IAS 2021

MPT issue: Contraceptive efficacy and safety and acceptability of IVR; and current evidence on anti-HSV-2 and anti-HIV IVR activity

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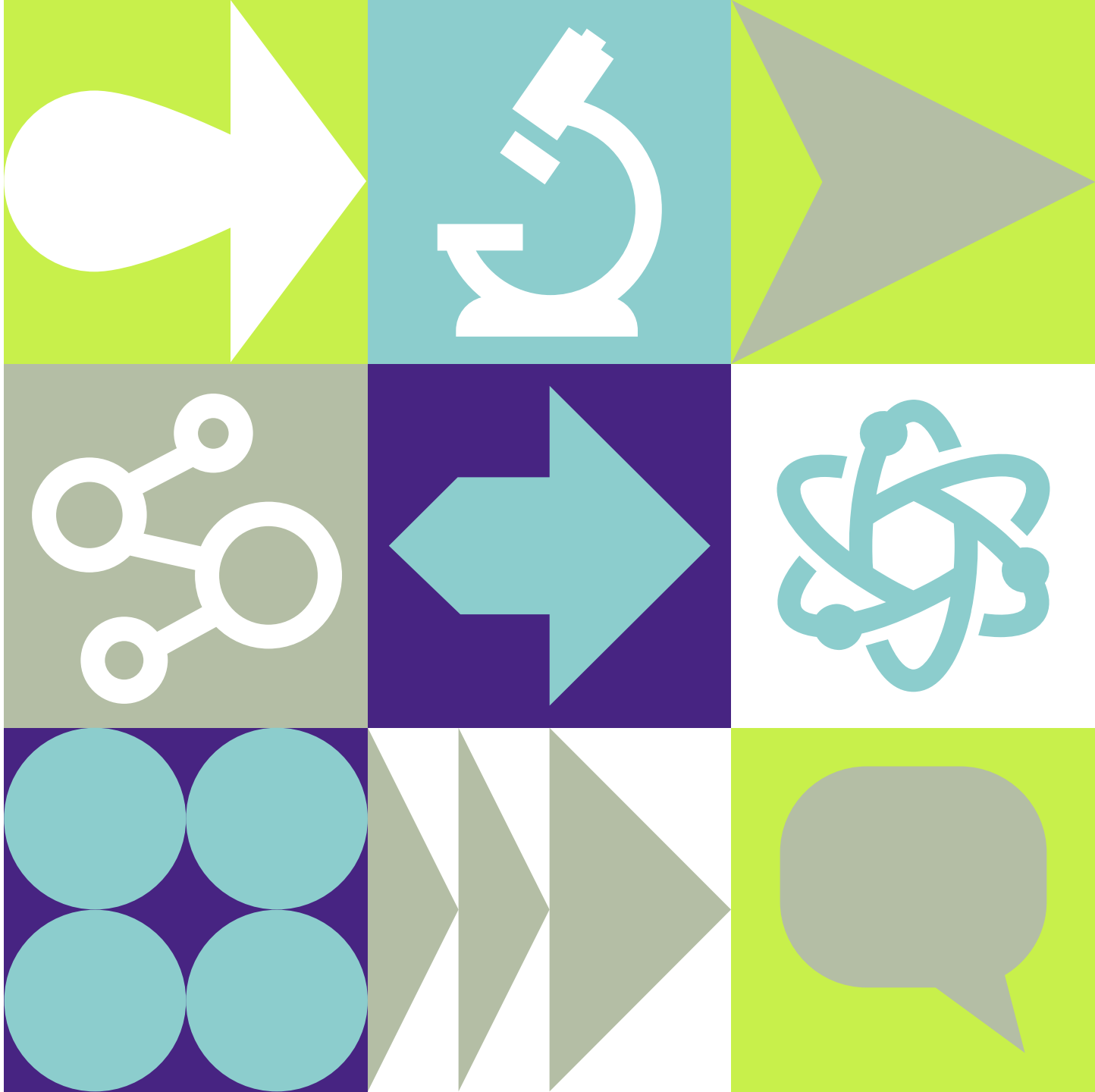
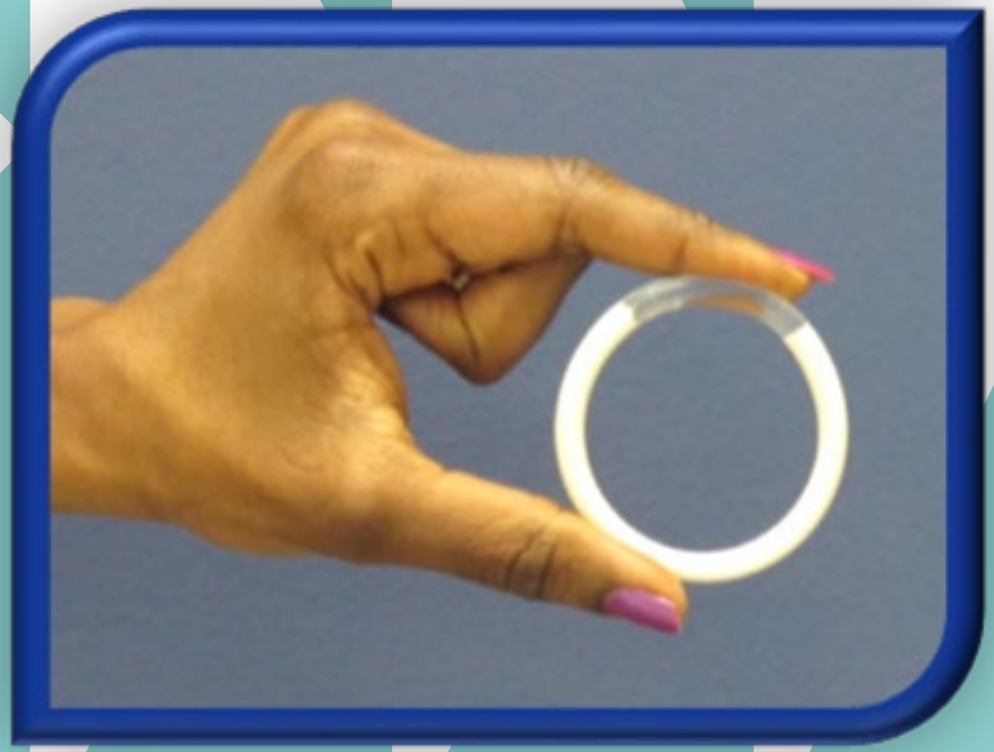


I have no conflicts of interest to disclose



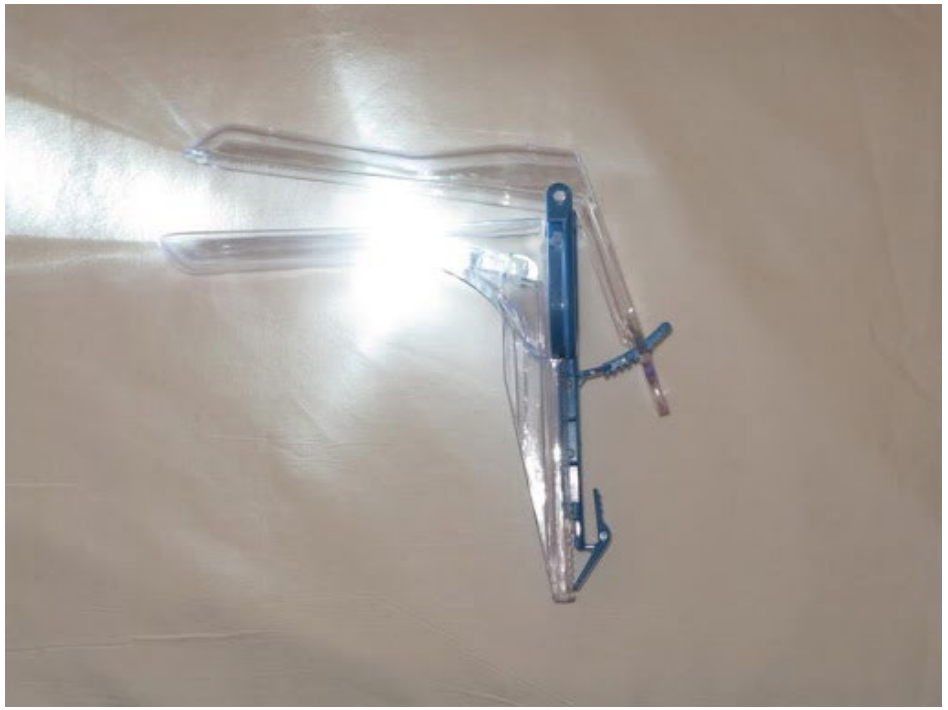
TFV (HIV/HSV2) and TFV/LNG (HIV/HSV2/FP) IVRs - Completed Phase I Studies

Study	#NCT	Products, Duration of Use, Number of Participants with all visits (N = 188)	Sites	References
CONRAD 128	NCT02235662	TFV, TFVLNG, Placebo; (2:2:1) 15 days continuous N = 50	CONRAD (Norfolk, VA) and Profamilia (Dominican Republic)	Thurman AR et al. PLoS One, 2018, 13(6): e0199778. Thurman AR et al. Plos One, 2019; 14(5) e0217229.
CONRAD 138 (ENRICH)	NCT03279120	TFVLNG (Continuous or Cyclic), Placebo (Continuous or Cyclic) (4:4:1:1); 90 days N = 40	CONRAD and Profamilia	Thurman et al. HIV R4P 2021
CONRAD 140	NCT02722343	F/TDF, TFV IVR (1:1); 14 days N = 22	CONRAD	Submitted to JAIDS
CONRAD 144	NCT03762382	TFV, TFVLNG, Placebo (2:2:1); 36 – 90 (median 68d) continuous N = 27	Kenya Medical Research Institute, Kisumu, Kenya	Mugo et al. HIV R4P 2021
MTN038	NCT03670355	TFV, Placebo (2:1) 90 days N = 49	San Francisco DOH, Univ. Pittsburgh, Univ. Alabama	Data under review, study completed

Completed Phase I Studies - Endpoints Tested

CLINICAL SAFETY:

- Incidence of TEAEs similar across treatment groups
- No colposcopic findings (CONRAD 128)
- No genital ulcers (CONRAD 128) even among sexually active women using product for up to 90 days (CONRAD 138, 144)



SUB CLINICAL SAFETY (Epithelial and immune markers)

No statistically significant changes from baseline at 90 days:

- **Ectocervical tissue histology or the density and phenotype of ectocervical lymphocytes or changes in phenotypes of these cells** (CD45, CD3, CD8, HLADR+, CD4+, CCR5+) (all p values > 0.07)

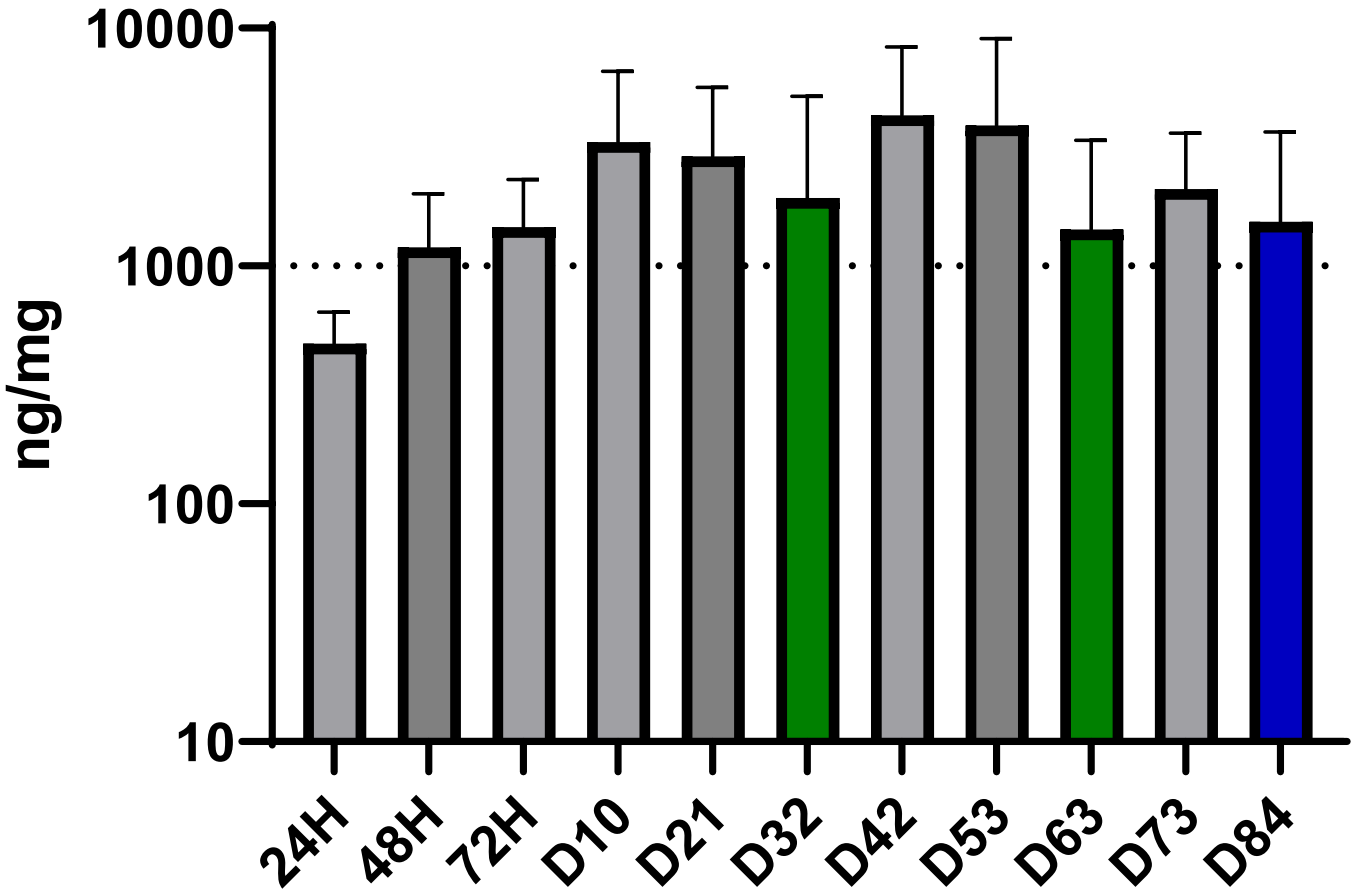
- **Secreted soluble proteins from the CV mucosa** (IP-10, GM-CSF, IL-10, IL-1α, IL-6, MIP-1α, RANTES, TNFα, IL-8, HBD2, SLPI, IL-1RA) (all p values > 0.12)

Impact on Menstrual Cycle (P only contraceptive)

Impact on cycle n (%) (users may report more than one impact)	Dosing Regimen and Agent						Month 1 p value	Month 3 p value
	TFV/LNG Continuous		TFV/LNG Interrupted		Placebo Continuous and Interrupted			
	Month 1 (n = 18)	Month 3 (n = 16)	Month 1 (n = 16)	Month 3 (n = 14)	Month 1 (n = 10)	Month 3 (n = 10)		
No change in cycle	8 (44.4)	6 (37.5)	6 (37.5)	6 (42.9)	5 (50.0)	6 (60.0)	0.81	0.52
Fewer days and/or lighter bleeding	6 (33.3)	5 (31.3)	6 (37.5)	5 (35.7)	4 (40.0)	2 (20.0)	0.93	0.70
Heavier and/or more days	4 (22.2)	4 (25.0)	4 (25.0)	2 (14.3)	1 (10.0)	0 (0.0)	0.63	0.22
More irregular menstrual bleeding	3 (16.7)	4 (25.0)	2 (12.5)	2 (14.3)	1 (10.0)	1 (10.0)	0.87	0.57

Andrea Thurman, MD

TFV PK in Vaginal Fluid

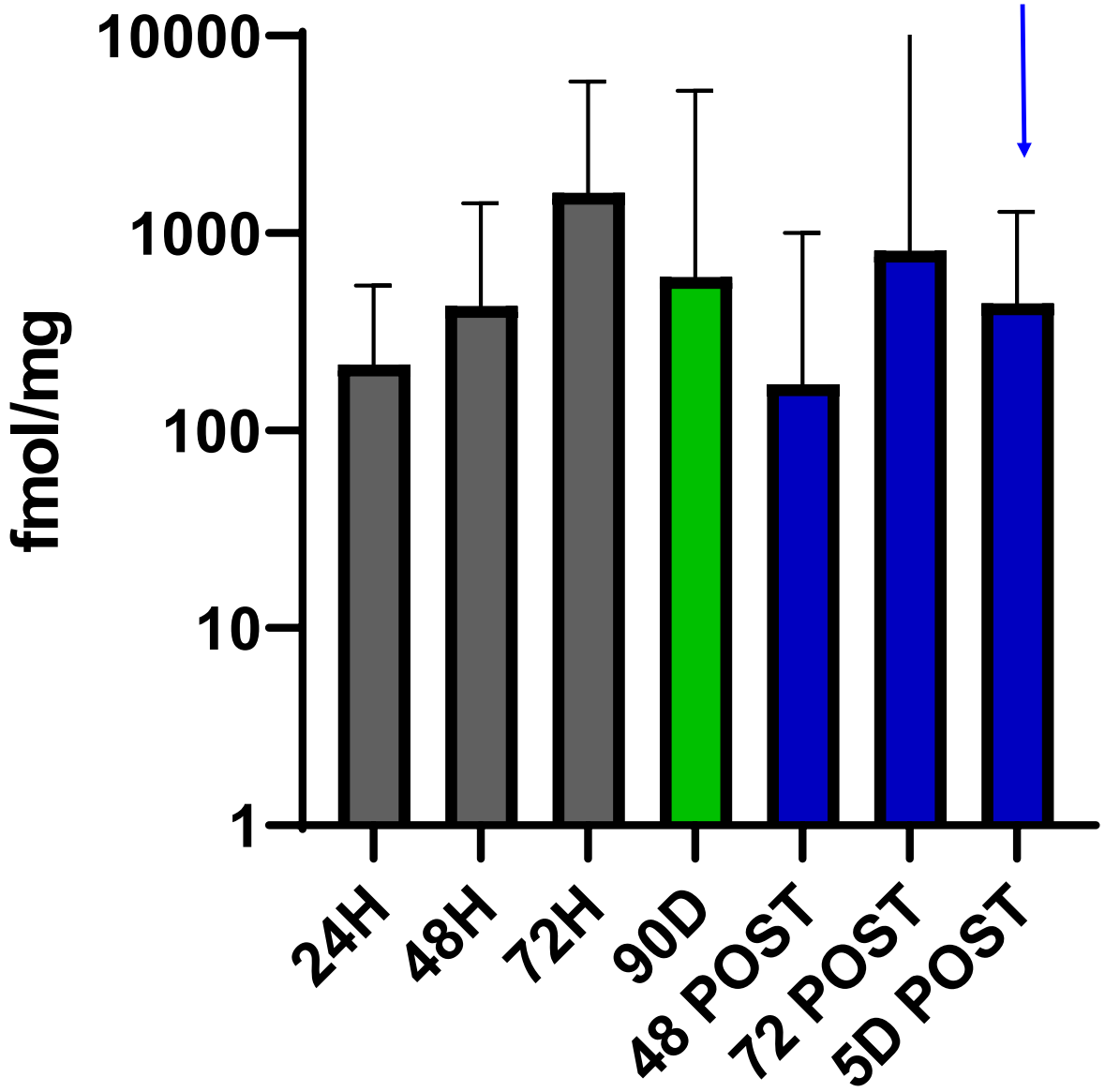


Dose of TFV is 8 – 10 mg/day

1000 ng/mL is TFV benchmark for TFV gel in CAPRISA 004

Green = Includes data from trough post 3d removal in cyclic
Blue = EOT

TFV-DP PK in Vaginal Tissue



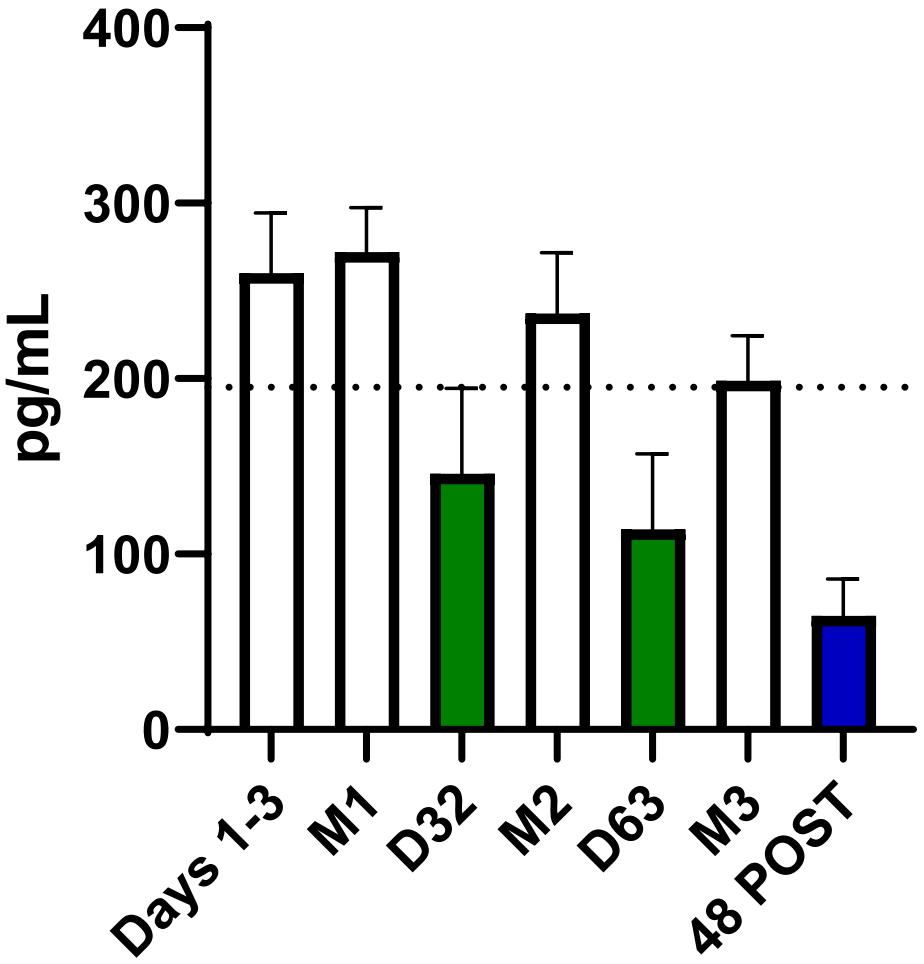
LONG TAIL for TFVDP = Forgiveness for IVR removals

1000 fmol/mg TFVDP in tissue benchmark from NHP SHIV challenge with TFV gel.

Black = Immediate Post IVR insertion
Green = End of Treatment
Blue = Post IVR Removal

LNG PK in Serum*

Unit dose of LNG is ~20 µg/day

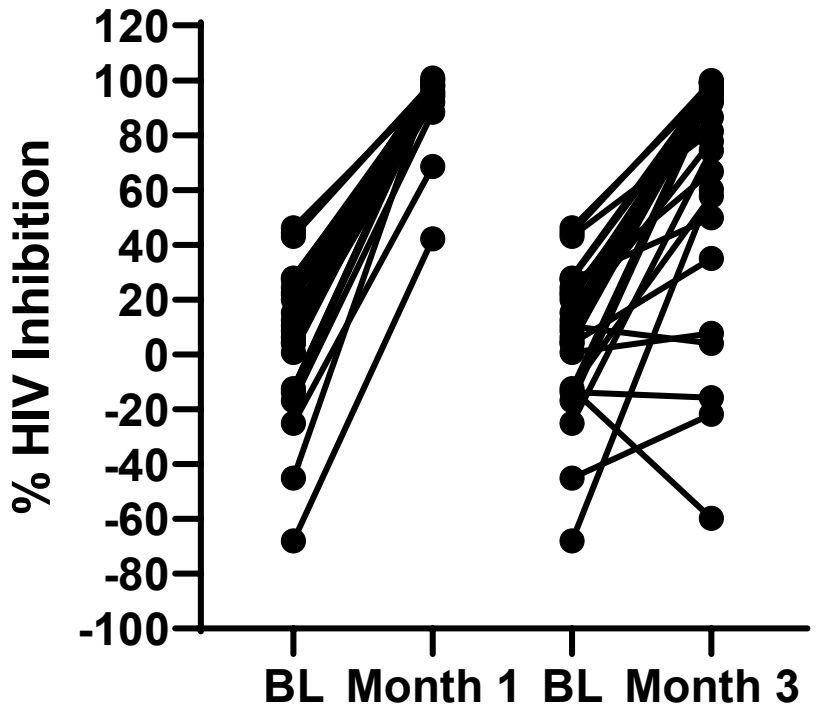


LNG 180 – 300 pg/mL, measured by RIA is the benchmark for systemically delivered LNG (Jadelle, Norplant)

* (pg/mL LC-MS/MS)

Days/months Post IVR Insertion
Green Bars contain trough values after 3d removals
Blue = 48 hours post removal

TFV Anti-HIV PD Modeled Ex Vivo



p < 0.01 change in pre-insertion to months 1 and 3

138 Study, Both Sites

HIV P24 endpoint	**HIV P24 antigen production** (pg/mL) from **placebo and baseline** ectocervical and vaginal tissue biopsies		**HIV P24 antigen production** (pg/mL) from ectocervical tissue biopsies after 3 months of **TFV/LNG IVR use**		P
	N	**Median**	N	**Median**	
SOFT	44	**300**	12	**6**	0.55
AUC	44	**1074**	12	**102**	0.23
CUM	44	**384**	12	**36**	0.55
Day 21	44	**140**	12	**6**	1.00

138 Study, EVMS Site Only

TFV Anti-Herpes Activity

CAPRISA 004: 15.5 cases/100 person years HSV-2 incidence. TFV VF concentrations of 10,000 ng/mL had 63% protection against HSV-2 vs. no TFV detected.

Abdool Karim SS et al. N Engl J Med. 2015;373(6):530-9.

VOICE: HSV-2 incidence 21 vs. 12/100 person years with positive TFV in plasma vs. negative TFV in plasma.

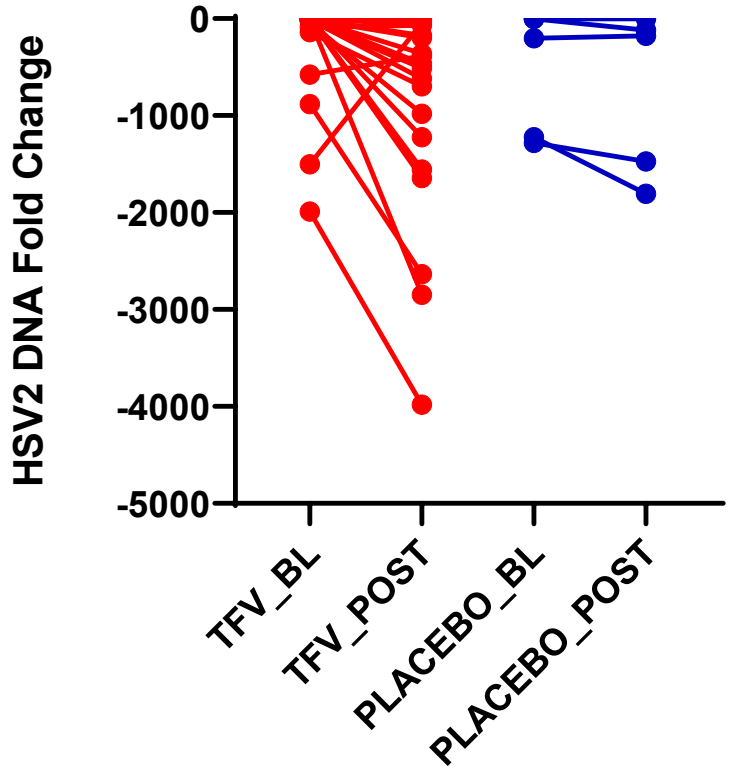
Marrazzo J et al. AIDS Res Hum Retroviruses. 2014;30 Suppl 1:A31.

In vitro anti-HSV-2 activity *(IC50)* (human lymphoid and CV tissues, keratinocytes, 3D rafts) is 10,000 – 200,000 ng/mL

Andrei G et al. Cell Host Microbe. 2011;10(4):379-89.

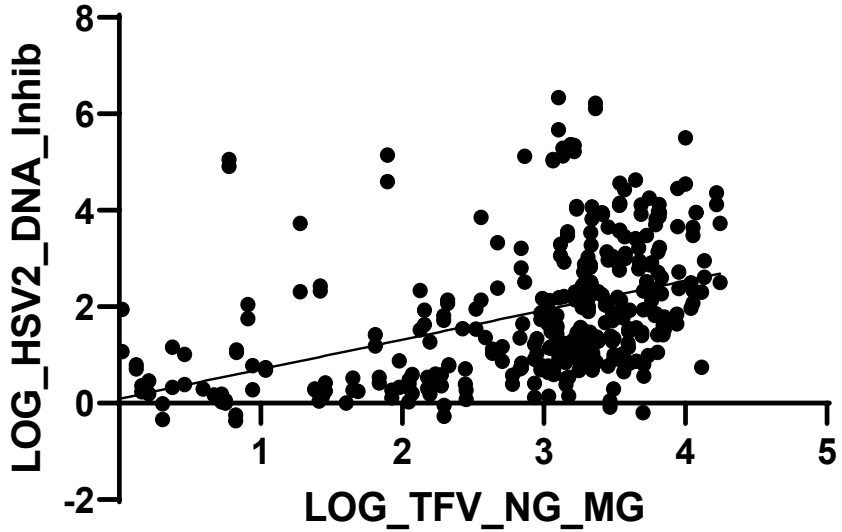
TFV Anti-HSV2 PD Modeled Ex Vivo

DNA HSV2 Fold Change with Placebo vs. TFV IVRs



Placebo p = 0.34
TFV Containing IVRs p < 0.01

HSV2 DNA Inhibition vs. VF TFV ACTIVE IVRs ONLY



R = 0.51, p < 0.0001

TX Group	HSV2 DNA Fold Inhibition		p
	< 20 fold	20 fold or more	
Placebo Both	83 (69%)	37 (31%)	< 0.01
TFVLNG Both	157 (42%)	215 (58%)	

HEC1A assay **CONRAD 138**

CONRAD 144 Study Kenya

IAS 2021
18 –21 July

LNG Surrogates of Contraceptive Efficacy

Period and Variable	TFV/LNG Continuous (n = 18)	TFV/LNG Interrupted (n = 17)	Placebo Continuous (n = 5)	Placebo Interrupted (n = 5)
Cervical Mucus Insler Score (Median, normal > 10)				
Month 1	6.0	5.0	11.0	12.0
Month 2	7.5	5.5	13.0	13.0
Month 3	7.0	7.0	12.0	13.0
Sperm Migration Assay (N and % Normal)				
Month 1	1 (5.6%)	2 (11.8%)	5 (100%)	3 (60.0%)
Month 2	4 (22.2%)	4 (23.5%)	4 (80.0%)	5 (100%)
Month 3	4 (22.2%)	4 (23.5%)	4 (80.0%)	5 (100%)
Monthly Ovulation by Serum Progesterone (N and % Ovulation)				
Month 1	7 (38.9%)	8 (47.1%)	5 (100%)	5 (100%)
Month 2	10 (62.5%)	8 (50.0%)	5 (100%)	5 (100%)
Month 3	10 (71.4%)	11 (68.8%)	5 (100%)	5 (100%)

All TFVLNG IVR users had AT LEAST ONE SURROGATE of contraceptive efficacy

CONCLUSIONS

- TFV/LNG and TFV IVRs are **safe** and do not cause epithelial disruption (ie, no genital ulcers)
- **Acceptable** in US, Kenyan and Dominican populations of women with minimal menstrual cycle changes due to micro-dose LNG
- TFV and LNG met **PK benchmarks**
- HIV and HSV PD models support in vivo **antiviral activity**
- LNG PD surrogates support in vivo **contraceptive activity**
- **Five clinical studies** completed, including one in Africa
- MPT ring performance supports **further clinical advancement**

Acknowledgements

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