P-S04

Hypo-osmolar Rectal Douche Delivered TFV Distributes TFV Differently Than Oral PrEP

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BACKGROUND

In spite of the oral PrEP with tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) rollout, the rate of new HIV infections remains a major hurdle. In the US alone, the rate of new infections has shifted to predominantly men having sex with men in rural settings where access to PrEP can be an issue, in addition to cost and the need for adherence. As an alternative, we have developed an on demand PrEP approach using TFV-based hypo-osmolar (HOsm) rectal douches that are congruent with sexual behavior. Using stringent intrarectal repeated exposures of macaques to SHIV, this approach has delivered significantly better protective efficacy from virus acquisition compared to oral daily TDF and TDF/FTC PrEP. We therefore attempted to delineate the parameters that my dictate such improved efficacy and tested safety of repeated TFV douching.

METHODS

Sodium based HOsm intrarectal douches were compared to oral daily PrEP for their ability to promote uptake of TFV into the tissue and circulation.

RESULTS

- Hosm rectal douching delivered better protection hrs post administration than oral daily TDF or TDF/FTC PrEP (human 300/200 eq dose, Fig. 1).
- HOsm formulation of TFV douche delivers ~5,000 fmol/mg TFV-DP at 1 hour 2500 fmol/mg TFV-DP in rectal tissues at 24 h post rectal douching.
- Daily oral PrEP only achieves ~200 fmol/mg at steady state (Fig 2)
- TFV-DP levels in all other tissues analyzed including colonic lymph nodes draining the rectal mucosa were between 10-30 fmol/mg (Fig 2).
- Single oral TDF and HOsm rectal TDF achieved the same peak of plasma TFV, but AUC were higher for the oral delivered TDF (Fig 2).
- Rapidly repeated HOsm rectal douching, 5x30 or 60ml was well tolerated
- Single vs repeated HOsm rectal douching achieved similar TFV and TFV-DP levels in colorectal tissues (no accumulation), but significantly higher plasma TFV levels with the higher 60 ml repeated dosing. (Fig 3B).

Figure 1: Efficacy trial against SHIV162p3

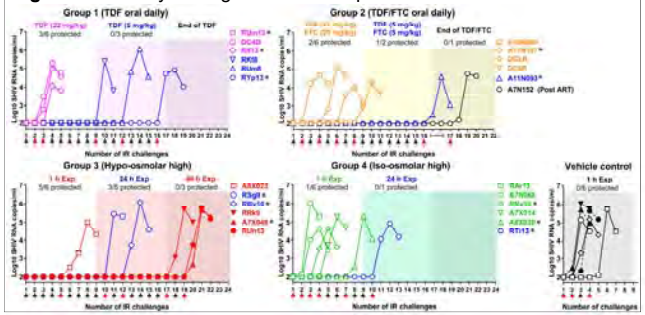


Figure 2: Single dose Rectal Formulation vs Oral TDF PK in Plasma and Tissue

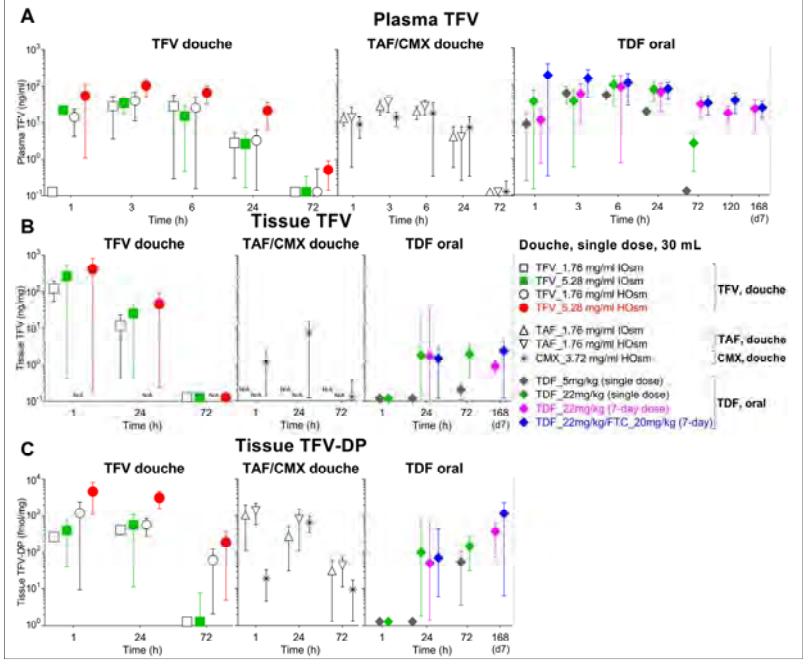


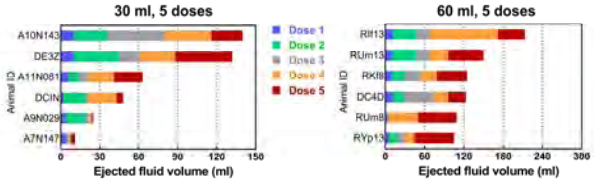
Table 1. Median Pharmacokinetic Parameters of Rectal Formulations vs Oral TDF

Single dose Enema formulation (mg/ml)	Plasma TFV (ng/ml) C_{max}	Plasma TFV (h) T_{max}	Plasma TFV (ng·h/ml) AUC24h	Tissue TFV (ng·h/mg) AUC24h	Tissue TFV-DP (fmol·h/mg) AUC24h
TFV, 1.76, IOsm	28	3	459	1,865	7,587
TFV, 5.28, IOsm	35	3	294	3,520	11,562
TFV, 1.76, HOsm	40	3	457	–	19,928
TFV, 5.28, HOsm	103	3	1,247	5,580	91,548
TAF, 1.76, IOsm	28	3	340	–	16,294
TAF, 1.76, HOsm	37	3	439	–	29,403
CMX, 3.72, HOsm	18	6	333	126	7,822
Oral regimen dose (mg/kg)					
TDF, 5, single dose	59	3	933	0	0
TDF, 22, single dose	99	6	1,927	20	1,139
TDF, 22, 7-day dose	87	6	1,703	21	611*
TDF, 22 (+FTC, 20), 7-day dose	177	1	2,595	17	861*

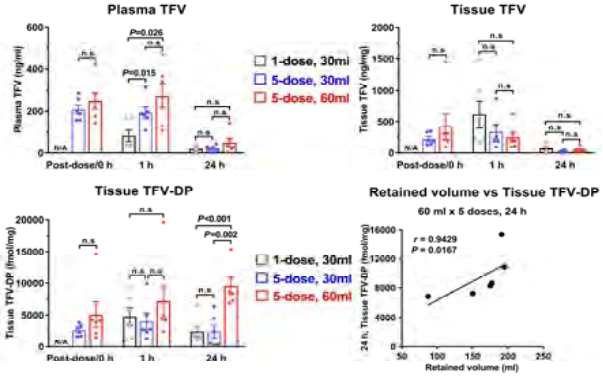
*P <0.001, single HOsm 5.28 douche **vs** Oral PrEP (AUC24h)
P =0.011, single HOsm 5.28 douche **vs** Oral steady-state PrEP (AUC7-day)

Figure 3: Repeat douching PK and Toxicity test of 5.28 HOsm

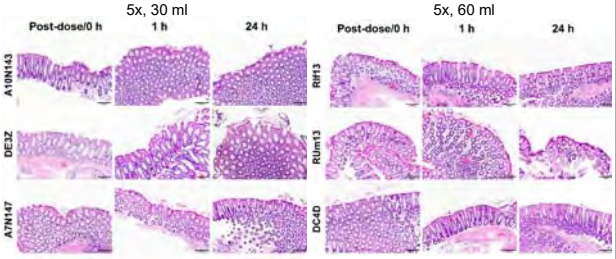
A. Ejected Fluid volumes after 5x Douching: 30 ml vs 60 ml



B. Plasma and Tissue PK: Single vs 5x Douching



C. No Detectable Mucosal Damage after 5x Douching



CONCLUSIONS

TFV 5.28 mg/ml HOsm douching showed the highest protection efficacy and appeared well tolerated even after multiple administration within 30 minutes. The most salient parameter potentially associated with protection from rectal infection appeared to be the considerably higher levels of TFV-DP at the mucosa but not in draining or distal lymphoid tissues, suggesting that drug levels at the portal of entry are critical for preventing mucosal virus acquisition.