CROI 2023: HIV Prevention Updates

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AETC AIDS Education & Training Center Program Mountain West

Data Considerations

Data in this presentation offer a limited perspective of how systemic, social, and economic factors impact health. We recognize that racism, not race, creates and perpetuates health disparities.

To Learn More:
https://www.cdc.gov/minorityhealth/racism-disparities

Cabotegravir

LEVI SYNDROME, PK DATA WITH MISSED DOSES

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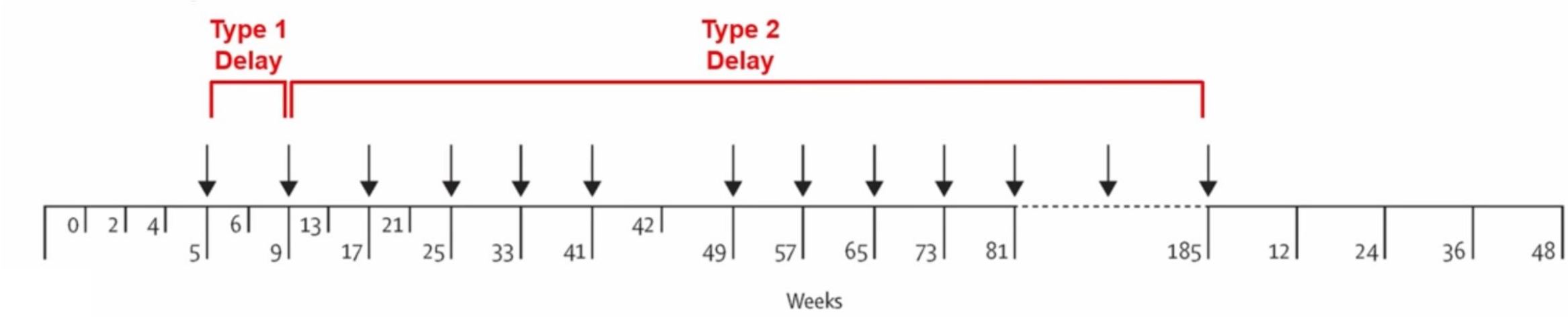
HPTN 084: Evaluation of delayed CAB-LA injections

- COVID disruptions led to missed/delayed injections
- Among those randomized to CAB arm during blinded period who had ≥1 delay:
  - Type 1 delay: 2nd injection (wk 9) took place 8-14 wks after first injection (wk 5)
  - Type 2 delay: Any subsequent injection took place 12-18 wks after the prior dose



Marzinke MA, et al. CROI 2023 Abstract 159

Therapeutic CAB-LA detected 12 weeks after missed injection

- 194/1614 participants (12%) had ≥1 delayed injection 224 total delays
  - 19 Type 1 delays btwn 1st and 2nd injection
  - 205 Type 2 delays while receiving injections every 2 months
- Median time from enrollment to injection delay: 49 wks
- Therapeutic concentrations maintained up to 12 weeks

[CAB] Trough	8-10 weeks Between Injections	10-12 weeks Between Injections	12-14 weeks Between Injections
	N=11	N=4	N=4
>8x PA-IC_{90}	10 (91%)	2 (50%)	0 (0%)
>4-8x PA-IC_{90}	1 (9%)	1 (25%)	1 (25%)
1-4x PA-IC_{90}	0 (0%)	1 (25%)	3 (75%)
<1x PA-IC_{90}	0 (0%)	0 (0%)	0 (0%)

Type 1 delays

Marzinke MA, et al. CROI 2023 Abstract 159

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Therapeutic CAB-LA detected 18 weeks after missed injection

- At 18 weeks (4.5 months) after 2nd injection, >85% of participants maintained therapeutic CAB levels
- Persons with BMI <26 (median for cohort) were more likely to maintain levels >8x PA-IC_{90} after a delay

[CAB] Trough	12-14 weeks Between Injections	14-16 weeks Between Injections	16-18 weeks Between Injections
	N=109	N=57	N=39
>8x PA-IC_{90}	95 (87%)	48 (84%)	24 (62%)
>4-8x PA-IC_{90}	12(11%)	6 (11%)	11 (28%)
1-4x PA-IC_{90}	1 (1%)	2 (4%)	2 (5%)
<1x PA-IC_{90}	1 (1%)	1 (2%)	2 (5%)

Type 2 delays

Marzinke MA, et al. CROI 2023 Abstract 159

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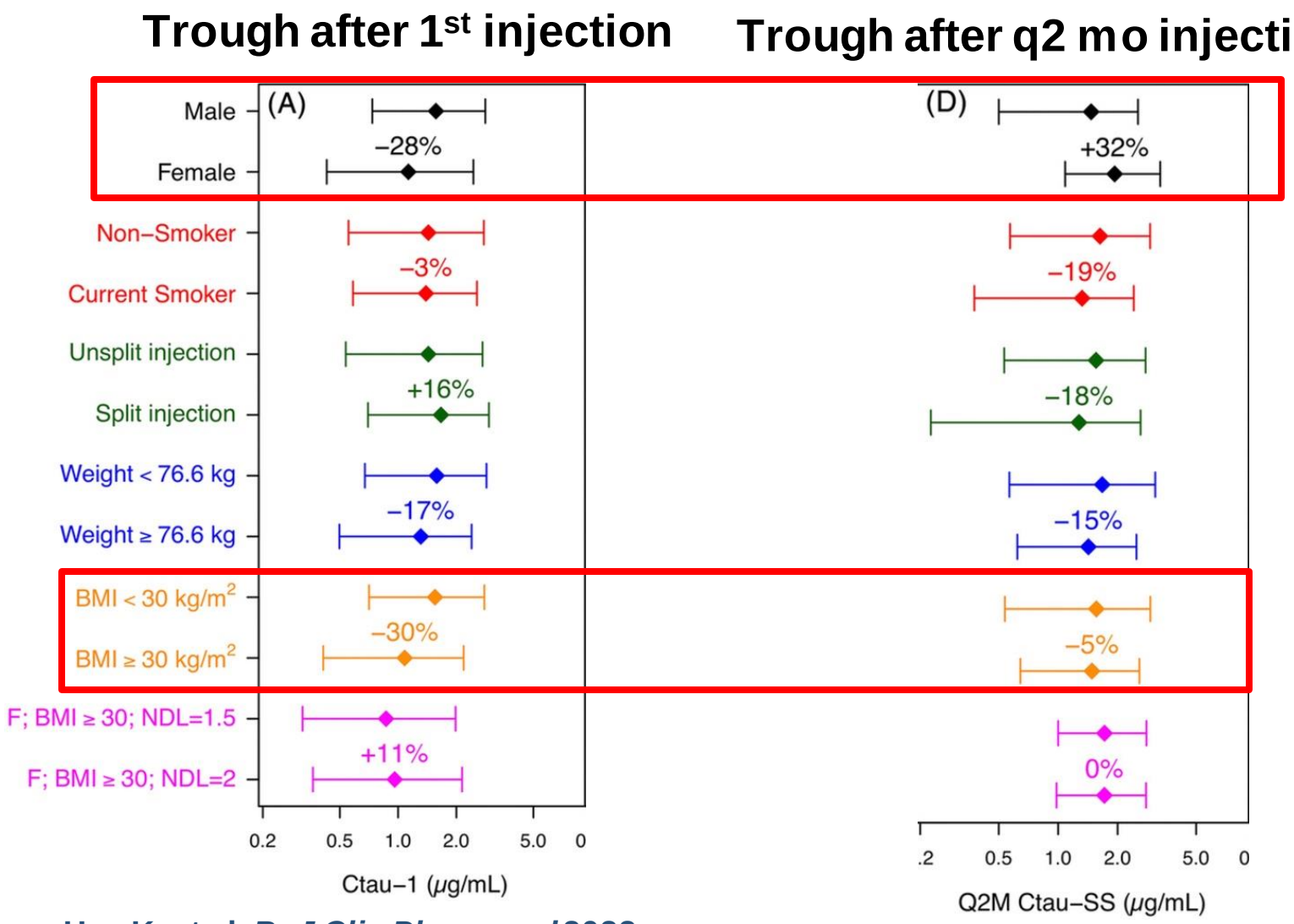
Factors associated with favorable PK for CAB-LA



- No association with age & race
- CAB accumulates in women at steady state; lower absorption rate constant
- BMI >30 associated with lower CAB troughs

Han K, et al. *Br J Clin Pharmacol* 2022

HPTN 084 PK data: Conclusions

- Despite delayed injections up to 6 weeks (12-14 weeks between injections), CAB-LA remained therapeutic at >4x inhibitory concentration in 98% and >8x in 87% of participants
- Up to 6 weeks “forgiveness” period may be feasible for AFAB persons receiving CAB-LA injections for PrEP
- Quarterly (q3 months) dosing strategy for AFAB persons ***may*** be plausible but needs to be studied

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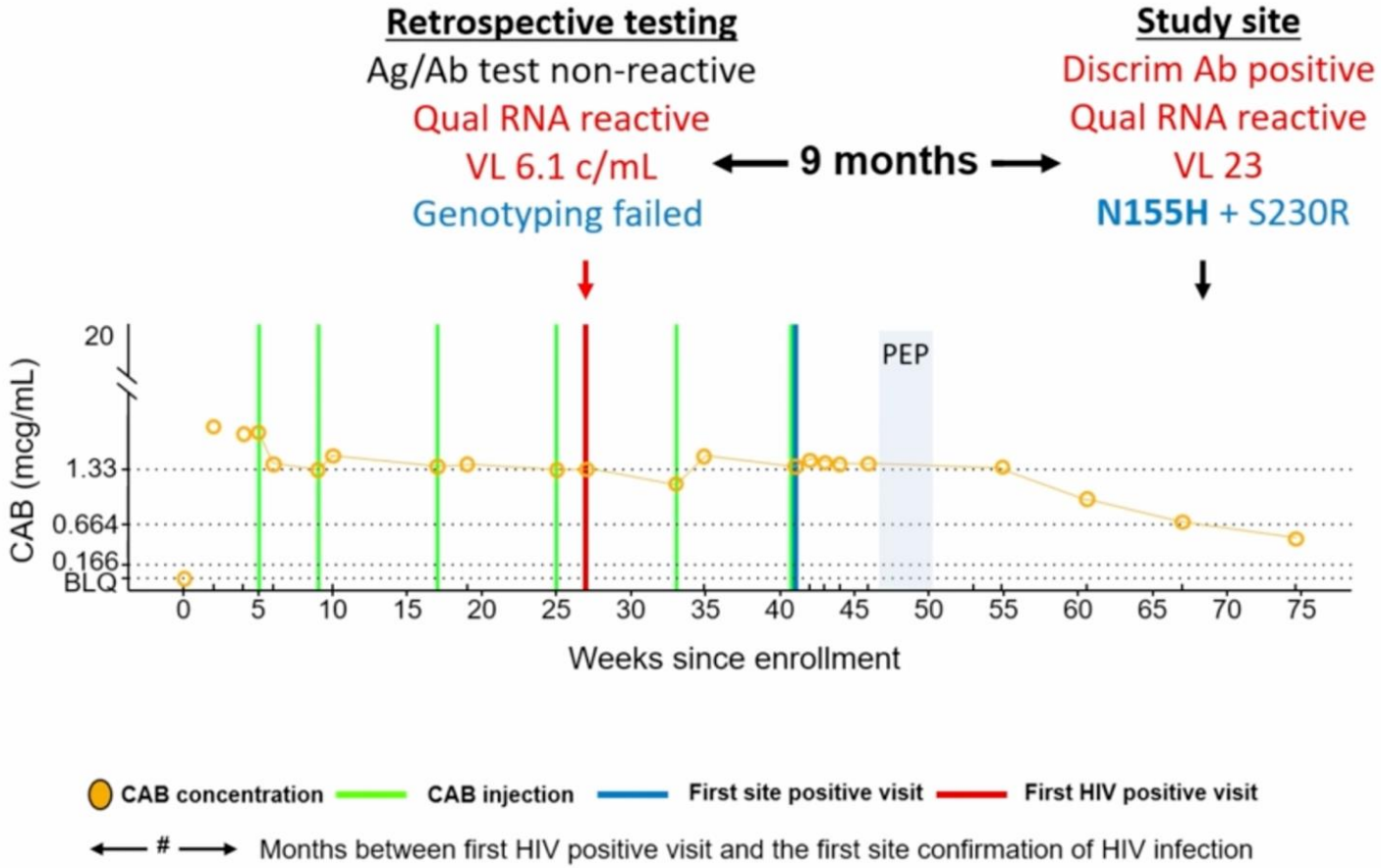
Long-acting early viral inhibition (LEVI) syndrome

- Viral suppression and delayed/decreased Ab formation → false negative Ag/Ab and rapid HIV tests
- In HPTN 083: 6 HIV infections of 2,282 participants despite on-time injections.
- Detection was delayed for 50% of new HIV infections



Eshleman S, et al. CROI 2023 Abstract 160

Acute HIV vs LEVI syndrome

	AHI	LEVI
Cause	Phase of natural HIV infection	Long-acting anti-viral PrEP agent (prototype: CAB-LA)
Onset	New infection	Infection during PrEP Initiation of PrEP agent during acute/early infection
Viral replication	Explosive	Smoldering
Symptoms	Fever, chills, rash, night sweats, muscle aches, sore throat, fatigue, swollen glands	Minimal, variable, often no symptoms reported
Detection	Ag/Ab assay, RNA assays (including less sensitive POC and pooled tests), DNA assays, total nucleic acid assays	Ultrasensitive RNA assay (often low or undetectable RNA, low/undetectable DNA, diminished/delayed Ab production)
Assay reversion	Rare	Common for many test types
Duration	1-2 weeks (until Ab detection)	Months (until viral breakthrough, drug clearance, or ART start); can persist months after the anti-viral agent is discontinued
Transmission	Very likely	Unlikely (except possibly through blood transfusion)
Drug resistance	No (unless transmitted)	Yes (can emerge early when viral load is low)

Eshleman S, et al. CROI 2023 Abstract 160

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LEVI syndrome: Conclusions

- Incident HIV infections were rare in HPTN 083 and 084 with timely injections
- INSTI resistance was detected in 10 of 18 cases when CAB was administered within 6 months of 1st (retrospective) HIV positive visit
- No INSTI resistance occurred when 1st (retrospective) HIV positive visit was >6 months from last CAB dose
- Sensitive VL assay is crucial component of monitoring while on CAB-LA as PrEP and can detect new HIV infection before INSTI resistance emerges
- Will LEVI syndrome occur with other long-acting prevention agents?

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CAB rapid fire!

- **HPTN 083 (Scott):** Dramatic reduction in HIV incidence with CAB-LA vs oral PrEP in Black MSM/TGW (HR 0.28, 95% CI: 0.096 – 0.834); low oral PrEP adherence (65% vs 81% in non-Black participants)
- **HPTN 083 (Clement):** 96% of 800 participants chose CAB-LA over oral PrEP in OLE
- **HPTN 084-01 (Hosek):** High interest, adherence in African AGYW <18 y/o. Safe and tolerable. No incident HIV infections. 92% chose CAB-LA in OLE
- **What we still don't know (Solomon)**
  - Phase III trials in PWID; interactions with substances of misuse, buprenorphine, etc.
  - Use in people who are released from jails/prison, unstably housed persons, etc.
  - Real-world acceptability – discontinuations due to ISRs
  - Need for oral ART to cover PK tail in persons who didn't want oral meds

Scott H, et al. Abstract 161; Clement M, et al. Abstract 994; Hosek S, et al. Abstract 162; Solomon S. Abstract 25

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Oral PrEP in Women

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Pooled efficacy and adherence for F/TDF among cis women

Aim: Evaluate efficacy (HIV incidence) and adherence among 6296 cis women across 11 demo projects in US, India, South Africa, Botswana, Kenya

Overall Adherence Scale	Objective Adherence* n = 237 (DBS, fmol/punch)		Subjective Adherence, n = 2887					
			ECM	PC	SR		SS	
≥7 Tablets	≥1250		≥7 Tablets				Excellent	
4–6 Tablets	700 – <1250	*or*	4–6 Tablets			or	Very Good / Good	
2–3 Tablets	350 – <700		2–3 Tablets				Fair	
<2 Tablets	<350		<2 Tablets				Poor / Very Poor	

*51 participants had only TFV plasma level data; those with TFV ≥40 ng/mL were assigned to the 4–6 Tablets group, and those with TFV <40 ng/mL to the <2 Tablets group
DBS, dried blood spot
Brooks K, Anderson, P. Clin Pharmacol Ther. 2018;104:1056-9

Marrazzo J, et al. CROI 2023 Abstract 163

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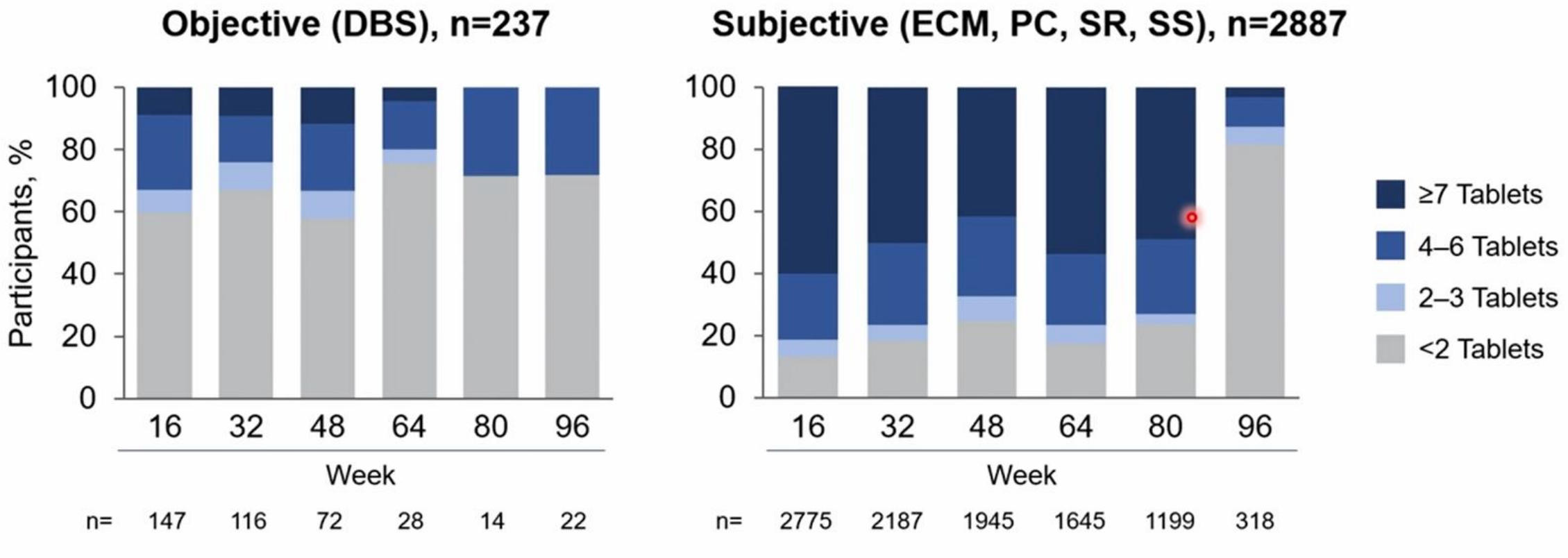
Discordance in adherence metrics among cis women



Adherence declines over time for both subjective and objective measures

Marrazzo J, et al. CROI 2023 Abstract 163

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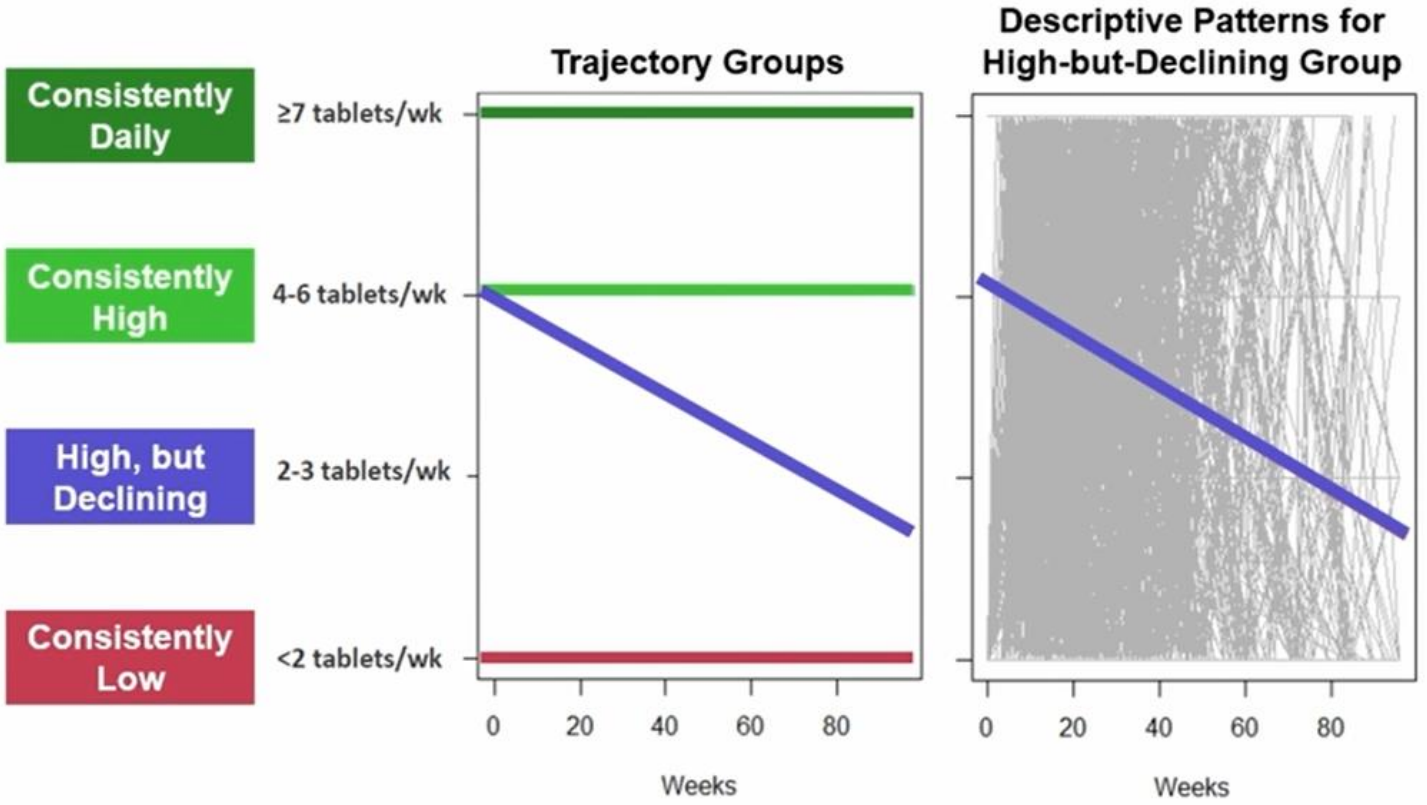
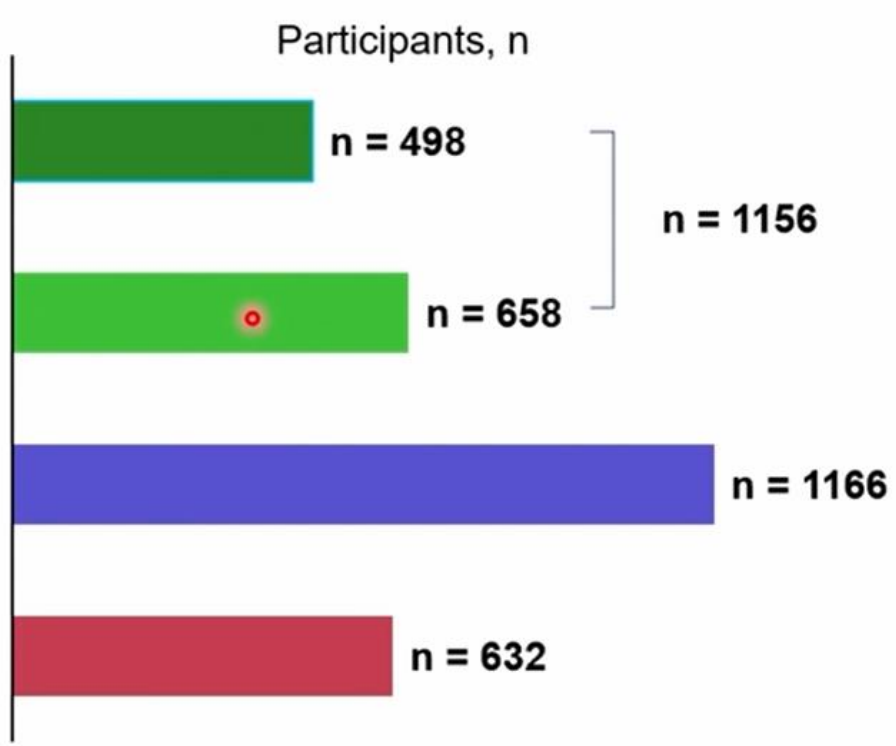
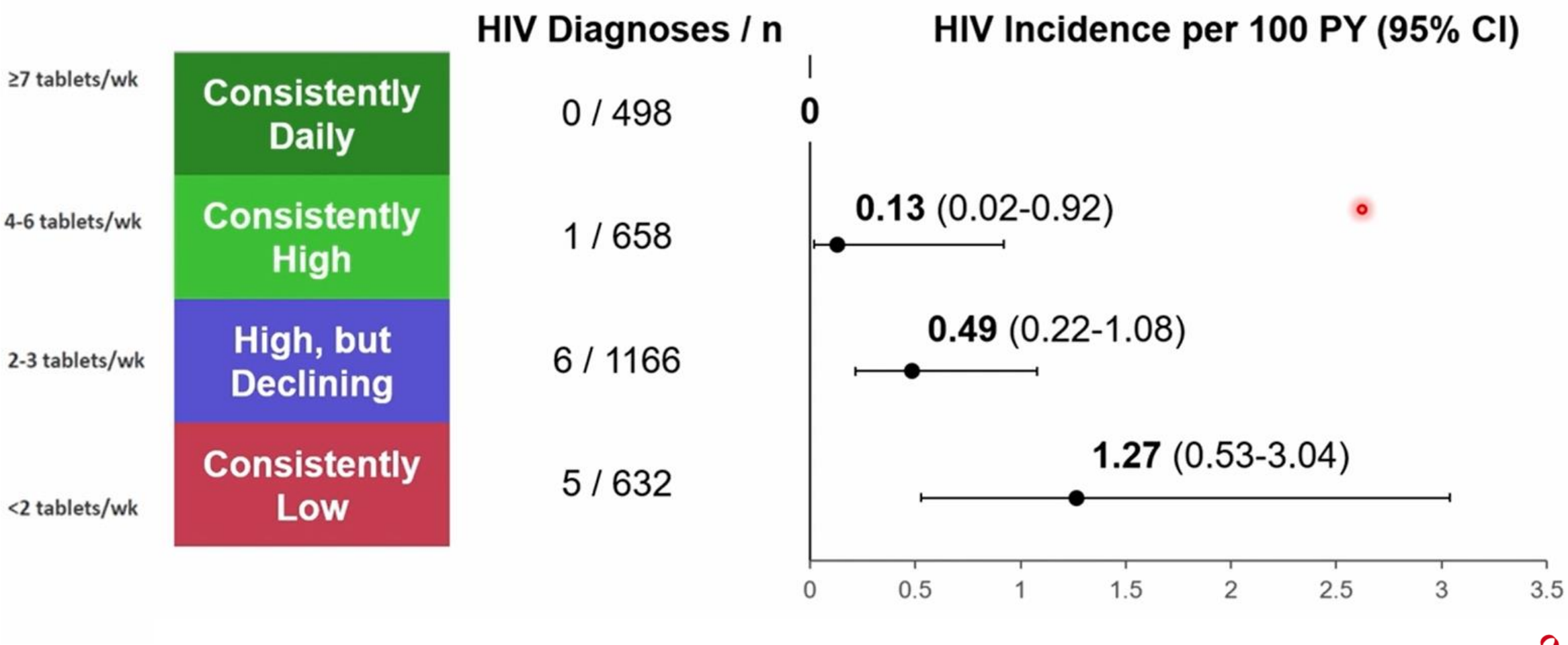
F/TDF adherence patterns among cis women





Marrazzo J, et al. CROI 2023 Abstract 163

HIV incidence by adherence category for cis women



Marrazzo J, et al. CROI 2023 Abstract 163

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Oral PrEP in cis women: Conclusions

- Even with low HIV incidence, better adherence associated with lower risk
- Given inconsistent adherence to oral PrEP, long-acting agents may be preferred for this population
- F/TDF is similarly effective for cis women taking ≥ 4 tablets vs 7 tablets/week

Could this shift the paradigm for counseling re: time to protection?

Is 4 pills/week enough for women as we have said for cis MSM?

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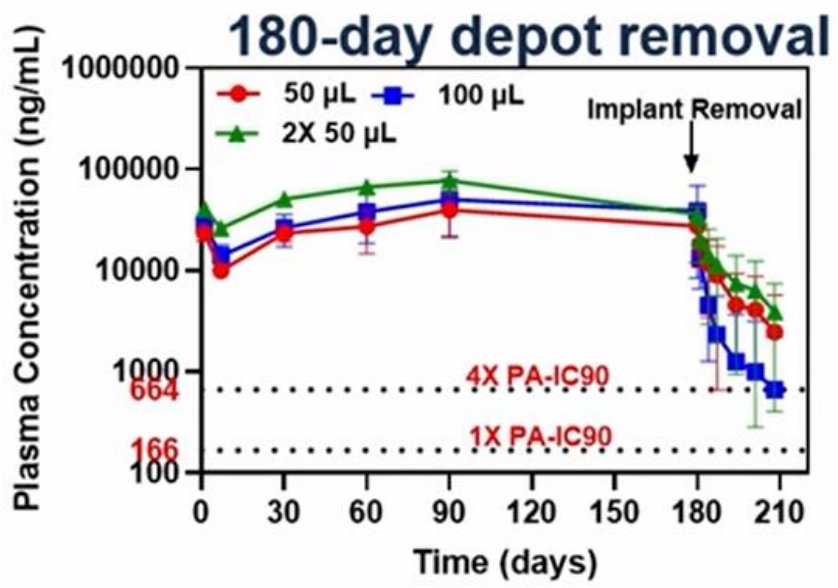
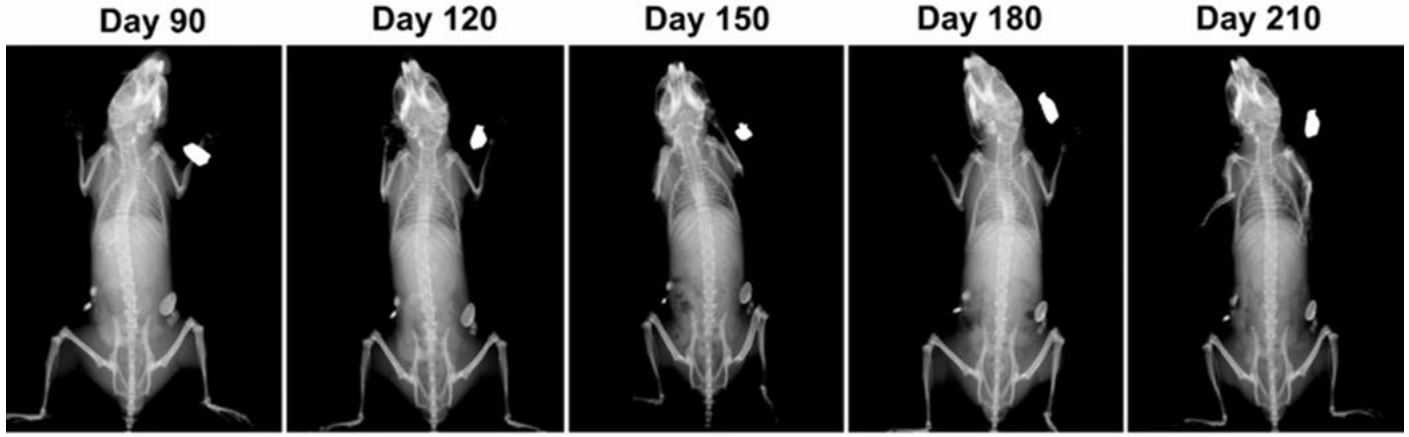
What's hot and new!

ANTIVIRAL RECTAL INSERTS, LONG-ACTING IMPLANTS & OTHER AGENTS, MICROBIOTA

Ultra-long acting in-situ forming implant with CAB

- SQ injection of biodegradable polymer mixed with solvent and drug(s) of choice
- Expected duration of action: 1 year at >4x PA-IC_{90} in female macaques and mice
- After implant removal at 180 days, CAB plasma levels drop but persist (25% drug and 15% polymer left) – PK tail data still pending





Young IC, et al. *Nature Comm*, 2023. Young I, et al. CROI 2023 Abstract 991

On-demand inserts for HIV PEP or PrEP

- Fast-dissolving product (TAF 20mg + EVG 16 mg) demonstrated efficacy in NHP SHIV challenges using 1 vaginal or 2 rectal inserts

- Phase 1, single-arm, OL study: PK/PD after use of 1 or 2 rectal inserts in humans
  - 1 drug-related AE – mild anal erythema
  - Rectal TFV plasma level peak was 12x lower than with oral dosing
  - EVG levels present 2-24 hrs, tenofovir sustained 48-72 hrs
  - Levels for TFV-DP exceeded those compared to steady state concentrations at 4 or 7 tabs/wk of oral TDF in HPTN 066

Dobard, et al. *eBioMedicine*, 2022. Makarova, et al. *eBioMedicine*, 2022. Riddler S, et al. CROI 2023 Abstract 164

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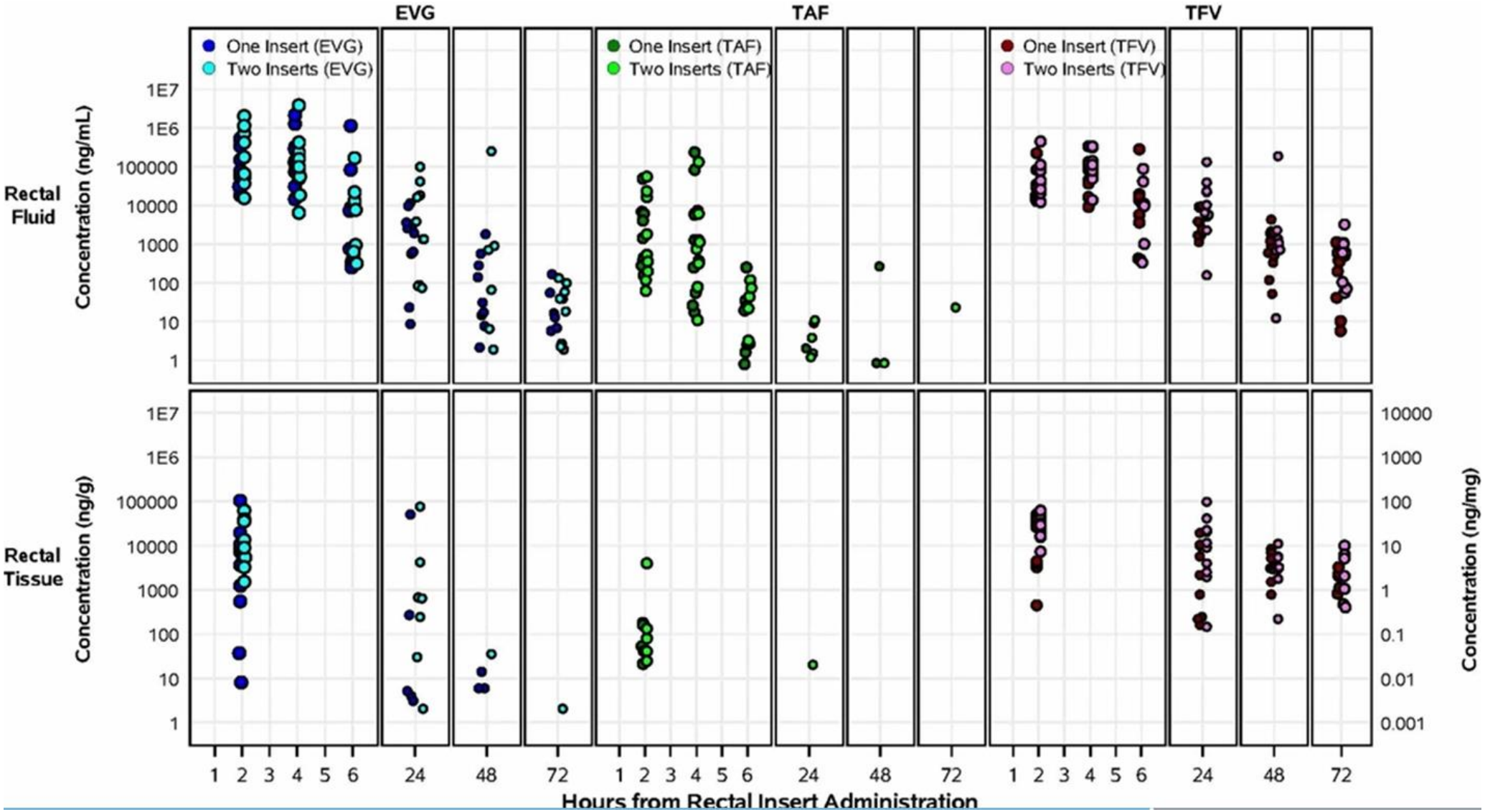
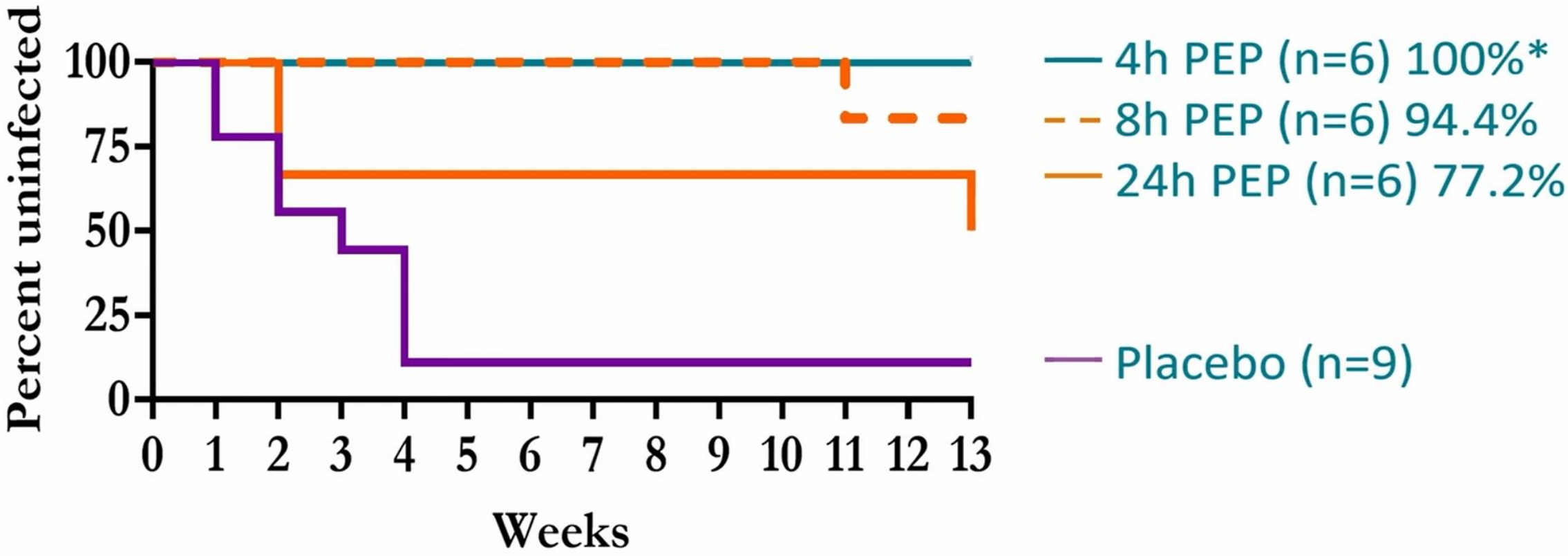
TAF/EVG inserts reach protective levels in rectal tissue



Riddler S, et al. CROI 2023 Abstract 164

TAF/EVG insert efficacy as PEP after vaginal SHIV exposure



High protection for inserts applied 4-8h after exposure with good effect even if given as 24-hour PEP

Dobard, et al. *eBioMedicine*, 2022. Makarova, et al. CROI 2023 Abstract 990

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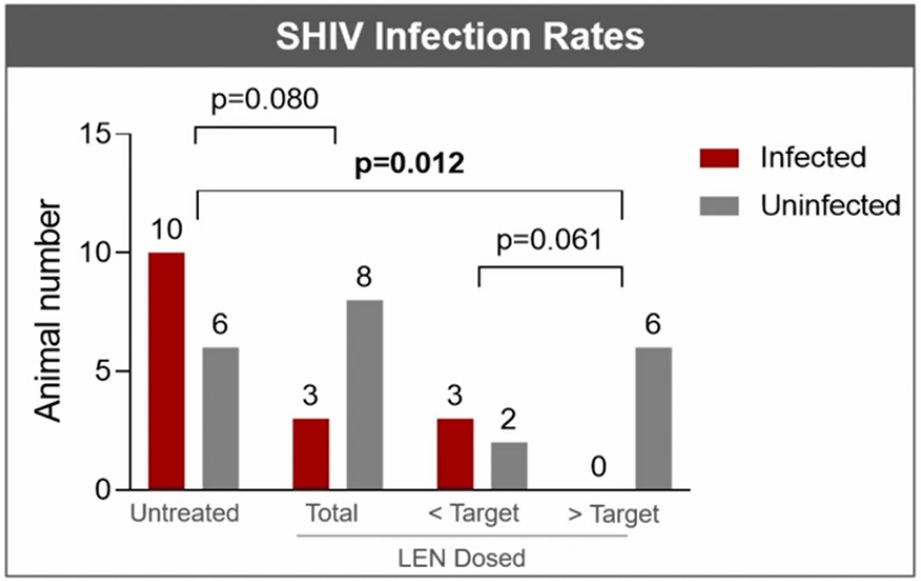
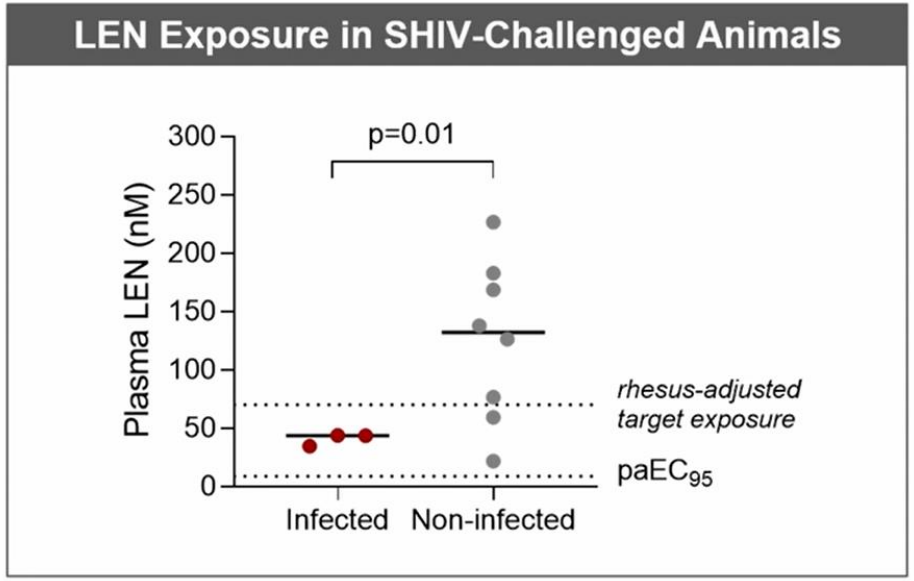
Lenacapavir and GS-CA1 for PrEP

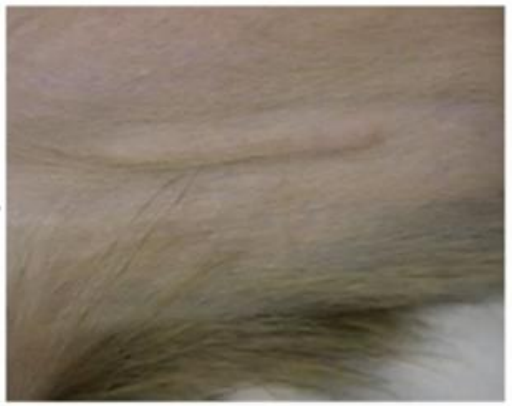
- SQ lenacapavir fully protected macaques after SHIV challenge 7 wks after SQ dosing (infection rate: 63% untreated vs 27% treated) if target levels reached
- PURPOSE-1 & PURPOSE-2 (soon: 3, 4) are phase 3 clinical studies of long-acting lenacapavir for HIV PrEP



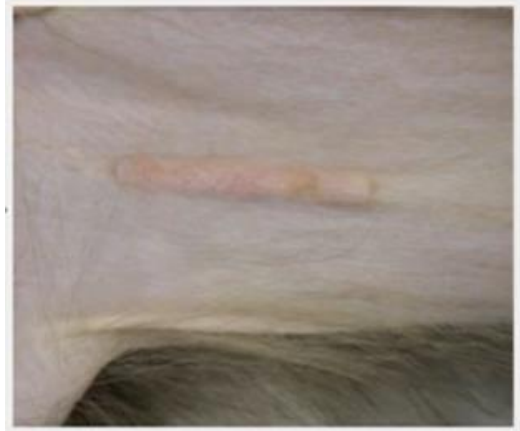


Bekerman E, et al. CROI 2023 Abstract 992

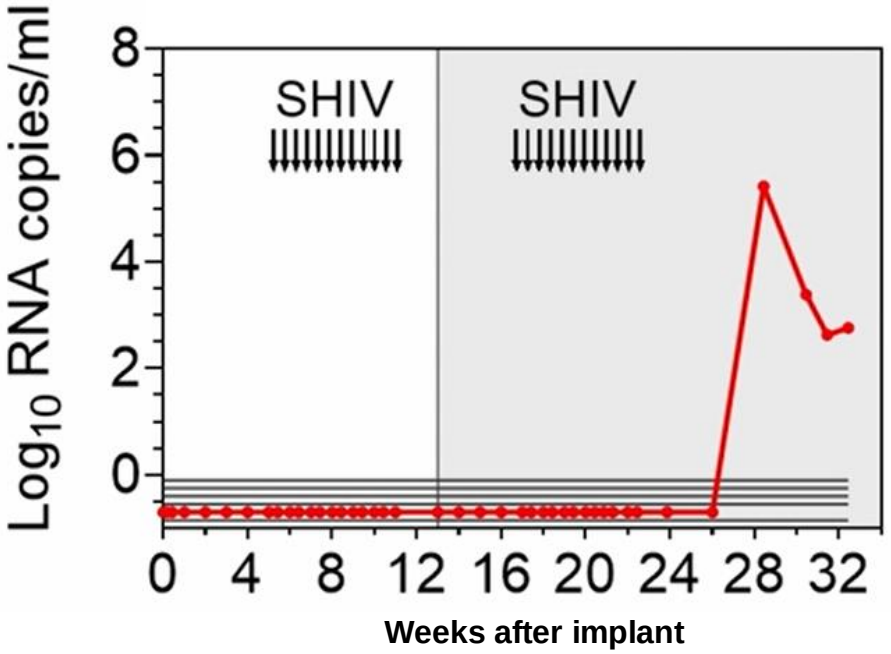
Biodegradable islatravir implants protect against vaginal SHIV



Week 13

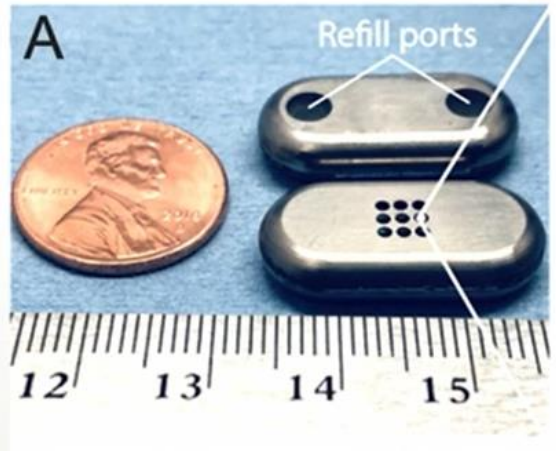


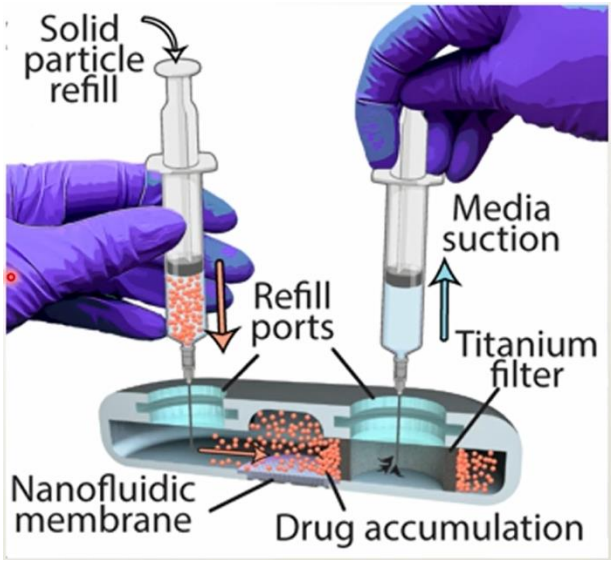
- 2 implants = 0.75 mg PO; 1 implant = 0.25 mg PO
- 5 of 6 animals protected when plasma ISL levels were therapeutic
- One breakthrough infection a/w low plasma ISL levels at week 28 (6 wks after last SHIV challenge)



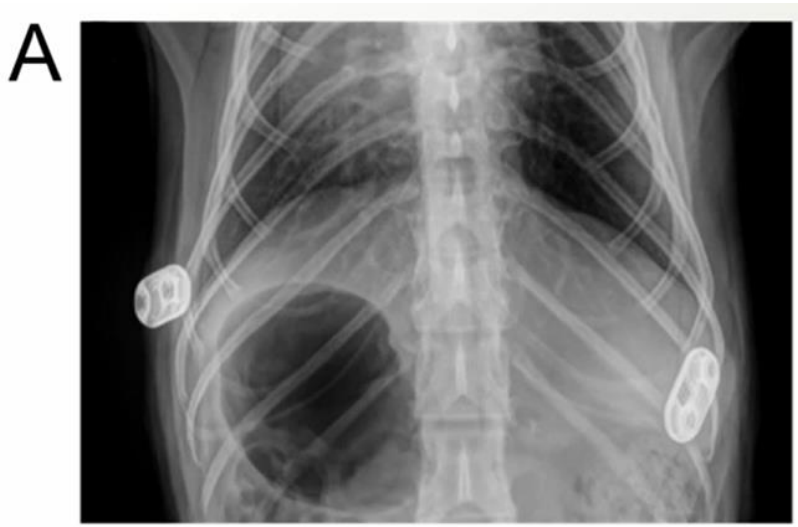
Daly M, et al. CROI 2023 Abstract 989; Matthews, et al. *JAIDS* 2021

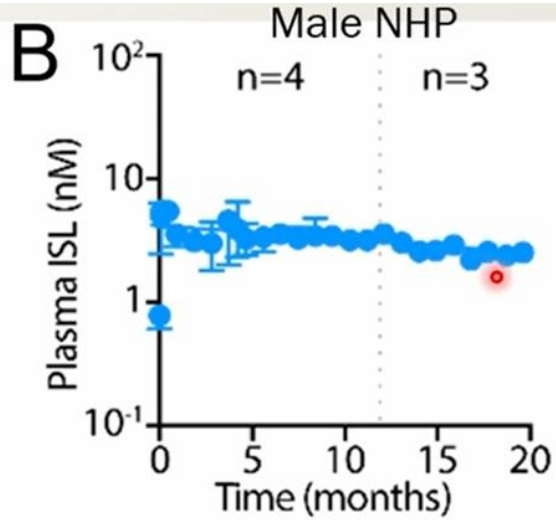
Multi-year refillable islatravir implants show promise





- ISL-TP levels above preventive level starting at 48hrs through 12 (rectal) and 20 (plasma) months in 4 NHPs
- Implants prevented 100% of infections in rectal and vaginal SHIV challenges
- No significant change in creatinine, AST/ALT or ALC





Di Trani et al. *Advanced Therapeutics*, 2022. Grattoni A, et al. CROI 2023 Abstract 165

Prevention potpourri

- While FTC + tenofovir AUC and Cmax were lower when F/TAF for PrEP was used with feminizing hormones, no clinically significant DDIs (Hiransuthikul, Abstract 996)
- Islatravir 60mg QM for PrEP associated with 20% and 7.5% mean decrease in ALC, respectively, for women vs MSM/TGW. After switching to OL F/TXF, counts rebounded to be similar to controls by 11-12 months (Squires, Abstract 192)
- Urine POCT for tenofovir has 91% PPV c/w DBS for TFV-DP (Mustanski, Abstract 979)
- High odds of PrEP disengagement if participant and partner both used meth (aOR 3.82) vs participant only (aOR 2.46) (Moran, Abstract 982)
- Tryptophan-metabolizing bacterial taxa including *Lactobacillus gasseri* and *Lachnospiraceae* inhibit HIV in cell culture nearly as well as ART (Jiang, Abstract 251)

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