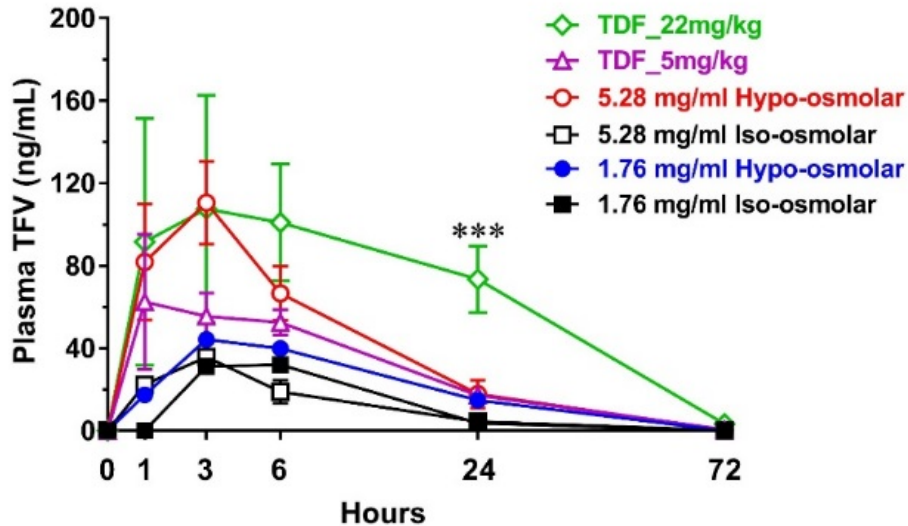


IP/CP-HTM DREAM U19, Francois Villinger, Univ Louisiana (Lafayette) CROI LB 2018

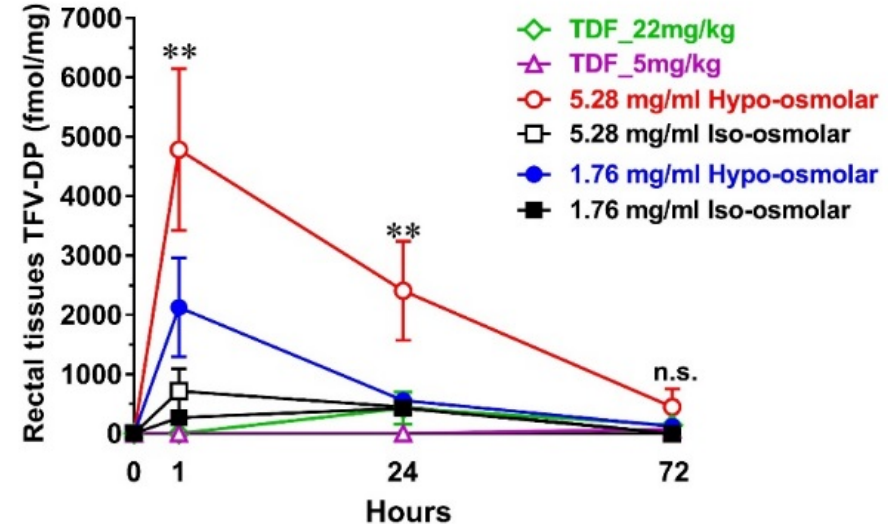


# NHP Oral TDF v. TFV Douche PK

## TFV concentrations in plasma



## TFV-DP concentrations in Rectal Tissues



- Plasma TFV concentrations similar
- Colorectal tissue TFV-DP far higher with rectal dosing (not steady-state)
- Steady-state oral TDF NHP studies underway

Francois Villinger, Univ Louisiana (Lafayette) CROI LB 2018



# DREAM-01 Data to Come



**DREAM**  
DEVELOPMENT OF A RECTAL ENEMA AS MICROBICIDE

What if you could get fresh down there AND prevent HIV?

Tell us what you think!

[CLICK HERE](#)

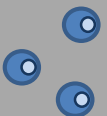
- Proteomics (Adam Burgener)
- Metabolomics (Anne Le)
- Microbiome (Jaques Ravel)
  
- Acceptability (Alex Carballo-Dieguez & Rebecca Giguere)
- DREAM Grindr Survey (*on deck*)



# Summary

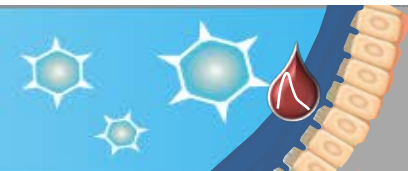
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- New methods developed to enable development
- Complex early studies informed development
- DREAM Pre-Clinical
  - Hypo-osmolar formulations increase tissue TFV-DP
  - Douche better than oral in NHP SHIV challenge
- DREAM-01 Clinical
  - ~85% complete, no safety signal
  - TFV-DP colon “target” exceeded by  $2-3\log_{10}$  in 1-3 hrs
  - Plasma TFV below & colon TFV-DP above NHP



# Acknowledgements

- NIH/DAIDS IP/CP-HTM Program
    - Jim Turpin, Hans Spiegel, Jeanna Piper, Cherlynn Mathias, James Cummins, Anabel Lowry
  - Johns Hopkins
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  - UCLA
    - Peter Anton, Julie Elliott, Terry Sanders
  - Columbia
    - Alex Carballo-Dieguez, Rebecca Giguere
  - Univ Louisville (Fayette)
    - Francois Villinger, Xiao Peng
  - Emory
    - Sanjeev Gumber
  - Duke
    - David Katz
  - CONRAD
    - Tim McCormack
- Study Volunteers
  - SAB
    - Jim Pickett
    - Tom Moench
    - Florian Hladik
    - Jose Romero
    - Rada Savic





Thank You!

