

DREAM

Developing Rectal Enema as Microbicide

Behaviorally-Congruent Rectal Microbicides

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JOHNS HOPKINS
M E D I C I N E

Overview

- PrEP Achilles Heel - Adherence
- Behaviorally-congruent Rectal Microbicide Development
 - Target product profile
 - Luminal PK
 - Dosing methods
 - Tissue PK
 - Intensive study design – PK, PD, Safety, Acceptability
- DREAM Program
 - Formulation enhancements
 - Broader objectives

Adherence Response

Formulation Changes in Development

| | |
|-----------|---|
| Phase III | <ul style="list-style-type: none">• “Periodic” Dosing<ul style="list-style-type: none">– Periodic oral TDF/FTC dosing (Ipergay)• Vaginal Ring (placebo-controlled) 1 month<ul style="list-style-type: none">– Dapivirine RCT (IPM & MTN-020) [CROI 2016] |
| IIB/III | <ul style="list-style-type: none">• Oral v. Injectable<ul style="list-style-type: none">– Cabotegravir Phase 2B/3 HPTN 083 (planning)• Periodic Dosing<ul style="list-style-type: none">– TFV/FTC oral event driven (HPTN 067)– TFV rectal gel MTN-017 (CROI 2016) |
| II | <ul style="list-style-type: none">• Injectable 2-3 month<ul style="list-style-type: none">– Rilpivirine q2 month HPTN 076 (ongoing)– Cabotegravir q3 month HPTN 077 (ongoing) |
| I | <ul style="list-style-type: none">• Behaviorally-congruent formulations – medicate existing product used parasexually<ul style="list-style-type: none">– Episodic enema TFV/prodrug (TDF, TAF, CMX-157) DREAM U19– Manual rectal gel dosing as lubricant (Manual gel dosing JHU; Adonis MTN-033) |
| Animal | <ul style="list-style-type: none">• Longer-acting Implantable<ul style="list-style-type: none">– TAF silicone/PVA rod OCIS U19– Various ARVs Northwestern U UM1 |

Behaviorally-Congruent

Lubricant & Enema/Douche Commonly Used in RAI

- Carballo-Dieguez A, Bauermeister J, Ventuneac A, Dolezal C, Balan I, Remien RH. The use of rectal douches among HIV-uninfected and infected men who have unprotected receptive anal intercourse: implications for rectal microbicides. *AIDS Behav* 2008;12:860-866.
- Carballo-Dieguez A, Bauermeister J, Ventuneac A, Dolezal C, Mayer K. *Why rectal douches may be acceptable rectal-microbicide delivery vehicles for men who have sex with men.* *Sex Trans Dis* 2009;36(11)
- Galea JT, Kinsler JJ, Imrie J, Nureña CR, Sánchez J, Cunningham WE. *Rectal douching and implications for rectal microbicides among populations vulnerable to HIV in South America: a qualitative study.* *Sex Transm Infect* 2013;0:1-3.
- Javanbakht M, Stahlman S, Pickett J, LeBlanc M-A, Gorbach PM. *Prevalence and types of rectal douches used for anal intercourse: results from an international survey.* *BMC Infectious Diseases* 2014;14:95.
- Noor SW, Rosser BRS. *Enema use among men who have sex with men: A behavioral epidemiologic study with implications for HIV/STI prevention.* *Arch Sex Behav* 2013, Epub ahead of print.

Behaviorally-Congruent Rectal Microbicide Target Product Profile

- Behaviorally-congruent? *Existing behavior & medicated product*
- Acceptable use? *Neutral to Enjoyable*
- Where? *Rectal ~15-20 cm, coincident with “HIV” surrogate distribution*
- How much? *Enough to achieve 85 fmol TFV-DP/10⁶ colon cells*
- How often? *Single dose, episodic use*
- How fast? *30 minutes to protection*
- How long? *7 days protection (???)*

Enema/Douche



Sexual Lubricant

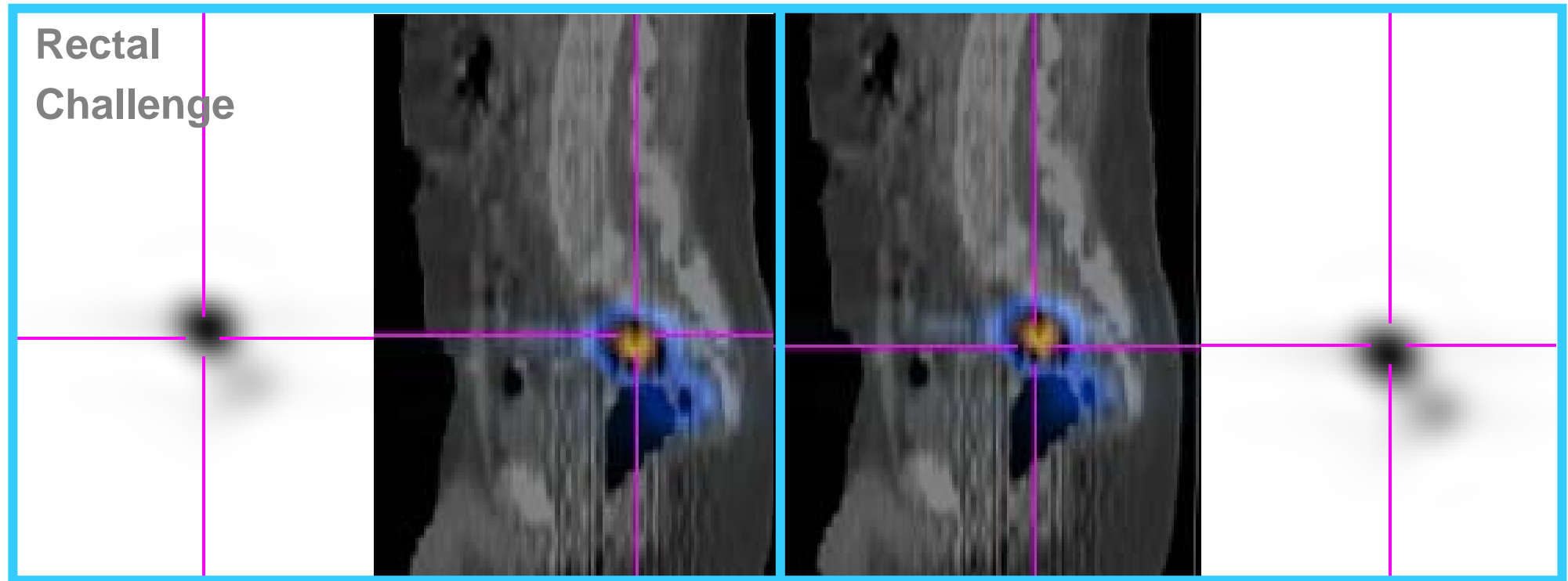


Selecting Luminal Distribution Targets

Localizing Cell-free & Cell-Associated HIV Targets

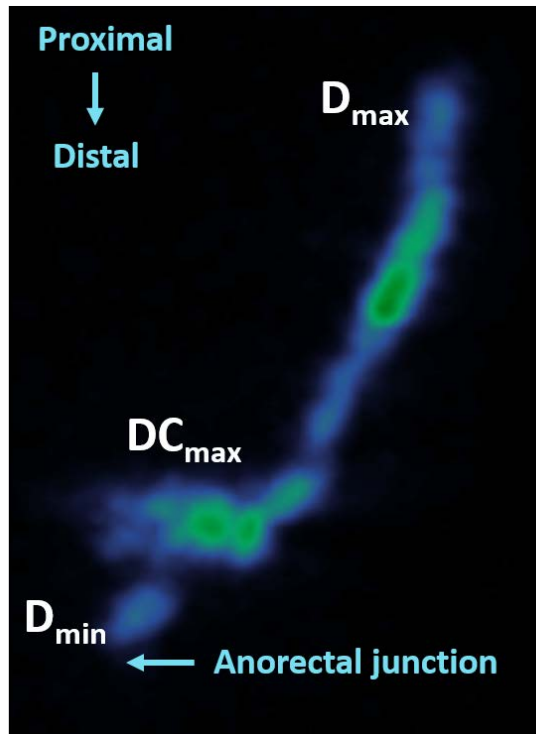
Cell-free HIV Surrogate
 ^{99m}Tc -Sulfur Colloid

Cell-Associated HIV Surrogate
 ^{111}In -Lymphocytes

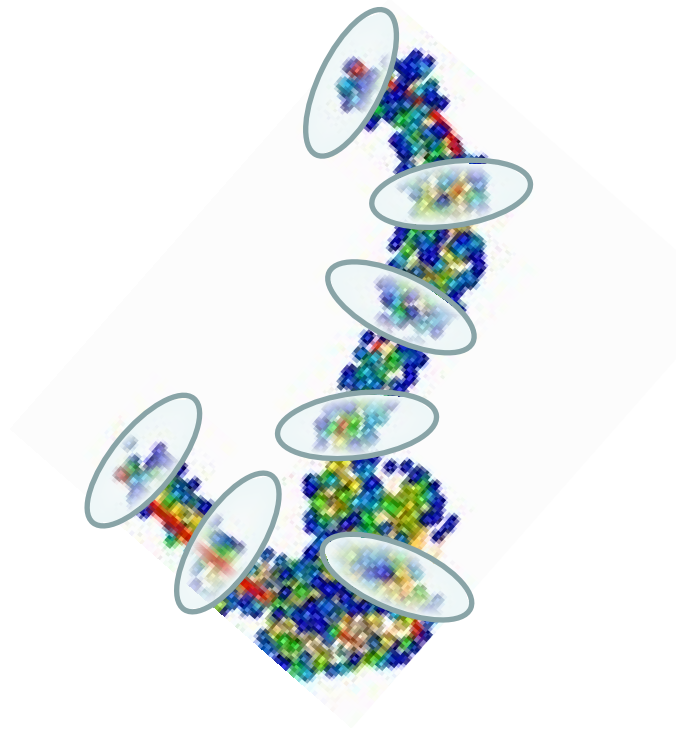


SPECT Image Analysis

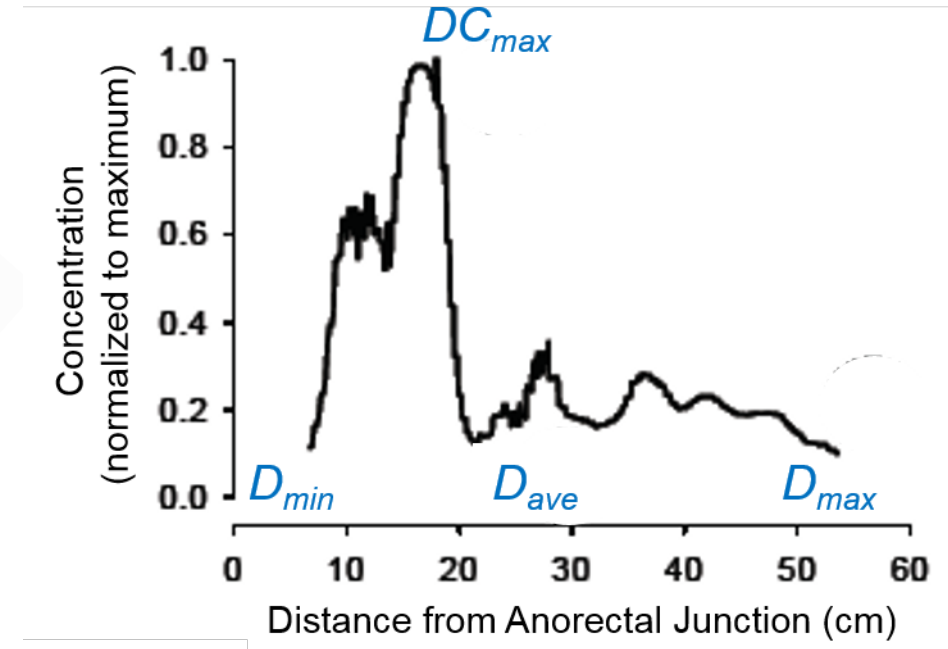
SPECT Emission Image → Tube-Fitting Algorithm → PK-Distance Parameters



- ^{99m}Tc -DTPA Distribution



- Fit 3-D centerline curve (red)
- Move disc along centerline
- Plot concentration v. distance



- D_{min} – distance to most distal signal
- DC_{max} – distance to max “concentration”
- D_{ave} – distance to “average” concentration
- D_{max} – distance to most proximal signal

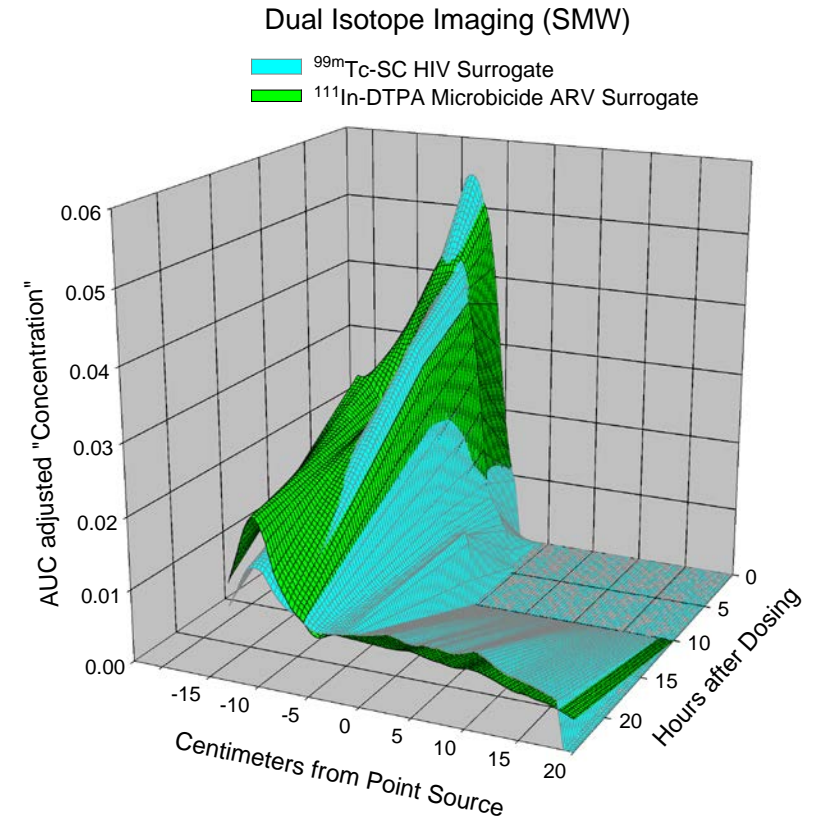
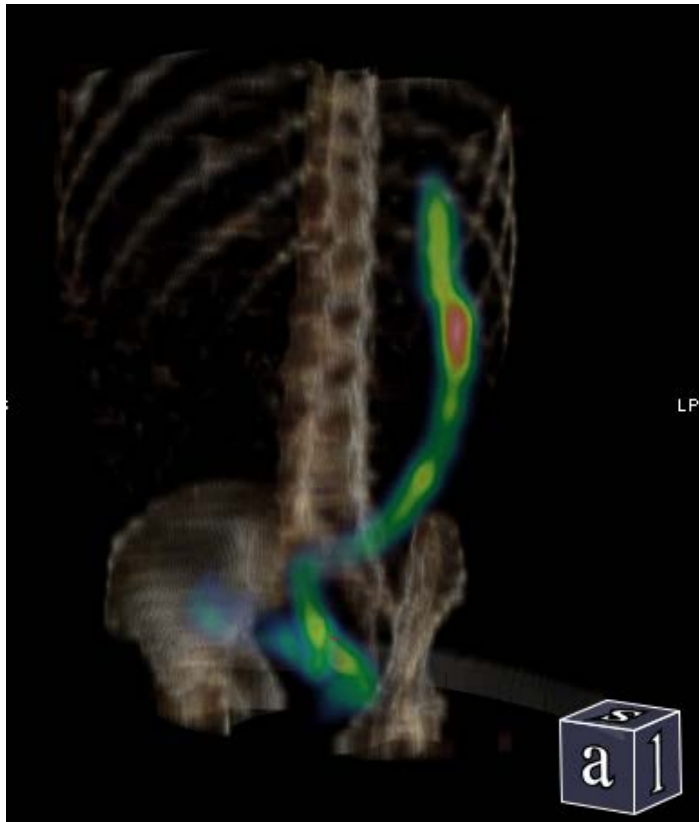
Assessing Luminal Vehicles

Comparing Luminal Drug & “HIV” Kinetics

“Microbicide” (^{111}In -DTPA)

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

Concentration-Distance-Time



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

85-90% HIV (2.5 mL) “covered” by Microbicide volumes (10 mL gel, 125 mL enema) tested to date

Assessing Luminal Vehicles

Rectal Formulations Luminal Distribution

| Study | CDC Imaging ¹ | P5-Aim2 ² | P5-Aim 2 ² | Manual Gel ³ | P5-Aim 1 ⁴ |
|-------------------|--------------------------|----------------------|-----------------------|-------------------------|-----------------------|
| Formulation | Gel | Gel | Fluid | Gel | Enema |
| Volume | 10 mL | 10 mL | 10 mL | 10 mL | 125 mL |
| Dose Method | Applicator | Applicator | Applicator | Manual/Phallus | Applicator |
| Osmolality | Hyper-osmolar | Iso-osmolar | Iso-osmolar | Iso-osmolar | Iso-osmolar |
| Post-dose | 4h | 4h | 4h | 4h | 4h |
| D _{max} | 14.0 (9.0–63) | 12.9 (11.6, 20) | 23.1 (14.9, 25.1) | 8.5 (8.5, 10.4) | 38.6 (23.8, 41.7) |
| DC _{max} | 6.0 (2.0–14) | 5.1 (2.0, 8.3) | 5.3 (3.3, 7.2) | 4.3 (2.3, 7.7) | 17.5 (8.2, 24.1) |
| D _{ave} | 6.7 (3.2–29) | 6.4 (4.7, 7.5) | 6.8 (4.7, 10.2) | 0.9 (0.5, 3.4) | 19.6 (9.8, 23.6) |
| D _{min} | - | -2.6 (-3.5, 0.8) | -3.8 (-3.8, -3.5) | 0.0 (-0.1, 1.0) | 2.0 (-1.3–3.4) |

median and range for CDC Imaging (BJCP 2012), IQR for all others.

D_{max}, greatest proximal distance at which radiolabel is detected

DC_{max}, distance at which greatest radiolabel concentration is detected

D_{ave}, mean residence distance (similar to mean residence time)

D_{min}, most distal location of radiolabel

All distances are relative to coccyx

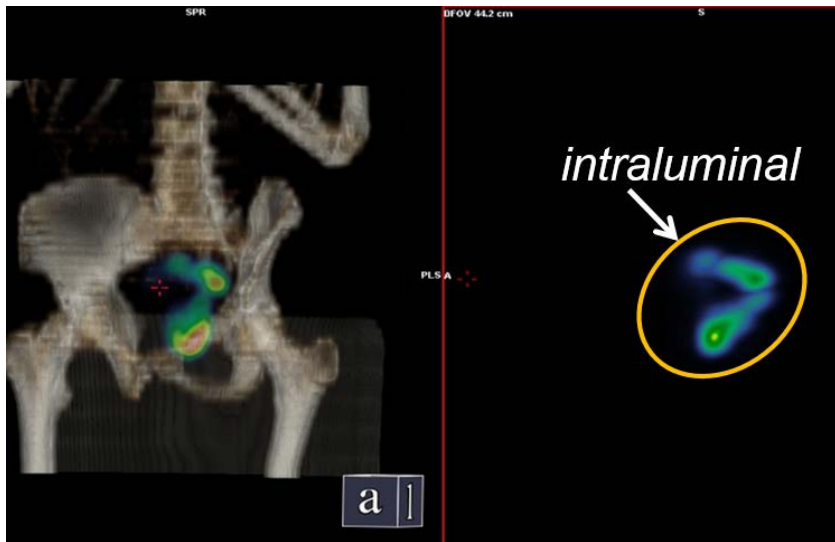
¹Cao, *et al*, BrJCP 2012; ²Leyva, *et al*. ARHR 2015; ³Shieh, *et al*. CROI 2016; ⁴Leyva, *et al*. ARHR 2013

Rectal HIV ~15 cm

Dosing Method

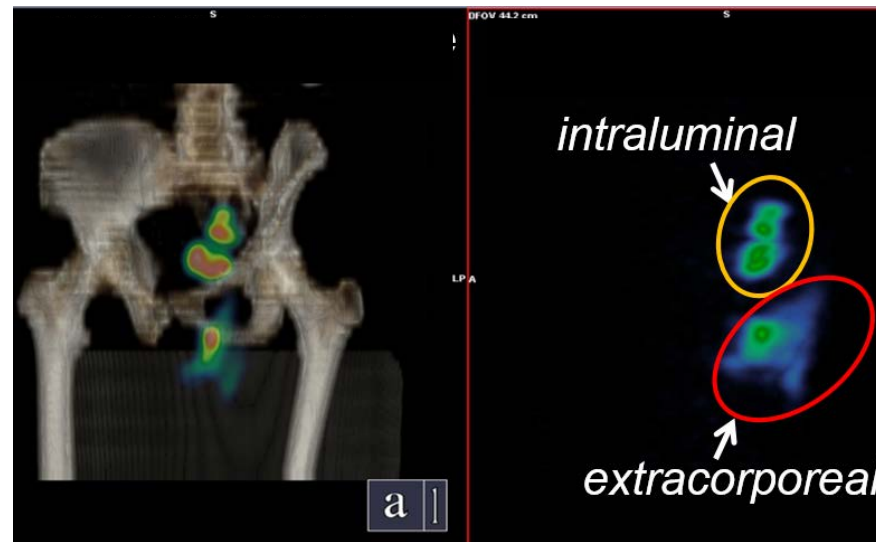
Applicator >> Manual Intraluminal Dosing Efficiency

“Not Well Liked”
Gel (HEC) via HTI
Intrarectal 3.5 mL



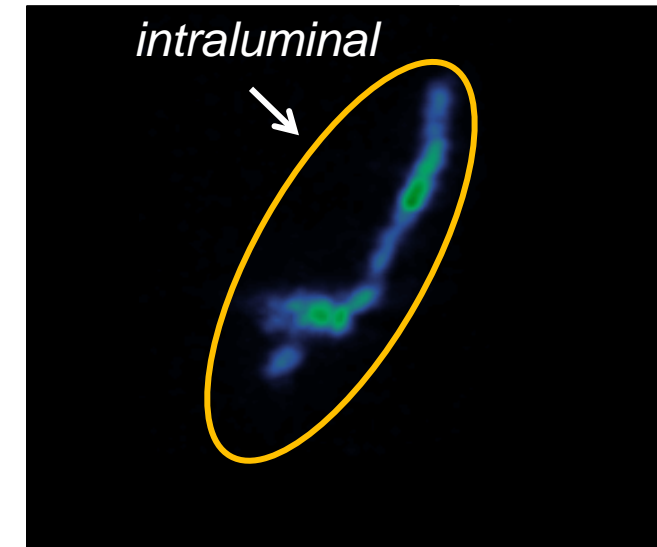
- Retention 88% (86%, 90%)
- Volume Delivered 3.1 (3.1, 3.1)

Behaviorally-Congruent
Wet™ Gel Lubricant
Manual/Phallus 10 mL



- Retention 3.6% (1.0%, 27.4%)
- Volume Delivered 0.3 (0.3, 0.4)
- *Requires TFV 10% for equivalence to 3.5 mL TFV 1% gel*

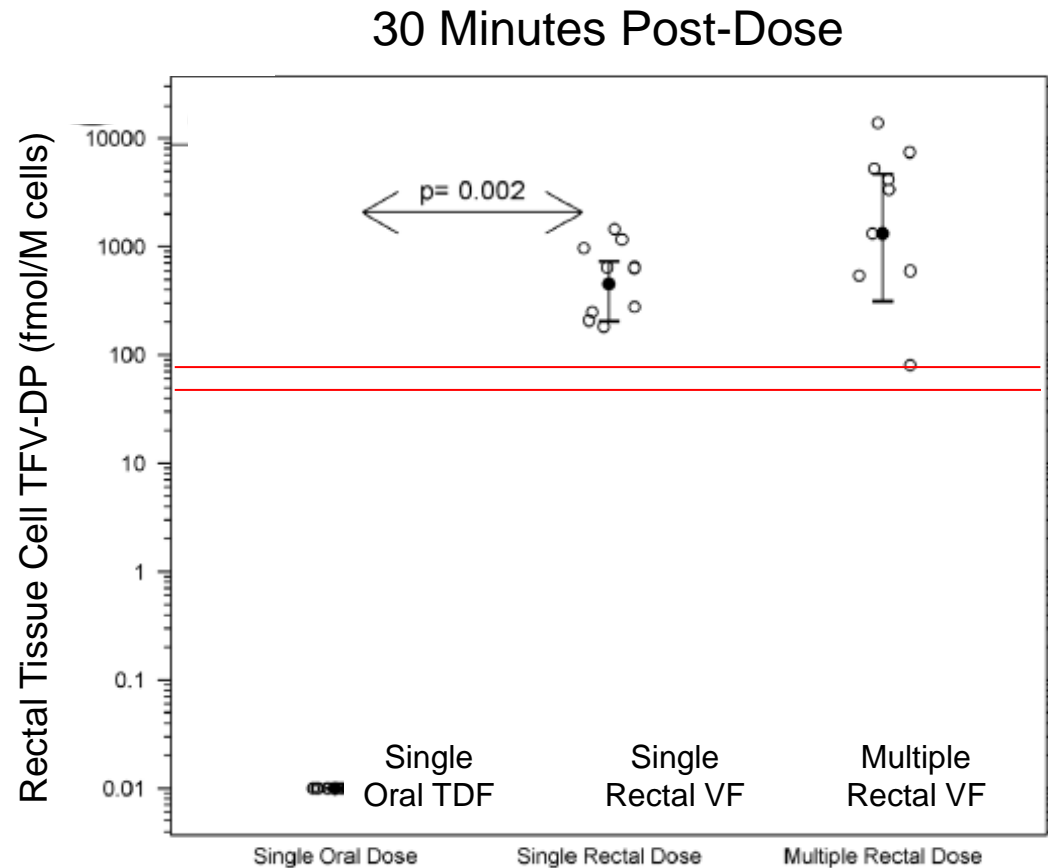
Behaviorally-Congruent
Enema (Normosol-R)
Intrarectal 125 mL



- Retention 60%
- Volume Delivered 75 mL

Colon Pharmacology – Time to “Protection”

Oral vs. Rectal Dosing TFV-DP Targets

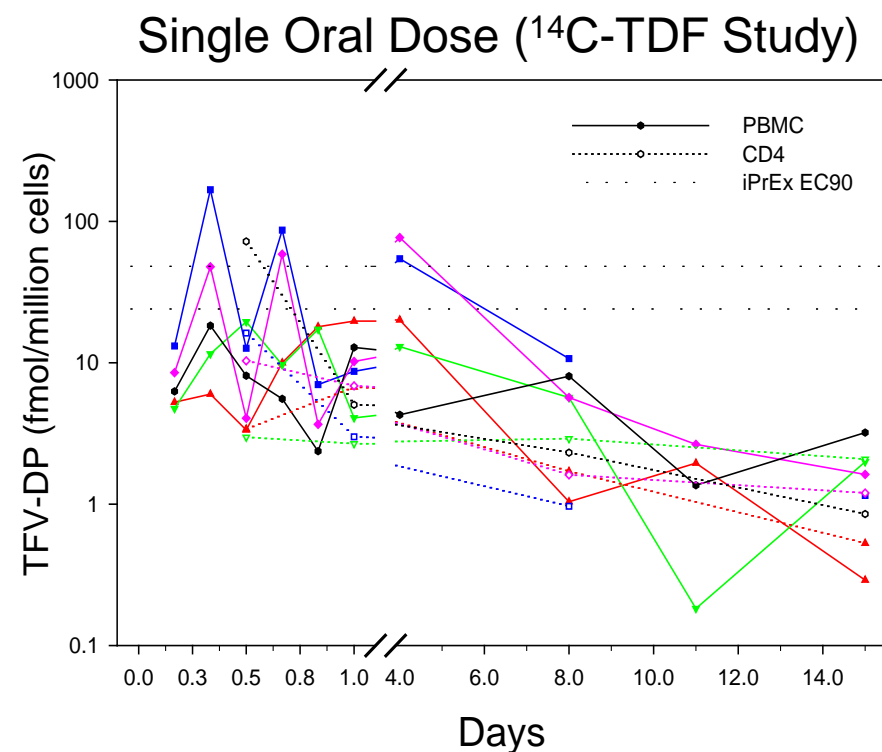


- Single dose TFV 1% rectal gel appears protective @ 30' v. 5d. w/ daily oral
- Steady-state accumulation ~5-fold (daily rectal dosing)
- Large variability in colon tissue

RMP-02/MTN-006 Yang, *et al.* PLOS One 2014

Colon Pharmacology – Duration of “Protection”

TFV-DP Kinetics in Colon Tissue



- Half-life estimates enable PK modeling
- Daily TDF dosing @ target @ 1 week
- Rectal TFV 1% gel c/w 1 week protection

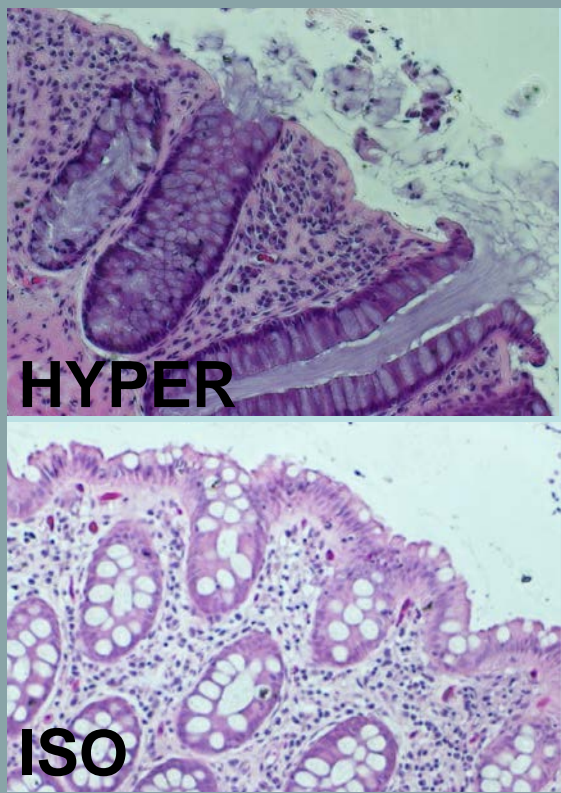
| Anatomic Location | Moiety | Units | Terminal Half-life Median (IQR) |
|-------------------|--------|---------|------------------------------------|
| Plasma | TFV | ng/mL | 69 (55, 77) |
| PBMC | TFV-DP | fmol/M | 48 (38, 76) |
| Blood CD4+ Cells | TFV-DP | fmol/M | 112(100, 118) |
| VT | TFV | ng/gm | 47 (38, 53) |
| VT | TFV-DP | fmol/gm | 53 (45, 68) |
| VT Total Cells | TFV-DP | fmol/M | 66 (43, 202) |
| VT CD4+ Cells | TFV-DP | fmol/M | 139 (121, 167) |
| CVL** | TFV | ng/mL | 40 (38, 43) |
| CVL Cells | TFV-DP | fmol/M | - |
| CT | TFV | ng/gm | 31 (24, 36) |
| CT | TFV-DP | fmol/gm | 34 (21, 40) |
| CT Total Cells | TFV-DP | fmol/M | 82 (43, 89) |
| CT CD4+ Cells | TFV-DP | fmol/M | 60 (52, 72) |
| Colon Brush | TFV | ng/mL | 20 (20, 21) |

Louissaint ARHR 2013

Intensive Multi-Domain Design

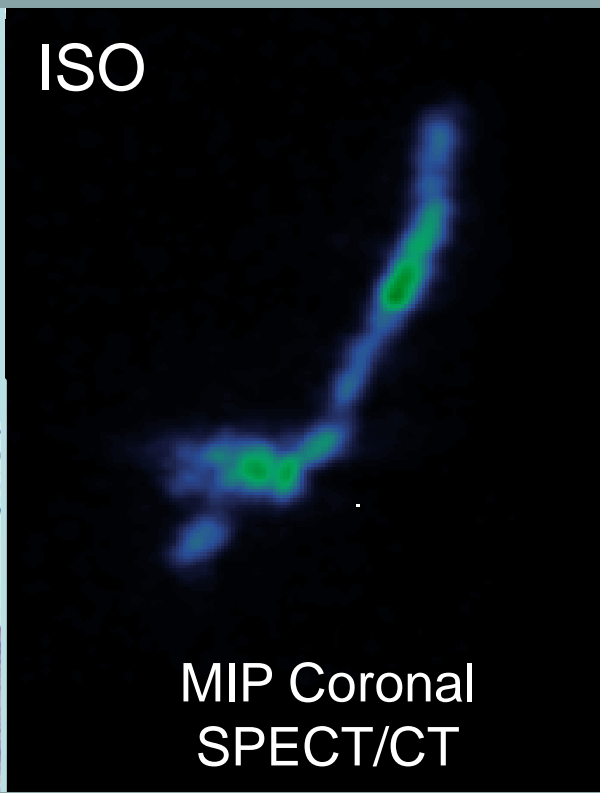
Enema Safety, PK, Acceptability

Toxicity



Distribution

ISO



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 |

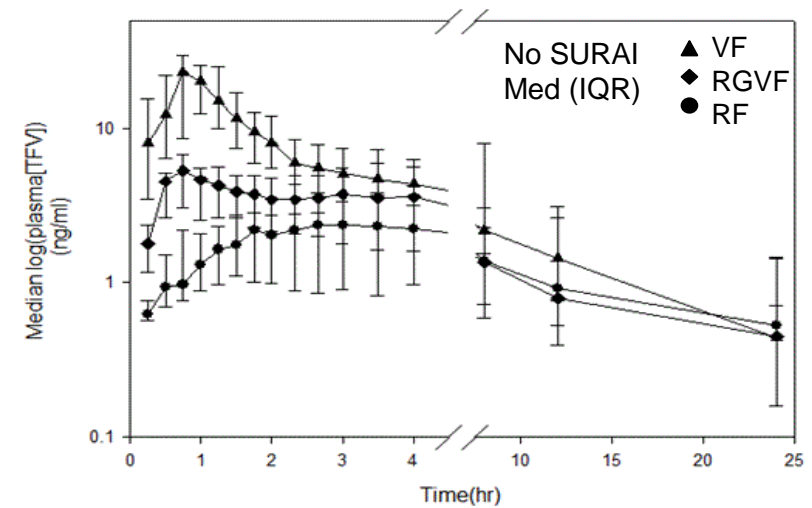
- 9 men, single dose cross-over
- Hyper-, iso-, hypo-osmolar enema
- Luminal PK, histology, acceptability favor iso-osmolar

Leyva, et al. ARHR 2013

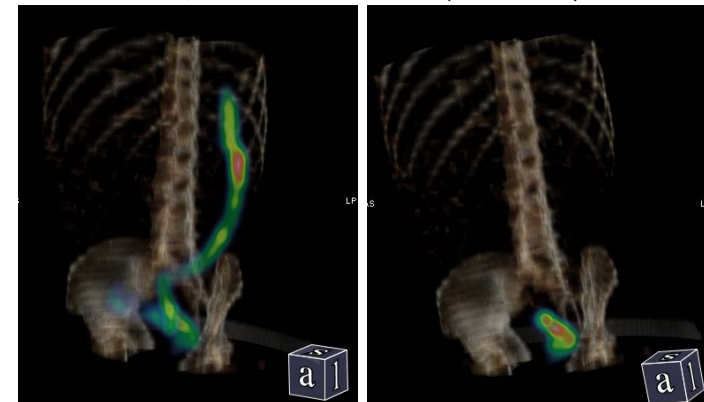
Intensive Multi-Domain Design

Rectal TFV 1% Gel Comparison – CHARM 01 & 02

- Single dose TFV 1% gel comparison, N=14, 9
 - VF 3,111 mOsm/kg (MTN-006)
 - RGVF 836 mOsm/kg (MTN-017)
 - RF 479 mOsm/kg
- Plasma
 - TFV (C_{max} , AUC) VF > RGVF > RF
 - &SURAI v. No SURAI No difference
- Colon Tissue MMC TFV-DP (CHARM 01)
 - TFV-DP VF > RGVF = RF
 - All products exceed tissue cell targets
- PD all formulations demonstrate *ex vivo* protection
- Luminal Distribution
 - D_{max} , D_{ave} VF > RGVF = RF
 - SURAI neutralized these differences
- Dual Isotope HIV v. Drug Distribution
 - 86% (SD 19%) “HIV” c/w “Microbicide”



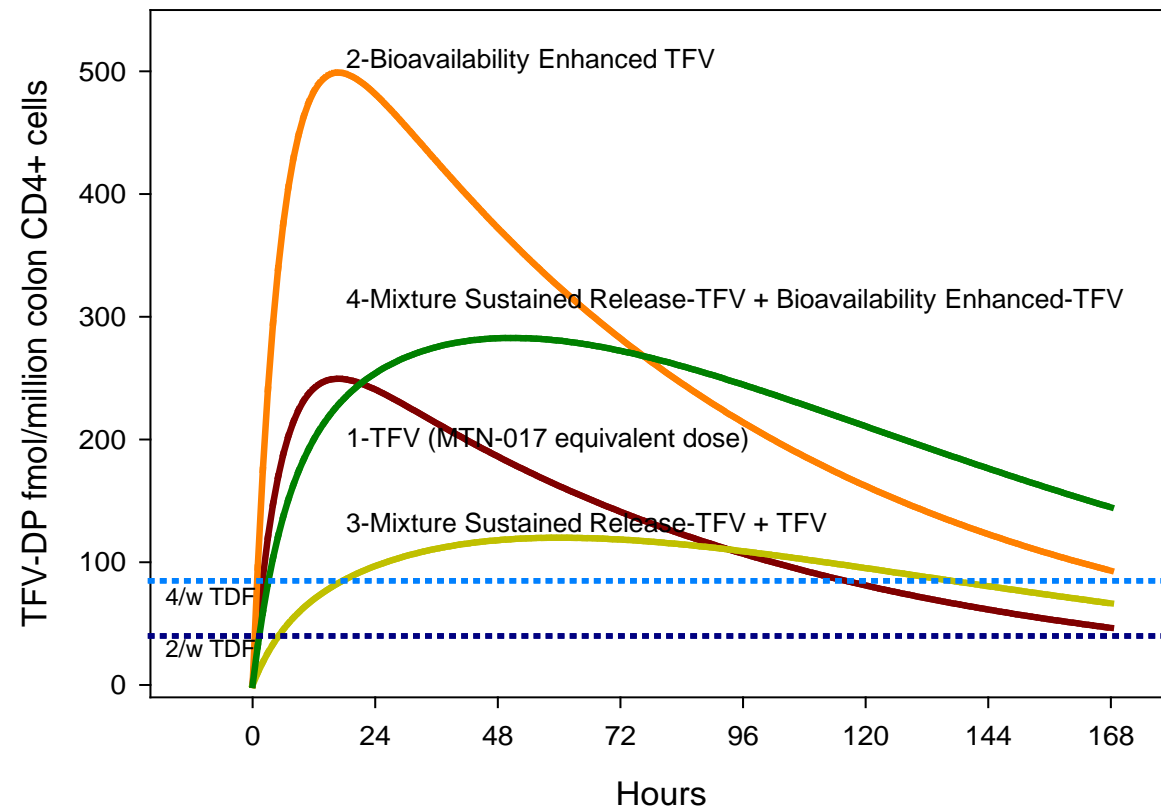
“Microbicide” ($^{111}\text{In-DTPA}$) “HIV” ($^{99\text{m}}\text{Tc-SC}$) in Semen



Rectal TFV gel (0h), SURAI (1h), SPECT/CT (2h)

DREAM: Enema Formulation Development

Single dose enhanced tenofovir enema for behaviorally-congruent PrEP



TFV enema PK Enhancements

- Bioavailability Enhancement (F)
 - Hypotonic vehicle
- Absorption Rate Enhancement (k_a)
 - TFV analogs (TDF, TAF, CMX-157)
- Sustained release (macaque only during DREAM Project)
 - Nanoparticle
 - Gelling agent

Reference Targets

- iPrEx PK/PD analyses (4 TDF doses per week, “4/w TDF”)
- Bridging iPrEx to PK studies
- Colon MMC/CD4+ cell TFV-DP



DREAM: Clinical Studies

- DREAM 01: Single dose, dose escalation, 3 formulations (1x, 3x, 9x), one week
 - PK – luminal distribution, blood/tissue/lumen
 - PD – ex vivo tissue HIV challenge
 - Safety – clinical, laboratory, transcriptomics/proteomics
 - Acceptability
- DREAM 02: Sequence effect (enema → semen vs. semen → enema)
 - DREAM 01 PK readouts
- DREAM 03: Optimal TFV (DREAM 01) v. Optimal TFV prodrug (pre-clinical)
 - DREAM 01 Readouts



DREAM: Program Targeted Outcomes

- Clinical
 - Best naked TFV or TFV prodrug enema
- Macaque
 - Best hypotonic nanoparticle thermoreversible enema
- Topical Dosing
 - 3-D drug penetration model (tissue MALDI)
- Microbicide development PK/PD surrogates
 - Allometric PK & PD scaling (human, macaque, mouse)
- Adherence
 - Quantitative rectal dose adherence monitoring
- Rectal microbicide clinical trial simulation



Thank You!

- Research Participants
- DREAM Team (U19)
- Drug Development Unit
- Clinical Pharmacology Analytical Lab
- NIH/DAIDS
 - Microbicide Trials Network (UM1)
 - Integrated Pre-clinical/Clinical Topical Microbicide Development (U19)
 - Hopkins Center for AIDS Research (P30)