

CROI 2023: HIV Prevention Updates

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Disclosures

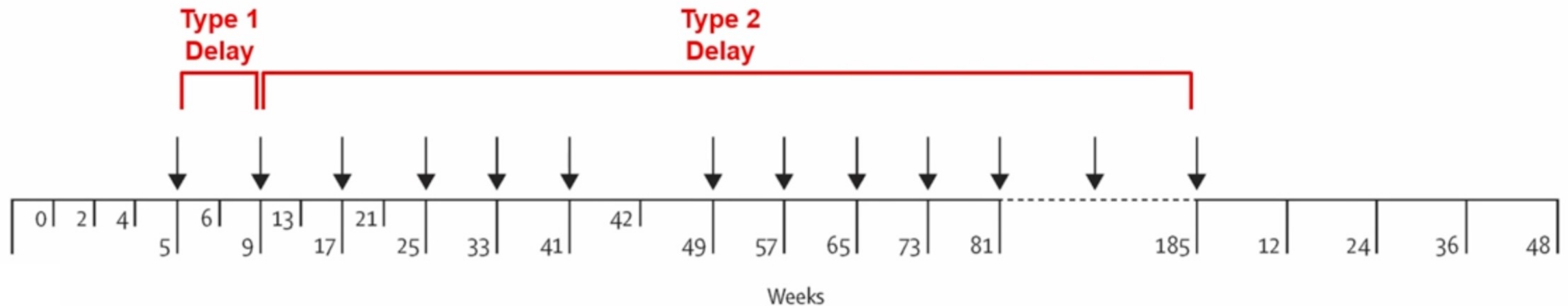
No conflicts of interest or relationships to disclose.

Cabotegravir

PK DATA WITH MISSED DOSES, HPTN UPDATES

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



Therapeutic CAB-LA detected 12 weeks after missed injection

- 194/1614 participants (12%) had ≥ 1 delayed injection
 - 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

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-IC₉₀ after a delay

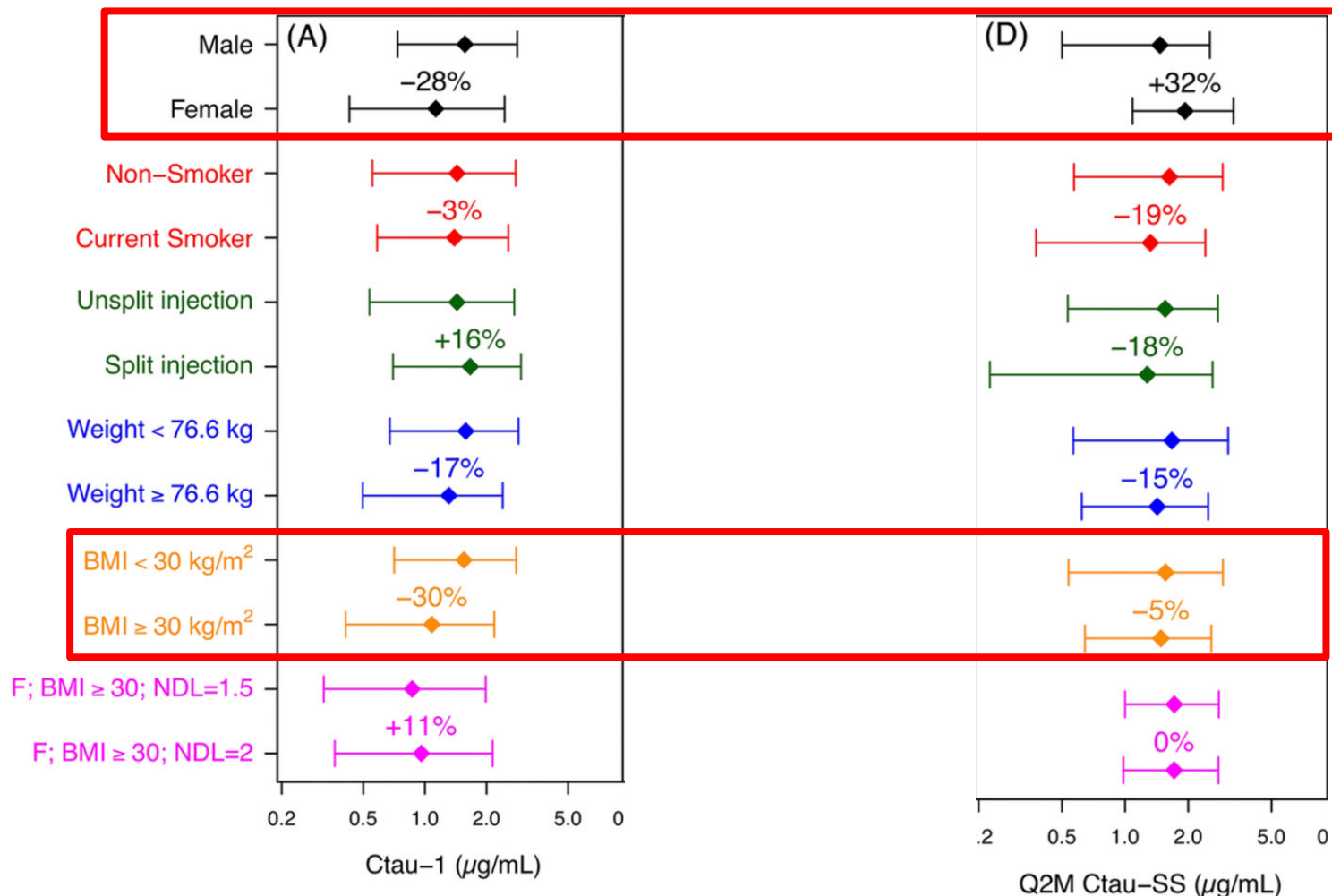
[CAB] Trough	12-14 weeks Between Injections	14-16 weeks Between Injections	16-18 weeks Between Injections
	N=109	N=57	N=39
>8x PA-IC ₉₀	95 (87%)	48 (84%)	24 (62%)
>4-8x PA-IC ₉₀	12(11%)	6 (11%)	11 (28%)
1-4x PA-IC ₉₀	1 (1%)	2 (4%)	2 (5%)
<1x PA-IC ₉₀	1 (1%)	1 (2%)	2 (5%)

Type 2 delays

Factors associated with favorable PK for CAB-LA

Trough after 1st injection

Trough after q2 mo injections x6



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





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

Oral PrEP in Women

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

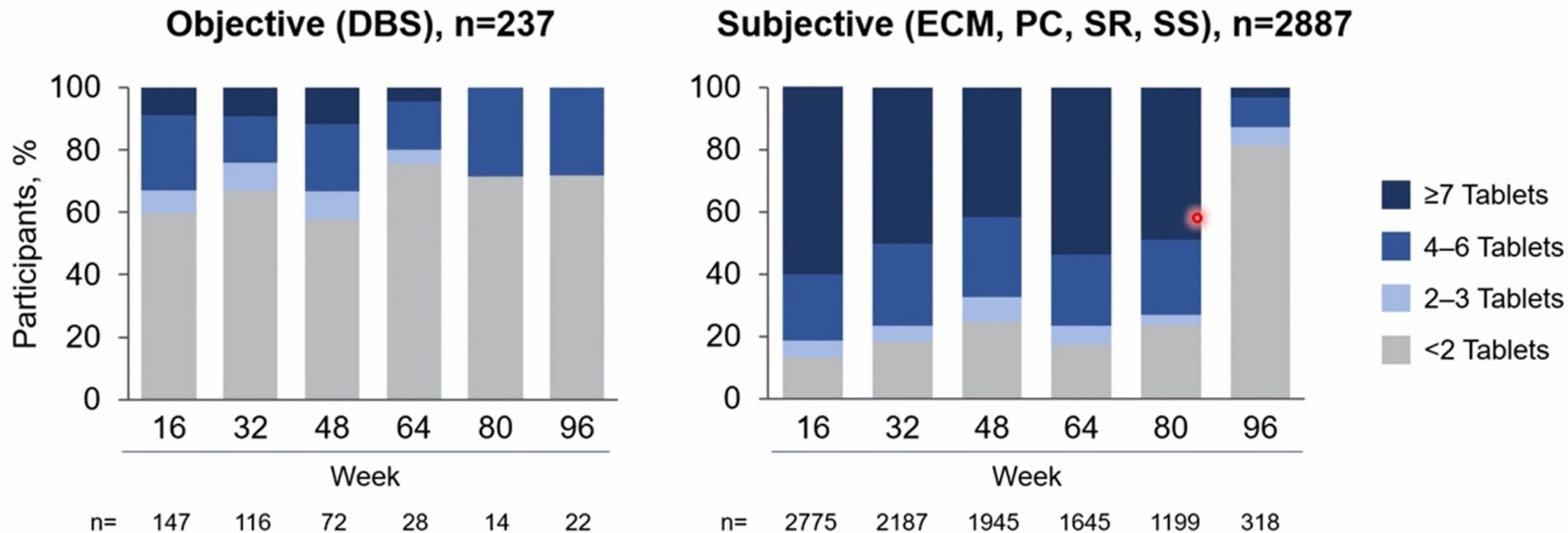
Overall Adherence Scale	Objective Adherence* n = 237 (DBS, fmol/punch)	Subjective Adherence, n = 2887			
		ECM 	PC 	SR 	SS 
≥7 Tablets	≥1250	≥7 Tablets			Excellent
4–6 Tablets	700 – <1250	4–6 Tablets			Very Good / Good
2–3 Tablets	350 – <700	2–3 Tablets			Fair
<2 Tablets	<350	<2 Tablets			Poor / Very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

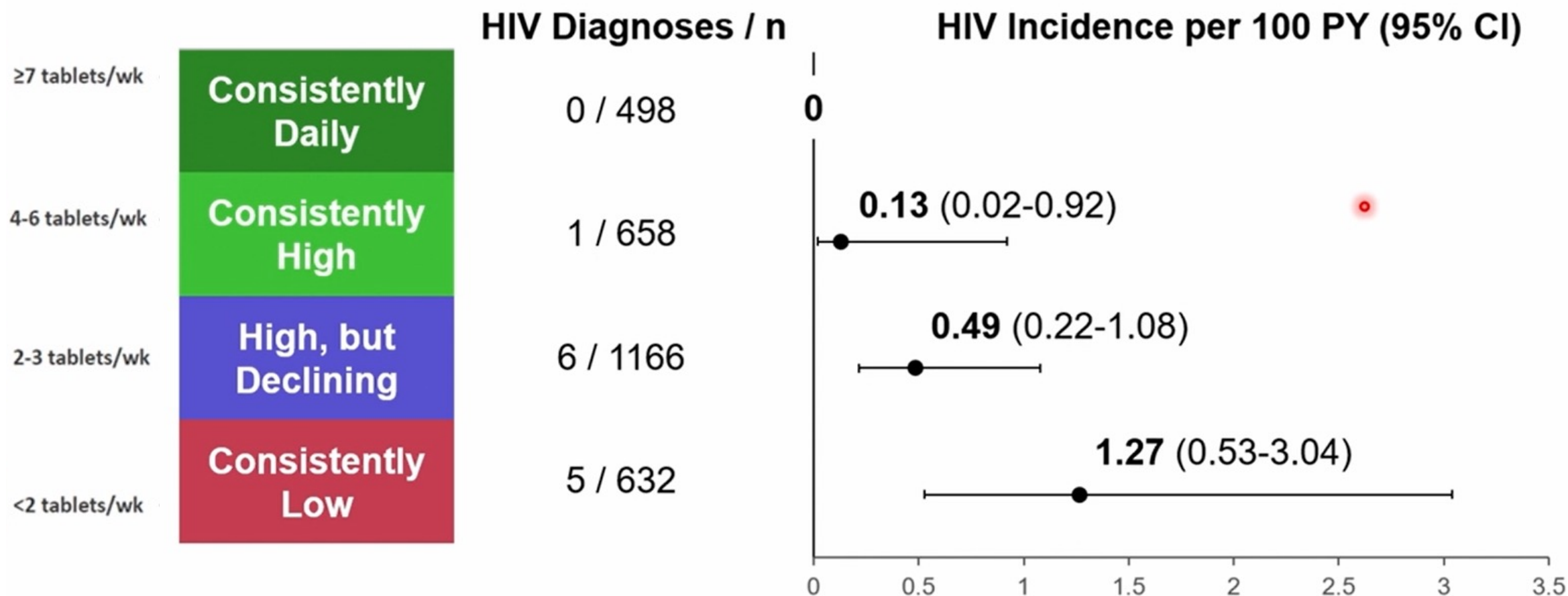
Brooks K, Anderson, P. Clin Pharmacol Ther. 2018;104:1056-9

Discordance in adherence metrics among cis women



Adherence declines over time for both subjective and objective measures

HIV incidence by adherence category for cis women



Oral PrEP in cis women: Conclusions

- F/TDF is similarly effective for cis women taking ≥ 4 tablets vs 7 tablets/week
- 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

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

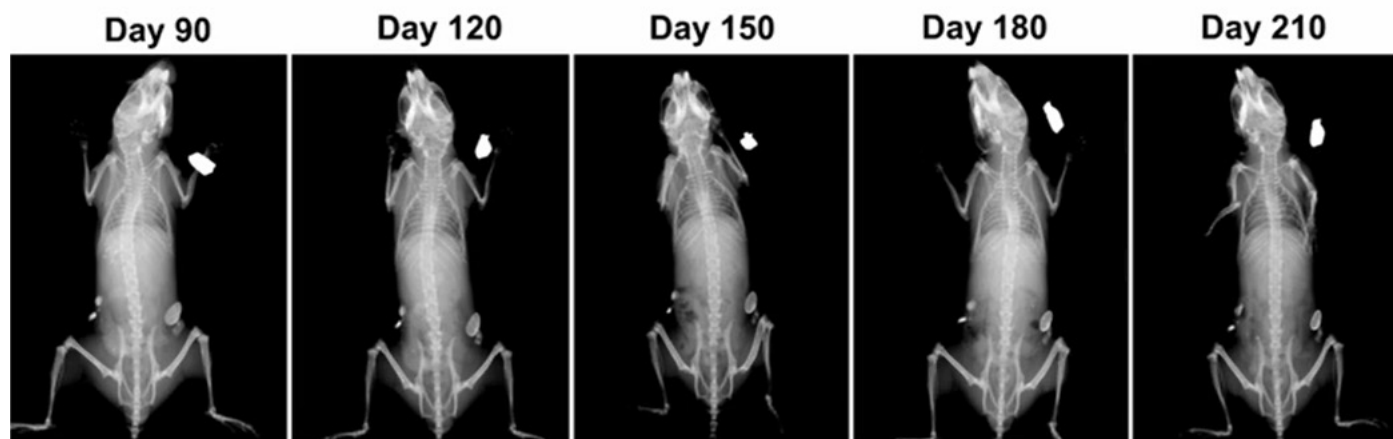
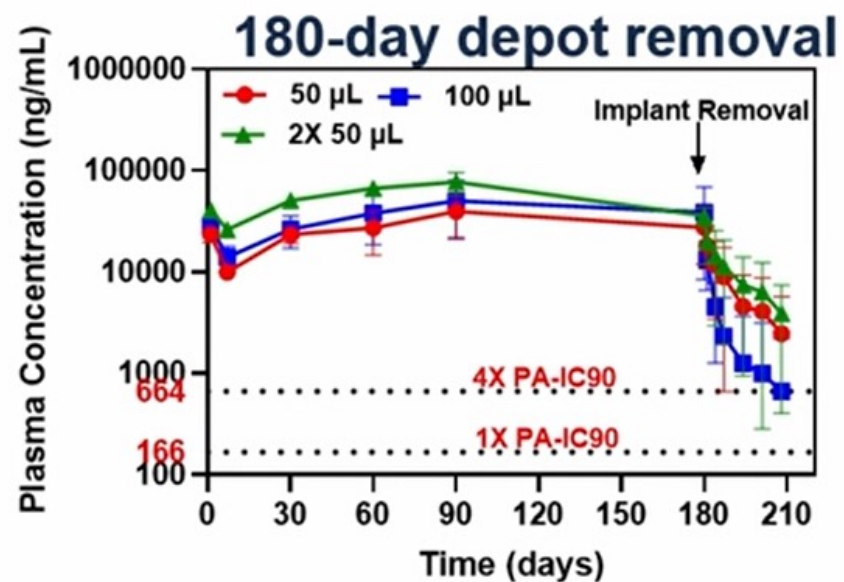
Is 4 pills/week enough for women as we have said for cis MSM?

The future of prevention

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

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-IC₉₀ 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

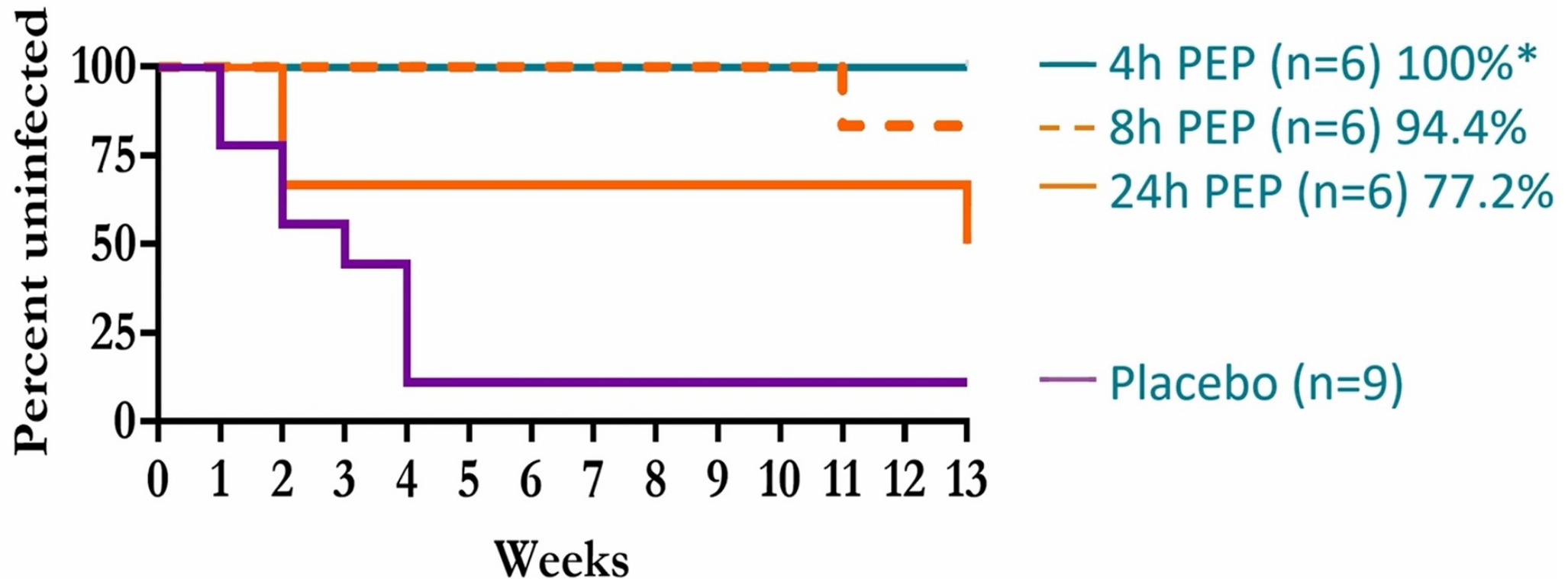


On-demand inserts for HIV PEP or PrEP

- Fast-dissolving TAF 20mg + EVG 16mg insert demonstrated efficacy in NHP SHIV challenges using 1 vaginal or 2 rectal inserts
- Phase 1, single-arm, OL study assessing PK/PD after use of 1 or 2 rectal inserts in humans
 - 1 drug-related AE – mild anal erythema
 - 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



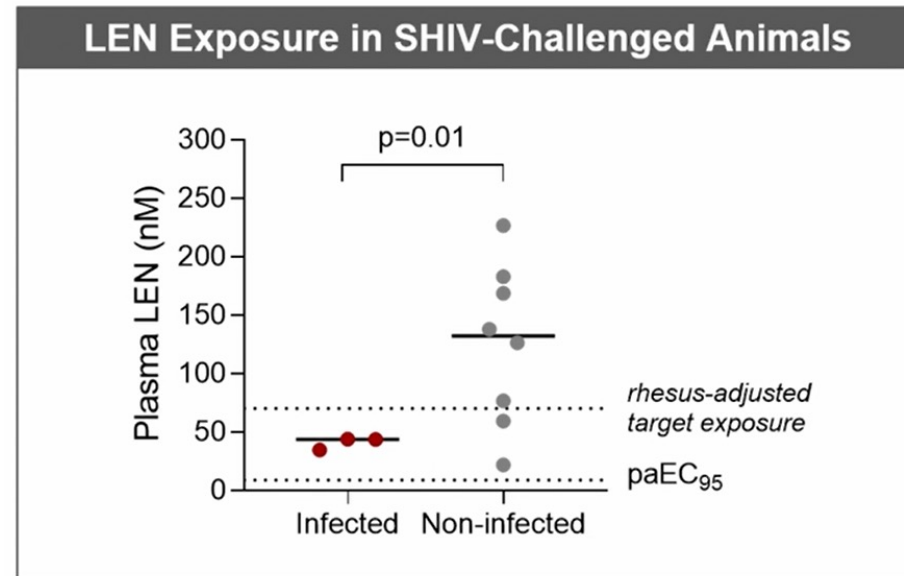
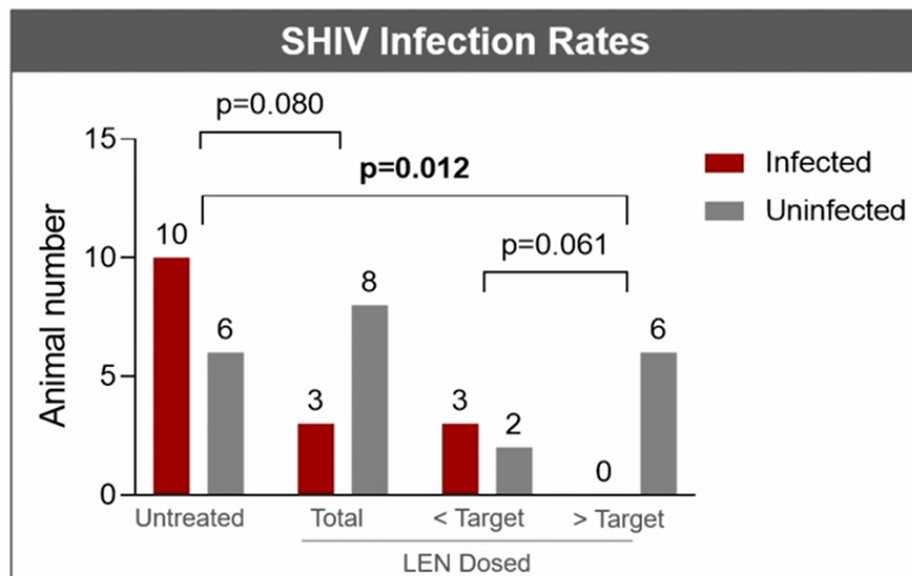
TAF/EVG insert efficacy as PEP after vaginal SHIV exposure



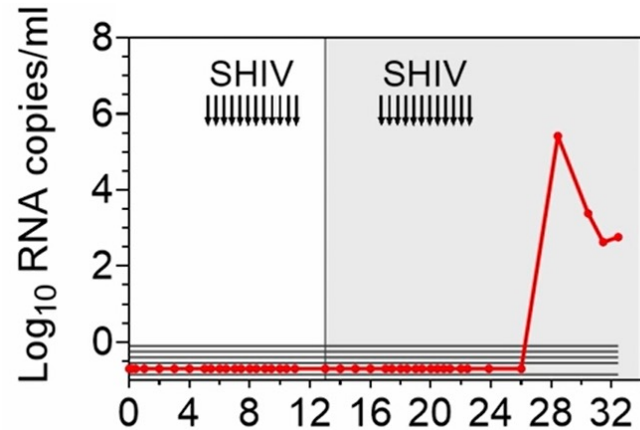
High protection for inserts applied 4-8h after exposure with good effect even if given as 24-hour PEP

Lenacapavir and GS-CA1 for PrEP

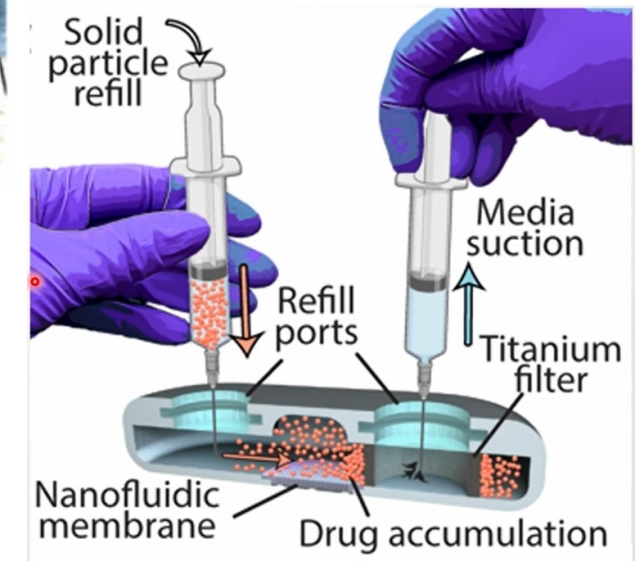
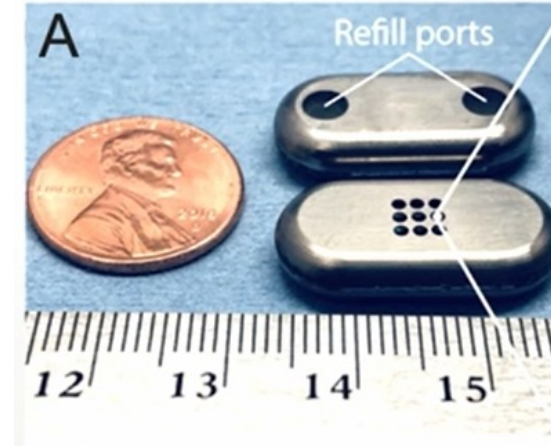
- Lenacapavir fully protected macaques after SHIV challenge 7 wks after SQ dosing (infection rate: 63% untreated vs 27% treated) if target levels reached
- PURPOSE-1 & PURPOSE-2 (soon: 3, 4) are phase 3 clinical studies of long-acting lenacapavir for HIV PrEP



Biodegradable and refillable islatravir implants show promise



Week 13



SHIV protection in 5 of 6 macaques when plasma ISL levels were therapeutic

100% of infections prevented in rectal + vaginal SHIV challenges with therapeutic levels to 20 months

Role of microbiome for HIV prevention?

Tryptophan-metabolizing bacterial taxa including *Lactobacillus gasseri* and *Lachnospiraceae* inhibit HIV in cell culture

