AETC AIDS Education & Training Center Program Mountain West

March 2025
AIDS Clinical Conference
2025 CROI Update

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CROI 2025: Updates in HIV Prevention & STIs

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Last Updated: 3/15/2025

Disclosures

Research support - Hologic

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MPOX

Project ECHO®

ACTG A5418

STOMP
Study of Tecovirimat for Mpox

Design and Sample Size	2:1 Randomized, Blinded, Placebo-controlled (n=530) Open label for children, persons with pregnancy or severe disease, severe immune suppression or severe skin disease (n≅250)
Study Population	Symptomatic mpox
Design	Superiority; randomized participants allowed open label tecovirimat for disease progression or severe pain at day 5
1^0 Outcome	Time to clinical resolution (all skins lesions scabbed or epithelialized; all visible mucosal lesions healed)
2^0 Outcomes	Daily pain score, HMPXV detection in various compartments, Pt reported outcomes
Duration	57 days (in person or fully remote enrollment)
Agent	Weight based oral Tecovirimat

12 March 2025

ACTG

Wilkin T, et al. CROI 2025 – OA 201

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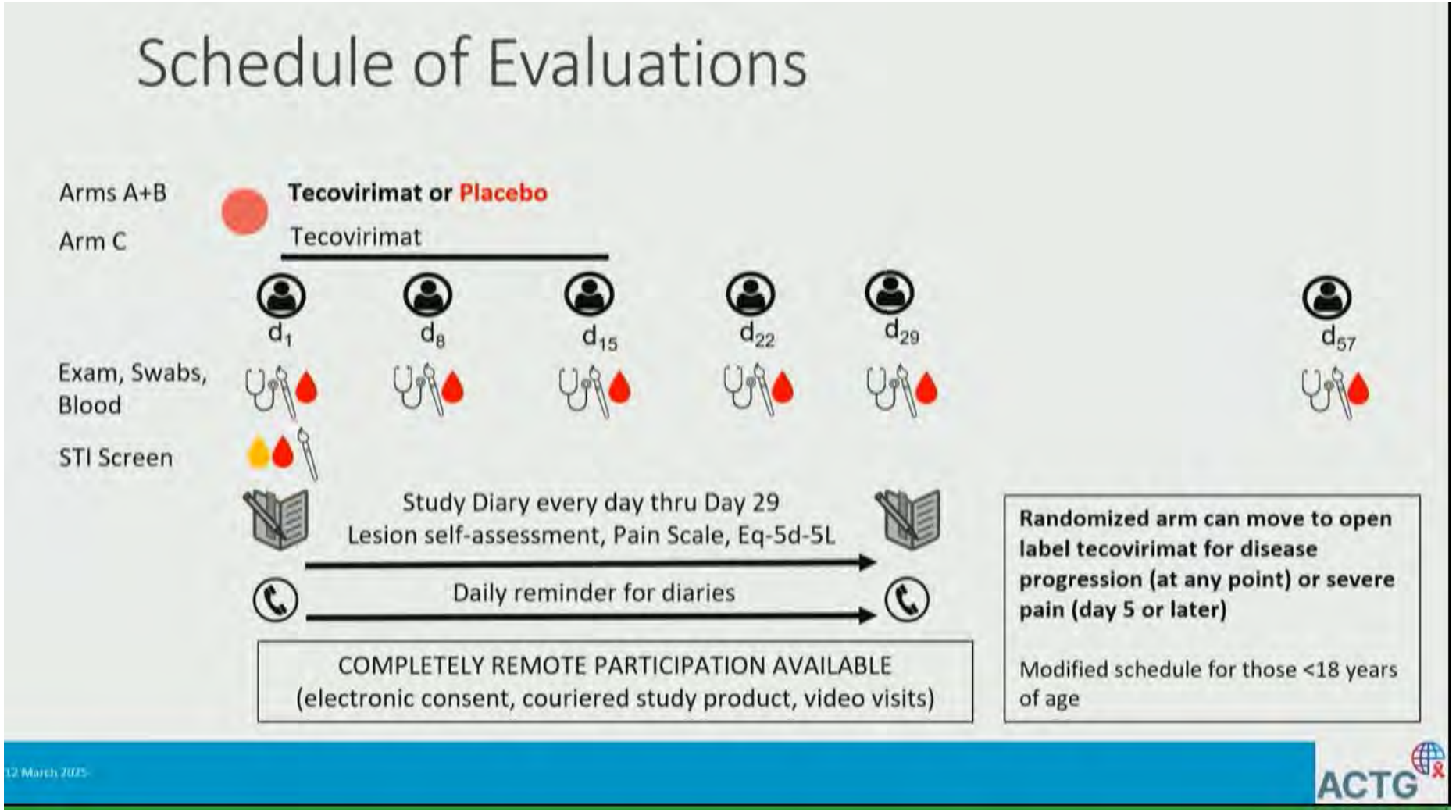
STOMP: Study procedures



Wilkin T, et al. CROI 2025 – OA 201
Fischer II WA, et al. CROI 2025 – OA 159

STOMP: Participant characteristics

Baseline characteristics for randomized population with lab-confirmed mpox (n=344)

	Tecovirimat (n=232)	Placebo (n=112)	Total (n=344)
Age	34 [27, 40]	34 [28, 41]	34 [28,40]
Male sex	228 (98%)	111 (99%)	339 (99%)
Remote enrollment	53 (23%)	28 (25%)	81 (24%)
White race	121 (52%)	61 (54%)	182 (53%)
Hispanic	107 (46%)	44 (39%)	151 (44%)

713 enrolled; 413 randomized; 68 excluded for lack of mpox diagnosis; 1 excluded enrollment violation; 344 analysis set

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Wilkin T, et al. CROI 2025 – OA 201

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STOMP: Participant characteristics

Baseline characteristics for randomized population with lab-confirmed mpox (n=344)

	Tecovirimat (n=232)	Placebo (n=112)	Total (n=344)
Days from symptom onset	8 [6, 10]	8 [6, 10]	8 [6, 10]
Severe pain (7-10 NRS)	81 (35%)	35 (32%)	116 (34%)
Lesion number	9 [5, 18]	8 [3, 17]	9 [4, 18]
Proctitis	85 (37%)	37 (33%)	122 (35%)
Living with HIV	86 (38%)	31 (28%)	117 (35%)
Prior smallpox vaccine	54 (23%)	24 (21%)	78 (23%)

713 enrolled; 413 randomized; 68 excluded for lack of mpox diagnosis; 1 excluded enrollment violation; 344 analysis set

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Wilkin T, et al. CROI 2025 – OA 201

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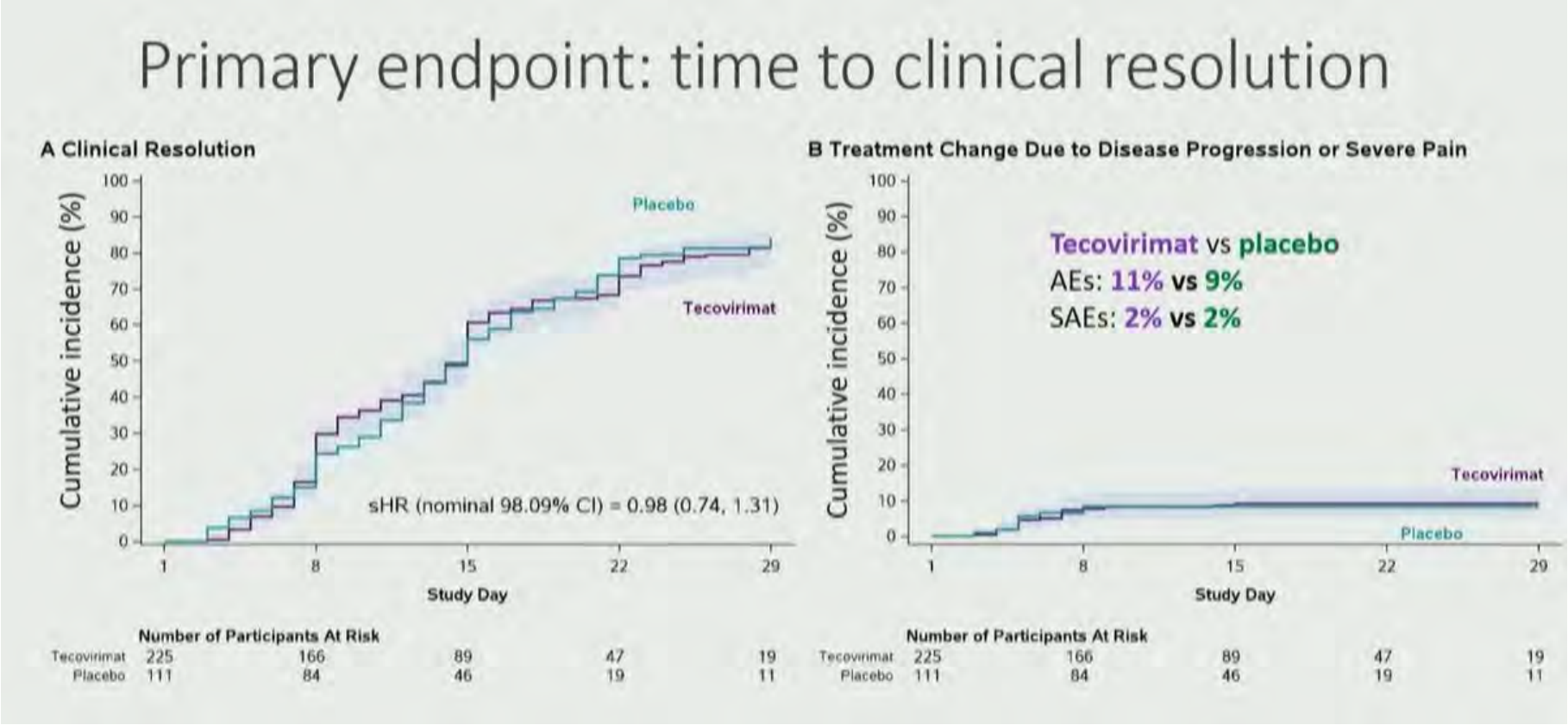
STOMP: Tecovirimat did not improve clinical outcomes

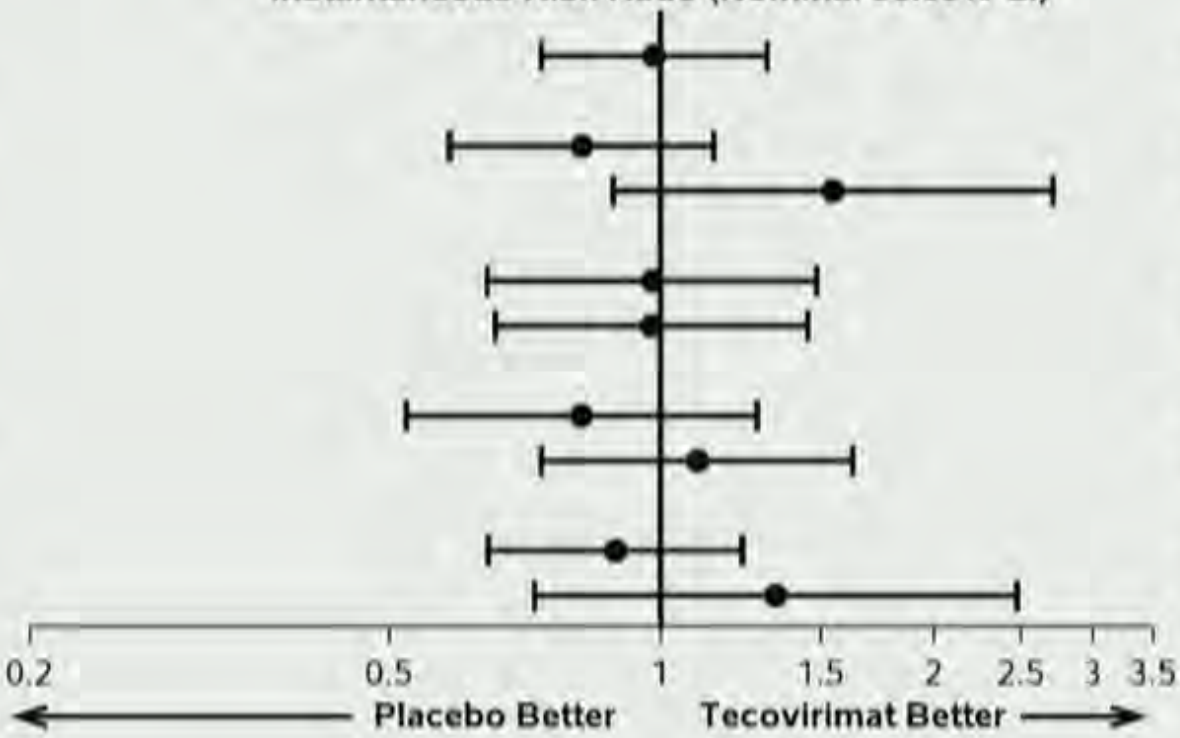


- Cumulative probability of clinical resolution by 28 days: 87% (95% CI: 80-92)
- Arm C: median time to clinical resolution from treatment initiation: 14 days (95% CI: 13-16)

Wilkin T, et al. CROI 2025 – OA 201
Fischer II WA, et al. CROI 2025 – OA 159

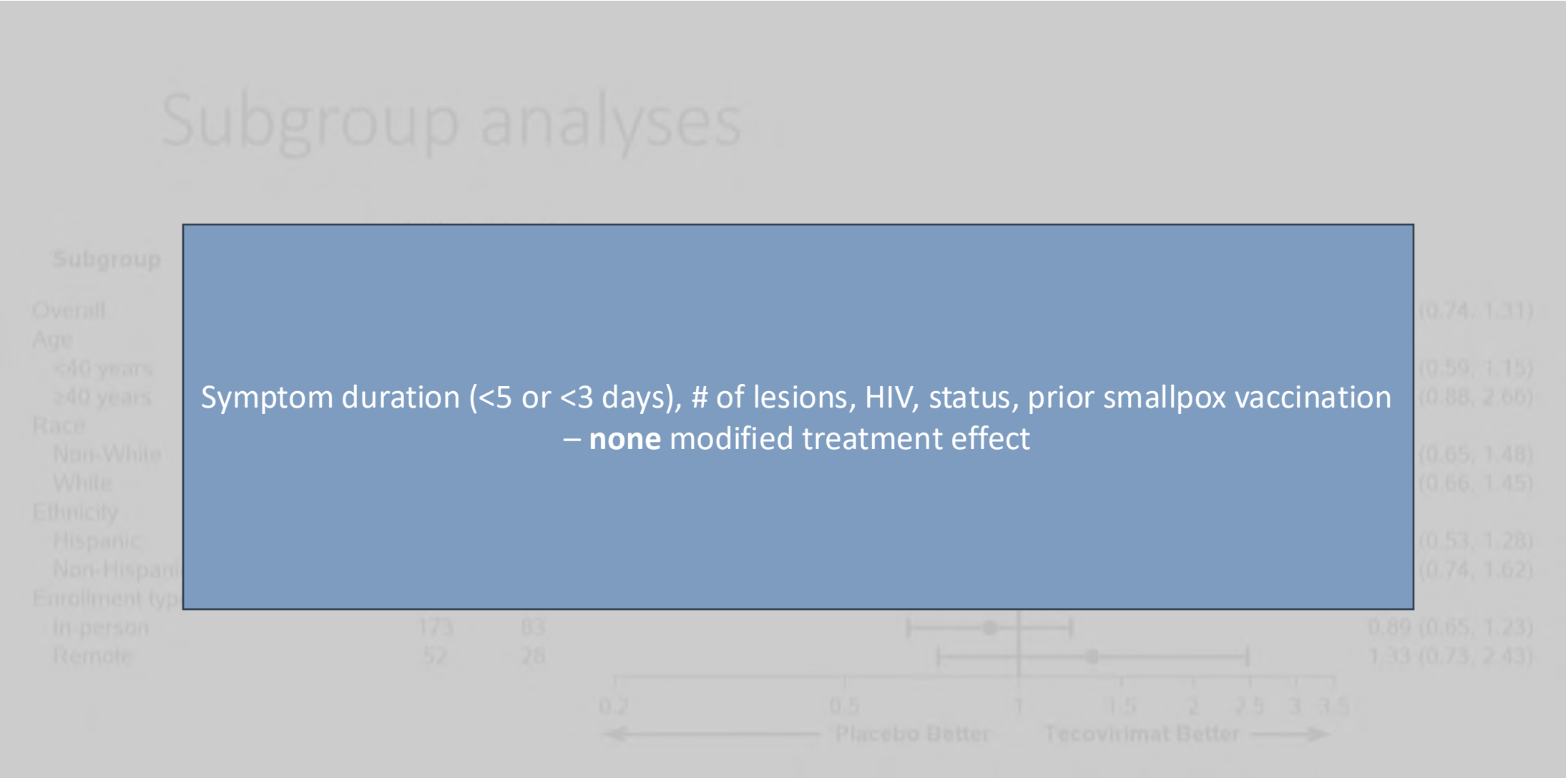
STOMP: No treatment effect modification in subgroup analysis

Subgroup	Active N	Placebo N	Instantaneous Risk Ratio (Nominal 98.09% CI)
Overall	225	111	0.98 (0.74, 1.31)
Age			
<40 years	165	79	0.82 (0.59, 1.15)
≥40 years	60	32	1.53 (0.88, 2.66)
Race			
Non-White	107	50	0.98 (0.65, 1.48)
White	118	61	0.98 (0.66, 1.45)
Ethnicity			
Hispanic	105	44	0.82 (0.53, 1.28)
Non-Hispanic	117	63	1.09 (0.74, 1.62)
Enrollment type			
In-person	173	83	0.89 (0.65, 1.23)
Remote	52	28	1.33 (0.73, 2.43)



Wilkin T, et al. CROI 2025 – OA 201

STOMP: No treatment effect modification in subgroup analysis



Symptom duration (<5 or <3 days), # of lesions, HIV, status, prior smallpox vaccination – **none** modified treatment effect

Wilkin T, et al. CROI 2025 – OA 201

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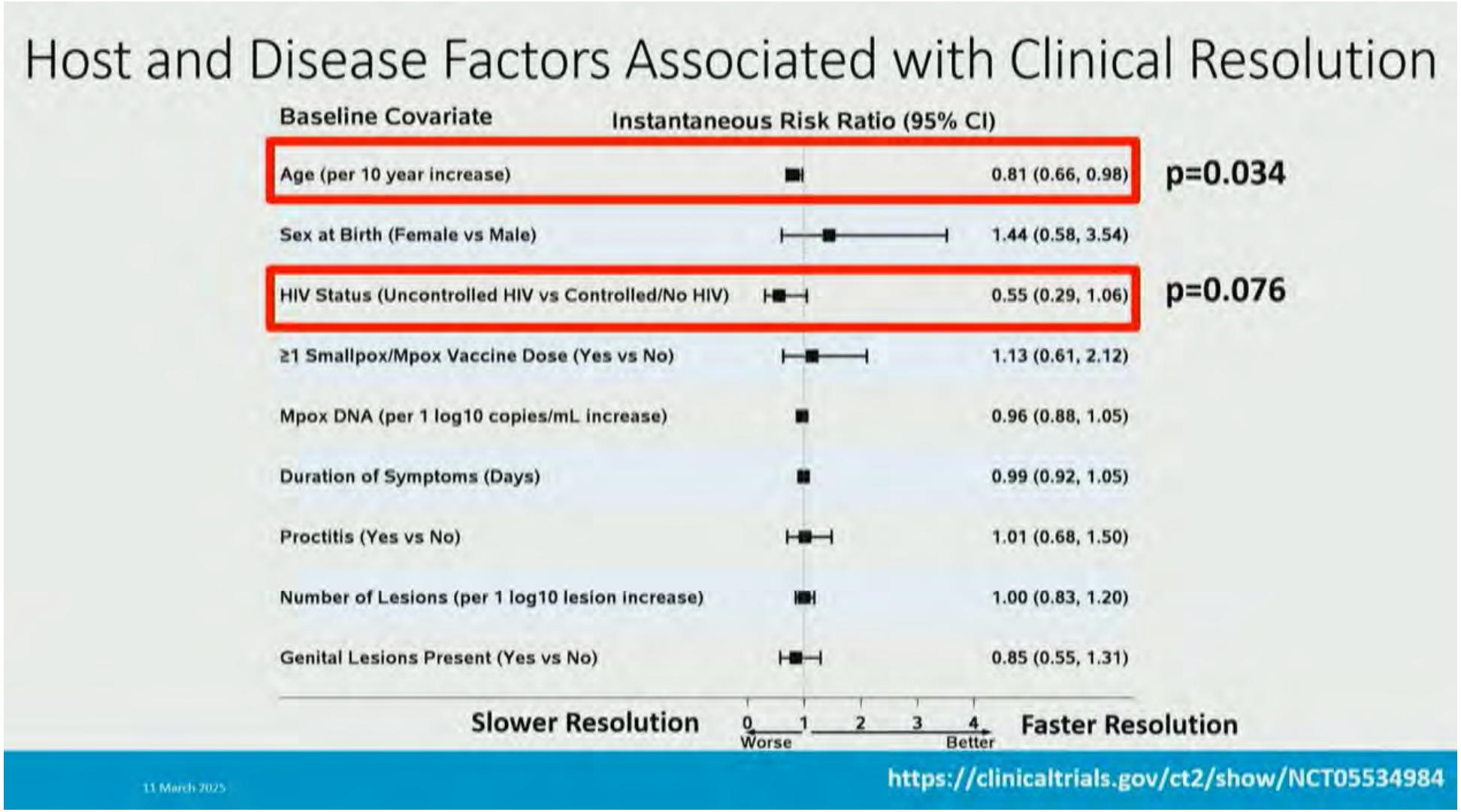
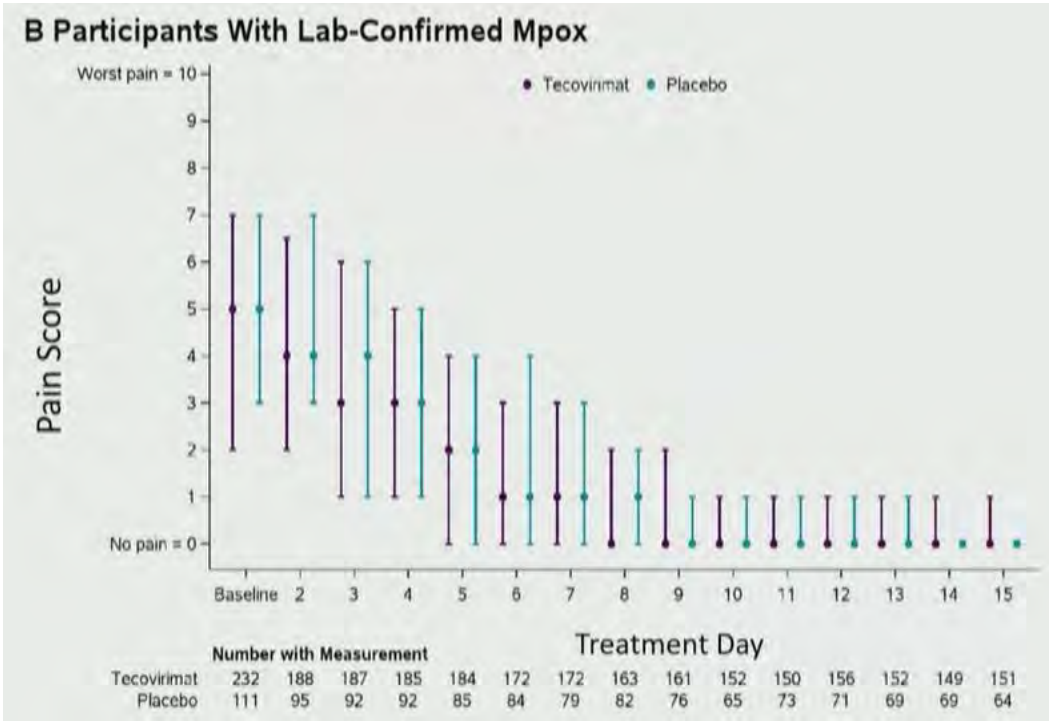
Clinical resolution slower with older age and uncontrolled HIV

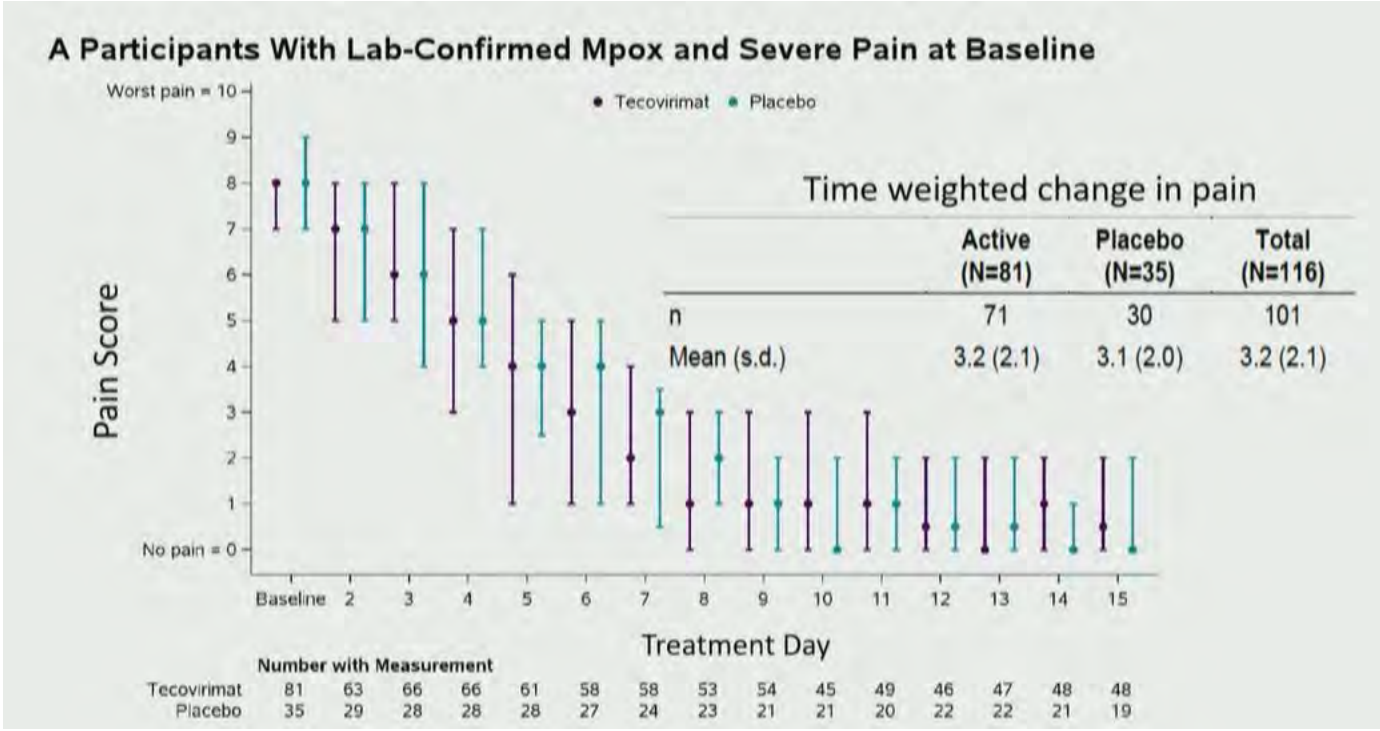


Fischer II WA, et al. CROI 2025 – OA 159

STOMP: Tecovirimat did not impact pain outcomes

- No difference in pain scores (11-point scale) over time in either group with severe pain at baseline





- Equivalent pain scores for all patients with lab-confirmed mpox

Wilkin T, et al. CROI 2025 – OA 201

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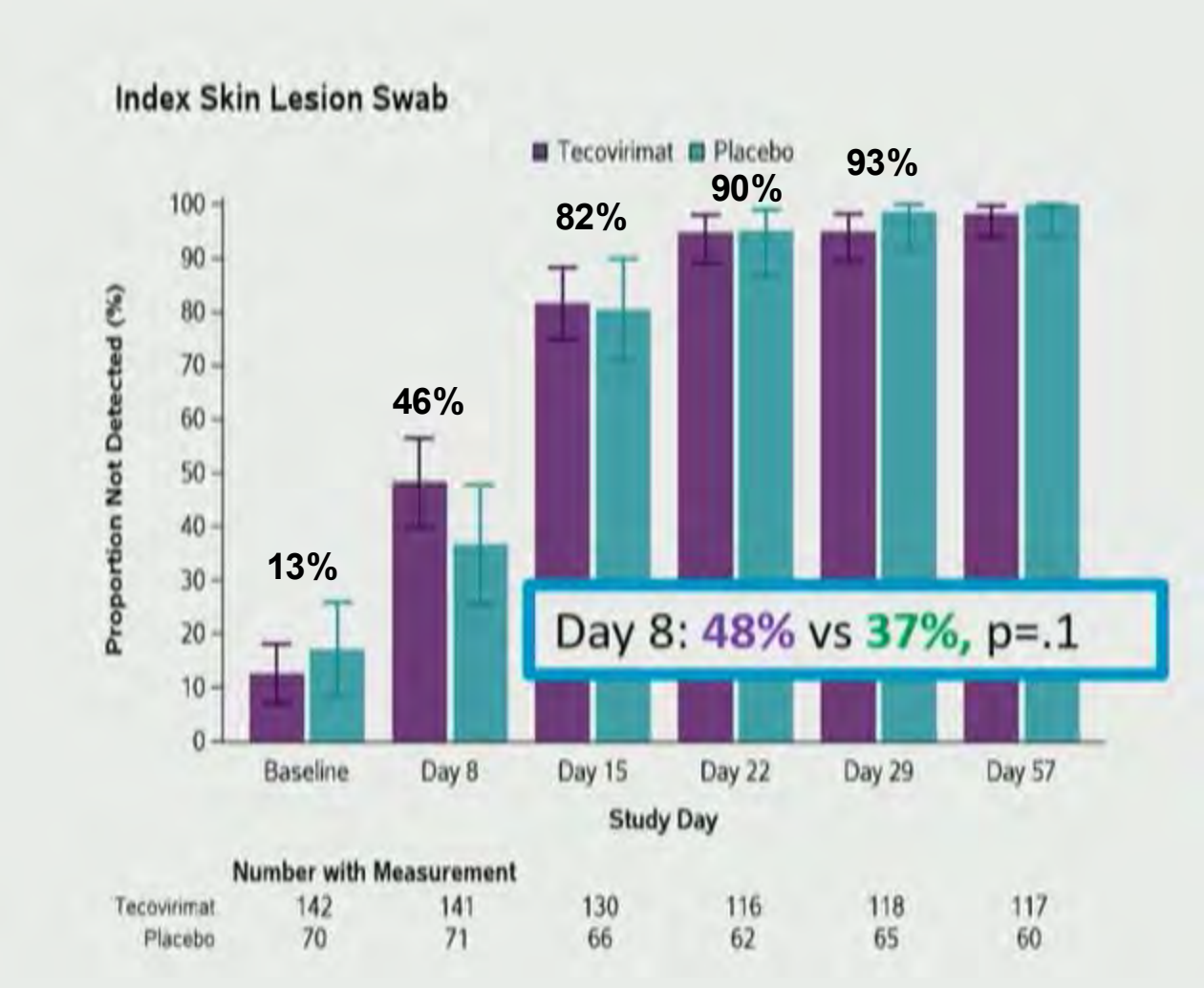
STOMP: Tecovirimat did not change lesion viral clearance

- Serial samples of index skin lesion and rectal swabs for study duration
- 10-15% had hMPXV-negative lesion at baseline; most negative by day 22
- Only trend toward difference was day 8 skin lesion results
  - 48% in tecovirimat cleared vs 37% in placebo
  - No difference for rectal samples



Wilkin T, et al. CROI 2025 – OA 201
Fischer II WA, et al. CROI 2025 – OA 159

Mpox and STOMP trial: Summary and conclusions

- Tecovirimat was safe but did not improve clinical outcomes in US population with clade II mpox
  - No faster resolution of mpox skin lesions or improved pain control (median 14d)
  - No significant reduction in hMPXV detection (trend toward ↓ at day 8)

- Now 2 negative clinical trials (PALM-007, clade I mpox); pending UNITY trial results soon

- Alternative agents and likely combination therapy should be used for mpox (e.g., brincidofovir + tecovirimat) – priority for immunocompromised populations

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DOXY FOR STI PREVENTION

Project ECHO®

Doxy-PEP: the Milan experience

- Doxy-PEP effective for CT and syphilis prevention in hospital-based clinic
  - Indications per clinic policy: ≥1 STI or condomless sex with ≥1 casual partner
  - Suggested use: “intensive” sexual activity (>5 partners)

- **Study aim:** Retrospective evaluation of benzylpenicillin, ceftriaxone, doxycycline use for bacterial STI treatment
  - Population: MSM with HIV or on PrEP receiving doxy-PEP in a real-world setting
  - Period: Aug 2022 – July 2024
  - Quantified as days of therapy (DOT) per 1000 person-days for users vs non-users
  - Analysis
    - Observed DOT after doxy-PEP Rx + DOT for incident STI treatment
    - Expected DOT for STI treatment in the absence of doxy PEP

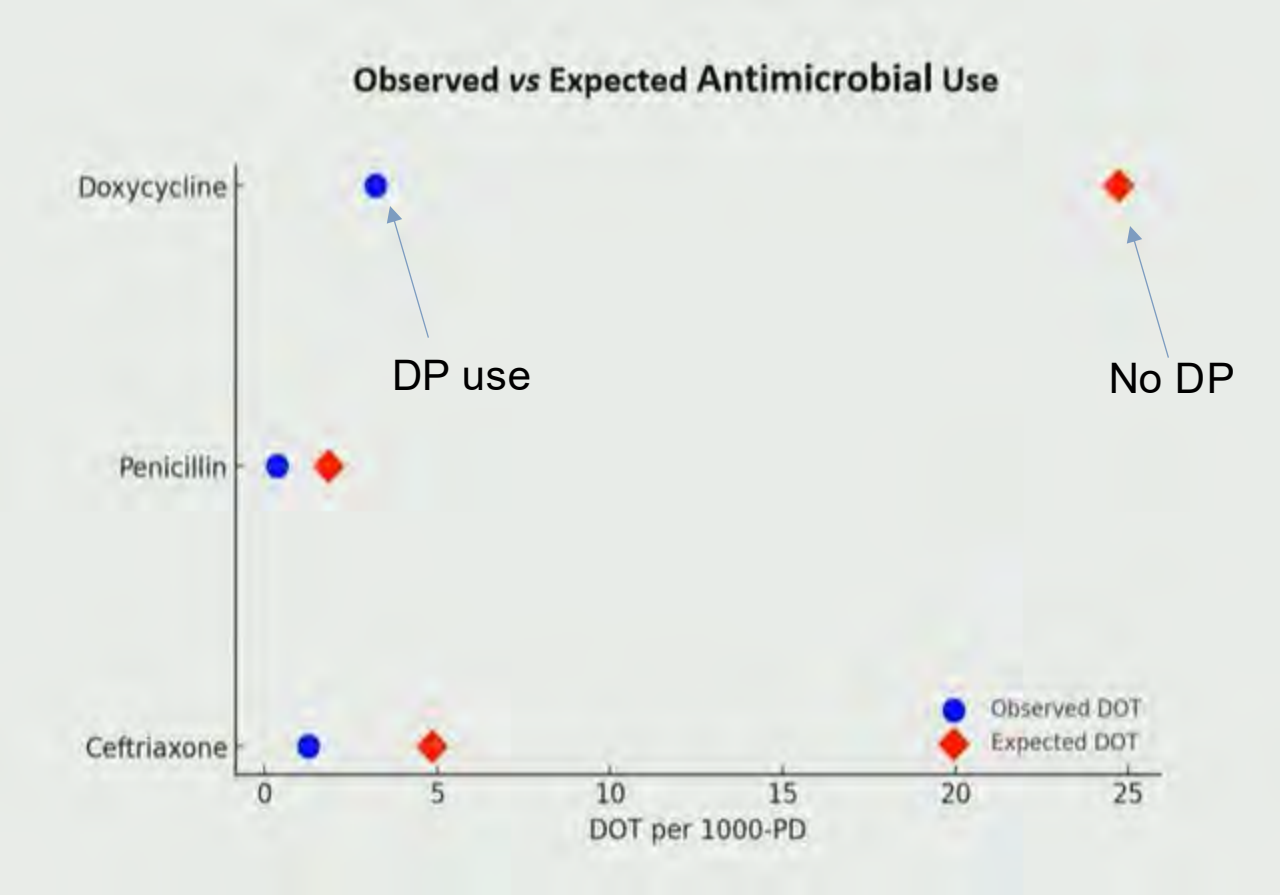
Raccagni AR, et al. CROI 2025 – OA 1284
Raccagni AR, et al. *Lancet Infect Dis* 2025

Doxy-PEP dramatically reduces antibiotic use for STI treatment

- Rx for 754 MSM, 222 (29.4%) of whom took ≥1 dose
- PWH 24% vs on PrEP 71%

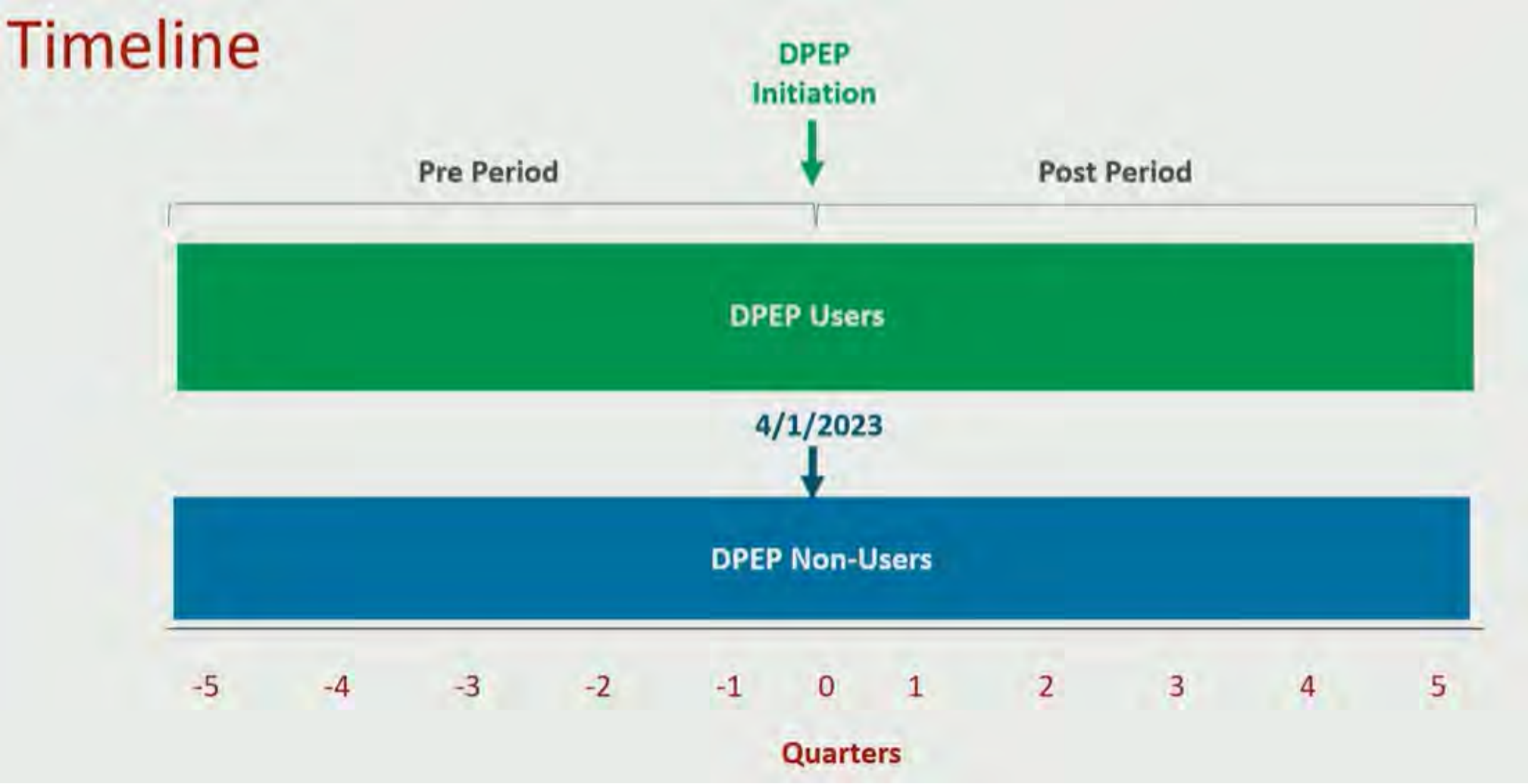
Doxy PEP timing	Median (IQR) f/u in users, mo	N, bSTI	N, by STI
Pre	16 (12-19)	401	Tp 70, CT 139, NG 192
Post	11 (7-13)	146	Tp 26, CT 32, NG 88
64% reduction in bacterial STI			

- Doxy-PEP group had lower DOT rate even when accounting for both therapeutic and prophylactic use



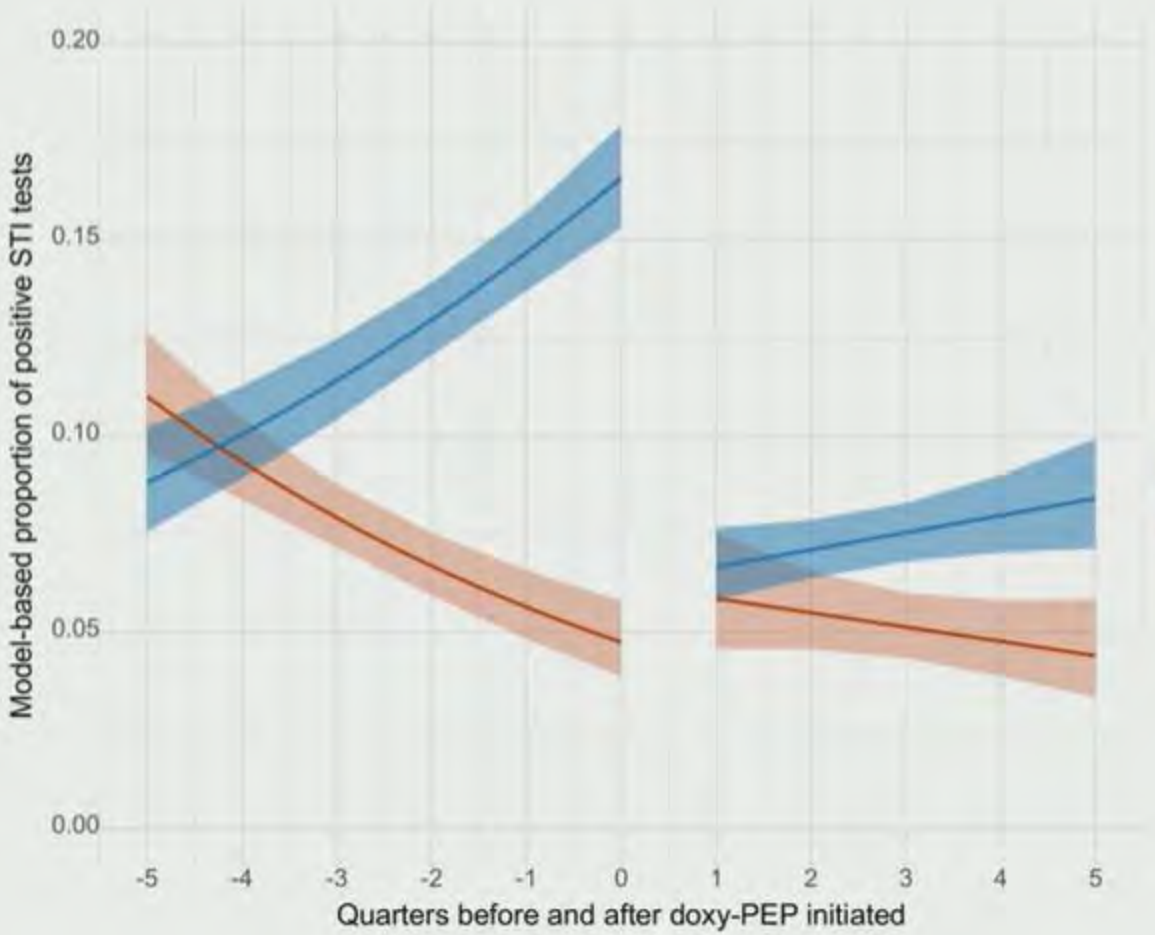
Raccagni AR, et al. CROI 2025 – OA 1284

Doxy-PEP effectiveness analysis update from San Francisco



Scott H, et al. CROI 2025 – OA 163

Sustained doxy-PEP effectiveness at Magnet SHC in SF



DPEP Users vs Non-Users	Odds Ratio	95% CI	p-value
Pre-Period	3.78	3.04 – 4.68	<0.001
Post-Period	1.01	0.67 – 1.55	0.917

	Odds Ratio	95% CI	p-value
Any STI	0.34	0.28 - 0.42	<0.001
Chlamydia	0.19	0.13 – 0.29	<0.001
Syphilis	0.11	0.02 – 0.54	0.006
Gonorrhea	0.56	0.44 – 0.71	<0.001

Scott H, et al. CROI 2025 – OA 163

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Doxy for STI prevention: Summary and conclusions

- Doxy-PEP use is rolling out across US and in some countries globally
- More work to reach those who are interested and could benefit
- Doxy-PEP reduced use of antibiotics needed for STI treatment in a real-world clinical setting
- Criteria for most appropriate use may require refinement for individual clinic or geographic populations

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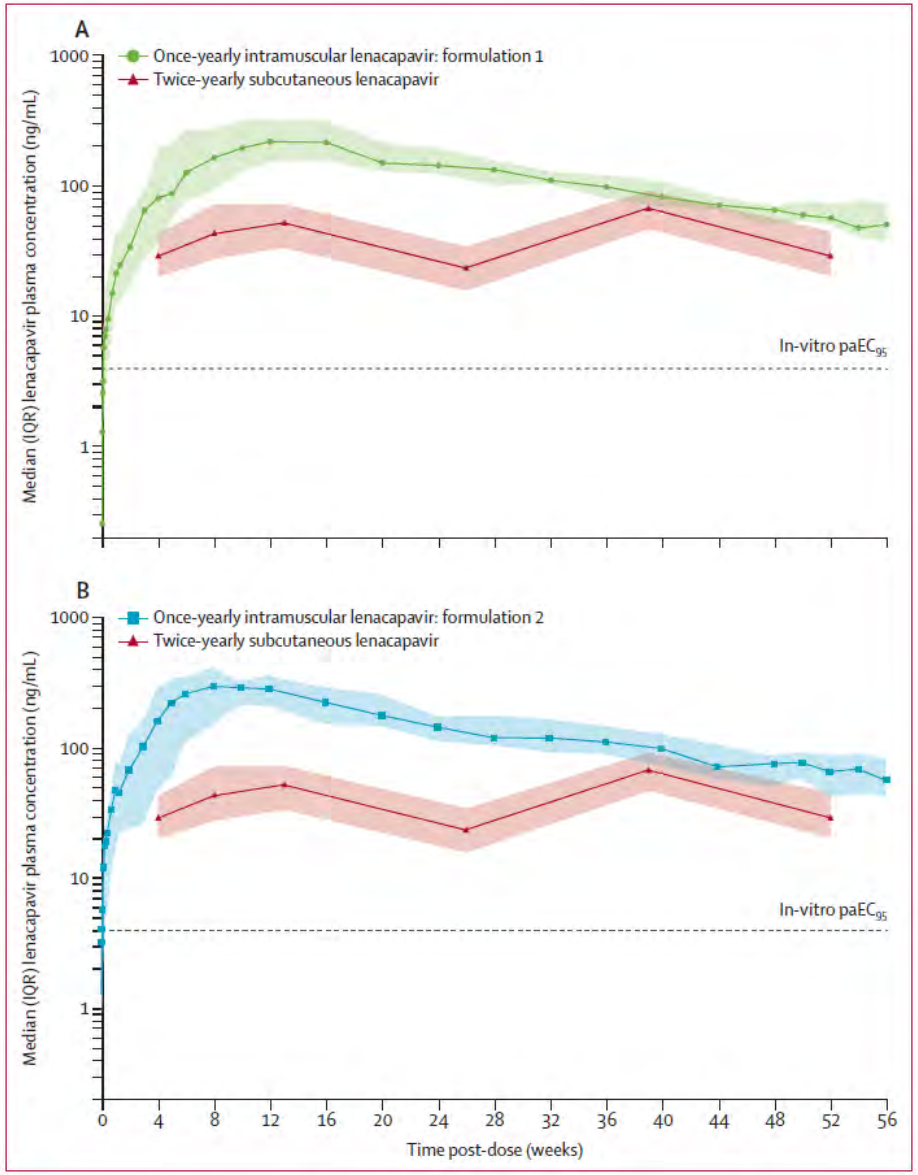
HIV PREVENTION: LENACAPAVIR

Project ECHO®

Phase 1 study of once-yearly LEN for PrEP

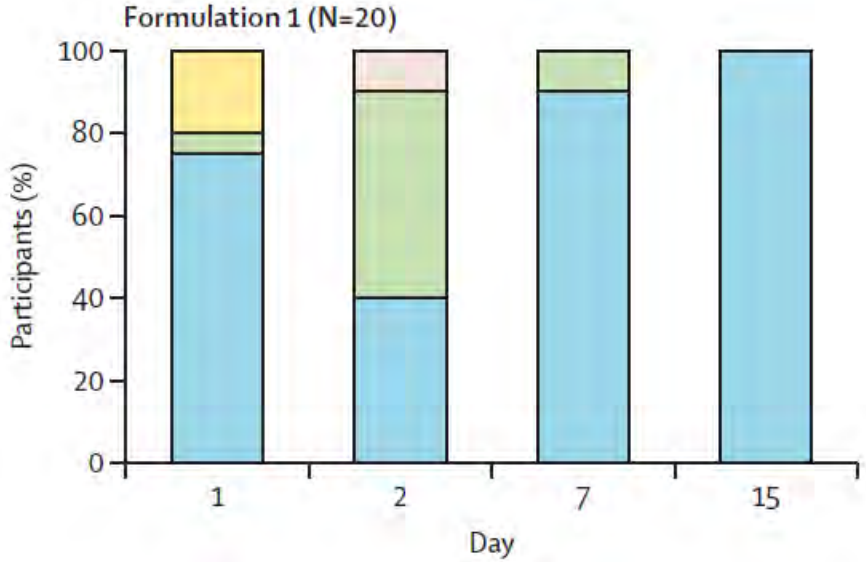
- Evaluated PK, safety, tolerability of LEN IM as 5000mg dose (two 5mL ventrogluteal injections)
  - **Formulation 1: 5% w/w ethanol (n=20)**
  - **Formulation 2: 10% w/w ethanol (n=20)**
- Ppts were representative of population; ages 33-37, BMI 26-28

	Lenacapavir formulation 1 (N=20)	Lenacapavir formulation 2 (N=20)
C_{max}, ng/mL	247·0 (184·0–346·0)	336·0 (233·5–474·3)
T_{max}, days	84·1 (56·1–112·0)	69·9 (55·3–105·5)
$AUC_{days\ 1–365}$, h*µg/mL	1011·1 (881·0–1490·2)	1274·0 (1177·3–1704·8)
$C_{trough\ (day\ 365)}$, ng/mL	57·0 (49·9–72·4)	65·6 (41·8–87·1)

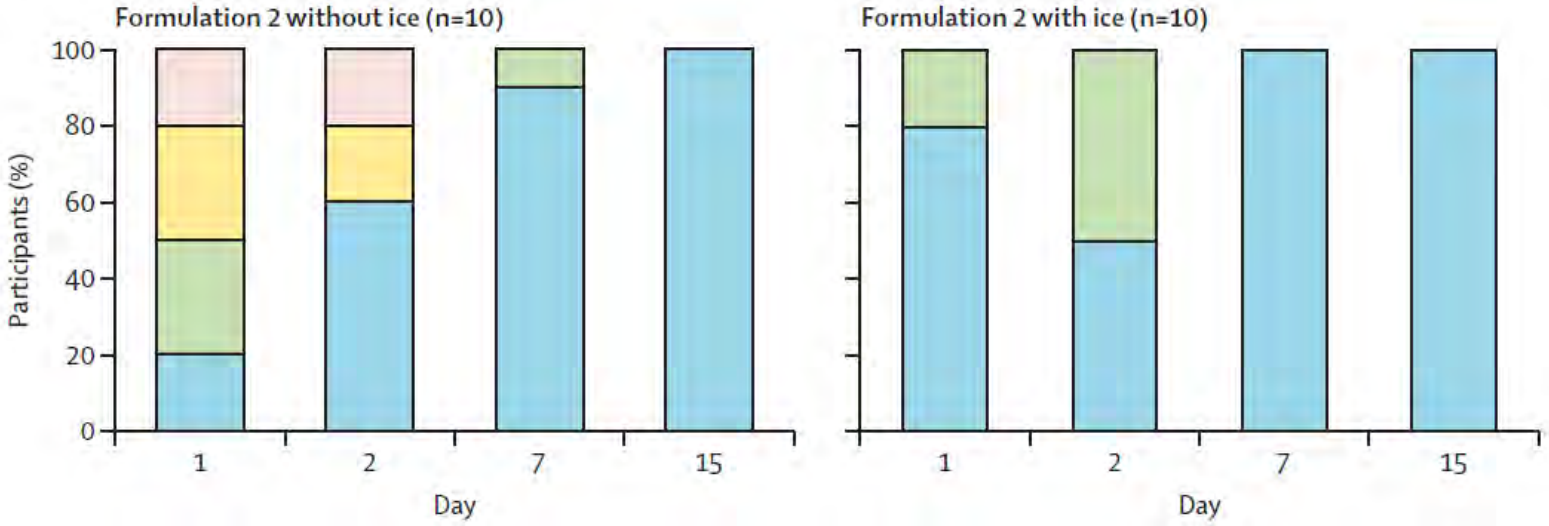


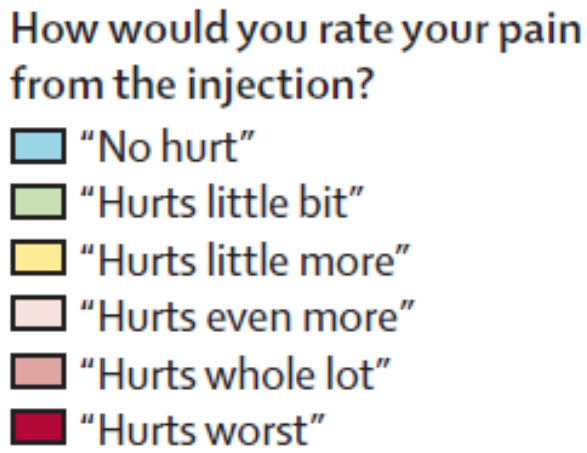
Singh R, et al. CROI 2024 – OA 154; Jogiraju V, et al. *Lancet* 2025

Injections site reactions common; better with ice before injection



- Study drug-related TEAEs common
  - 85% in formulation 1: injection site pain, bruising, swelling
  - 80% in formulation 2: injection site pain, gait disturbance, headache, “feeling hot,” dizziness





Singh R, et al. CROI 2024 – OA 154
Jogiraju V, et al. *Lancet* 2025

Lenacapavir: Summary and conclusions

- Once-yearly IM LEN maintained plasma concentrations beyond 12 months at levels above that known to be efficacious for twice-yearly SC LEN for PrEP
- Intramuscular LEN was safe, but injection site pain was common, resolved after a few days and was improved with pretreatment using ice
- Planned phase 3 study for once-yearly IM LEN for PrEP is already planned and may be able to use an even lower dose
- LEN could have significant public health impact for ending HIV epidemic if it is available, scalable and acceptably priced

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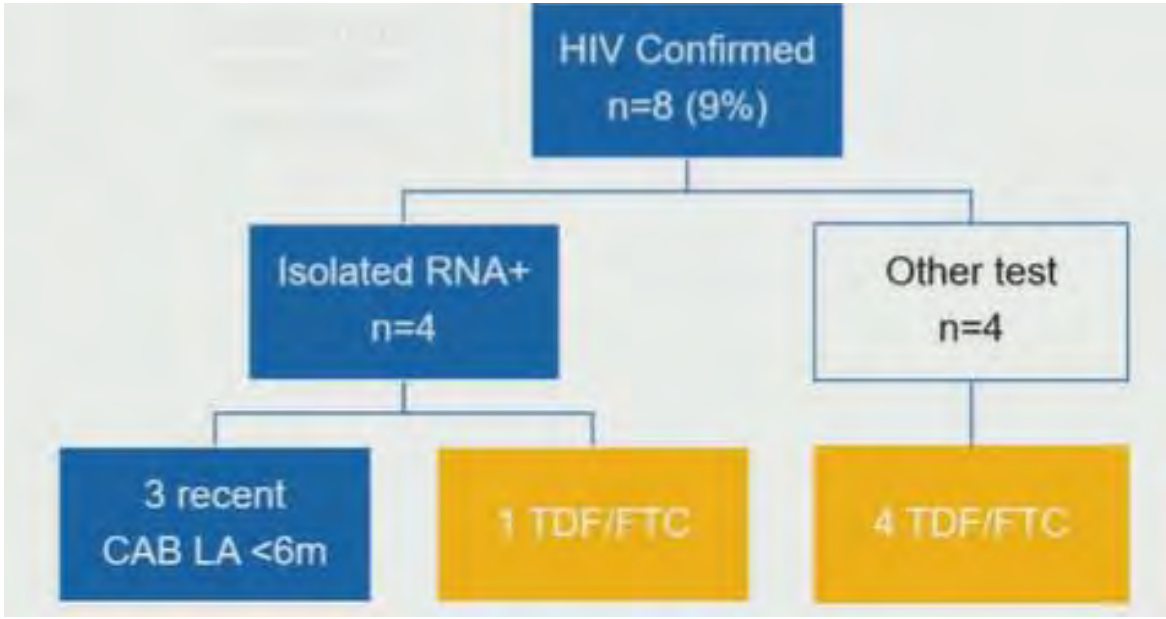
HIV PREVENTION: CABOTEGRAVIR

Project ECHO®

Challenges with diagnosing HIV in setting of CAB-LA

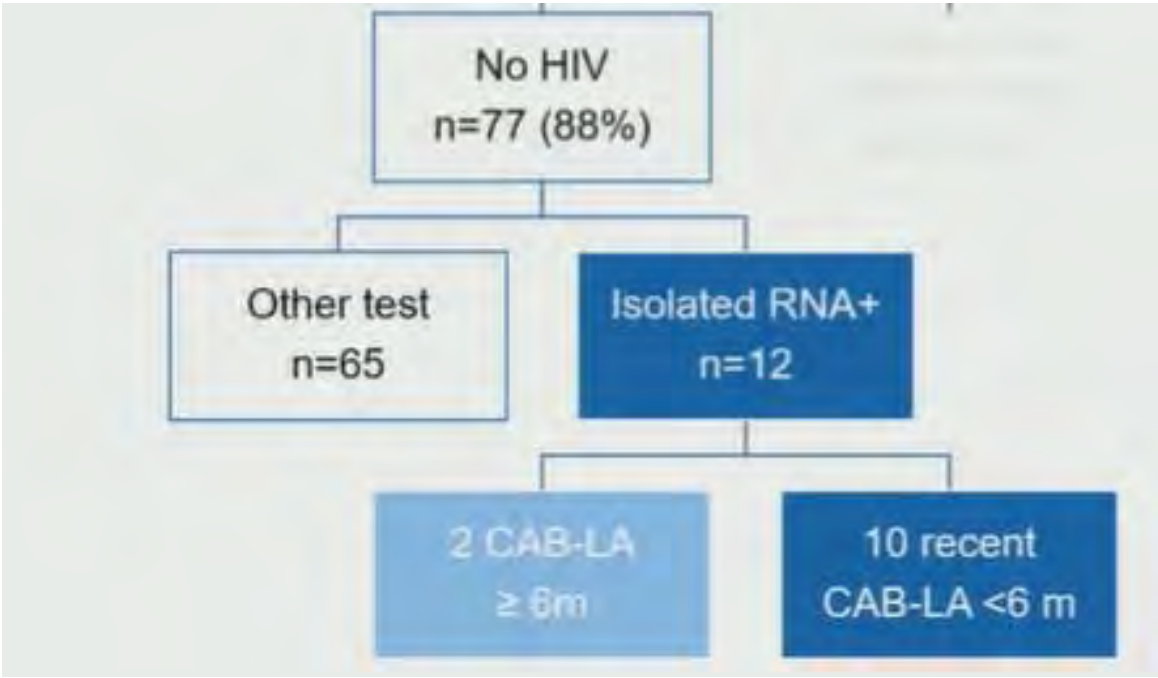
- Analysis of HPTN 084 OLE data evaluating HIV RNA performance for screening
  - Included 2,462 ppts in 24,244 visits with RNA screening = 3,229 person-years
  - 87 (4%) ppts had ≥1 reactive HIV test requiring adjudication
    - No HIV (n=77, 88%)
    - Unable to determine (n=2, 3%)
    - **HIV confirmed (n=8, 9%) as true cases**
  - For isolated HIV RNA cases:
    - RNA <LOQ with recent CAB use (quant unhelpful re: FP vs TP)
    - Oral F/TDF: RNA = 1000 c/mL



Delaney-Moretlwe S, et al. CROI 2025 – OA 195
Delaney-Moretlwe S, et al. *Lancet* 2022

Challenges with diagnosing HIV in setting of CAB-LA

- HIV excluded (n=77, 88%) as false cases
  - **12 (15%) had false positive RNA**
  - 5/12 (42%) had >10wk injection delays
  - Most had recent CAB use in past 6 mo
  - All had CAB paused at some point



Delaney-Moretlwe S, et al. CROI 2025 – OA 195; Delaney-Moretlwe S, et al. *Lancet* 2022

HPTN 084: Frequent HIV RNA false positives with CAB use

	FPR (95% CI)	PPV (95%)	Sensitivity* (95% CI)
Overall	75% (47.6%, 92.7%)	25% (7.3%, 52.4%)	62.5% (24.5%, 91,5%)
CAB-LA use < 6 m	76.9% (46.2%, 95.0%)	23.1% (5.0%, 53.8%)	100.0% (29.2%, 100.0%)
CAB-LA use ≥ 6m	100% (15.8%, 100.0%)	0% (0%, 84.2%)	0%

*Sensitivity based on HIV RNA with other screening tests

Delaney-Moretlwe S, et al. CROI 2025 – OA 195

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CAB-LA: Summary and conclusions

- Single isolated HIV RNA test performs poorly for diagnosing HIV infection in context of CAB-LA use
- Most isolated positive HIV RNA tests are expected to be false positives given low HIV incidence in setting of highly effective CAB-LA
- HIV RNA may not be cost effective as screening test and has potential for negative clinical consequences including prolonged PrEP interruptions

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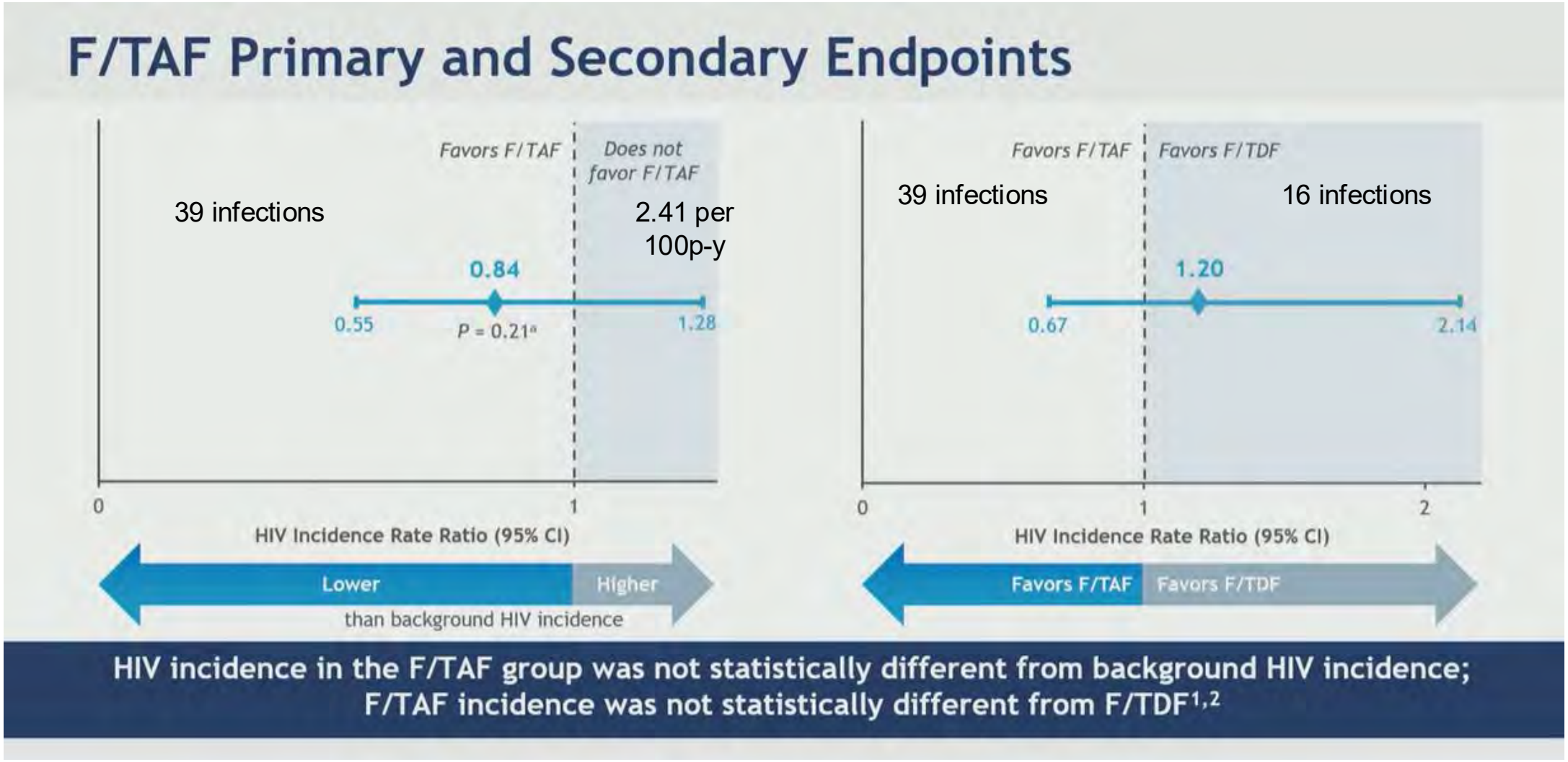
HIV PREVENTION: PrEP FOR WOMEN

Project ECHO®

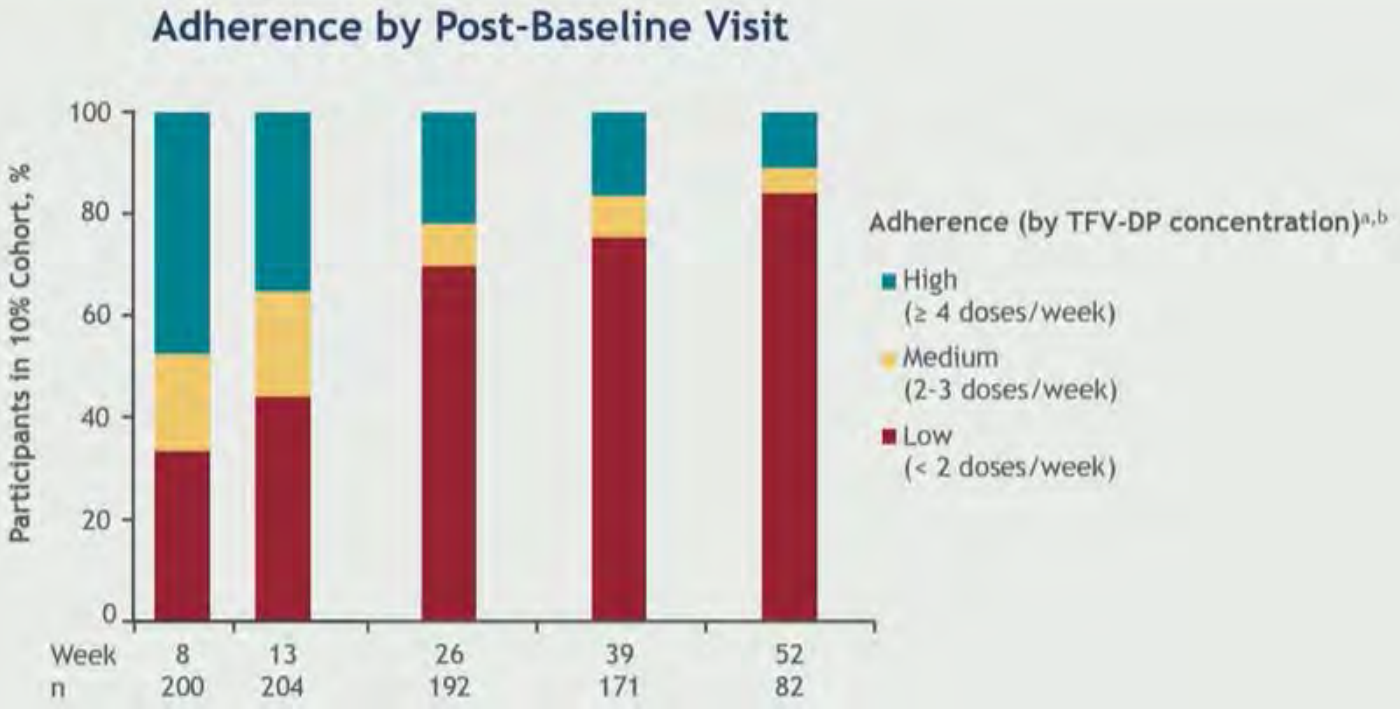
Lack of efficacy for F/TAF in women in the PURPOSE 1 trial



Kiweewa FM, et al. CROI 2025 – OA 194; Bekker LG, et al. *NEJM* 2024

Low adherence to F/TAF in women in the PURPOSE 1 trial

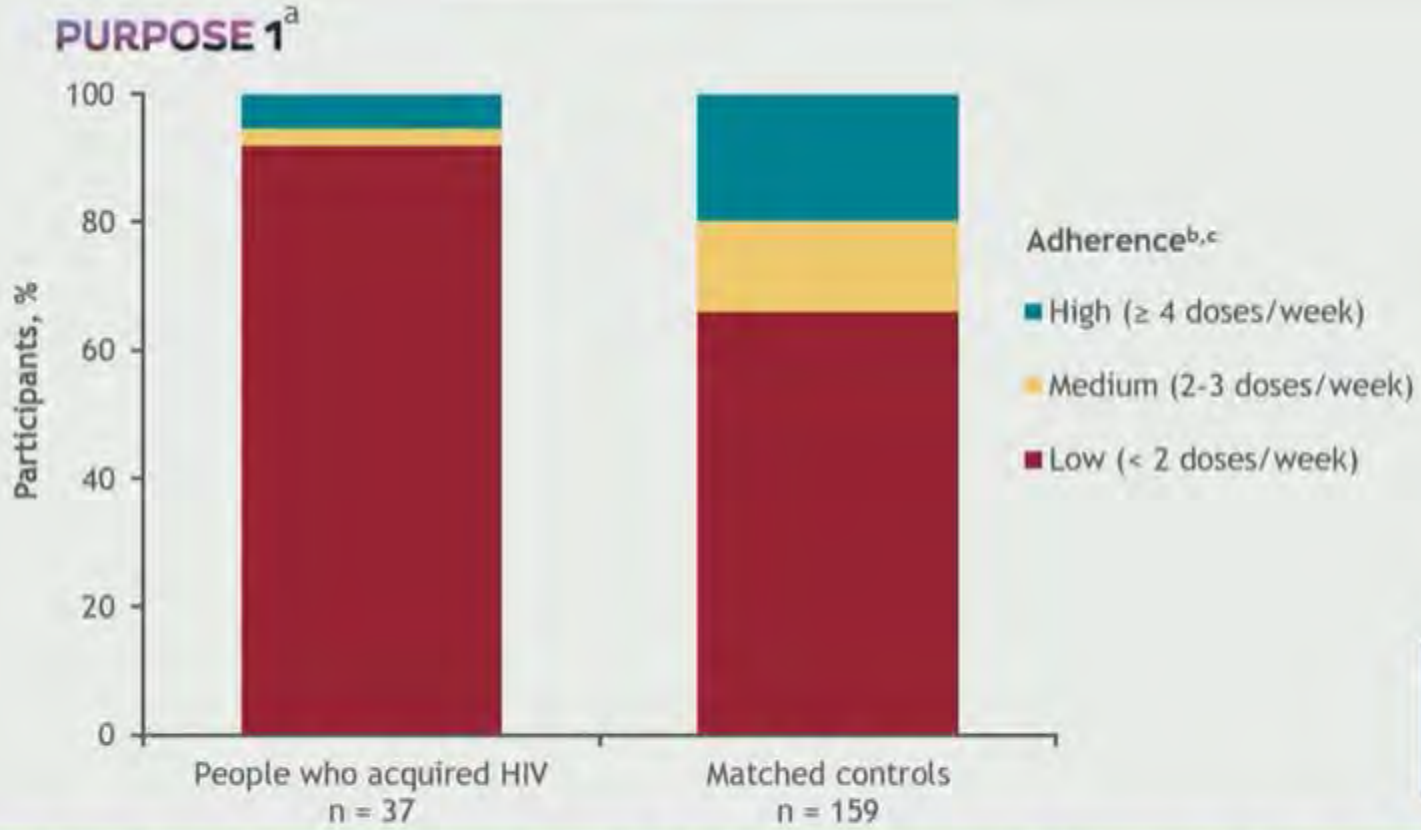
Adherence to Oral F/TAF Was Low

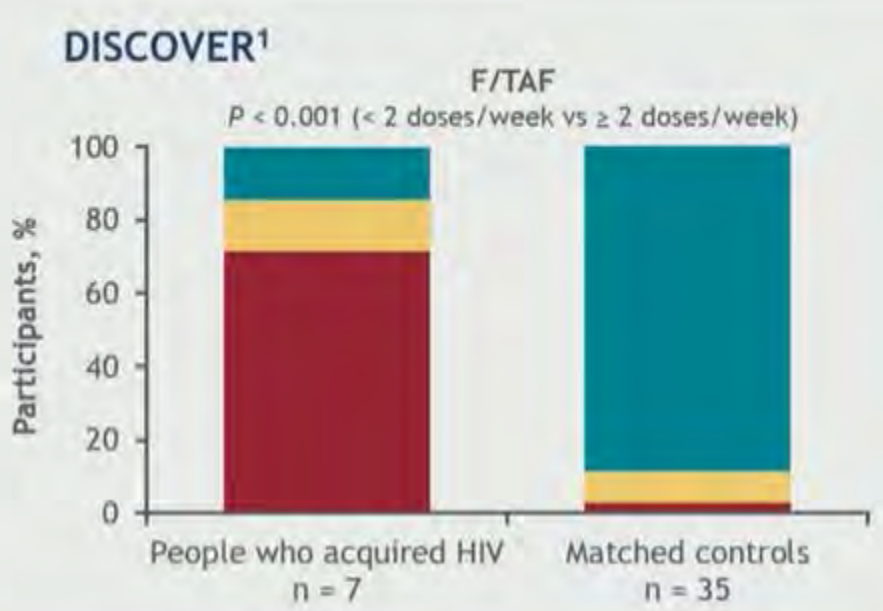


Most participants in the F/TAF group had low adherence to oral tablets, and adherence declined over time[1,2]

Kiweewa FM, et al. CROI 2025 – OA 194; Bekker LG, et al. *NEJM* 2024

Lower odds of HIV a/w medium or high F/TAF adherence





F/TDF adherence-efficacy analyses from post-approval studies in women also show increased efficacy with increased doses/week[2]

Odds of HIV acquisition were 89% lower among cisgender women in PURPOSE 1 who took ≥ 2 pills per week (odds ratio: 0.11; 95% CI: 0.012-0.49; *P* = 0.0006)[3,4]

Kiweewa FM, et al. CROI 2025 – OA 194; Bekker LG, et al. *NEJM* 2024

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New PURPOSE 1 takeaways

- All but 1 case of incident HIV in PURPOSE 1 was due to low F/TAF adherence
- Emergent ARV resistance was rare (1 case of TFV + FTC transmitted RAM)
- F/TAF did not cause a delay in HIV diagnosis as few had detectable HIV VL
- Medium or high adherence to F/TAF is efficacious for HIV prevention in women

Kiweewa FM, et al. CROI 2025 – OA 194; Bekker LG, et al. *NEJM* 2024

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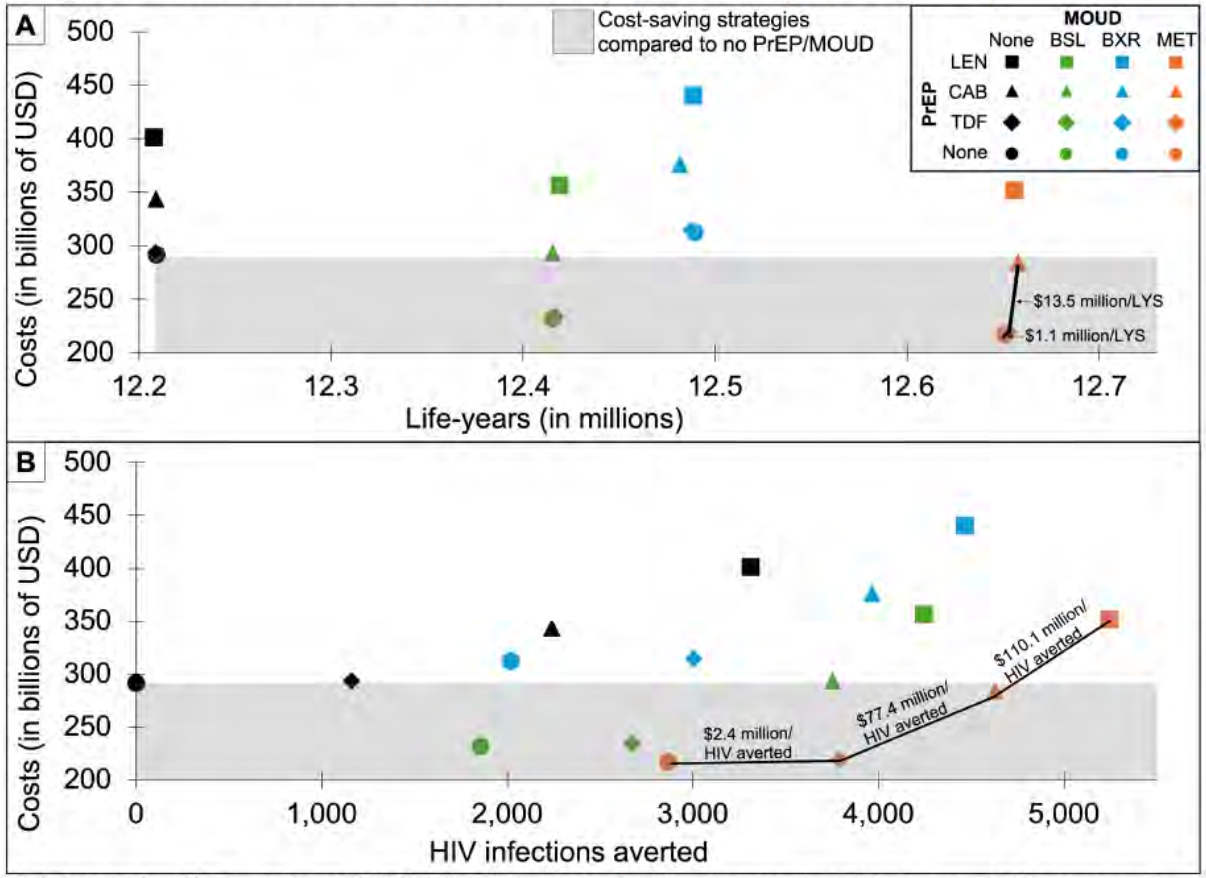
HONORABLE MENTION

Project ECHO®

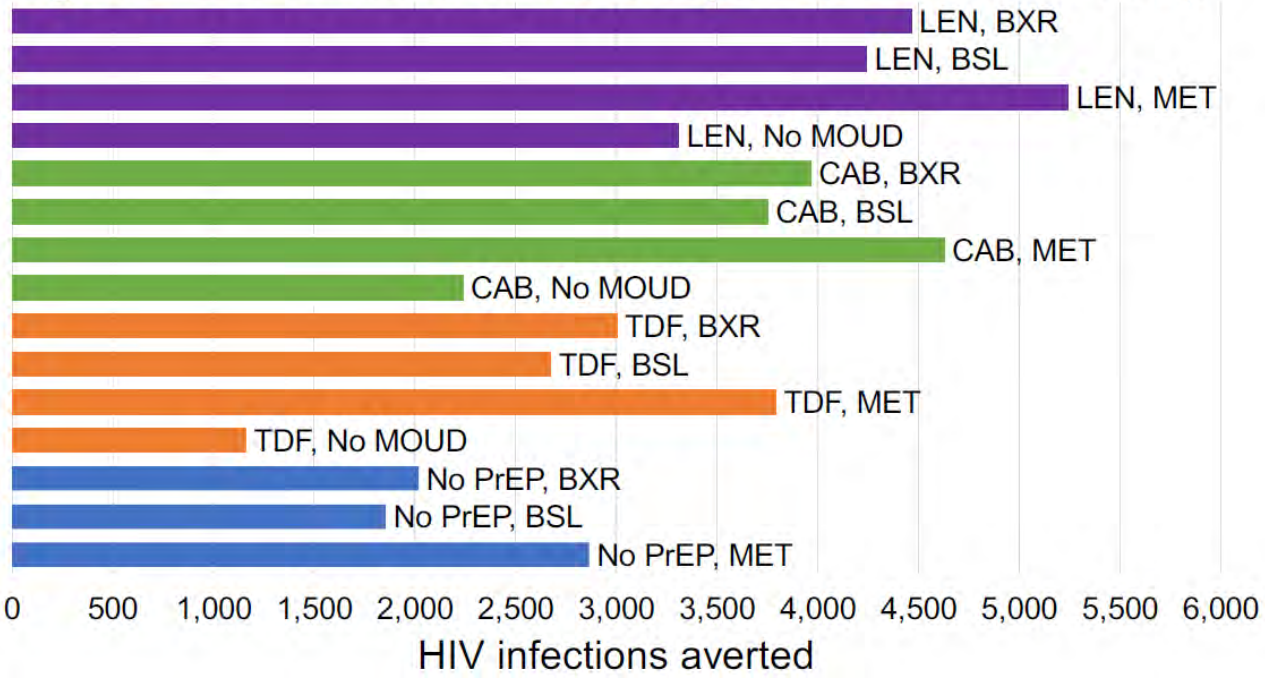
PrEP +/- MOUD reduces morbidity and mortality for PWID with OUD but is not cost effective at current PrEP prices

Figure 3. Cost-effectiveness (efficiency frontiers)



PrEP strategies: TDF = daily oral TDF/FTC; CAB = bimonthly IM cabotegravir; LEN = biannual SQ lenacapavir
MOUD strategies: MET = daily oral methadone; BSL = daily SL buprenorphine; BXR = monthly SQ buprenorphine

Figure 2. HIV infections averted (vs. No PrEP or MOUD)



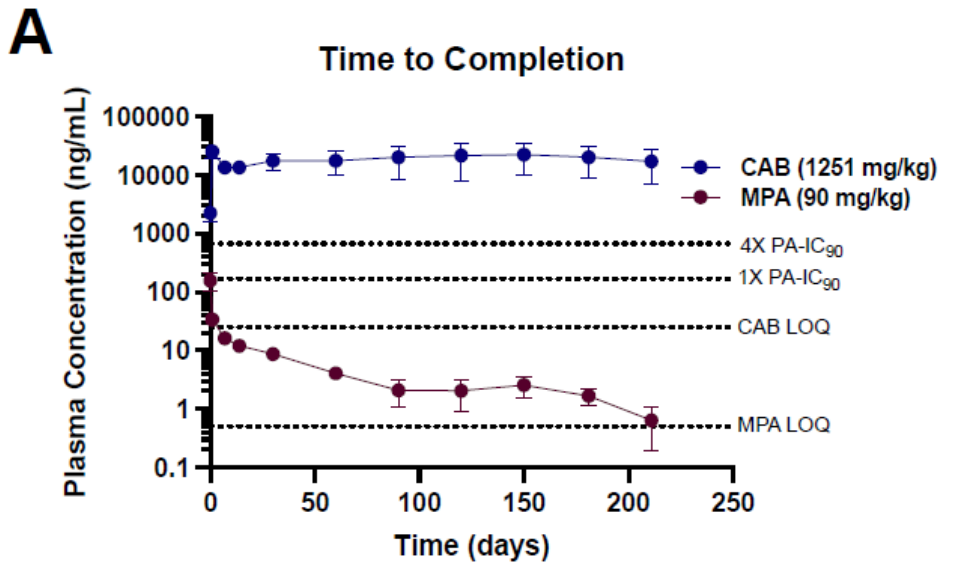
PrEP	US$ cost/interval
Oral F/TDF	$300/yr
IM CAB	$23,214 bimonthly
SQ LEN	$39,000 biannually

Chiosi J, et al. CROI 2025 - Poster 1294

Future of HIV, STI and pregnancy prevention

- Grindr survey of 827 MSM with HIV in 46 US states/territories *(Martinson, Poster 1358)*
  - 59% aware of doxy-PEP, 13% prescribed
  - Of 306 meeting CDC criteria
    - 20% prescribed and taking
    - 90+% not on doxy-PEP were interested and would start if offered by provider

- Multipurpose interventions for women and girls
  - Biodegradable, removable in-situ forming implants with CAB + MPA maintained therapeutic levels for 210 and 180d, respectively, in mice *(King, Poster 1236)*
  - Islatravir intravaginal ring was 100% efficacious in pigtail macaques SHIV challenged x12 wks *(Srinivasan, Poster 1238)*



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CROI 2025 Report Back: Treatment Updates

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Last Updated: 18 March 2025

Disclosures

No conflicts of interest or relationships to disclose.

Outline

- LA CAB-RPV
  - CARES 96 Week Data
  - More Observational Data
  - Outcomes in PWH with Viremia
  - CAB-RPV in Pregnancy
  - Stopping CAB-RPV
- DOR-ISL

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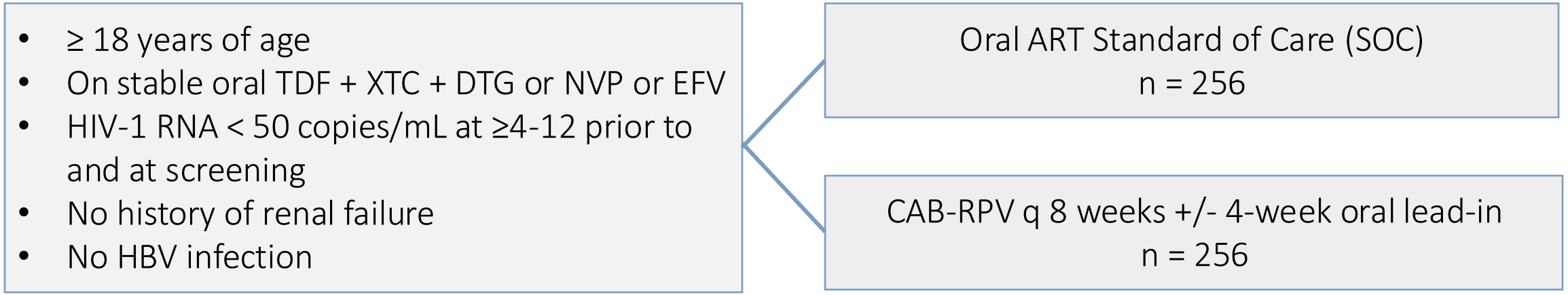
LA CAB-RPV Updates

Project ECHO®

CARES: Study Design

- Phase 3b, Randomized, Open-Label, Active-Controlled, Non-Inferiority Study



- HIV-1 RNA checked every 24 weeks
- Due to a public health approach to enrollment, resistance analysis performed during therapy and proviral DNA was performed for archived resistance on stored PBMCs
- Study sites in Uganda, Kenya, and Tanzania

Kityo CM et al, CROI 2025 #202.

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CARES: Key Baseline Characteristics

Characteristic	CAB + RPV LA (n=255)	Oral ART (SOC) (n=257)	Overall (n=512)
BMI ≥ 30 kg/m^2, n (%)	57 (22)	52 (20)	108 (21)
Time on 1st line ART regimen, median (IQR), years	8 (4-13)	7 (4-13)	8 (4-13)
Prior exposure to NNRTI, n (%)	189 (74)	191 (74)	380 (74)
INSTI regimen at screening	231 (91)	240 (93)	471 (92)
Archived DNA analysis[*+]			
Viral subtype A1, n/n (%)	*116/218 (53)*	*120/215 (56)*	*236/433 (55)*
RPV resistance mutations, n/n (%)	*14/208 (7)*	*16/193 (8)*	*30/401 (7)*
CAB resistance mutations, n/n (%)	*8/99 (8)*	*12/103 (12)*	*20/202 (10)*

*Retrospective, batched sequencing performed on archived viral DNA extracted from PBMCs stored at baseline
+Viral subtype, RAMs, and drug susceptibility determined using the Los Alamos National Laboratory Panel, IAS-USA 2022 mutations list, and Stanford algorithm respectively. APOBEC-related mutations were excluded.

Kityo CM et al, CROI 2025 #202.

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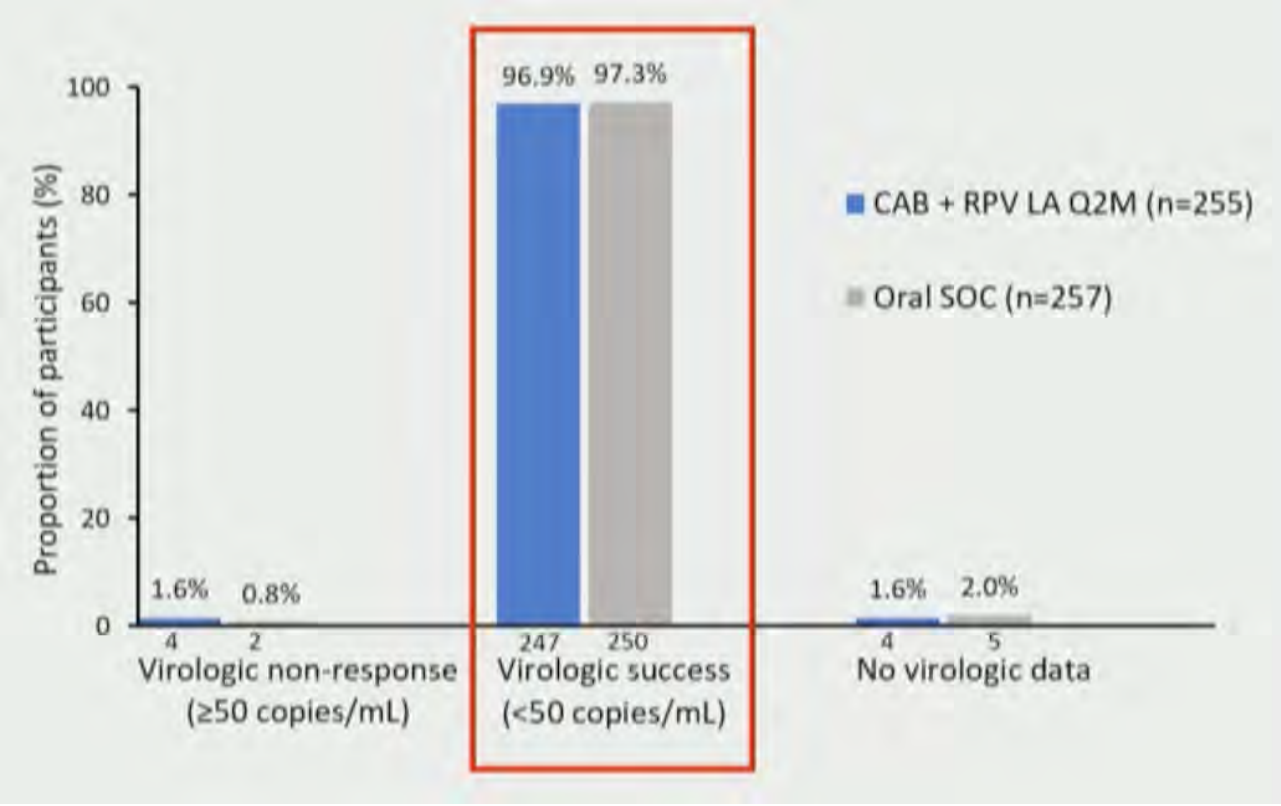
CARES: Week 96 Results

- LA CAB-RPV demonstrated noninferior virologic efficacy as compared to oral standard of care ART
- 77% had an injection site reaction (ISR)
- Over 99% on LA CAB-RPV preferred injectable to daily oral therapy
- 81% of participants received injections within the 7-day target window
- 4 cases of virologic failure (1.6%)



Kityo CM et al, CROI 2025 #202.

CARES: Virologic Failures at Week 96

Confirmed virological failure (VL ≥ 200 copies/ml x 2)	CAB + RPV LA 4 (1.6%)	Oral ART 0	Difference (95% CI) 1.6% (0.4 to 4.2)

	Participant 1	Participant 2	Participant 3	Participant 4
At confirmed virological failure				
Week of failure	48	48	**72**	**72**
Viral load, copies/ml	8,608 and 1612	44,984, no repeat	798 and 563	259 and 16,161
RPV mutations (level) ††	V108I, E138K (intermediate)	K103N/S, V106V/A, E138A, M230M/L (high)	Test Failed	E138A (low)
CAB mutations (level CAB, DTG) ††*	E92E/V, N155H, L74M (intermed., potential low)	G118R (high, high)	Test Failed	Q148R (M50I) (high, low)
At baseline				
RPV mutations (level) †	Nil	K103N/S, E138A (low)	E138K (low)	Nil
CAB mutations (level) †	L74M (low)	Nil	Test Failed	Nil
Viral subtype †	A1	D	A1	C
BMI, kg/m^2	25.9	22.0	22.2	19.9

Kityo CM et al, CROI 2025 #202.

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CARES: Conclusions

- At Week 96, LA CAB-RPV q 8 weeks administered in public health settings in sub-Saharan Africa was non-inferior in virologic efficacy to oral standard of care, had a good safety profile, and was well tolerated

- 4 cases of VF occurred in the LA CAB-RPV arm, with emergence of INSTI-R and NNRTI-R

- This remains an important contribution not only regarding broad implementation in sub-Saharan Africa using a public health approach, but also in individuals with high exposure to NNRTIs and pre-treatment resistance, and different subtypes of HIV-1

Kityo CM et al, CROI 2025 #202.

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Key Highlights from CAB-RPV Observational Data

1. Viral Suppression (VS) in the OPERA Cohort
2. VS in Women in the OPERA Cohort
3. VS in the TRIO Cohort

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Key Highlights from CAB-RPV Observational Data

- **VS in OPERA Cohort[1]**
  - Of 2,618 PWH who started CAB-RPV, 83% were on CAB-RPV at end of study period
  - With a median follow up of 11 months, 95% had VS
  - After a median of 7 months, 21 (1%) had confirmed virologic failure (CVF)
- **VS in Women in the OPERA Cohort[2]**
  - Of 532 women who started CAB-RPV, 78% were on CAB-RPV at end of study period
  - With a median follow up of 12 months, 94% had VS, and 5 (≤ 1.3%) had CVF
- **VS in the TRIO Cohort[3]**
  - Of 1198 virally suppressed PWH, 79% were on CAB-RPV at the end of the study period
  - With a median follow up of 12 months, 95% had VS, and 15 (1.6%) had CVF
    - 5/15 CVF had genotypic data
      - 3 had RPV-R (Y181C+G190S; K101E; Y181C), 1 of whom had CAB-R (S147G+N155H)

1-Sension M et al, CROI 2025 #674. 2-Altamirano JA et al, CROI 2025 #676. 3-Sax PE et al, CROI 2025 #675.

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Outcomes Among PWH Initiating CAB-RPV with Viremia

1. Ward 86: 370 PWH on CAB-RPV – 129 (35%) initiated with HIV RNA > 30 copies/mL[1]
   - 97.9% achieved and maintained VS at 48 weeks
   - No statistically significant difference in VS between those VS or with viremia at baseline

2. Ponce Clinic: 361 PWH on CAB-RPV – 81 (22%) initiated with HIV RNA > 50 copies/mL[2]
   - 69% on CAB-RPV only, 28% on CAB and/or RPV + LEN, 2% on CAB/RPV + LEN + IBA
   - 92% (72/79) achieved VS
   - Of the 6 who did not achieve VS:
     - 2 had VF with NNRTI and INSTI resistance associated mutations (RAMs)
     - 2 had persistent low-level viremia
     - 2 had HIV RNA levels 1000-3000 without RAMs

1-Gistand NL et al, CROI 2025 #689. 2-Colasanti JA et al, CROI 2025 #690.

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CAB-RPV in Pregnancy

- Little is known about the safety, efficacy, and outcomes of CAB-RPV use in pregnancy

- Multicenter retrospective chart review of pregnant women prescribed LA CAB-RPV
  - 23 women received LA CAB-RPV during pregnancy (11 q4w, 12 q8w)
    - 73% initiated prior to pregnancy, 27% switched to it during pregnancy
  - Viral suppression at delivery
    - Among those who stayed on CAB-RPV, 20/21 had HIV RNA < 200 copies/mL
    - One person had a HIV RNA > 1000 copies/mL
  - Neonatal outcomes
    - 81% of newborns received zidovudine only post-delivery
    - No cases of vertical transmission

Short WR et al, CROI 2025 #1015

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Why do people stop CAB-RPV?

- Ward 86 retrospective chart review of 437 PWH starting CAB-RPV
  - Median time on treatment 553 days
  - 69 (16%) discontinued treatment
    - 30% were on q8w dosing
  - Among those who started with VS, most common reason for discontinuation was pain
  - Among those who started viremic, lateness [of injections] and virologic failure drove discontinuation

Table 1. Reasons for Discontinuation, Stratified by HIV VL at LA-CAB/RPV Initiation

Reason for Discontinuation	Overall (n=69)	HIV VL <50 copies/mL (n=47)	HIV VL ≥50 copies/mL (n=22)
Injection site pain	14	10	4
Injection site pain with other side effect/concern*	11	9	2
Other side effect/concern*	14	11	3
Residential treatment for mental health/substance use or incarceration	5	5	-
Need to come to clinic for injections	2	2	-
Allergic reaction	1	1	-
Relocation	2	2	-
Lateness leading to provider discontinuation	8	2	6
Provider discontinuation for HIV RNA blip	1	1	-
Loss to follow up	3	3	-
Virologic failure	7	1	6
Declined ART but remained in care	1	-	1

*Other side effect/concern (not mutually exclusive): flu-like symptoms (7), weight gain (2), fatigue (2), patient concern about efficacy (3), mistrust/misunderstanding (2), muscle spasms (1) injection site abscesses (1), bloating (1), sleep/appetite concern (1), patient desire for control of HIV treatment (1), feeling "stuck in a jar" (1), wanted to "take a break" (1), feeling like "too much medicine" in body (1), discomfort with subcutaneous lenacapavir injections given for intensification of treatment regimen

Christopolous KA et al, CROI 2025 #683.

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Why do people stop CAB-RPV?

- UCSD Owen Clinic retrospective chart review of 465 PWH starting CAB-RPV
  - Median time on treatment 164d
  - 92 (19.7%) discontinued treatment
    - >90% of those who restarted oral ART had VS
  - 1 person developed NNRTI-R during PK tail
    - Baseline HIV RNA 44 copies/mL, no RAMs
    - After 2 injections, lost to follow up
    - Re-established care after 9 months
      - HIV RNA: 36,300 copies/mL
      - Genotype: Y181C
      - Concurrent proviral DNA: A98G, E138Q, V179I, Y181C, M230L

Reason for stopping LAI CAB/RPV	n (%)
Injection site reaction (ISR)	26 (28.3)
Side effect other than ISR	11 (12.0)
Difficulty coming in for injections	8 (8.7)
Lost to follow-up but returned to care*	7 (7.6)
Lost to follow-up and did not return	5 (5.4)
Insurance challenges	10 (10.9)
Virologic Failure	6 (6.5)
Concern about HBV reactivation	2 (2.2)
Deceased	5 (5.4)
Pregnancy	2 (2.2)
Other/Not documented	10 (10.9)

Faggiano T et al, CROI 2025 # 685.

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DOR-ISL

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ISL-DOR

- Islatravir (ISL) is a nucleoside reverse transcriptase translocation inhibitor (NRTTI)
  - Prior studies with higher doses ISL had declines in CD4 T-cell and total lymphocyte count (TLC)
  - Studies being repeated with lower dose ISL (0.25mg) with DOR

- Among 513 VS PWH on B/F/TAF randomized 2:1 to DOR/ISL QD (342) vs. continued B/F/TAF (171), VS was high and DOR/ISL was non-inferior at 48w[1]
  - 2 PWH in ISL-DOR had HIV RNA > 200 copies/mL but no treatment emergent resistance
  - 2 PWH on ISL-DOR and 1 on B/F/TAF discontinued due to decrease in CD4 T-cell or TLC

- Among 551 VS PWH on baseline ART (bART) randomized 2:1 to DOR/ISL QD (366) vs. continued bART (185), VS was high and DOR/ISL was non-inferior at 48w[2]
  - 5 PWH in ISL-DOR arm had VF but no treatment emergent resistance

1-Colson A et al, CROI 2025 #204A. 2-Orkin C et al, CROI 2025 #204B.

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Conclusions

1. Week 96 CARES data demonstrated that LA CAB-RPV was non-inferior to oral SOC in sub-Saharan Africa.
2. In observational cohorts of individuals on CAB-RPV, VS remains high, including in people starting viremic.
3. LA CAB-RPV may be a viable option in pregnancy, but more studies are needed.
4. In clinics with large numbers on CAB-RPV, approximately 15-20% of PWH have discontinued injections, mostly due to pain/injection site reactions.
5. DOR-ISL appears efficacious and safe at a dose of 100mg/0.25mg in phase 3 trials.

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CROI 2025 Update: Co-Occurring Conditions

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Last Updated: 3/17/25

Disclosures

No conflicts of interests or relationships to disclose

CROI Updates: Co-Occurring Conditions

- Updates in HIV and TB management
- Updates in ART and weight gain
- Updates in HBV vaccination

HIV and TB co-infection

DOLPHIN-Moms: PK of Dolutegravir and HIV Viral Suppression with 1HP or 3HP in Pregnancy

- For women with HIV, active TB risk is highest during and just after pregnancy
- For PWH needing TB preventive therapy (TPT): **3HP (3 months of weekly isoniazid and rifapentine with daily DTG)** and **1HP (1 month of daily isoniazid and rifapentine with BID DTG)** have similar efficacy, increased adherence, and fewer adverse events compared to 6H (6 months of daily isoniazid)
  - **Pregnant women excluded from all trials**
  - **Pregnant women have 25-30% lower DTG troughs than non-pregnant**
- Both WHO and US CDC recommend daily isoniazid for TB preventive therapy in pregnant women with HIV
  - BUT: Increased adverse pregnancy events with 6H in pregnant versus post partum

What happens to PK of dolutegravir in 1HP and 3HP in pregnant women?

Mathad et al. CROI 2025; Slide acknowledgements Dr. Sylvia LaCourse and DOLPHIN Moms team

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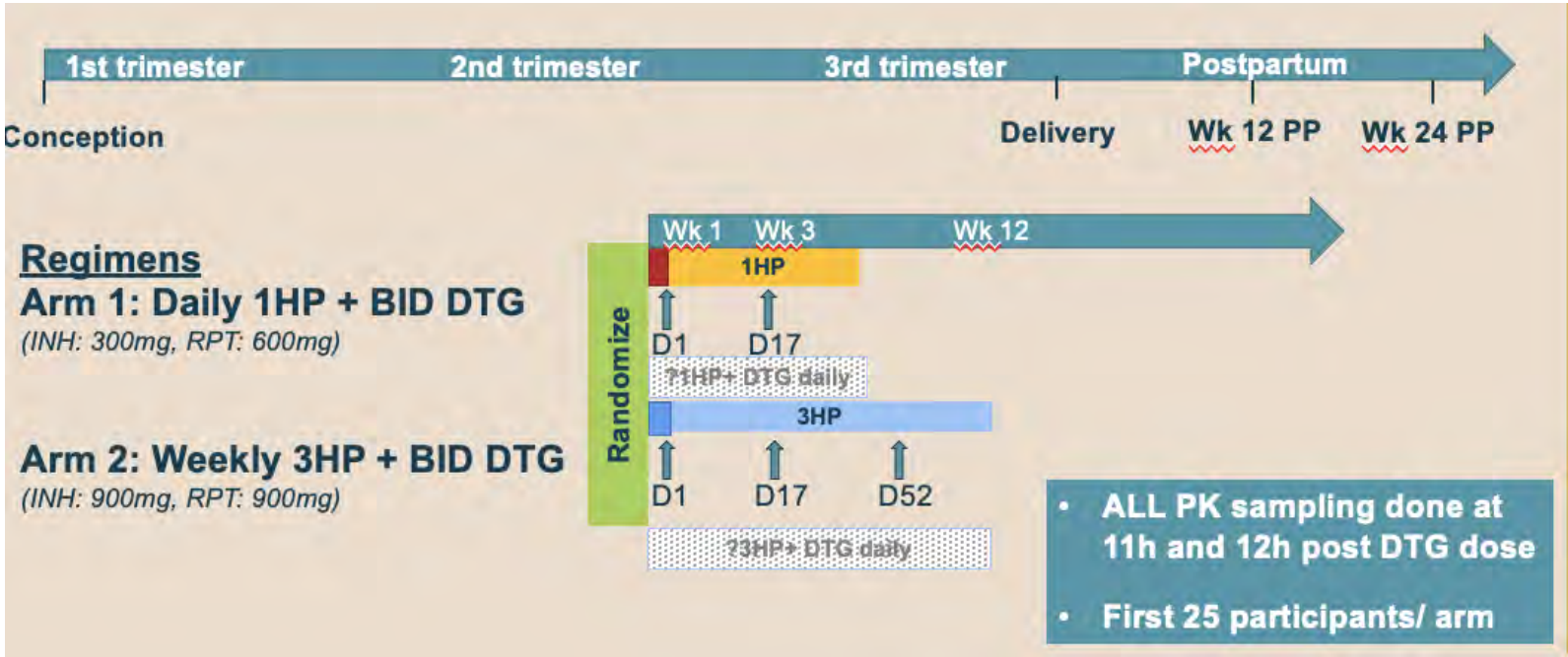
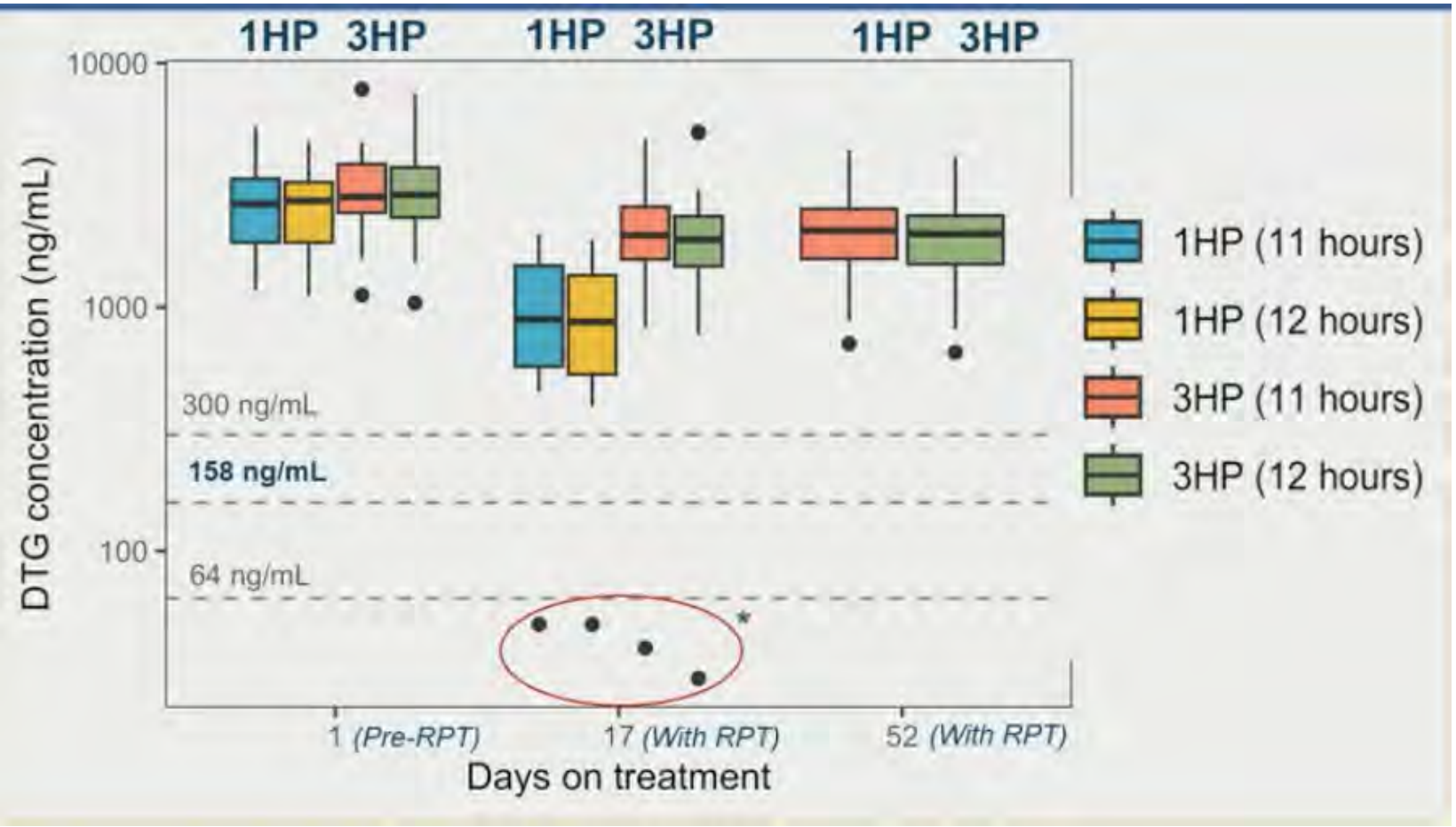
DOLPHIN-Moms: PK of Dolutegravir and HIV Viral Suppression with 1HP or 3HP in Pregnancy

- Phase II RCT of 1HP and 3HP and pharmacokinetics of DTG
  - Ongoing study in South Africa
  - Pregnant women at 20-34 weeks of gestation
  - ART: DTG based for a month or more with VS
- Primary PK Outcome
  - Population plasma PK parameters of DTG +/- 1HP or 3HP
- Secondary Outcomes
  - Viral suppression
  - Daily versus BID DTG with 1HP or 3 HP



DOLPHIN-Moms: PK of Dolutegravir and HIV Viral Suppression with 1HP or 3HP in Pregnancy



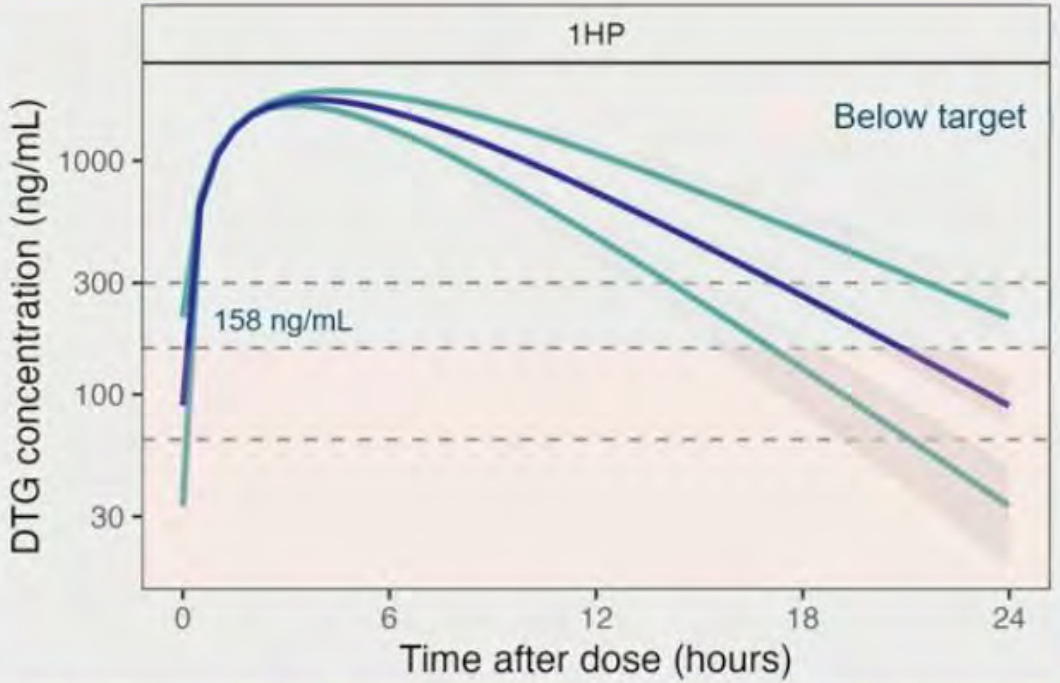
Day 1: **No difference** in [DTG] between arms

Day 17: **Significant difference** in [DTG] as compared to day 1 AND between arms

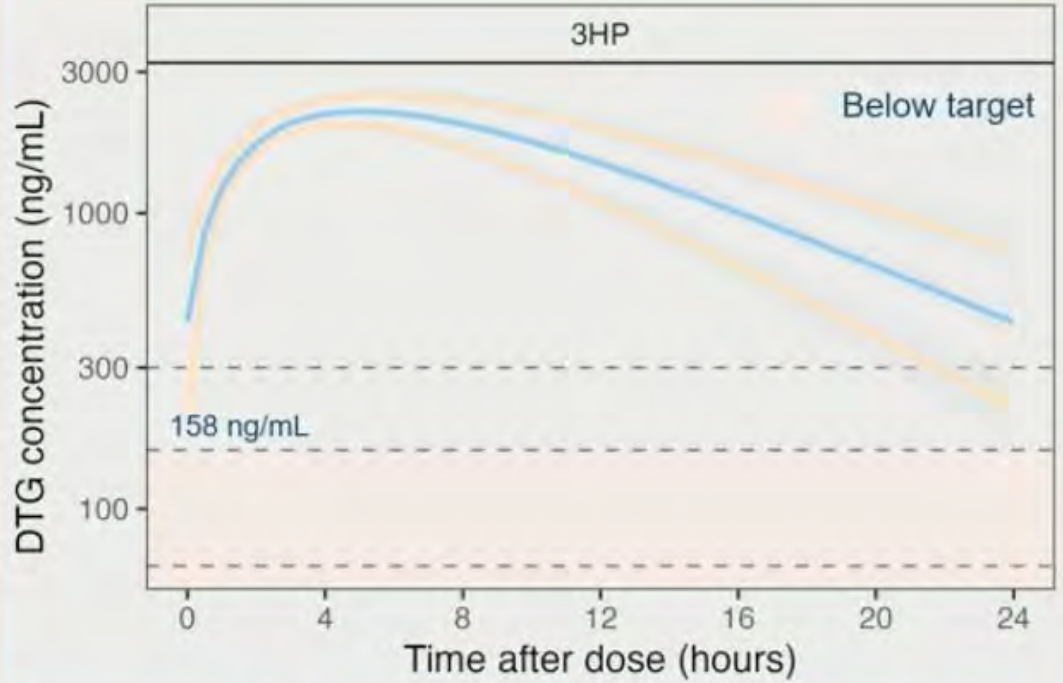
Day 52: Stable levels (3HP)

***All therapeutic DTG levels except for those with adherence difficulties**

DOLPHIN-Moms: Simulations of DAILY DTG with 1HP and 3HP



TROUGHS ng/mL	5% of data	50% of data	95% of data
5% CI	18.4	73.2	166
50% CI	33.2	89.4	214
95% CI	50.2	119	299



TROUGHS ng/mL	5% of data	50% of data	95% of data
5% CI	169	384	635
50% CI	220	427	745
95% CI	291	502	912

DOLPHIN-Moms: PK of Dolutegravir and HIV Viral Suppression with 1HP or 3HP in Pregnancy

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Takeaways

- In pregnant women with HIV, **BID DTG with either 1HP or 3HP resulted in appropriate DTG troughs and continued viral suppression**

- In simulation models of daily DTG:
  - 1HP: DTG troughs below acceptable threshold, suggesting need for BID DTG with this regimen in pregnancy
  - 3HP: All DTG troughs above acceptable threshold, suggesting that daily DTG can be given with this regimen in pregnancy

- **Ongoing:** enrollment of an additional 25 women on **3HP and once daily DTG with PK sampling**

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TAF Achieves Adequate Intracellular Tenofovir-DP Concentrations with Rifampicin Based TB therapy

- FDA labeling recommends against coadministration of TAF + rifampin
- Open label, three period sequential PK study in people with VS on rifampin containing TB therapy
- Standard dosed TAF achieved **higher TFV-DP intracellular concentrations compared to TDF (standard of care)** in patients with HIV-associated, rifampicin sensitive TB

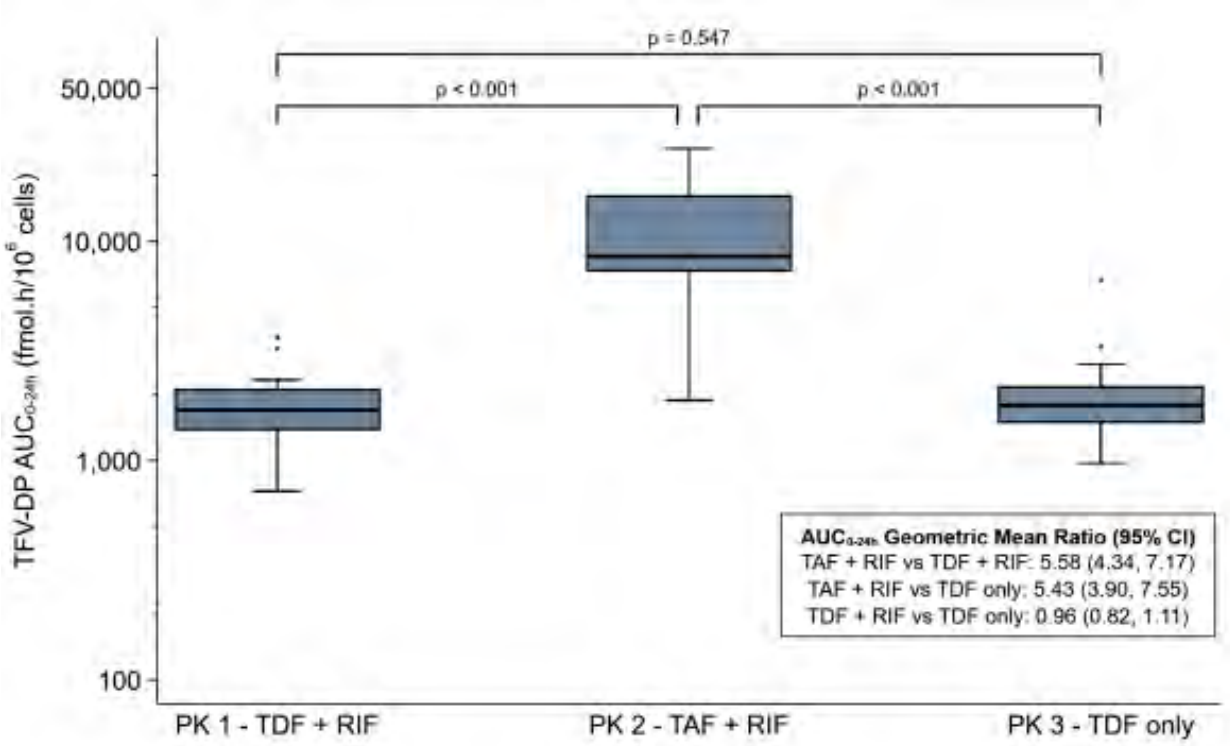

Figure 1: Intracellular Tenofovir Diphosphate 24-Hour Area Under the Concentration-Time Curve by Treatment Period

Mpofu et al. Poster #646 CROI 2025

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Weight Gain

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Weight Gain on ART

- Some weight gain expected with ART initiation[1]
- Signals for independent weight gain effects of INSTI + TAF, with greatest weight gain in combination[2,3]
  - **True in both switch and ART-naïve start**
- Mechanism? Unknown!
  - **Weight suppressive effects of EFV, TDF**
  - **Synergy between TAF and INSTIs**
- Is weight gain on ART reversible? We don't know! No definitive RCT data

1 Pantazis et al. Lancet HIV 2024
2 Venter et al. NEJM 2019
3 Sax et al. CID 2020

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Switch to DTG/3TC vs. B/F/TAF (PASO-DOBLE)

In PASO-DOBLE, switching ART **to DTG/3TC vs B/F/TAF in PWH with VS** was associated with less weight gain.

Poster #661 Tiraboschi et al: Switch to DTG/3TC vs B/F/TAF: Efficacy and Weight Changes by Predefined Subgroups

- Subgroup analysis of efficacy and **clinically meaningful weight changes (>5% from baseline)**
- Significant lower proportions of PWH with significant weight gain in DTG/3TC arm in:
  - females, age 35-50 years, Latin-American ethnicity
  - Pre-switch CD4 >= 500/mm3
  - TDF, FTC, and NNRTI containing regimens

Poster #897 Di Gregorio et al.: Body Composition Changes in People With HIV Switching to DTG/3TC or BIC/TAF/FTC

- Analysis of body composition in both arms via whole body DXA and abdominal CT
- Significant increase in fat compartments and decrease in lean mass compartments in all groups; changes were greater in BIC/TAF/FTC group versus DTG/3TC group
- TDF and EFV at baseline associated with significant difference in visceral and total fat mass changes

Martinez et al, AIDS 2024

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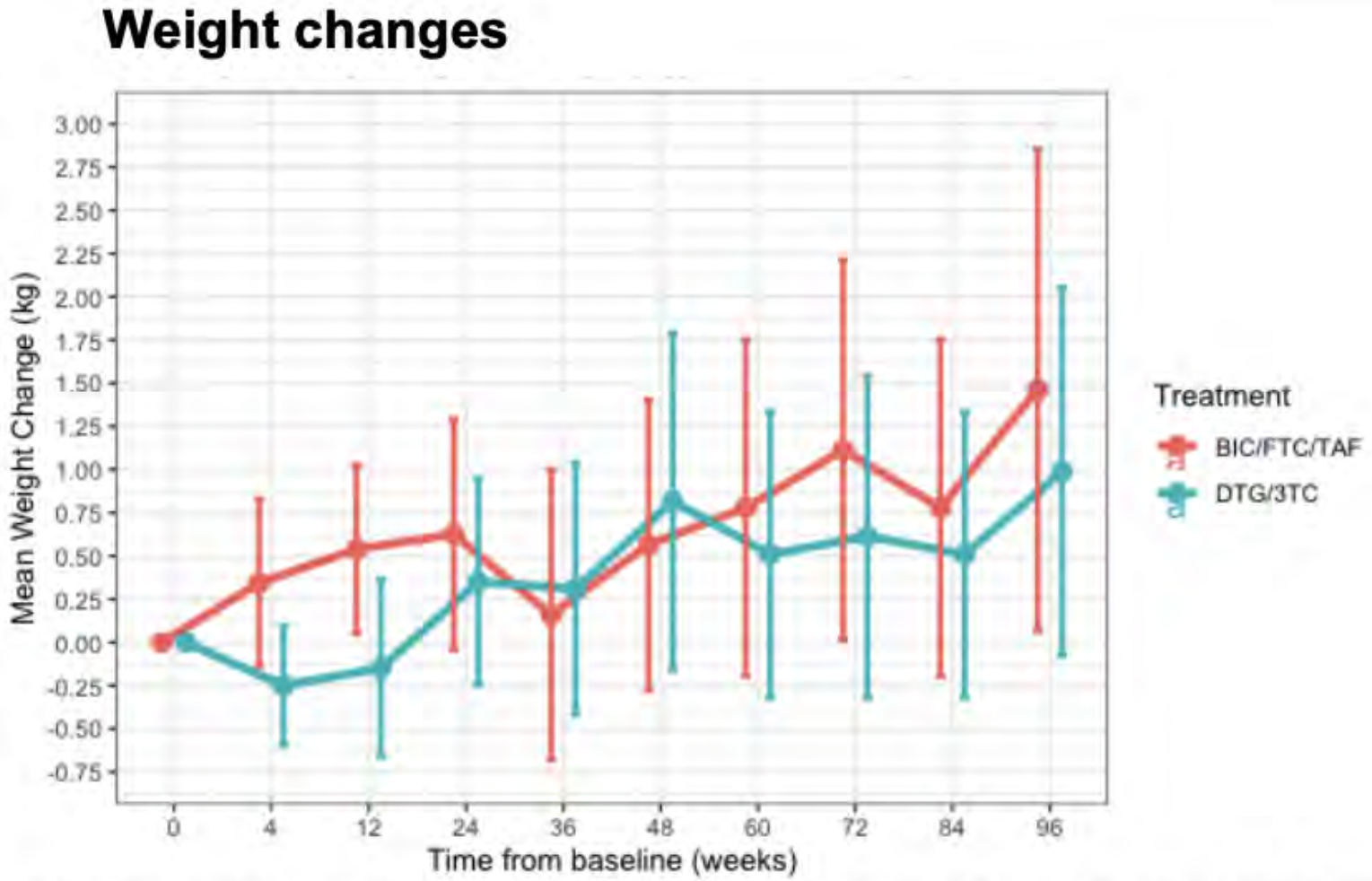
Impact of Switching From DTG/3TC to BIC/FTC/TAF on Weight, Cholesterol, and Inflammation in HIV

- INSTINCT Trial: Effect of switching from DTG/3TC to BIC/TAF/FTC on systemic inflammation up to 96 weeks
- No difference in weight changes between groups



Mean weight at baseline 77 kg and the overall mean weight change was 1.22 kg, (95% CI 0.31-2.13) with no difference between groups.

Serrano-Villar et al. CROI 2025, Poster #668

Weight Gain Rapid Fire

- **Poster #890** Pedersen et al.: Weight and Body Composition After Switch to DTG/3TC from DTG/3TC/ABC
  - Switching to two drug ART (DTG/3TC) by discontinuing abacavir for 48 weeks did NOT change body weight, fat distribution, or metabolic parameters in PWH

- **Poster #893** Milic et al.: Body Composition Changes in PWH Switching From or Maintaining TDF-Based Regimens
  - After 2 years of follow-up, TDF maintenance a/w slight reduction in BMI and total lean mass; switching to TAF a/w increase in BMI and stabilization of lean and fat mass

- **Poster #894** Mavarani et al: Risk Factors Associated With Extreme Weight Gain in PWH
  - Association with higher risk of >10% weight gain within 5 years in PWH: younger age, higher baseline CD4/CD8 ratio, switch to TAF, switch off TDF (trend)

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Takeaways

- HIV and ART related weight gain is multifactorial
- More evidence that initiation of TAF + INSTI (2nd gen) is associated with more weight gain than INSTI alone, suggesting synergistic or additive effect, but-
- Switching from INSTI to combination of TAF + INSTI does not appear to drive further weight gain
- TDF continues to be associated with attenuation of some metabolic and mass effects
- **What do we do about weight gain?**

Hepatitis B Vaccination in PWH

B-Enhancement of HBV Vaccination in Persons Living With HIV (BEe-HIVe): Study Design

HBV vaccine seroprotection rates (SPR) in persons with HIV (PWH) are lower than in adults without HIV with conventional HBV vaccine (HepB-alum)[1]

- **Entry Criteria Arm A and B**
  - PWH and age 18-70 years
  - On ART & HIV-1 RNA <1,000 copies/mL
  - CD4 >100 cells/mm^3
  - Negative HBV surface Ab (sAb)
  - No history of hepatitis B
  - Not pregnant
- **Arm A (Vaccine Non-Responders)**
  - Serum Hep B sAb <10 mIU/mL
  - HBV vaccination (>168 days prior)
- **Arm B (Vaccine Naïve)**
  - Hep B sAb negative (<45 days)

Arm A: HBV Vaccine Non-Responders	
HepB (CpG)	2 doses: 0, 4 weeks
HepB (CpG)	3 doses: 0, 4, and 24 weeks
HepB (Eng-B)	3 doses: 0, 4, and 24 weeks

Arm B: HBV Vaccine Naive	
HepB (CpG)	3 doses: 0, 4, and 24 weeks

Source: Marks K, et al. ID Week. October 19-23, 2022; Washington, D.C. Poster LB749.; National HIV Curriculum

ACTG 5479 (BEe-HIVe): Prior Results

Arm A (vaccine non response)[1]

- PWH with non-response to conventional HBV vaccine achieved **superior SPR** as compared to 3 doses of HepB-alum
- Three doses of HepB-CpG achieved high proportion of SPR with HBsAb titers > 1000 mIU/mL (78%)

Arm B (vaccine naïve)[2]

- **100% of PWH** receiving 3-dose series HepB-CpG (Heplisav-B) vaccine **achieved seroprotective response** (SPR, HBsAb ≥ 10 mIU/mL), 84% HBsAb ≥ 1000 mIU/mL
- **98.5% achieved SPR after two doses**, though at lower titers (28% HBsAb ≥ 1000 mIU/mL)

72 week durability data for both arms

[1]Marks KM, et al. JAMA 2025
[2]Marks KM, et al. Clin Infect Dis 2023

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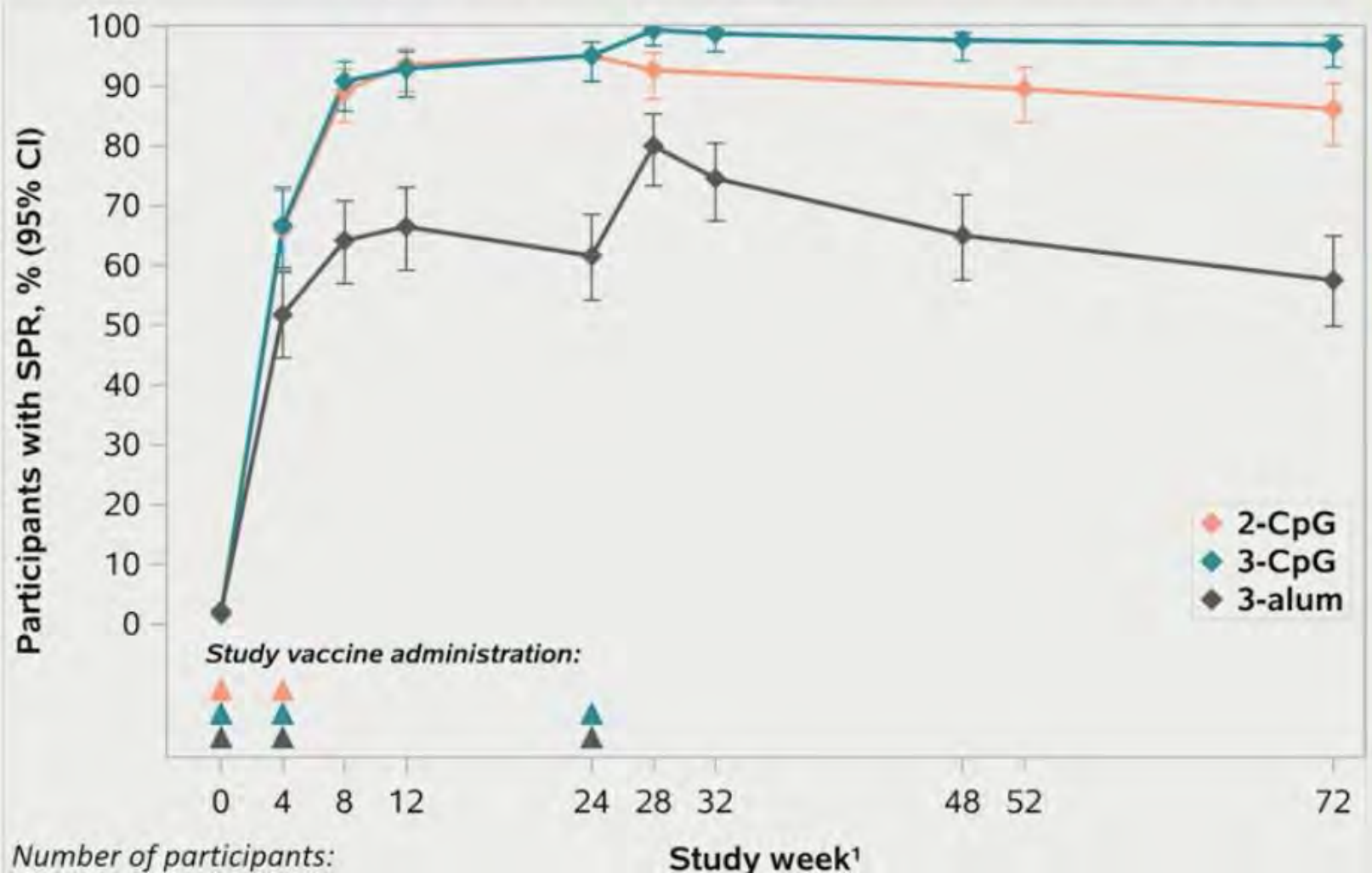
BEe-HIVe: Group A 72 week Results

Group A: Proportion with Anti-HBs ≥ 10 at Study Visits



End of study Anti-HBs ≥ 10

97.2% of 3-CpG (n=177)

86.1% of 2-CpG (n=173)

57.5% of 3-alum (n=174)

The proportion who achieved SPR at any time on study but had anti-HBs <10 by study end was:

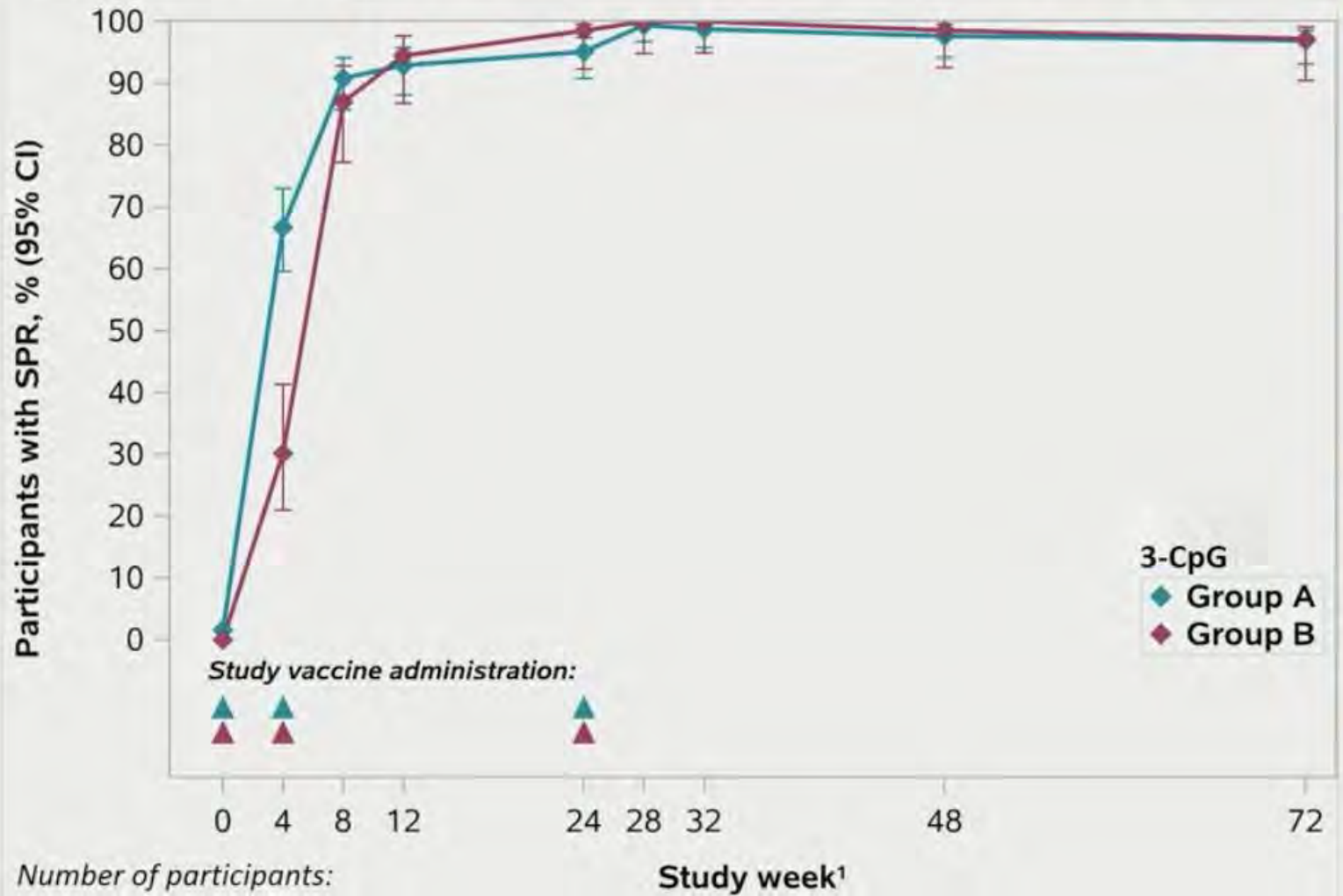
2.1% for 3-CpG

10.7% for 2-CpG

22.0% in 3-alum

BEe-HIVe: Group B 72 week Results

Group B: Proportion with Anti-HBs ≥ 10 at Study Visits



End of study anti-HBs ≥10
97.3% 3-CpG (n=74)

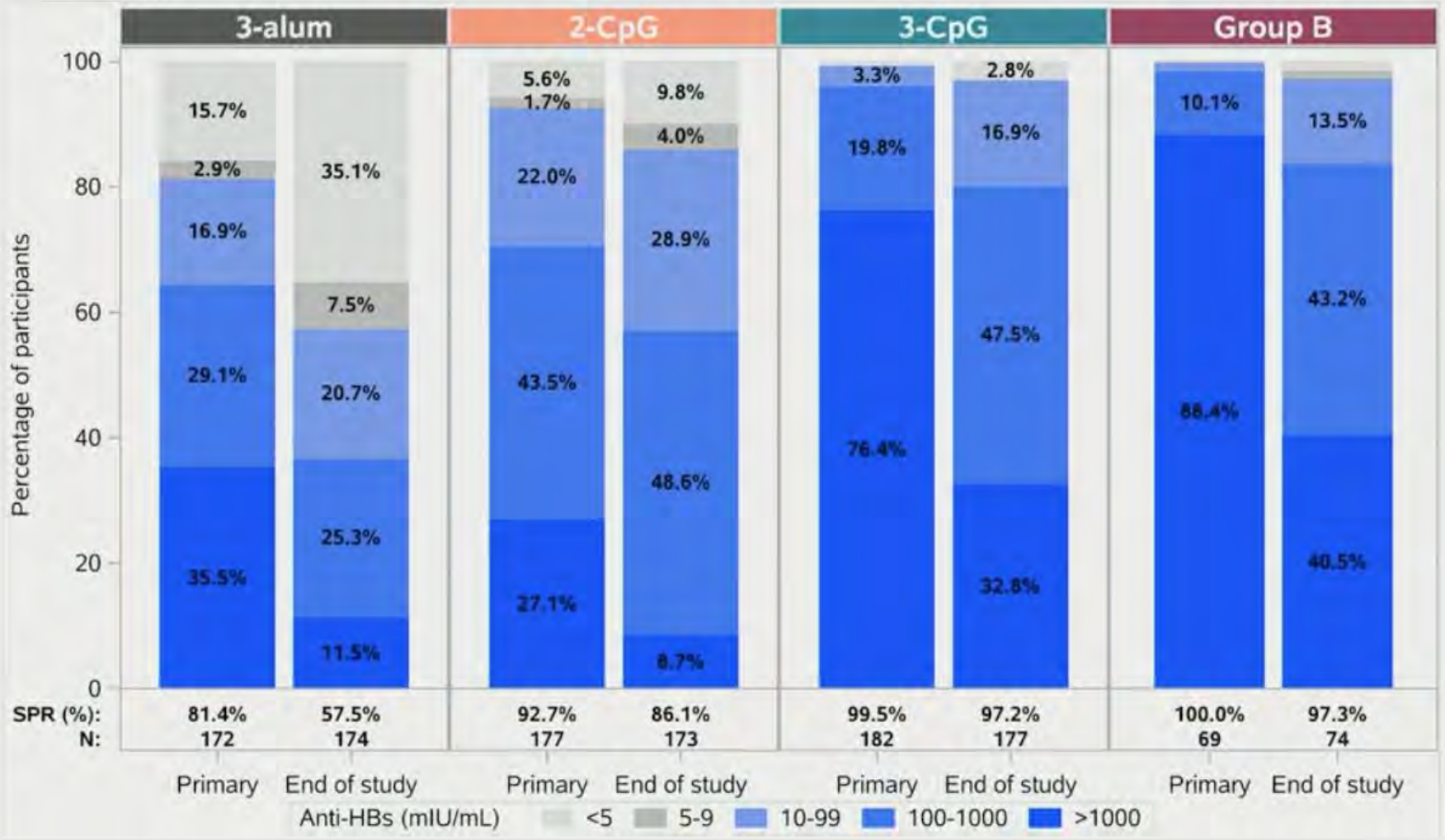
For comparison,
97.2% in Grp A 3-CpG (n=177)

Group B Durability

- Primary SPR proportion
  100% (CI: 94.7%, 100%)
- End of study SPR proportion
  97.3% (CI: 90.7%, 99.3%)

BEe-HIVe: 72 week Results

Group A & B: Distribution of Anti-HBs titers*



Higher primary anti-HBs titers were more likely to lead to SPR by end of study (EOS).

EOS SPR:

- 100% of those with titers > 1000 at primary response
- 0% with titers <100 in 3-alum at primary response
- 61% with titers <100 in 2-CpG at primary response
- Not enough people with titer <100 at primary response in 3-CpG arms to say!

Takeaways

- In PWH, higher end of study seroprotection was achieved with HepB-CpG over HepB-alum, and among CpG, 3 doses over 2 doses
- HepB-CpG led to durable seroprotection both in vaccine-naïve and prior vaccine non responders
- NB: Low CD4 and HIV viremia not well represented in the study

Co-Occuring Conditions: Take Home Points

- In pregnant women with HIV, BID DTG with either 1HP or 3HP was favorable from a PK perspective- and daily dosing of DTG with 3HP might be
- There is increasing data that ART related weight gain is complex; need more data regarding impact of regimen switch
- HepB-CpG (Heplisav-B) is superior to conventional HBV vaccination in PWH and is highly durable

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Questions?

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