UNC
INSTITUTE FOR GLOBAL HEALTH
& INFECTIOUS DISEASES

CROI 2025 – What Matters Most

A NATAP UPDATE

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CROI 2025: What Matters Most

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PREVENTION

- Oral PrEP
  - PrEP to Need Ratio and HIV diagnoses
  - Disparities in PrEP uptake
  - High female prevalence areas
- LA-CAB uptake
  - Kaiser
  - PILLAR
  - HIV RNA screening ART Response after LA-CAB
    - 083
- Lab testing before and during PrEP
- LEN annual
- DOXY-PEP
  - DC Cohort
  - SF Experience

HIV TREATMENT

- CAB/RPV
  - OPERA
  - SF SPLASH & Homeless Individuals
  - Why people stop
  - CARES Trial
- Switch to DOR/ISL
  - BFTAF->
  - ART->
- ISL+LEN Weekly
  - Resistance
- bNAbs
  - TAB+ZAB+LEN
  - NSL6 + CAB - EMBRACE
- BIC+LEN – ARTISTRY
- New ART
  - MK-8527
  - VH-184
  - Others

HIV COMPLICATIONS

- PASO-DOBLE update
- BMI and VAT (VAMOS) Plus BRI
- OPERA - HTN and ART
- NA-ACCORD/IdEA - INSTI and DM
- REPRIEVE
  - Biomarkers and plaque
  - Risk for functional decline
  - Cognition
- What Semaglutide does
  - SLIM-LIVER
  - Cognition
  - Alcohol
- Letermovir – Good news?
- CoRIS – Really good news

MPOX

- Clade 1 resurgence
- STOMP
- Vaccination response

Thank You!

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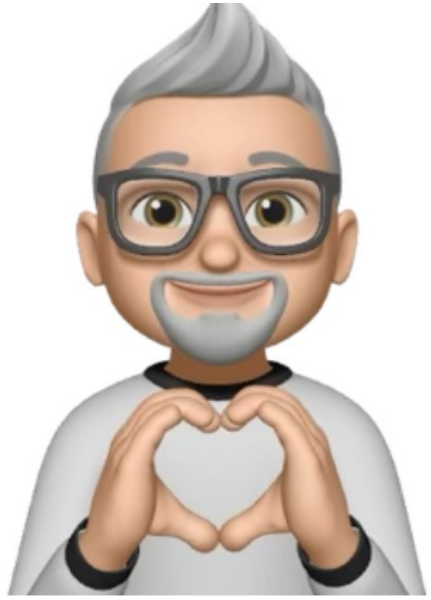
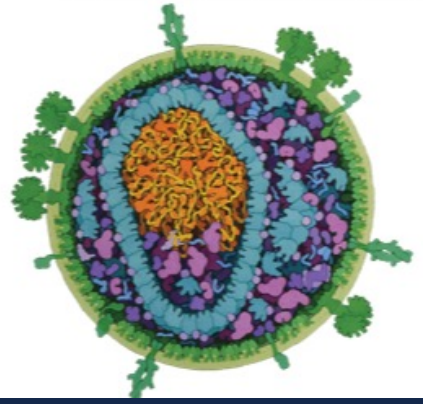
Acknowledgement

The vast majority of practice-changing and life-enhancing data to be presented was generated or supported by the US Federal government through the NIH, the CDC and other agencies staffed by people dedicated to our health and well-being.

Thank you, Federal Workers, for your passionate commitment and for creating what has been the **greatest** engine of research in the world.





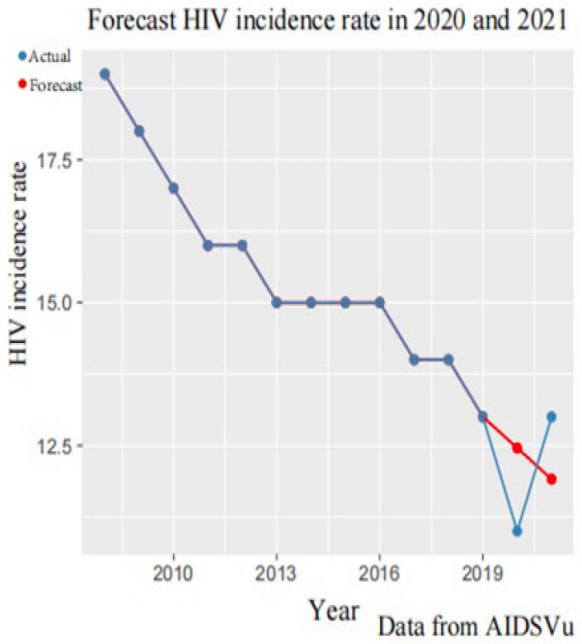
CROI

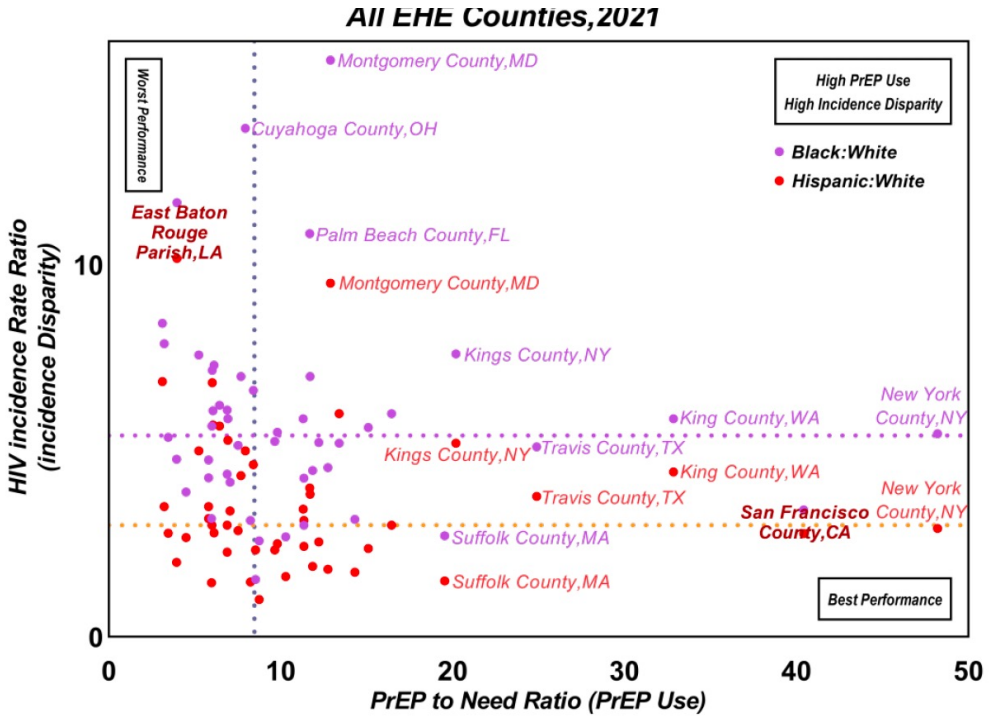
Conference on Retroviruses and Opportunistic Infections

Prevention

HIV PrEP – How are we doing?

- PrEP to Need Ratio (PNR) = PrEP prescriptions/New HIV diagnosed
- High PNR is good (Lots of PrEP and few new diagnoses)
- Objectives:
  - What is the association between changes in PNR over time and HIV incidence 2012-21 in EHE jurisdictions





Xia G, et al.

HIV PrEP – How are we doing?

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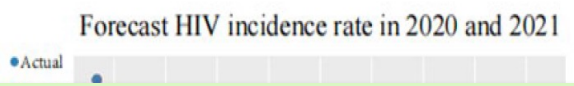

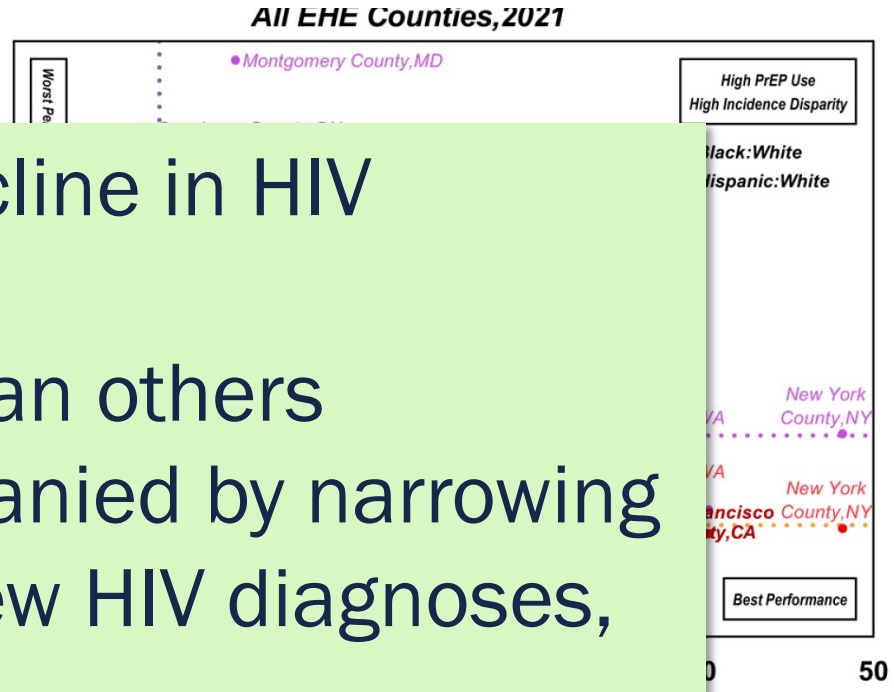

- Better PNR was associated with decline in HIV diagnoses
- But some places do much better than others
- Better PNR was not always accompanied by narrowing of racial and ethnic disparities in new HIV diagnoses, reflecting unequal access to PrEP
- We need to do better

Xia G, et al.

HIV PrEP – How are we doing?

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- What is driving PrEP disparities?
- Objectives:
  - Calculate measure of socioeconomic segregation based on race, income, & education and associate with PrEP uptake

Methods

Index of Concentration at the Extremes (ICE)

- The ICE quantifies segregation by measuring the concentration of individuals at opposite ends of the socioeconomic spectrum[4–6]:

$$ICE = \frac{A_i - P_i}{T_i}$$

i is a geographic area or unit
A_i is the number of residents categorized to the most privileged extreme
P_i is the number of residents categorized to the most underprivileged extreme
T_i is the total population in the area

Table 1. Attributes of ICE Scores

Attribute	1. ICE Race	2. ICE Income	3. ICE Education	4. ICE Race & Income
Privilege extreme (A_i)	Non-Hispanic White	Annual household income ≥$100K	Education ≥ college graduate	Non-Hispanic White with income ≥$100K
Underprivilege extreme (P_i)	Non-Hispanic Black	Annual household income <$25K	Education < high school	Non-Hispanic Black with income <$25K

ICE, Index of Concentration at the Extremes.

- Four ICE scores were calculated for >32,000 USA Zip Code Tabulation Areas (ZCTAs) using American Community Survey data (2022; 5-year data) **(Table 1)**
  - ICE values range from -1 (entire population is in the most underprivileged group) to 1 (entire population is in the most privileged group)
  - ZCTAs were categorized into quintiles (Q) based on sample distributions of ICE values
  - Q1 represents the most underprivileged communities and Q5 represents the most privileged communities

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HIV PrEP – How are we doing?

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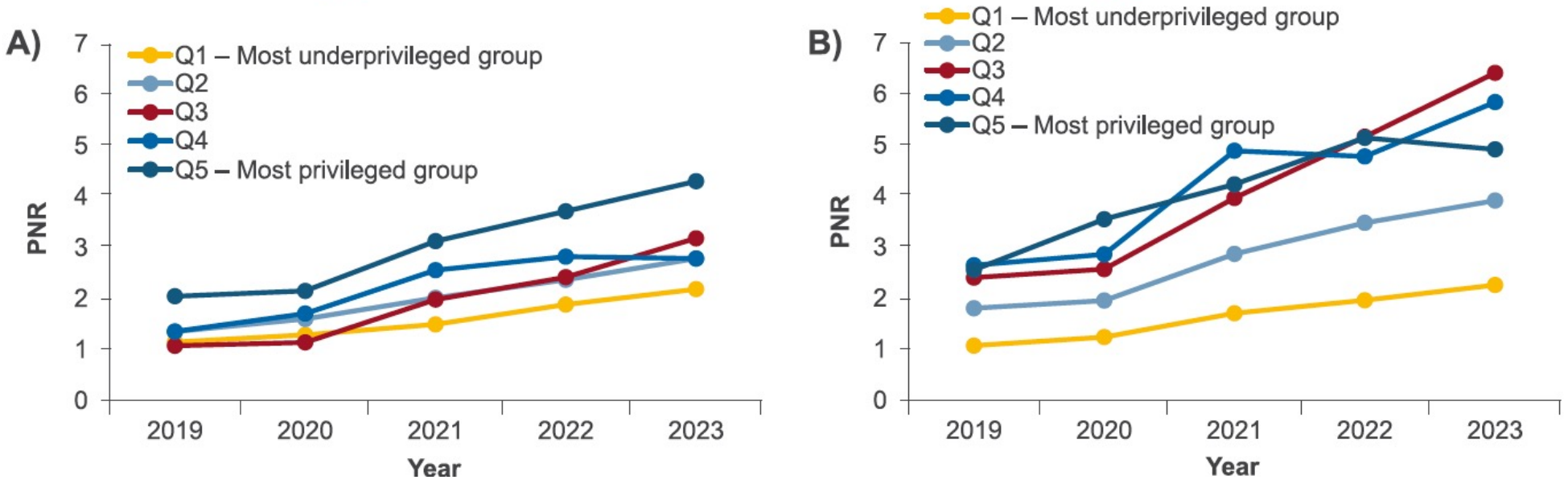
Analytic Cohort

- The number of PrEP claims (2019–2023; N=4,521,267) and individuals who newly initiated PrEP (2019–2023; N=529,016) were obtained from the IQVIA Longitudinal Access and Adjudication Dataset and linked with ICE indices

Figure 2. PNR Trends by Racialized Economic Segregation for (A) ICE Income Quintile, (B) ICE Race Quintile, (C) ICE Combined Race/Income Quintile, and (D) ICE Education Quintile



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HIV PrEP – How are we doing?

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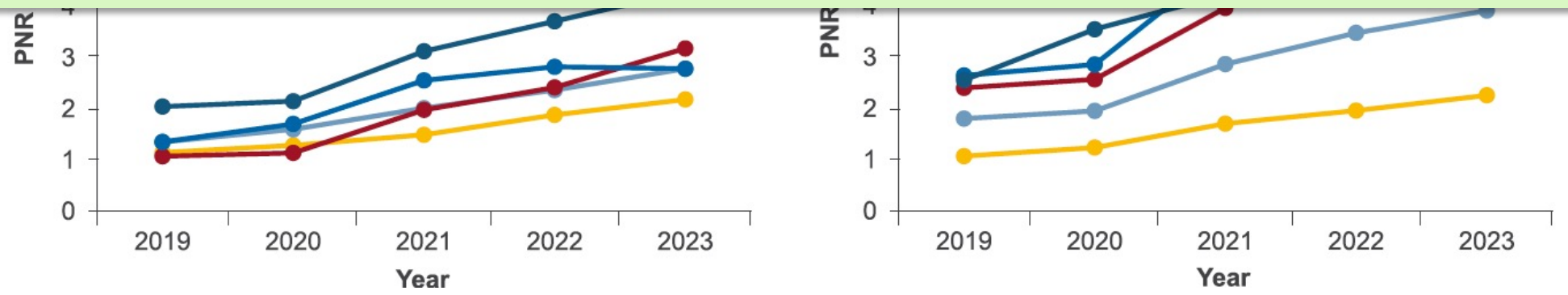
- Greatest unmet PrEP need is in the least privileged communities
- Disparities are widening over time!



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HIV PrEP – How are we doing?

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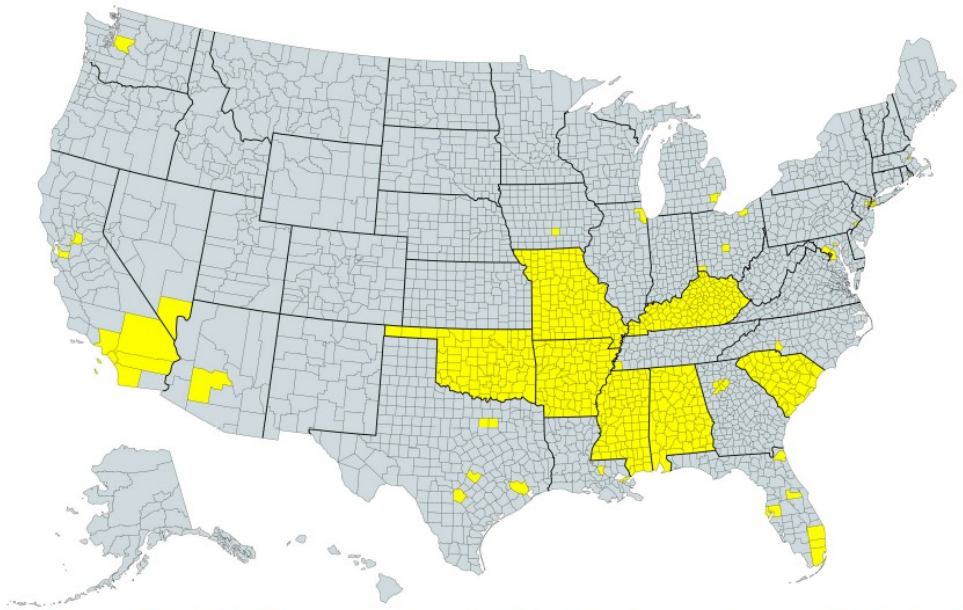
- PrEP uptake by US cis-women is low
- The 57 EHE jurisdictions were selected based on overall HIV prevalence
- Objectives:
  - Does EHE under-represent places where female to male prevalence and new diagnoses of HIV is relatively high?

Inclusion Criteria

For HIV and PrEP data, U.S. counties were excluded based on AIDSVu criteria including:

- Thresholds for county population size, HIV case counts (including HIV prevalence, new diagnoses)
- Unstable rates of HIV cases in county
- Presence of correctional facility in county



A total of **810 counties** were included in the HIV PR ratio analysis (**Table 1, Figure 2**)

A total of **93 counties** were included in the HIV NDR ratio analysis (**Table 1**)

Figure 1: 56 *EHE* jurisdictions (yellow) in the continental U.S. (57th Puerto Rico not shown)

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HIV PrEP – How are we doing?

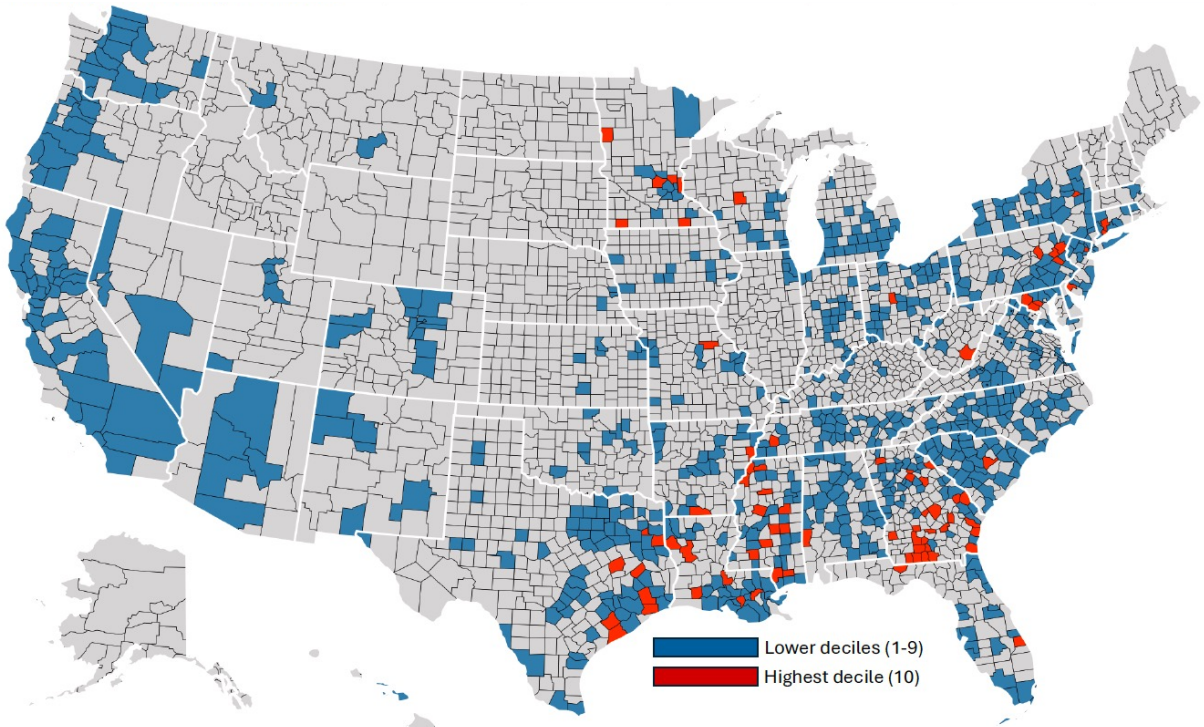

Figure 2: Counties included in the analysis of female-to-male HIV prevalence rate ratio in 2022 are shown in red or blue as highest (red) or all lower (blue) deciles. Gray counties were excluded from analysis.

Results

Table 1: Characteristics of lowest vs highest female to male HIV prevalence ratio deciles in US

	Prevalence Rate n=810 counties			New Diagnosis Rate n=93 counties		
Counties ranked from highest to lowest decile of female-to-male	Lowest Decile (n=81)	Highest Decile (n=81)	*P* value	Lowest Decile (n=9)	Highest Decile (n=9)	*P* value
National female-to-male HIV PR or NDR ratio	0.29		N/A	0.23		N/A
Range of county-level female-to-male HIV PR or NDR ratios	0.07-0.19	0.54-1.10	N/A	0.11-0.14	0.39-0.73	N/A
Counties in U.S. South	15 (19%)	60 (74%)	<0.001	2 (22%)	8 (88%)	0.004
Counties designated as rural	76 (7%)	41 (51%)	<0.001	None	None	N/A
Counties designated as *EHE* by county- or state-level status	12 (15%)	18 (22%)	0.23	6 (67%)	1 (11%)	0.02

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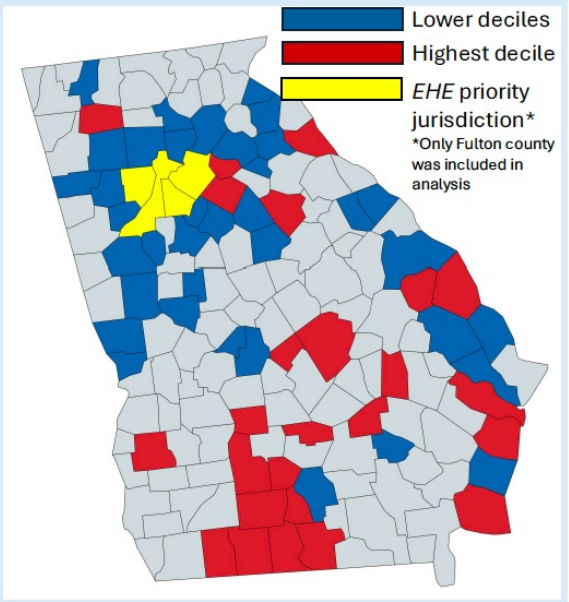
HIV PrEP – How are we doing?



A case study: 91% (58/64) of Georgia counties included in the analysis, have a female-to-male HIV PR ratio that is higher than the national average of 30%

Figure 3: Counties in the top decile of female-to-male HIV prevalence rate (PR) ratio (red) vs all lower deciles (blue) vs *EHE* counties (yellow). Gray excluded.

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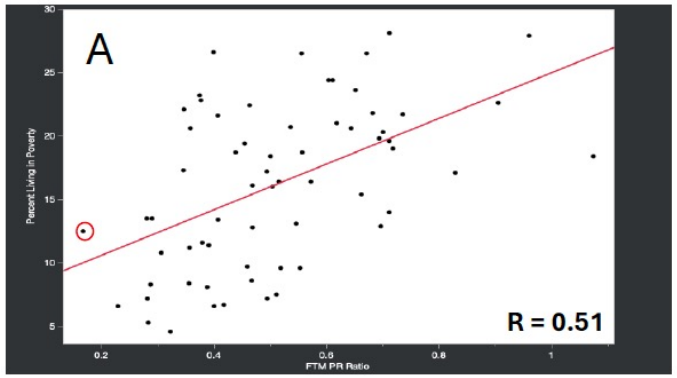
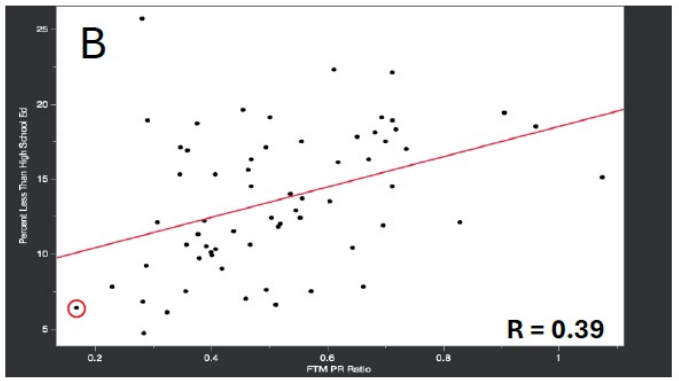
Female to male prevalence ratio was correlated with:

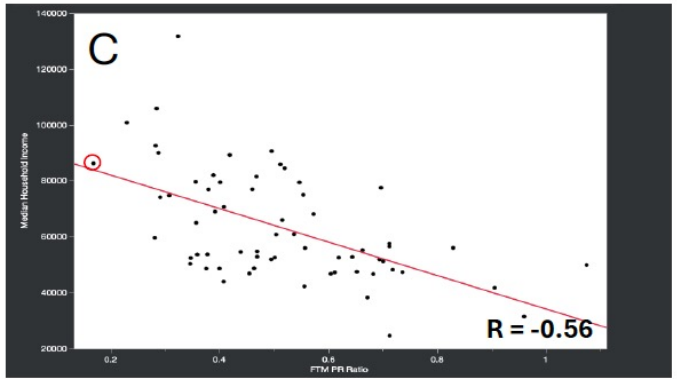
% in county living in poverty



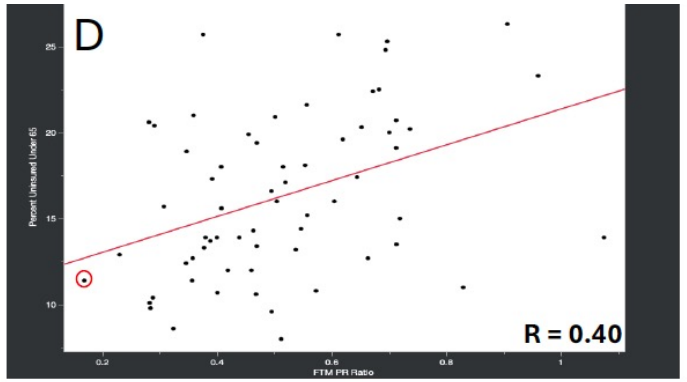
% in county with <HS degree



Median income

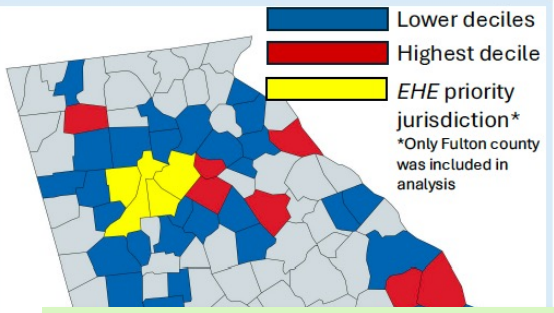


% in county <65 and uninsured



Red circle is Fulton county – only EHE county

HIV PrEP – How are we doing?



HIV PR ratio that is higher than the national average of 30%

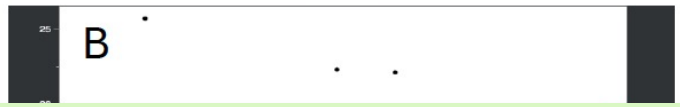
Figure 3: Counties in the top decile of female-to-male HIV prevalence rate (PR) ratio (red) vs all lower deciles (blue) vs *EHE* counties (yellow). Gray excluded.

Vaidya A, et al.

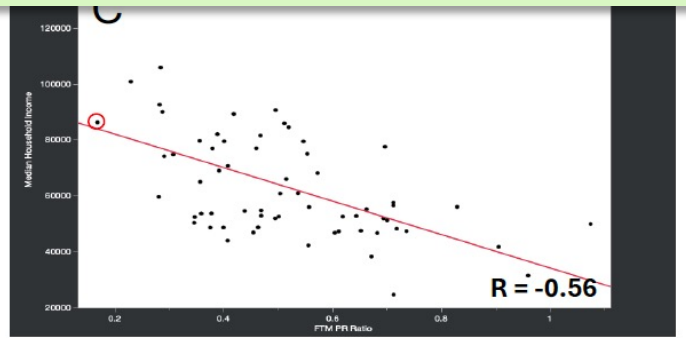
Female to male prevalence ratio was correlated with:

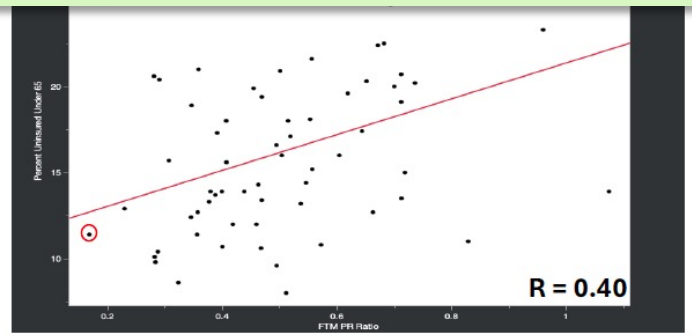
% in county living in poverty

% in county with <HS degree



- EHE largely does not cover counties where female to male prevalence of HIV is high
- Poverty, less education, and underinsurance were associated with higher female to male prevalence of HIV





Red circle is Fulton county – only EHE county

HIV LA-PrEP – How are we doing?

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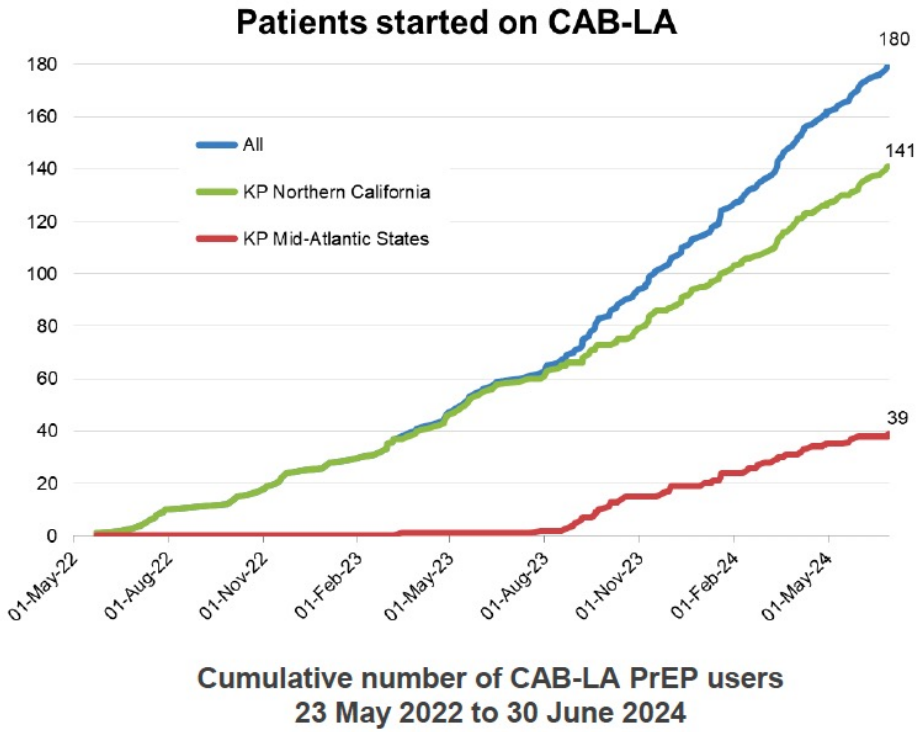
- LA-CAB PrEP uptake and persistence – Kaiser Permanente CA, MD, VA (5.4M members)
- Objectives:
  - Uptake and persistence of LA-CAB
  - Compare patients getting LA-CAB vs oral PrEP
- LA-CAB started May 2022 in CA and March 2023 in Mid-Atlantic

N=23,311
PrEP users
during study period

↓

N=180 (0.8%)
prescribed CAB-LA



Cumulative number of CAB-LA PrEP users
23 May 2022 to 30 June 2024

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HIV LA-PrEP – How are we doing?

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Results *CAB-LA users vs oral PrEP only users*

Characteristic at baseline	Oral-PrEP only users (N=23,131)	CAB-LA users (N=180)	P-value
Age, years, mean (SD, range)	37.4 (11.6)	39.1 (11.5)	0.042
Insurance type			0.014
Commercial	20630 (89.2)	148 (82.2)	
Medicaid	1848 (8.0)	27 (15.0)	
Medicare	586 (2.5)	5 (2.8)	
Other	67 (0.3)	0 (0.0)	
Race and ethnicity			<0.001
White alone, non-Hispanic	9627 (41.6)	54 (30.0)	
Asian alone, non-Hispanic	3620 (15.7)	17 (9.4)	
Black or African American alone, non-Hispanic	2354 (10.2)	34 (18.9)	
Native Hawaiian or other Pacific Islander alone, non-Hispanic	140 (0.6)	2 (1.1)	
American Indian or Alaska Native alone, non-Hispanic	297 (1.3)	1 (0.6)	
Multiracial, non-Hispanic	90 (0.4)	0 (0.0)	
Unknown, non-Hispanic	1548 (6.7)	10 (5.6)	
Hispanic	5455 (23.6)	62 (34.4)	
Sex			0.761
Female	1372 (5.9)	13 (7.2)	
Male	21612 (93.4)	166 (92.2)	
Unknown	147 (0.6)	1 (0.6)	
History of bacterial STI at KP prior to baseline			
Any STI	6471 (28.0)	81 (45.0)	<0.001
Syphilis	3707 (16.0)	52 (28.9)	<0.001
Gonorrhea	2366 (10.2)	33 (18.3)	<0.001
Chlamydia	2341 (10.1)	28 (15.6)	<0.001
History of clinical diagnoses prior to baseline			
Hypertension	3064 (13.3)	40 (22.2)	<0.001
Osteopenia	129 (0.6)	1 (0.6)	0.977
Osteoporosis	48 (0.2)	1 (0.6)	0.310
Diabetes	1216 (5.3)	12 (6.7)	0.399

CAB-LA users:

Slightly older

Less likely to have private insurance

More likely to be Black or Hispanic !

More likely to have had a bacterial STI

More likely to have hypertension

Trager M, et al.

HIV LA-PrEP – How are we doing?

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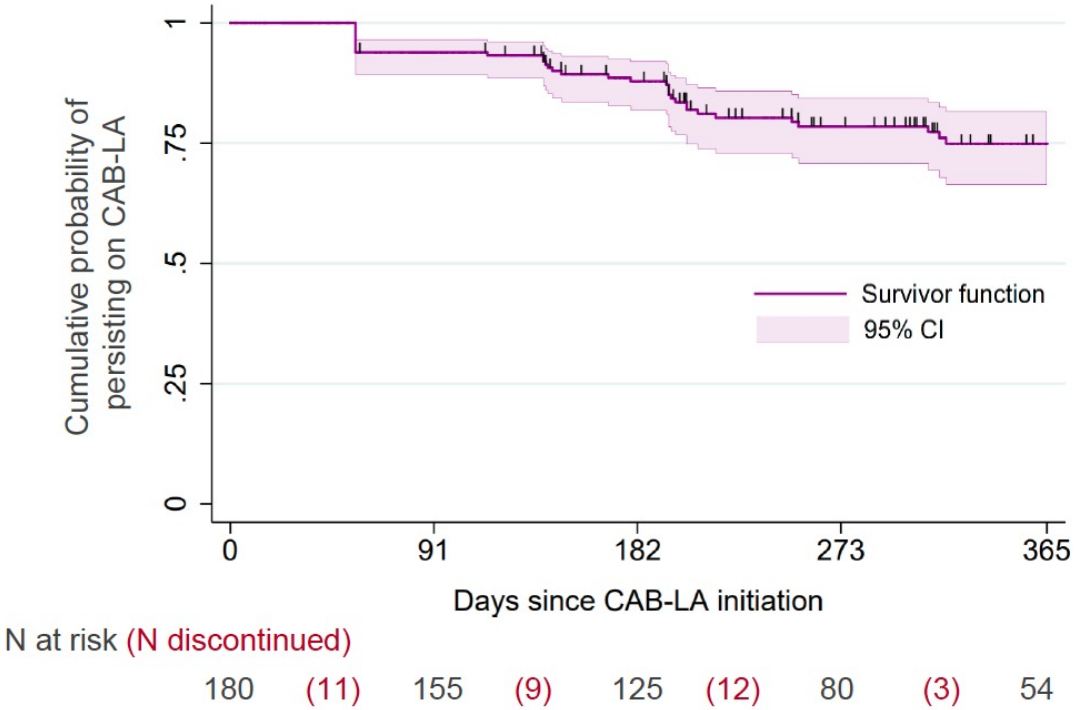
Results *CAB-LA persistence*



	Number at risk	Discontinued CAB-LA	Censored*	Survivor function (95% CI)
Baseline to 6 months	180	20	35	87.9% (81.3-92.1)
6 months to 12 months	125	15	56	74.9% (66.3-81.6)

Cumulative probability of persisting on CAB-LA at:

6 months = 87.9%

12 months = 74.9%

Of the 35 individuals who discontinued CAB-LA:

- 12 (34.3%) had oral PrEP prescribed after stopping CAB-LA
- 2 (5.7%) had oral PrEP prescribed during CAB-LA use

| Vertical lines represent an individual censored

* Individuals censored at disenrollment from health plan or end of study period (30 Jun 2024)

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No HIV infections among LA-CAB users even after discontinuation

HIV LA-PrEP – How are we doing?

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Results *CAB-LA persistence*

	Number at risk	Discontinued CAB-LA	Censored*	Survivor function (95% CI)

- LA-CAB uptake was low (<1% of PrEP users)
- LA-CAB more likely in people with public insurance and those who are Black or Hispanic
- 75% remained on PrEP after 1 year
- Oral PrEP was late to start in LA-CAB discontinuers

Days since CAB-LA initiation

N at risk (N discontinued)

180 (11) 155 (9) 125 (12) 80 (3) 54

| Vertical lines represent an individual censored

* Individuals censored at disenrollment from health plan or end of study period (30 Jun 2024)

Of the 35 individuals who discontinued CAB-LA:

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Trager M, et al.

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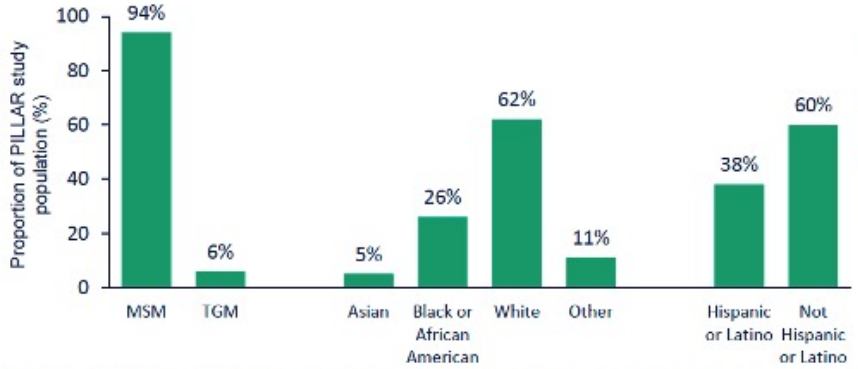
HIV LA-PrEP – How are we doing?

- PILLAR – Implementation study of LA-CAB
- Industry sponsored
- 17 US clinics (11 with enhanced support) in EHE locations
- Outcomes included LA-CAB administration metrics and interviews

PILLAR Enrollment Reflected US National HIV Demographics[1]



Protocol-defined enrollment targets exceeded:

	Target	Achieved
Black or Latino participants*	50%	60%
TGM participants	2–4%	6%

- 201 diverse participants enrolled and initiated CAB LA; median age (interquartile range) was 35 (29–44) years, 6% were TGM, 26% were Black, and 38% were Hispanic
- In total, 22% of participants had not received oral PrEP in the last 6 months prior to receiving CAB LA, demonstrating the potential for CAB LA to expand PrEP uptake

*Eight participants were both Hispanic or Latino and Black or African American. CAB, cabotegravir; LA, long-acting; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; TGM, transgender men; US, United States.
1. Centers for Disease Control and Prevention. HIV Diagnoses, Deaths, and Prevalence. 2024. Available from: https://www.cdc.gov/hiv-data/nhss/hiv-diagnoses-deaths-prevalence.html?CDC_AAref_Val=https://www.cdc.gov/hivlibrary/reports/hiv-surveillance/vol-34/index.html Accessed January 2025

Khan T M, et al.

HIV LA-PrEP – How are we doing?

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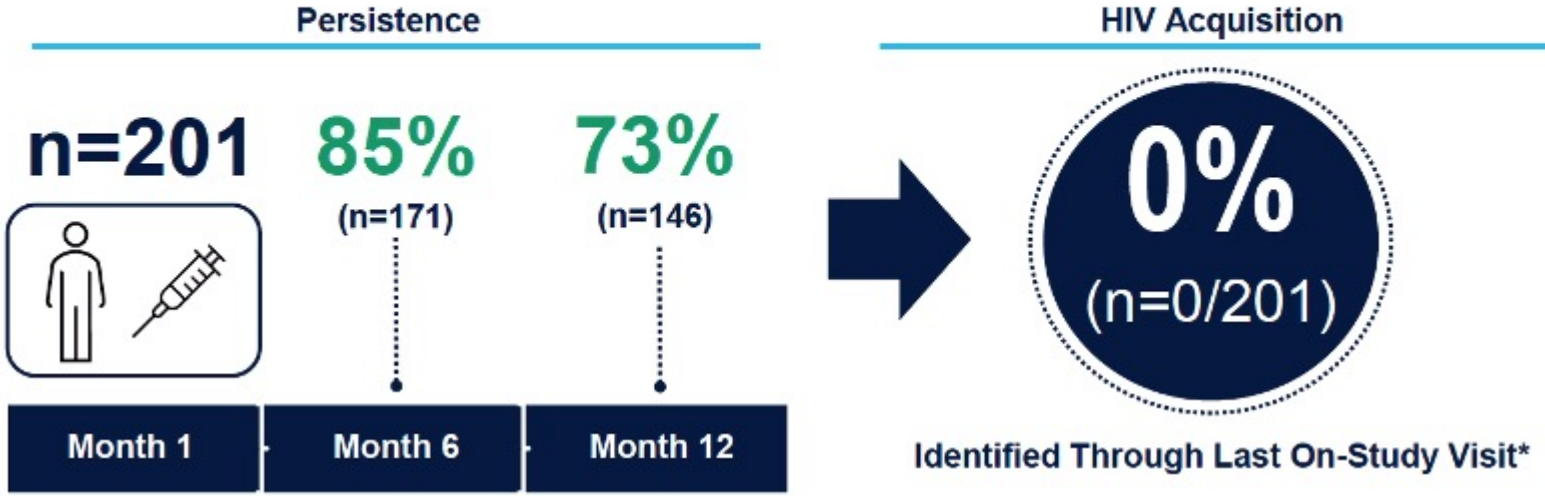
High Persistence and No Cases of HIV Acquisition Through Month 12



- A total of 72% (n=144/201) of participants completed all injections within the study. Six (3%) participants missed an injection and received oral CAB (n=1) or alternative PrEP (n=5)
- Most participants in the study (94%, n=131/139) did not find attending Q2M clinical visits difficult†

*Includes all participants up to their last visit on study. †"Very easy", "easy" or "neither easy or difficult".
CAB, cabotegravir; PrEP, pre-exposure prophylaxis; Q2M, every 2 months.

Khan T M, et al.

HIV LA-PrEP – Screening for HIV infection

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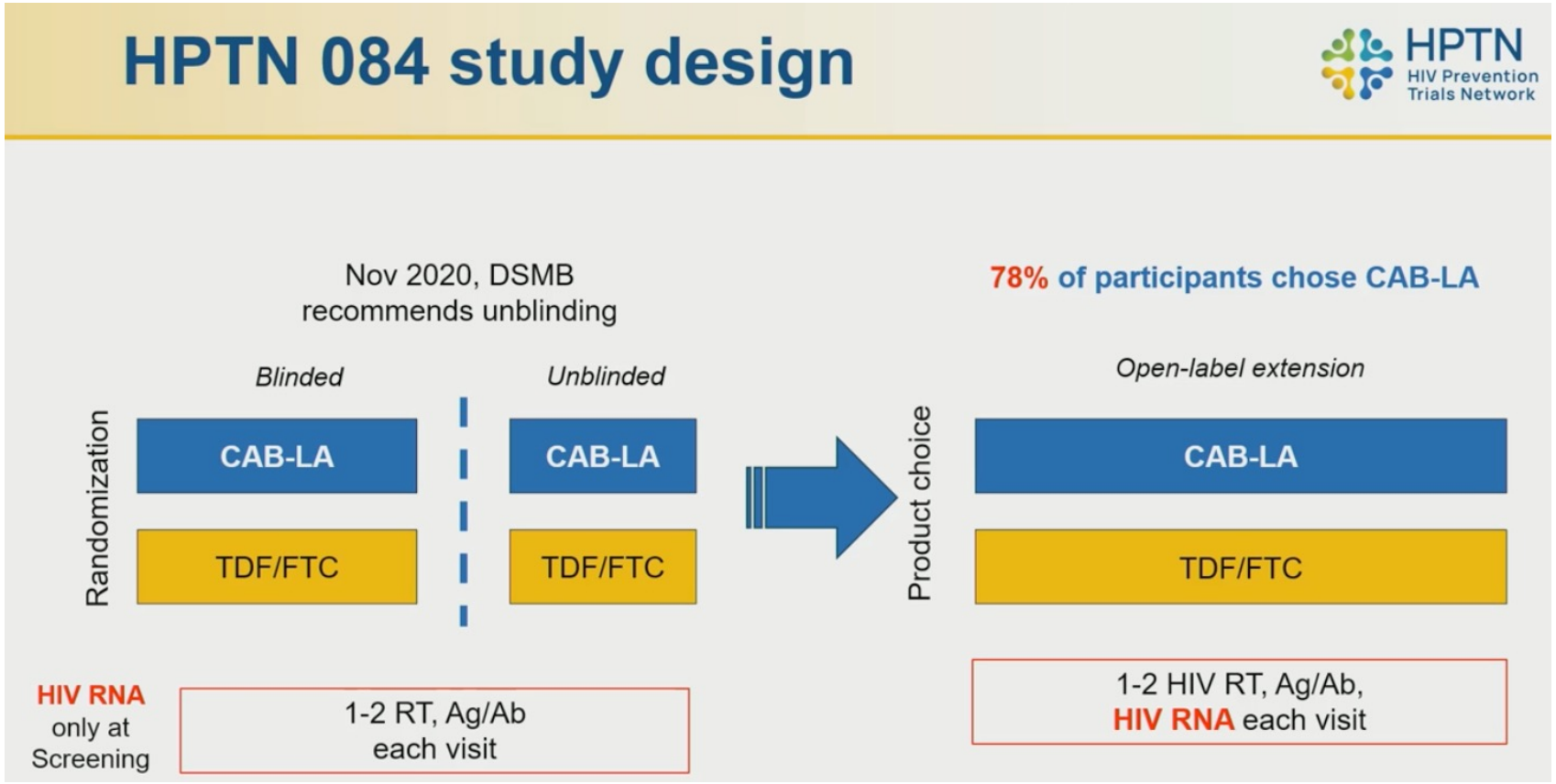
- HPTN 084 Trial compared LA-CAB and oral TDF/FTC in cis-women
- LA-CAB could delay detection of infection.
- HIV RNA recommended for monitoring
- How well does it do?



Delany-Moretlwe, et al.

HIV LA-PrEP – Screening for HIV infection

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Attributes of a good screening test

HPTN HIV Prevention Trials Network

When selecting a screening test, there is a need to balance
the benefits of early treatment for those with undetected infection
vs **the harm to those that do not need treatment**

Ideally a screening test should

- Should be capable of detecting infection at an early stage
- accurately identify those with disease i.e. high sensitivity
- Have a high positive predictive value i.e. it accurately predicts the presence of infection
- Results should be easy to interpret with clear cut-off for what constitutes a positive test
- Should be reasonably priced
- Should be widely available

Based on Wilson and Junger, 1968

HPTN 084

Delany-Moretlwe, et al.

HIV LA-PrEP – Screening for HIV infection

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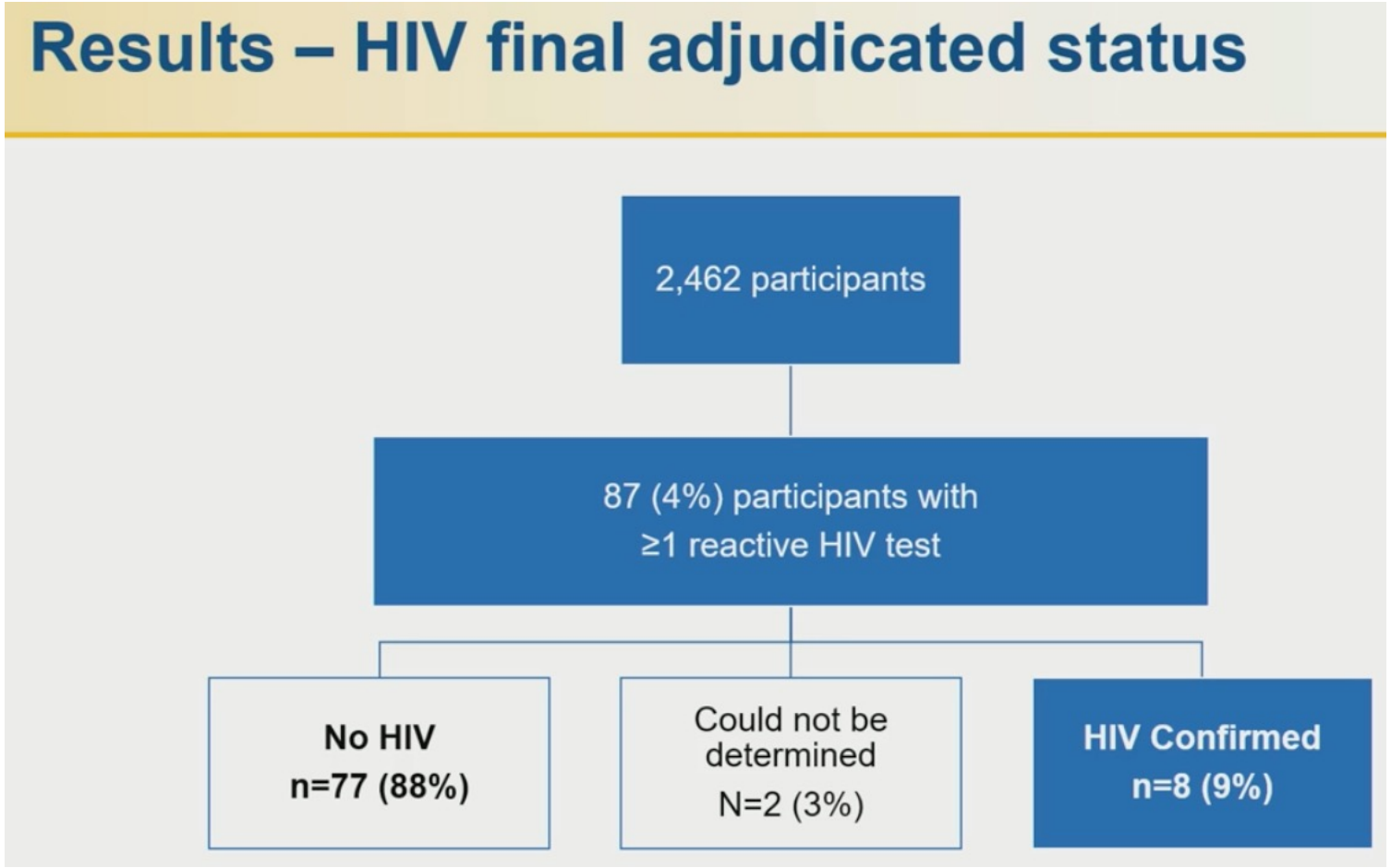
Results – HIV final adjudicated status



Delany-Moretlwe, et al.

HIV LA-PrEP – Screening for HIV infection

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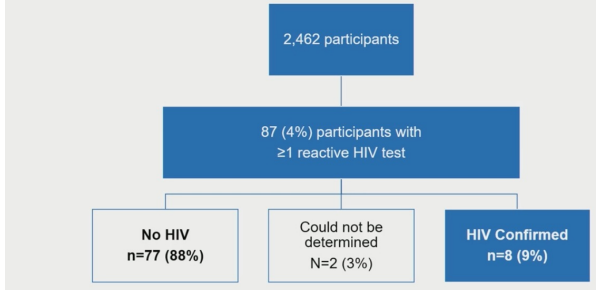
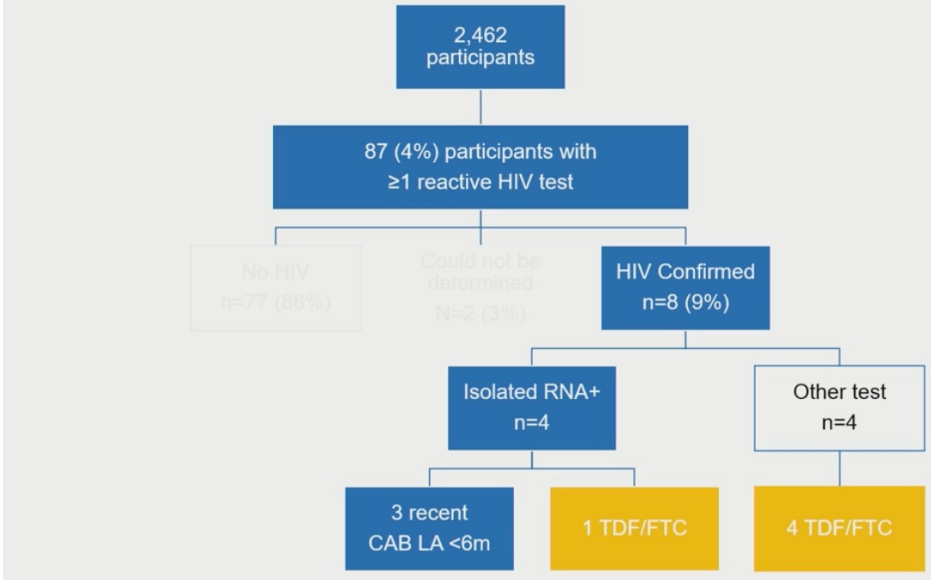
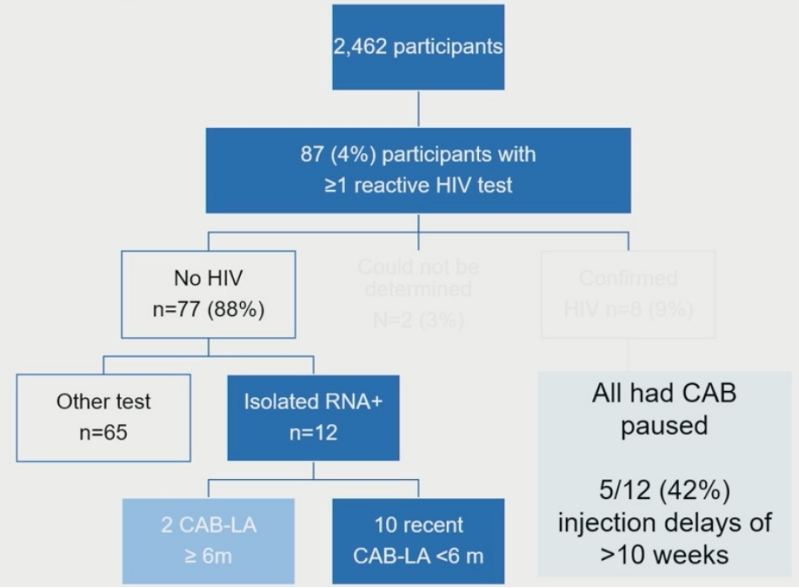
Results – HIV final adjudicated status



Results – true positive



Results – false positive



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HIV LA-PrEP – Screening for HIV infection

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HIV RNA performance characteristics

HPTN HIV Prevention Trials Network

	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 is based on HIV RNA with other screening tests

HPTN 084

Delany-Moretlwe, et al.

HIV LA-PrEP – Screening for HIV infection

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HIV RNA performance characteristics

HPTN HIV Prevention Trials Network

- HIV RNA performed poorly in detecting HIV infections in people on LA-CAB where infections were rare
- 75% false positive rate
- Performance even worse 6+ months after initiation
- Given operational issues and expense as well as the consequences of a positive test, HIV RNA for infection monitoring should be reconsidered

Sensitivity is based on HIV RNA with other screening tests

084

Delany-Moretlwe, et al.

HIV PrEP – How are we doing?

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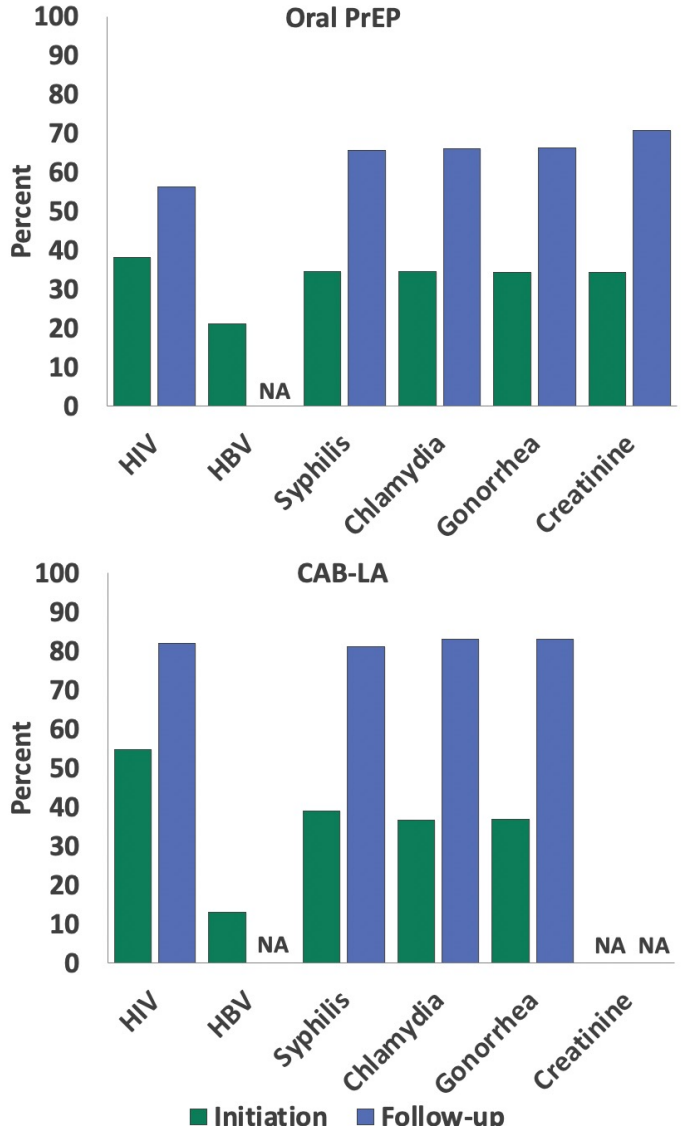
- Lab testing for HIV and other STIs is recommended prior to and during PrEP initiation for obvious reasons
- **CDC** study looked at adherence to lab testing recommendations in an analysis of >35,000 US PrEP users (2022-23) in a commercial database

Hoover K, et al.



RESULTS

- Among 35,132 oral PrEP users, 38% received lab-based HIV testing at initiation
  - Among 12,370 persons with oral PrEP use ≥3 months, 56% received a first follow-up lab-based HIV test since PrEP initiation at a median time of 89 days (IQR: 62-120)
- Among 453 CAB-LA PrEP users, 55% received lab-based HIV testing at initiation
  - Among 370 persons with PrEP use ≥3 months. 82% received a first follow-up HIV test since PrEP initiation at a median of 42 days (IQR: 33-84)

HIV LA-PrEP – Where are we going?

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- Lenacapavir (LEN) is a long acting antiretroviral administered SQ every 6 months approved for use in heavily treated people with HIV
- Studied extensively in the PURPOSE trials as PrEP and expected to be approved this year
- PK data presented on LEN given IM in two different doses YEARLY

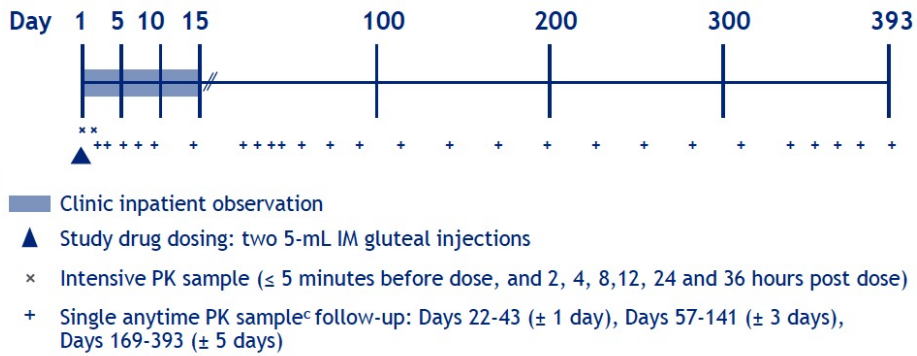
Study Design

Open-label, Phase 1 study evaluating the PK, safety, and tolerability of a single 5000 mg[a] IM dose of two free-acid LEN formulations: Formulations 1 and 2

Cohort 1: Formulation 1 (5% EtOH; n = 20)

Cohort 2: Formulation 2[b] (10% EtOH; n = 20)

Study Population
- Healthy participants with a low likelihood of HIV acquisition
- Aged 18-55 years
- BMI ≤ 35.0 kg/m²



Safety Assessments
- Laboratory evaluation
- Investigator-reported AEs
- Participant-reported outcomes including pain measures on a qualitative scale

PK Analysis/Outcomes
- PK ($AUC_{Days\ 1\text{-}365}$, C_{max}, T_{max}, and C_{trough})
- Compared LEN concentrations between once-yearly IM and twice-yearly SC LEN

[a] 2 × 5 mL of 500 mg/mL. [b] Half of participants who received Formulation 2 were pretreated for approximately 10 minutes with an ice pack at the site of injection. [c] A single anytime PK sample was collected on Days 3, 4, 6, 8, 10, 15, 22, 29, 36, 43, 57, 71, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 351, 365, 379, and 393, and at the early termination visit (if applicable).
AE, adverse event; AUC, area under the concentration-time curve; $AUC_{Days\ 1\text{-}365}$, area under the concentration-time curve for the once-yearly dosing interval calculated from days 1-365; BMI, body mass index; C_{max}, observed peak plasma concentration; C_{trough}, estimated trough concentration at the end of 364 days; EtOH, ethanol; IM, intramuscular; LEN, lenacapavir; PK, pharmacokinetic; T_{max}, time to reach peak plasma concentration.

Jogiraju V, et al.

HIV LA-PrEP – Where are we going?

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Participant Demographics

	LEN Formulation 1 n = 20	LEN Formulation 2 n = 20
Age, years (Q1, Q3)	37 (29, 50)	33 (29, 45)
Assigned male sex at birth, n (%)	13 (65)	13 (65)
Assigned female sex at birth, n (%)	7 (35)	7 (35)
Race, n (%)		
Black or African American	3 (15)	5 (25)
White	17 (85)	15 (75)
Ethnicity, n (%)		
Hispanic or Latine	20 (100)	16 (80)
Not Hispanic or Latine	0	4 (20)
Weight, kg (Q1, Q3)	73.6 (68.6, 86.8)	77.1 (72.5, 85.6)
BMI, kg/m^2 (Q1, Q3)	26.5 (24.1, 29.4)	28.0 (24.9, 30.0)

Jogiraju V, et al.

HIV LA-PrEP – Where are we going?

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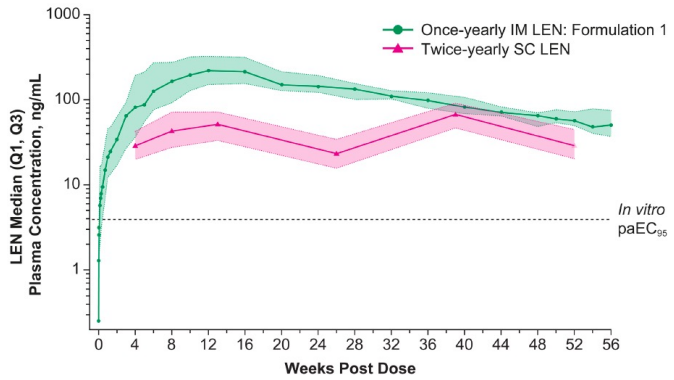
Once-yearly IM Formulation 1 Compared With Twice-yearly SC LEN

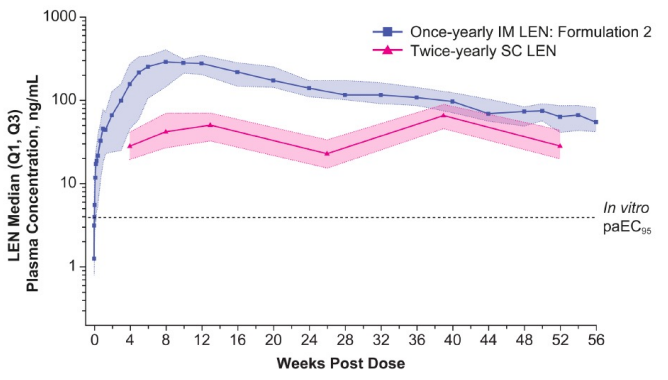


PK Parameter, median (Q1, Q3)	LEN Formulation 1 (n = 20) 5000 mg (2 × 5 mL of 500 mg/mL with 5% EtOH)
C_{max}, ng/mL	247 (184, 346)
T_{max}, days	84.1 (56.1, 112)
$AUC_{Days\ 1\text{-}365}$, h*µg/mL	1011 (881, 1490)
$C_{trough\ (Day\ 365)}$, ng/mL	57.0 (49.9, 72.4)

Concentrations with once-yearly IM LEN were higher than twice-yearly SC LEN for 56 weeks

Horizontal dashed line at 3.87 ng/mL represents *in vitro* $paEC_{95}$. SC LEN 927 mg on Day 1 and at the end of 26 weeks, with oral LEN 600 mg on Days 1 and 2, in PURPOSE 1 and PURPOSE 2. PK parameters; n = 15 (C_{max} and T_{max}) and n = 13 ($AUC_{Days\ 1\text{-}365}$ and C_{trough}).
AUC, area under the concentration-time curve; $AUC_{Days\ 1\text{-}365}$, AUC for the once-yearly dosing interval calculated from Days 1-365; C_{max}, peak plasma concentration; $C_{trough\ (Day\ 365)}$, trough concentration at Day 365; EtOH, ethanol; IM, intramuscular; LEN, lenacapavir; $paEC_{95}$, protein-adjusted 95% effective trough concentration; PK, pharmacokinetics; Q1, first quartile; Q3, third quartile, SC, subcutaneous; T_{max}, time to reach peak plasma concentration

Once-yearly IM Formulation 2 Compared With Twice-yearly SC LEN



PK Parameter, median (Q1, Q3)	LEN Formulation 2 (n = 20) 5000 mg (2 × 5 mL of 500 mg/mL with 10% EtOH)
C_{max}, ng/mL	336 (234, 474)
T_{max}, days	69.9 (55.3, 105)
$AUC_{Days\ 1\text{-}365}$, h*µg/mL	1274 (1177, 1705)
$C_{trough\ (Day\ 365)}$, ng/mL	65.6 (41.8, 87.1)

C_{max} was at least 3-fold lower than LEN concentrations previously studied without safety concerns[1]

Concentrations with once-yearly IM LEN were higher than twice-yearly SC LEN for 56 weeks

Horizontal dashed line at 3.87 ng/mL represents *in vitro* $paEC_{95}$. SC LEN 927 mg on Day 1 and at the end of 26 weeks, with oral LEN 600 mg on Days 1 and 2, in PURPOSE 1 and PURPOSE 2. PK parameters; n = 15 (C_{max} and T_{max}) and n = 19 ($AUC_{Days\ 1\text{-}365}$ and C_{trough}).
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1. Jogiraju V, et al. *Antimicrob Agents Chemother*. 2024;68:e0134423.

Jogiraju V, et al.

HIV LA-PrEP – Where are we going?

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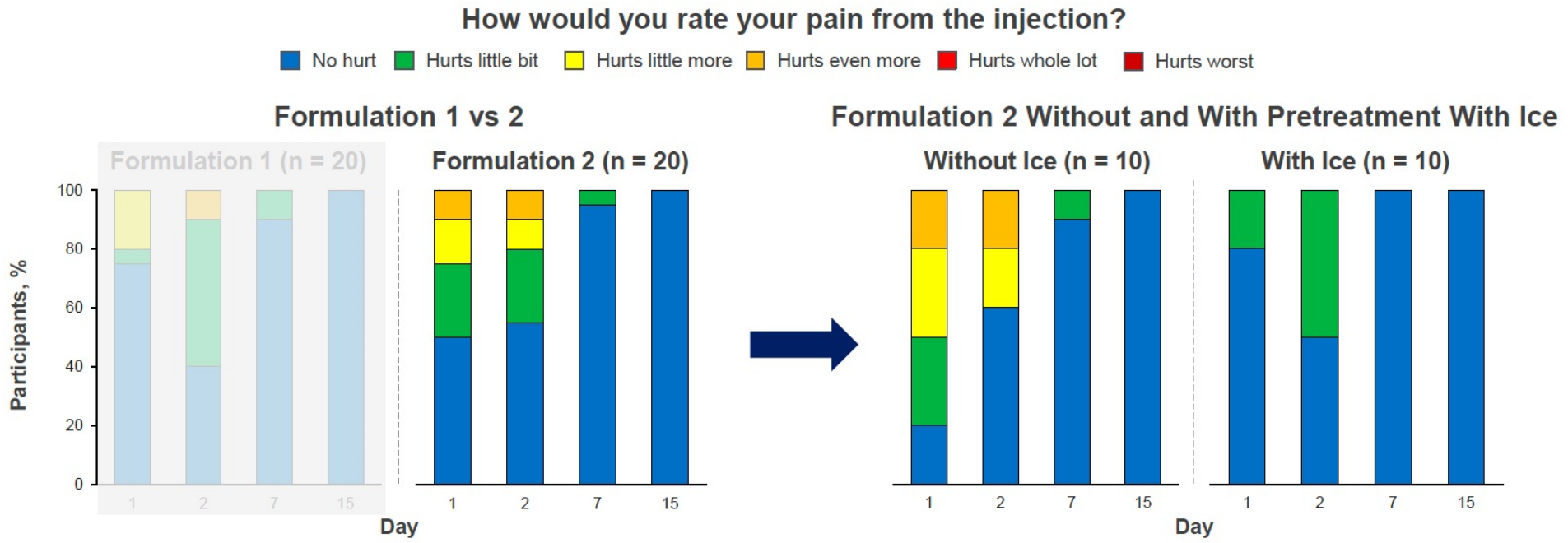
Participant-Reported Injection-Site Pain Decreased With Ice Pretreatment

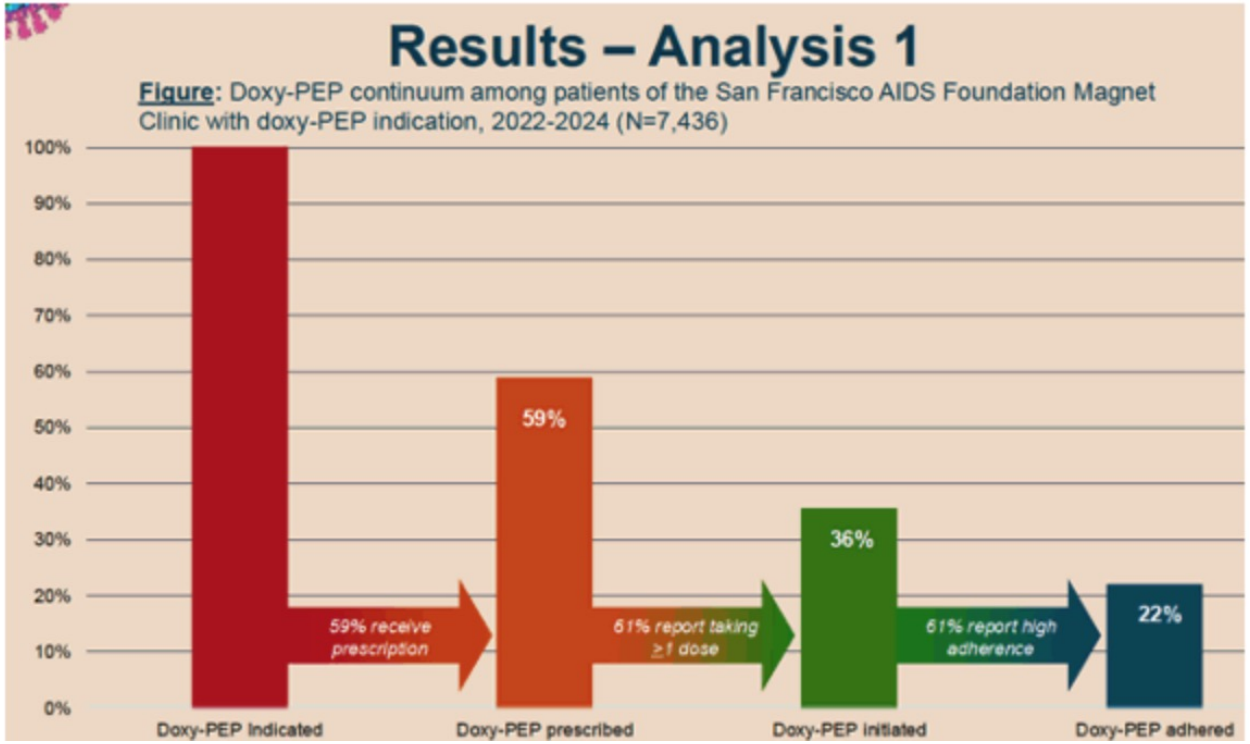


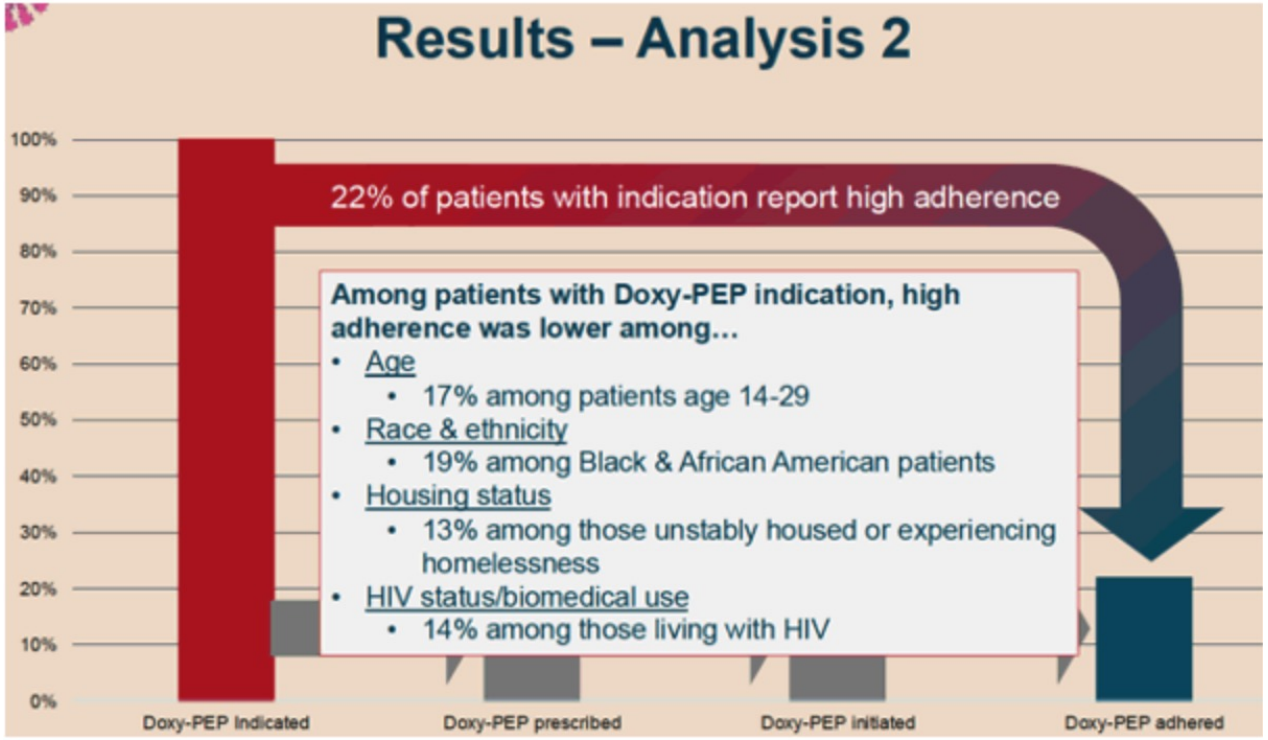
Most participants reported no or mild pain, which typically resolved within 1 week
Pretreatment with ice decreased pain ratings on Days 1 and 2 for Formulation 2

Jogiraju V, et al.

DoxyPEP

- DC Cohort: Of 1,564 PWH who were MSM or TGW with STI in previous year, only 64 (4%) prescribed DoxyPEP [Castel A, et al]
- SF AIDS Foundation Magnet Clinic: DoxyPEP continuum [Barry M, et al]





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UNC SCHOOL OF MEDICINE

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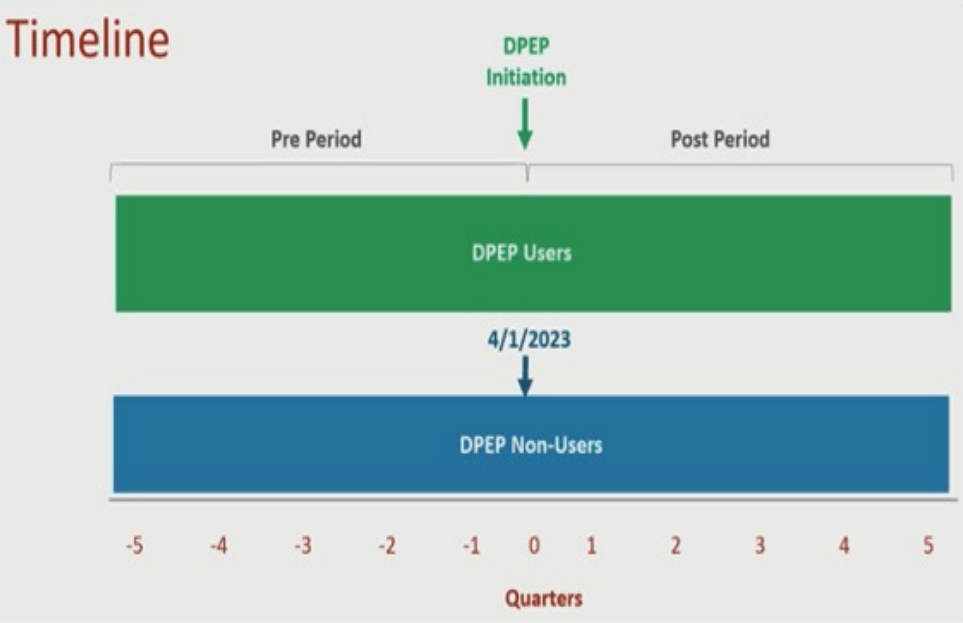
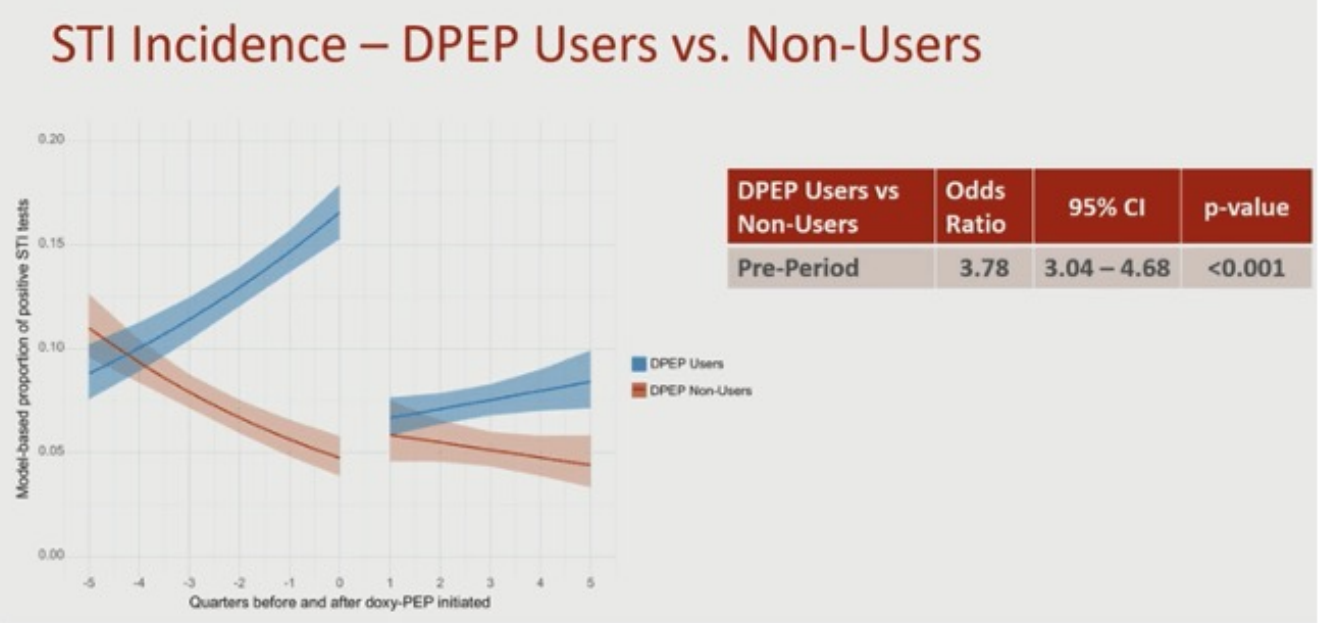
- SF AIDS Foundation Magnet Clinic: DoxyPEP continuum [Barry M, et al]
  - Comparison of STI 2,524 DoxyPEP users with 2.068 non-users [Scott H, et al]





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

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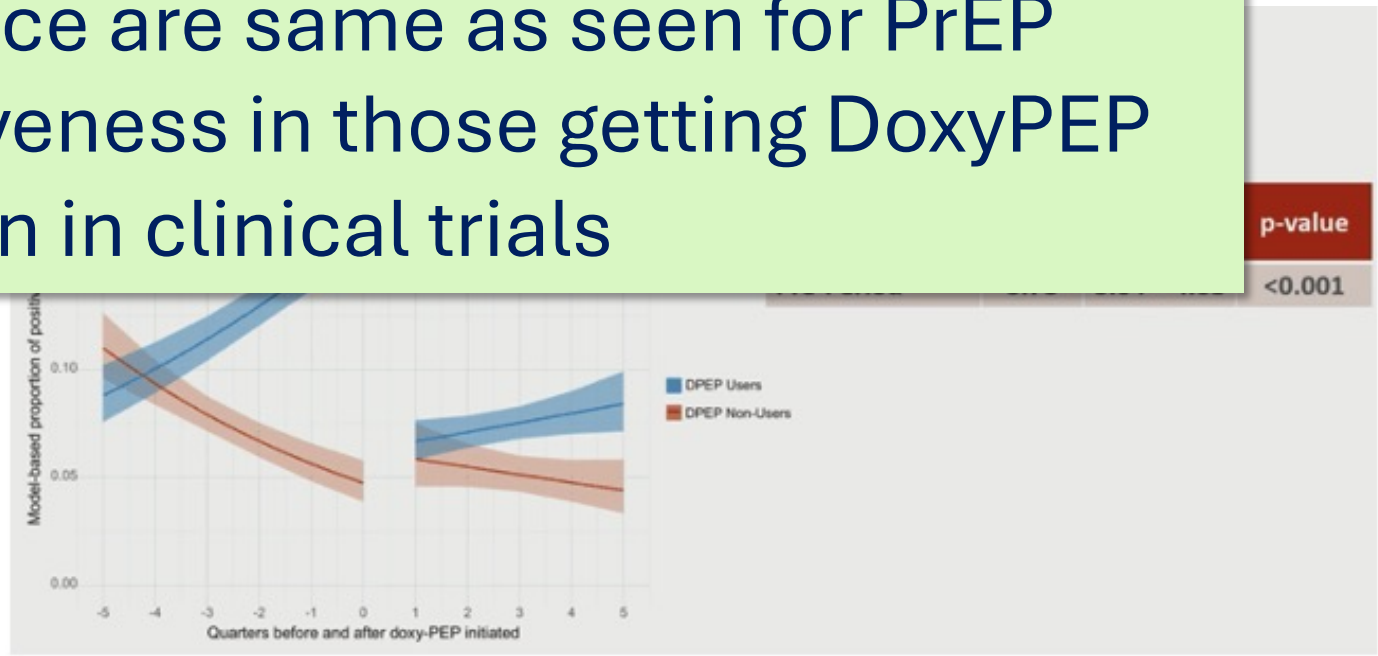
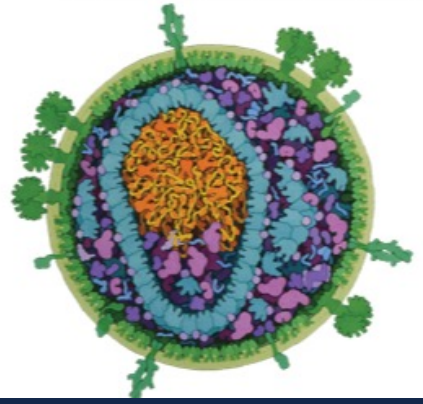
  - Com

- DoxyPEP under-prescribed
- Barriers to persistence are same as seen for PrEP
- Realer world effectiveness in those getting DoxyPEP is similar to that seen in clinical trials





CROI

Conference on Retroviruses and Opportunistic Infections

Treatment

HIV LA-ART – How are we doing?

UNC SCHOOL OF MEDICINE

- OPERA Cohort (101 clinics in 23 US states/territories; 14% of PWH)
- 2,858 patients with suppressed viral load initiated LA-CAB

Table 1. Demographic and clinical characteristics at CAB+RPV LA initiation (N = 2,858)

	Individuals with ≥ 1 injection
Age, median years (IQR)	39 (31, 51)
Female, n (%)	448 (16%)
Black race, n (%)[a]	1,199 (42%)
Hispanic ethnicity, n (%)[a]	853 (30%)
Married or domestic partner, n (%)[a]	486 (17%)
Injection drug use, n (%)	86 (3%)
MSM, n (%)	1,619 (57%)
Care in Southern US, n (%)	1,577 (55%)
Payer, n (%)[b]	
Medicare	342 (12%)
Medicaid	945 (33%)
Commercial Insurance	1,954 (68%)
Ryan White/ADAP	900 (31%)
Cash	85 (3%)

Sessions M, et al.

Table 2. Persistence and adherence among complete initiators (N = 2,618)

	Complete initiators
Months of follow-up, median (IQR)	11 (6, 18)
Receiving CAB+RPV LA at time of analysis, n (%)[a]	2,179 (83%)
Received 2nd initiation injection on-time	2,188 (84%)
Individuals with ≥ 1 maintenance injection, n (%)	2,360
Received all maintenance injections on-time	1,475 (62%)
≥ 1 delayed maintenance injections, n (%)	711 (30%)
≥ 1 missed maintenance injections, n (%)	279 (12%)

[a] Including individuals who discontinued and reinitiated during the study period

HIV LA-ART – How are we doing?

UNC SCHOOL OF MEDICINE

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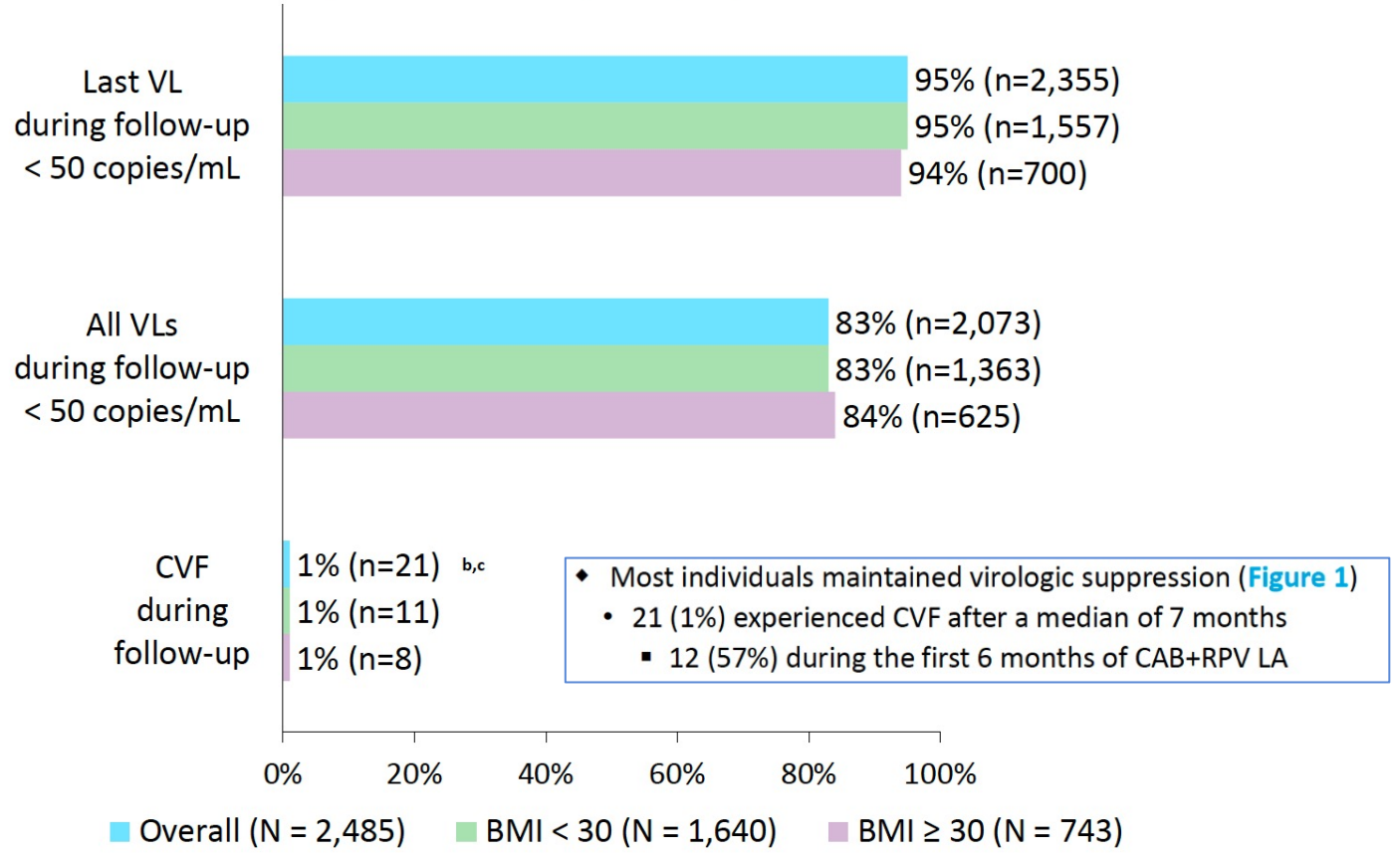
Sessions M, et al.

Figure 1. Virologic outcomes among complete initiators with ≥ 1 VL during follow-up; overall and stratified by BMI at initiation (N = 2,485)[a]



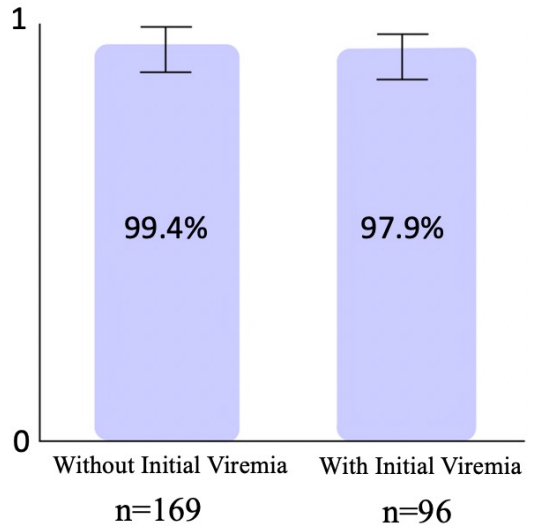
[a] Among those with 6, 12, and 24-month VLs available, VL < 50 copies/mL was observed in 954/1,015 (94%), 511/538 (95%), and 85/89 (96%), respectively
[b] After a median of 7 months (IQR: 3, 9)
[c] 12 (57%) experienced CVF during the first 6 months of follow-up

HIV LA-ART – How are we doing?

UNC SCHOOL OF MEDICINE

- Updated data from UCSF clinic on CAB/RPV use in people w/wo viral suppression: 370 individuals (129 not suppressed).

Figure 1. Viral Suppression outcomes at 48 weeks in those who started LA ART with and without viremia at baseline with at least 48 weeks of observation (n=265)



Five people were lost to follow-up who had at least 48 weeks of observation following initiation, 3 in the viremic group

Median time to achieve VS (≤200 copies/ml) in those with viremia was **32 days** (95% CI 30-45; **Figure 2**)

Rates of current or past substance use (OR = 1.22, 95% CI 1.11-1.34, p < .001) and unstable housing (OR = 1.11, 95% CI 1.01-1.23, p = .031) higher than in those starting LA ART with initial viremia; PWH with initial viremia were also more likely to have CD4 counts <200 cells/mm3 (OR = 1.22, 95% CI 1.09-1.36, p < .001) at initiation (**Table 1**)

Gistand N, et al.

HIV LA-ART – How are we doing?

UNC SCHOOL OF MEDICINE

- SF Dept of Health Clinic offering ART to people experiencing homelessness.

RESULTS

- N=94 unique PWH had at least two clinical encounters at MXM and were not established in HIV primary care elsewhere between January-December 2023
- Of these PWH, n=20 received LA-ART and n=89 received SOC (e.g., daily oral ART) for ≥1 month—including 15 patients who transitioned from oral to LA-ART during 2023*

Figure 1. PWH Included in this Analysis

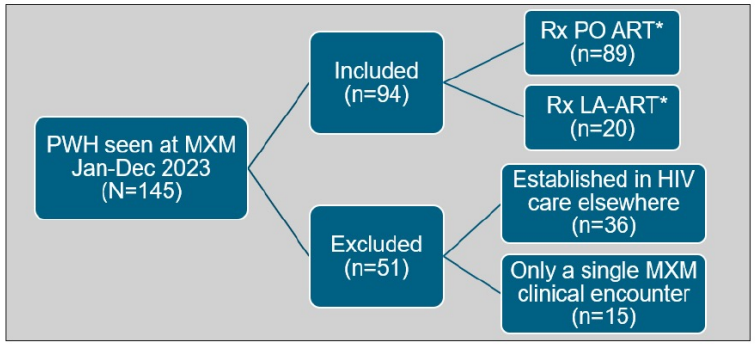


Table 1. Baseline Characteristics

	SOC (n=89)	LA-ART (n=20)
Age (mean, SD)	43.5 (12.4)	41.5 (9.6)
Cisgender male	64%	60%
Transgender or non-binary	18%	30%
Non-white race or ethnicity	72%	75%
Mental health co-morbidities		
Stimulant use disorder	71%	75%
Opioid use disorder	27%	30%
Primary psychotic disorder	27%	40%
Other mental health disorder	48%	60%

O'Conner K, et al.

HIV LA-ART – How are we doing?

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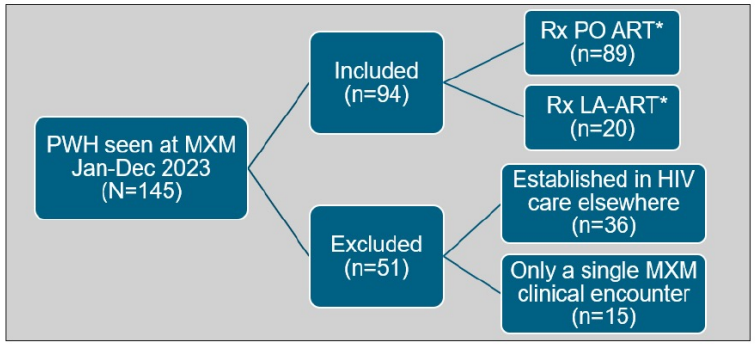
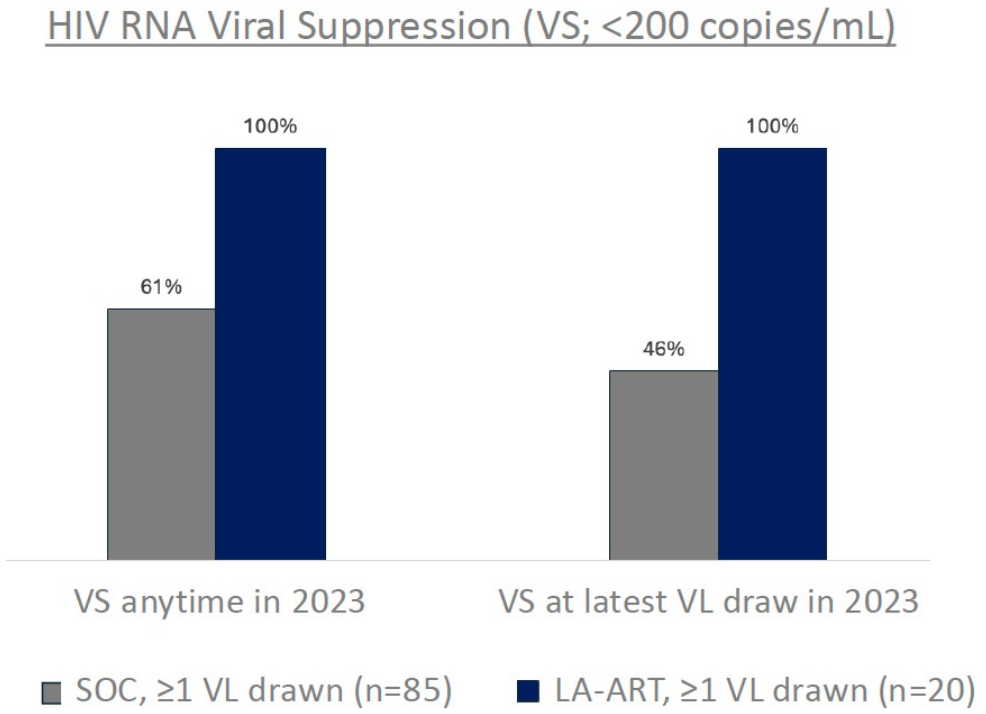




O'Conner K, et al.

HIV LA-ART – How are we doing?

UNC SCHOOL OF MEDICINE

- UCSF Clinic – 437 patients prescribed CAB/RPV: **69 (16%) discontinued. Why?**

  - Discontinuation rates similar for those w/wo viremia at initiation
  - At DC, median number shots was 6
    - 10% DC after 1st shot
    - 30% were on every 2M schedule
  - **For those w viral suppression at initiation, pain was most common cause of DC**

Christopolous K, et al.

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

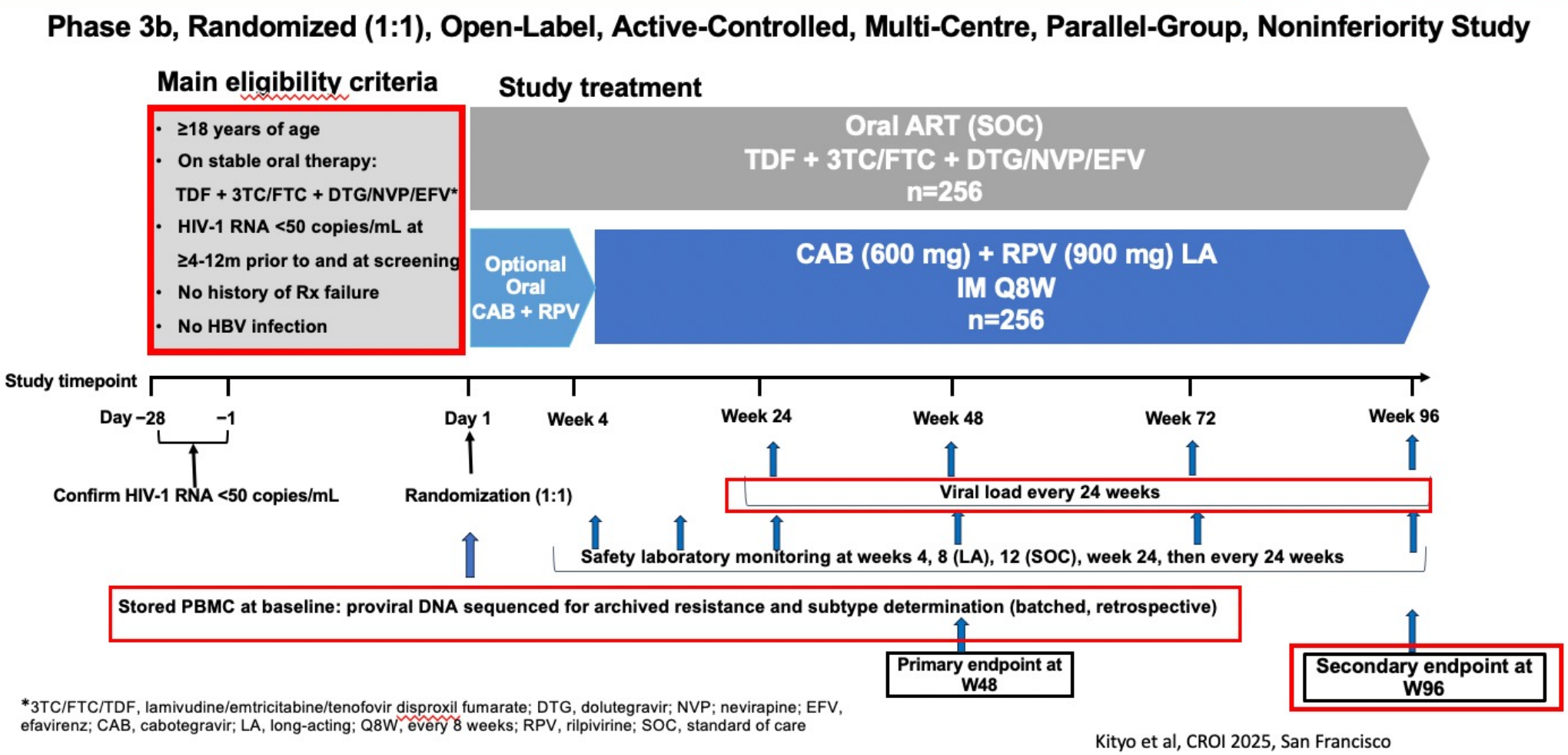
Reason for Discontinuation	Overall (n=69)	HIV VL <50 copies/mL (n=47)	HIV VL ≥50 copies/mL (n=22)
Injection site pain	14	10	4
Injection site pain with other side effect/concern*	11	9	2
Other side effect/concern*	14	11	3
Residential treatment for mental health/substance use or incarceration	5	5	-
Need 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

HIV LA-ART – How are we doing?

UNC SCHOOL OF MEDICINE

- CARES Trial – 96 Week Data



Kityo et al, CROI 2025, San Francisco

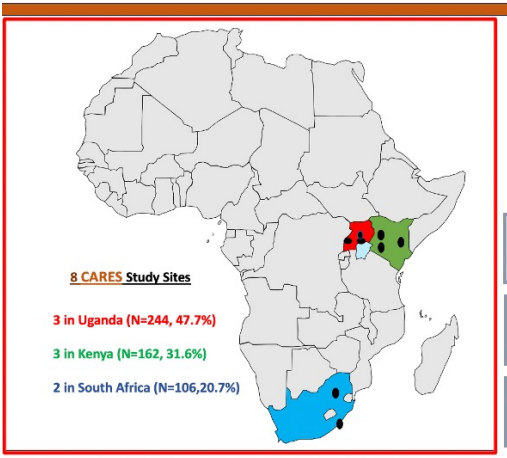
Mutuluuza C, et al.

HIV LA-ART – How are we doing?

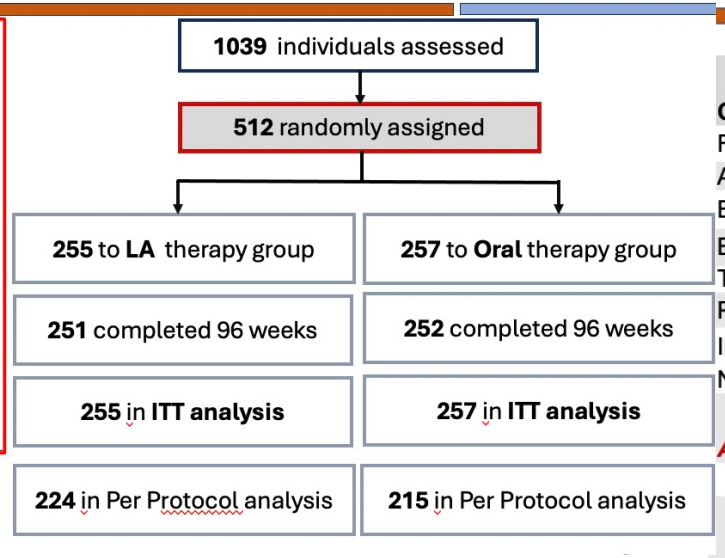
UNC SCHOOL OF MEDICINE

- CARES Trial – 96 Week Data

Enrollment & Retention



98% retention at Week 96



Baseline Characteristics

Characteristic	CAB + RPV LA (n=255)	Oral ART (SOC) (n=257)	Overall (N=512)
Female sex, n (%)	146 (57)	149 (58)	295 (58)
Age, median (IQR), years	43 (36-51)	42 (35-49)	42 (35-51)
BMI≥30 kg/m², n (%)	57 (22)	51 (20)	108 (21)
Black race, n (%)	254 (>99)	256 (>99)	510 (>99)
Time on first-line ART, 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)
NNRTI regimen at screening	24 (9)	17 (7)	41 (8)
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)
RPV intermediate/high-level resistance, n/n (%)	4/208 (2)	8/193 (4)	12 /401 (3)
CAB resistance mutations, n/n (%)	8/99 (8)	12/103 (12)	20/202 (10)
CAB intermediate/high-level resistance, n/n (%)	3/99 (3)	2/103 (2)	5/202 (2)

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

Mutuluuza C, et al.

HIV LA-ART – How are we doing?

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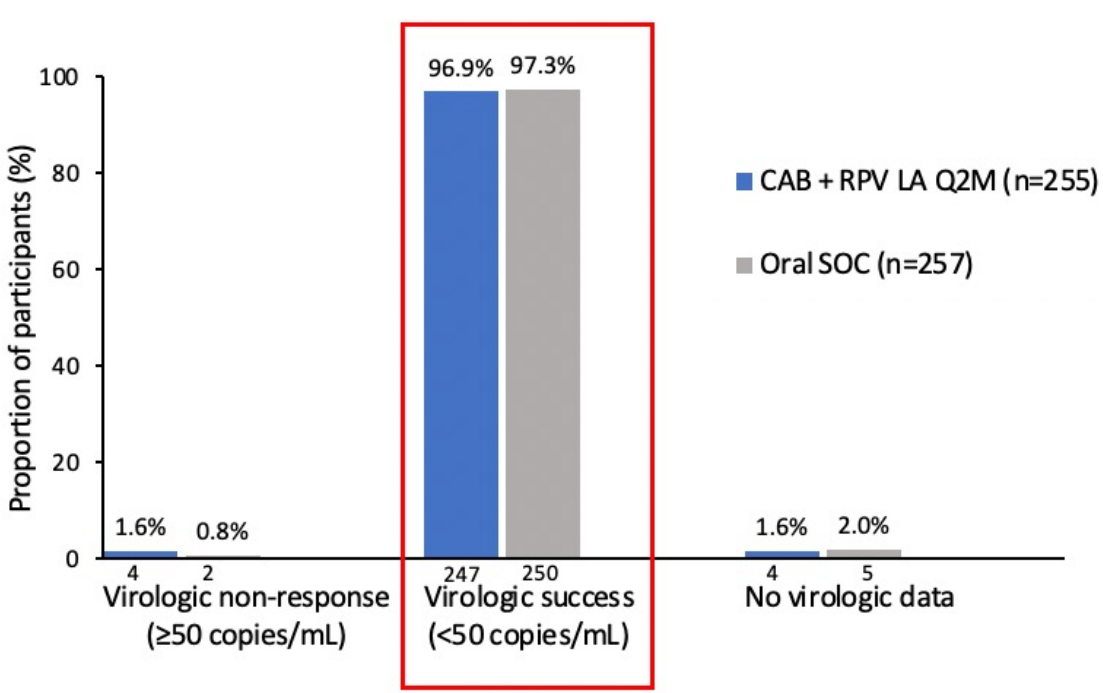
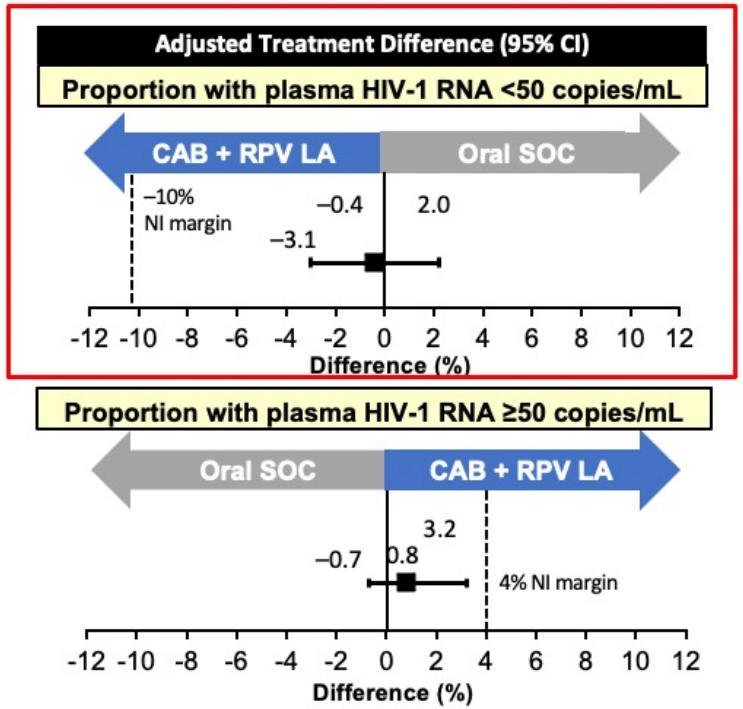
- CARES Trial – 96 Week Data





Primary outcome - proportion with plasma HIV-1 RNA <50 copies/mL:

- Main analysis (ITT): adjusted difference -0.4% (95% CI, −3.1 to 2.0), **meeting the non-inferiority criterion**
- Sensitivity analysis (per-protocol): adjusted difference -1.3% (95% CI, -4.2 to -0.1) **confirming non-inferiority**

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HIV LA-ART – How are we doing?

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Participants with Virological Failure

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

*Participants 1,3 and 4 resuppressed on TLD
†† RNA sequencing performed on plasma collected at confirmed virologic failure. Interpreted using Stanford algorithm
† Retrospective, batched sequencing performed on archived viral DNA extracted from PBMCs stored at baseline

Kityo et al, CROI 2025, San Francisco

Mutuluuza C, et al.

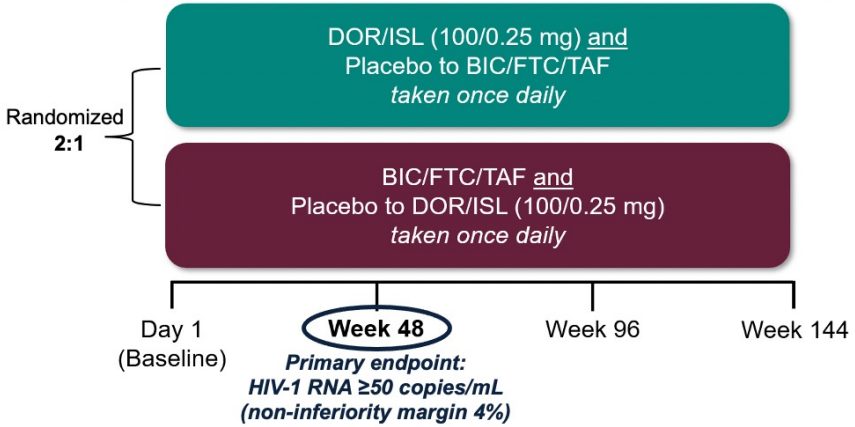
HIV ART – DOR/ISL

- Islatravir is a nucleoside reverse transcription translocation inhibitor (NRTTI) in development
- Two switch trials to oral daily DOR/ISL presented:
  - BFTAF (Biktarvy) -> DOR/ISL Blinded
  - Baseline Oral ART -> DOR/ISL Open Label

Double-Blind DOR/ISL vs Continuing BIC/FTC/TAF

Population
- Adults with HIV-1 RNA <50 copies/mL for ≥3 months on BIC/FTC/TAF
- CD4 count ≥50 cells/mm³ and total lymphocyte count ≥650 cells/mm³
- No history of treatment failure on any regimen
- No known resistance to DOR*
- No active HBV infection

*V106A/M, V108I, Y188L, H221Y, P225H, F227C/L/V, M230I/L, L234I, P236L or Y318F



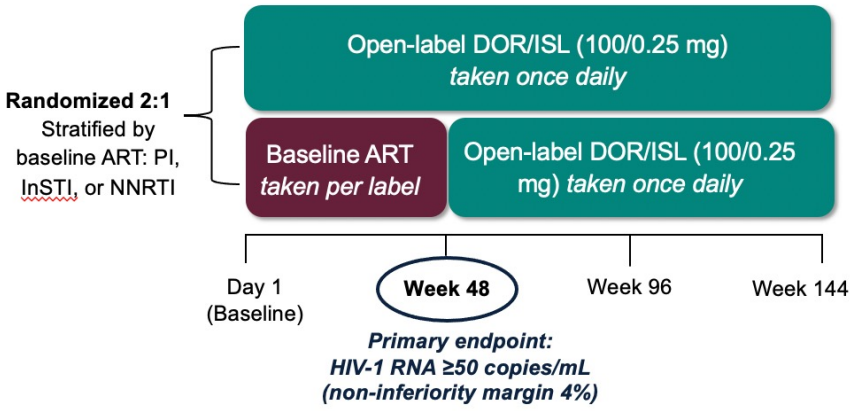
Discontinuation was required for confirmed decline in total lymphocytes (≥30% and to <1000 cell/mm³) or in CD4 count (<350 cells/mm³ from baseline ≥500, ≥30% and to <350 from baseline ≥350, or to <200 from baseline ≤349)

MK8591A-052

Open-Label DOR/ISL vs Continuing Baseline ART

Population
- Adults with HIV-1 RNA <50 copies/mL for ≥3 months on stable, oral 2- or 3-drug ART
- CD4 count ≥50 cells/mm³ and total lymphocyte count ≥650 cells/mm³
- No history of treatment failure on any regimen
- No known resistance to DOR*
- No active HBV infection

* V106A/M, V108I, Y188L, H221Y, P225H, F227C/L, M230I/L, L234I, P236L or Y318F



Discontinuation was required for confirmed decline in total lymphocytes (≥30% and to <1000 cells/mm³) or in CD4 count (<350 cells/mm³ from baseline ≥500, ≥30% and to <350 from baseline ≥350, or to <200 from baseline ≤349)

PI, protease inhibitor; InSTI, integrase strand-transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor.

MK8591A-051

Colson A, et al; Orkin C, et al.

HIV ART – DOR/ISL

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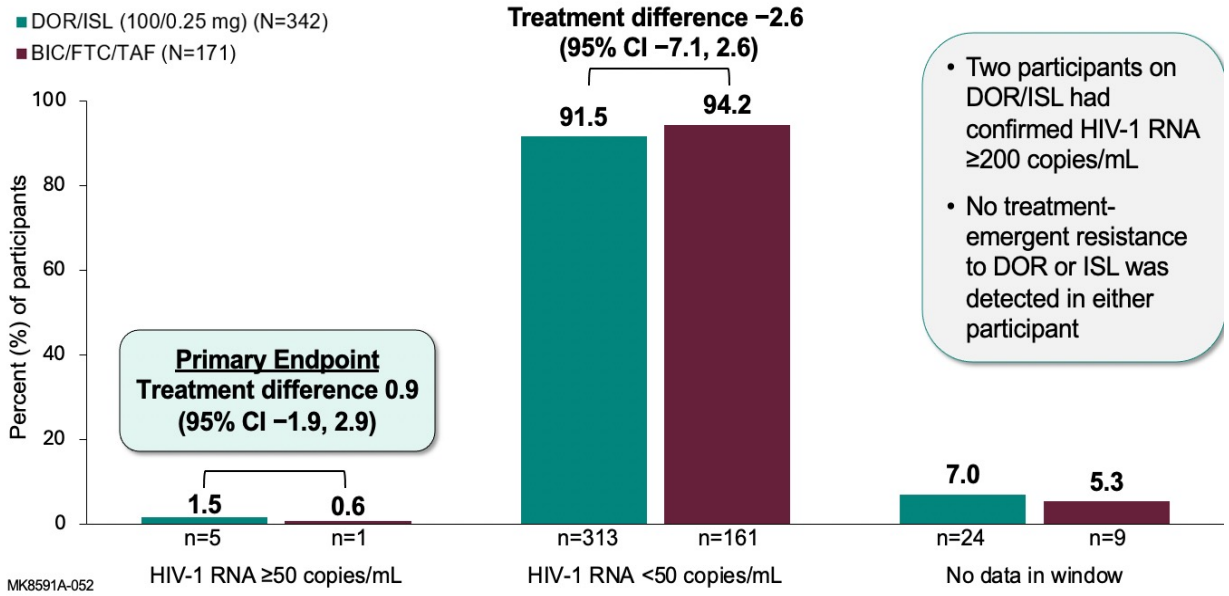
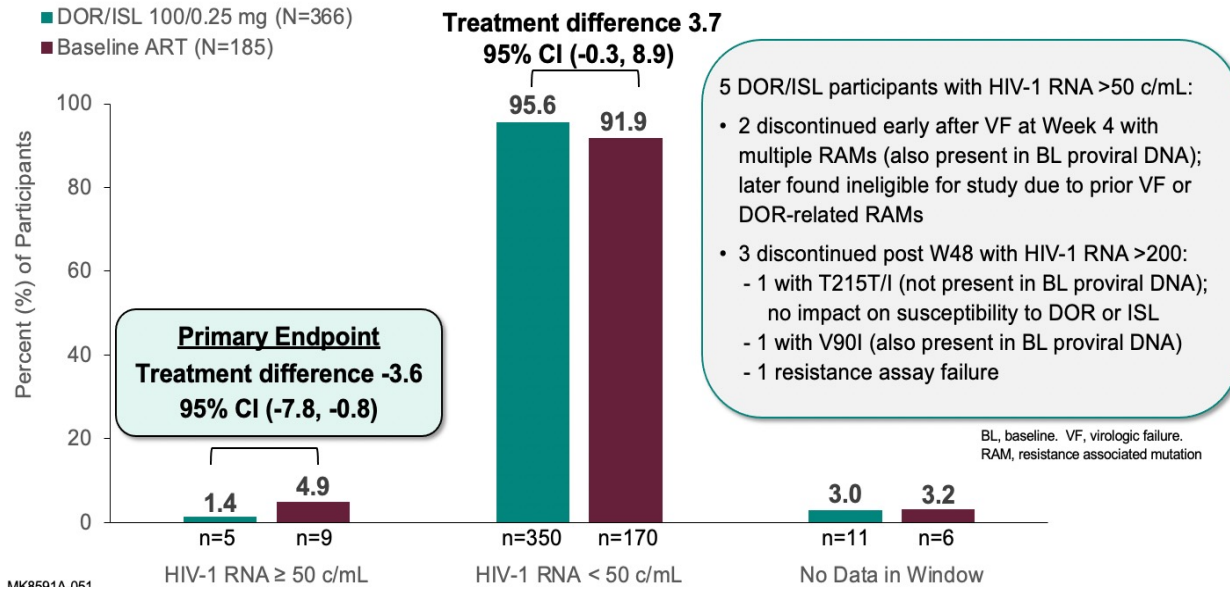
DOR/ISL Non-Inferior to BIC/FTC/TAF at Week 48
US FDA Snapshot Algorithm



DOR/ISL Non-Inferior to Baseline ART at Week 48
US FDA Snapshot Algorithm



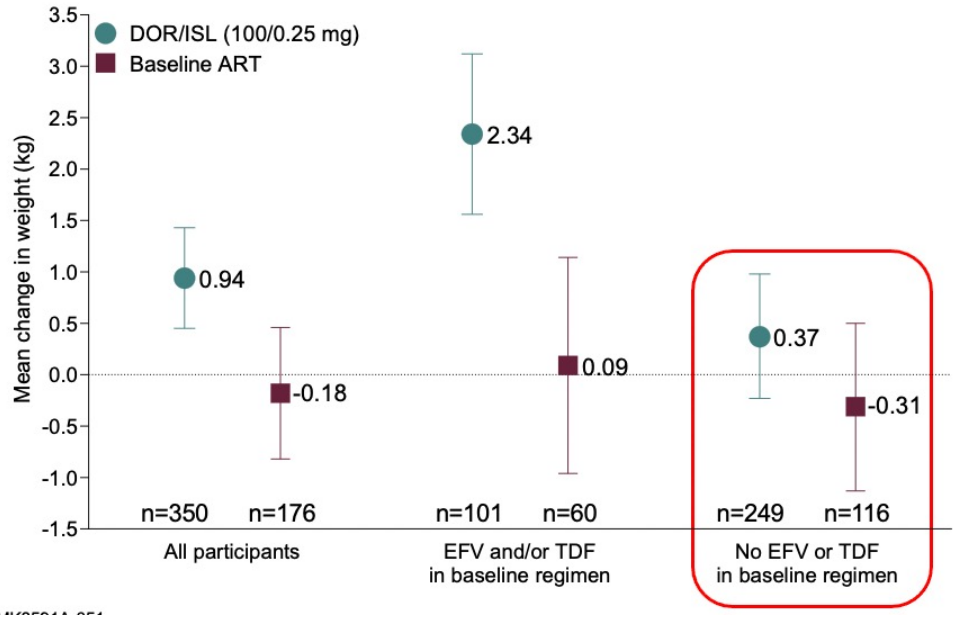
Colson A, et al; Orkin C, et al.

HIV ART – DOR/ISL

- No impact of DOR/ISL on lymphocyte or CD4 counts
- 2 cases of low-level HBV viremia and 2 acute HBV infections in DOR/ISL arm of the BFTAF trial
- DOR/ISL safety/tolerability ~ to comparators
- **Mean weight change:**
  - No difference DOR/ISL vs BFTAF: -0.03 kg vs 0.28 kg
  - Increase after switch from baseline ART driven by removal of weight suppressing ARVs

Weight Gain Driven by Removal of Weight Suppressive ART

Mean change (95% CI) in weight (kg) from baseline to week 48



For baseline regimens without EFV or TDF, difference between DOR/ISL and baseline ART = 0.82 kg (95% CI: -0.22, 1.87)

Colson A, et al; Orkin C, et al.

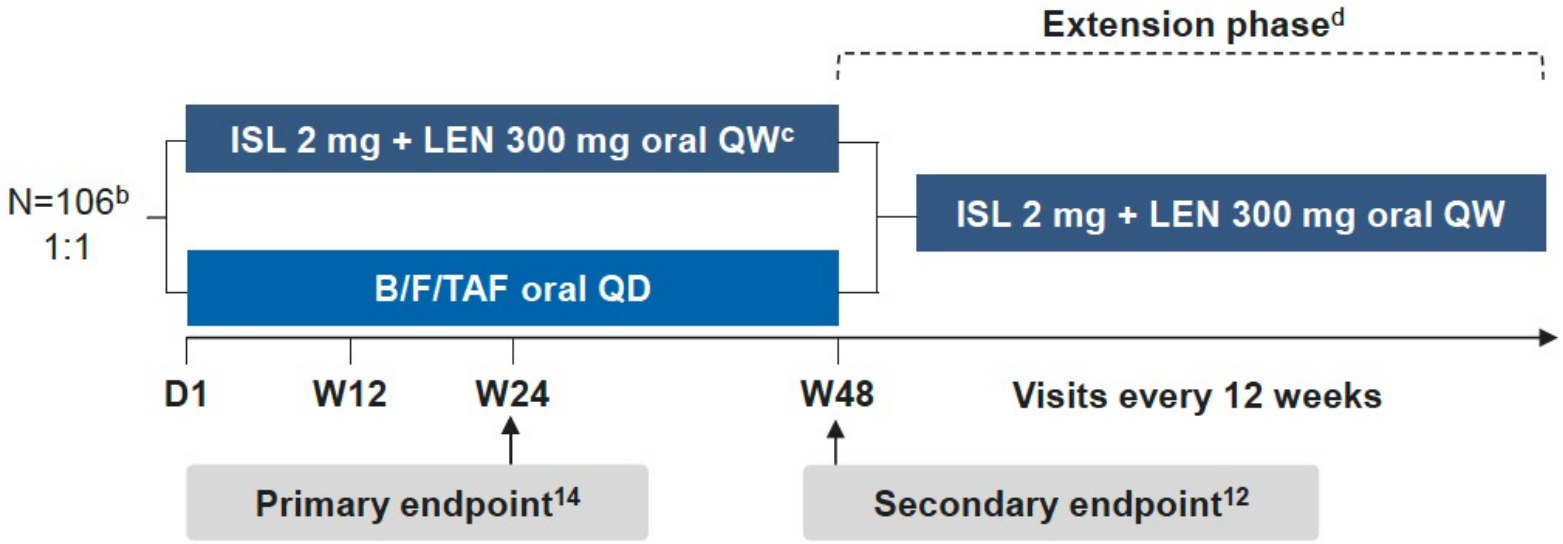
HIV ART – ISL/LEN

- ISL and LEN can be administered orally weekly
- Some data collected among PWH indicate many prefer weekly therapy
- In a Phase II trial ISL/LEN QW was non-inferior to BFTAF at 48 weeks
- Resistance profile presented

Figure 1. Study Design

Key eligibility criteria

- Aged ≥18 years
- On B/F/TAF for >6 months
- HIV-1 RNA <50 copies/mL for >6 months
- No history of virologic failure
- CD4+ T-cell count ≥350 cells/µL
- Lymphocyte count ≥900 cells/µL
- No HBV infection
- No NRTI or NNRTI resistance[a]



Vanderveen L, et al

HIV ART – ISL/LEN

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Figure 2. Virologic Outcomes at Week 48 by FDA Snapshot Algorithm[12,13]

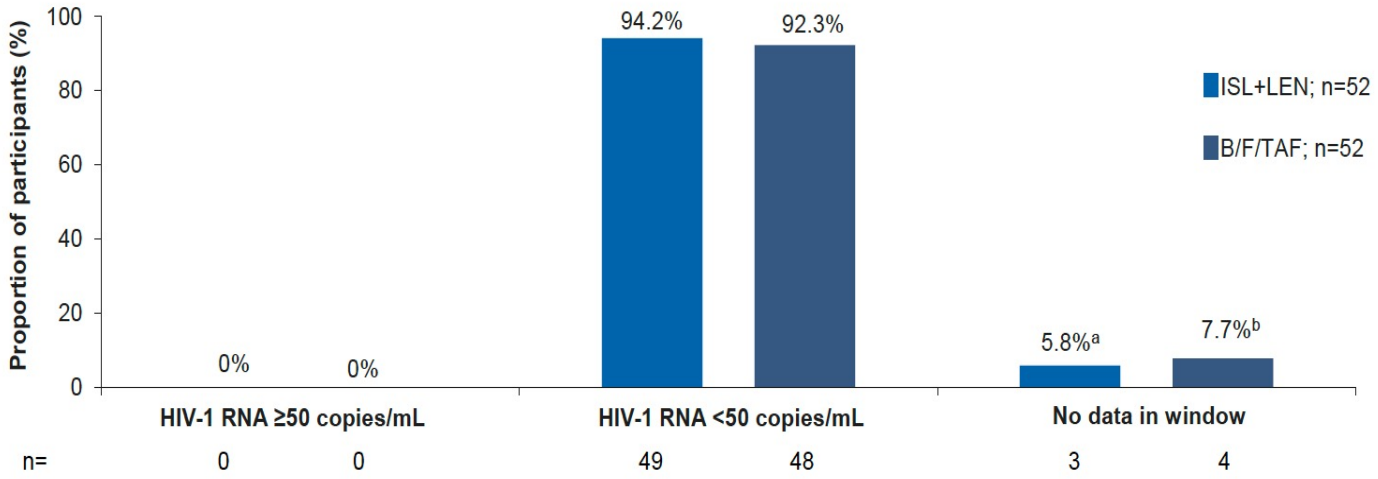
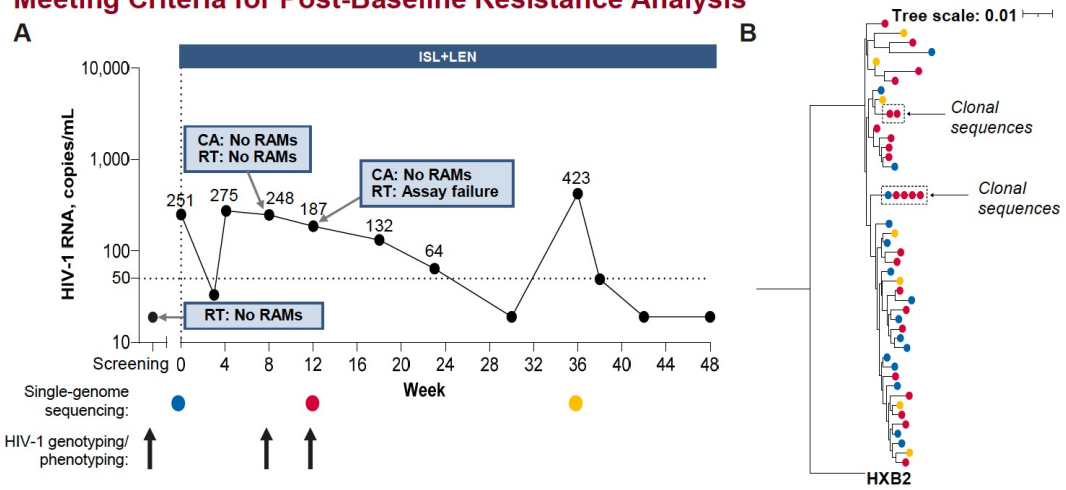


Figure adapted from Colson A, et al. IDWeek 2024.
[a]Two participants discontinued due to adverse events not related to study drug and one participant discontinued due to other reasons not related to study drug; all participants had HIV-1 RNA <50 copies/mL at study discontinuation. [b]Three participants discontinued due to other reasons not related to study drug and had HIV-1 RNA <50 copies/mL at study discontinuation; one participant had missing data during window but remained on study drug.
B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; FDA, Food and Drug Administration; ISL, islatravir; LEN, lenacapavir.

- Pre-existing ARV resistance was uncommon and all with NRTI and NNRTI resistance remained suppressed
- One ISL/LEN participant with viremia that started at baseline.
  - No resistance
  - Adequate plasma drug levels
  - Resuppressed on ISL/LEN

Figure 3. Virologic Analysis (A) and Phylogenetic Tree (B) of Participant Meeting Criteria for Post-Baseline Resistance Analysis

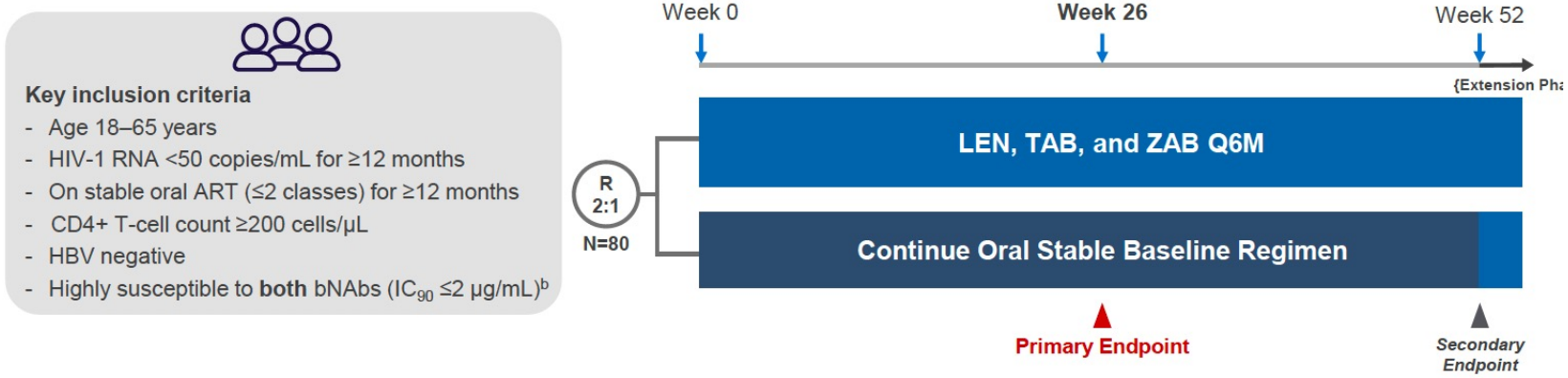


Vanderveen L, et al

HIV ART – bNAbs

- A critical mass of long-acting agents are needed to craft regimens that can be administered every 6 months along with LEN
- bNAbs can have extended half-lives
- Some HIV strains not neutralized by these antibodies
- Phase 2 trial of LEN plus two bNAbs:
  - Teropavimab and Zinlirvimab

Phase 2 Study Design[a]



Primary Outcome (Efficacy): HIV-1 RNA ≥50 copies/mL at Week 26 per FDA snapshot algorithm

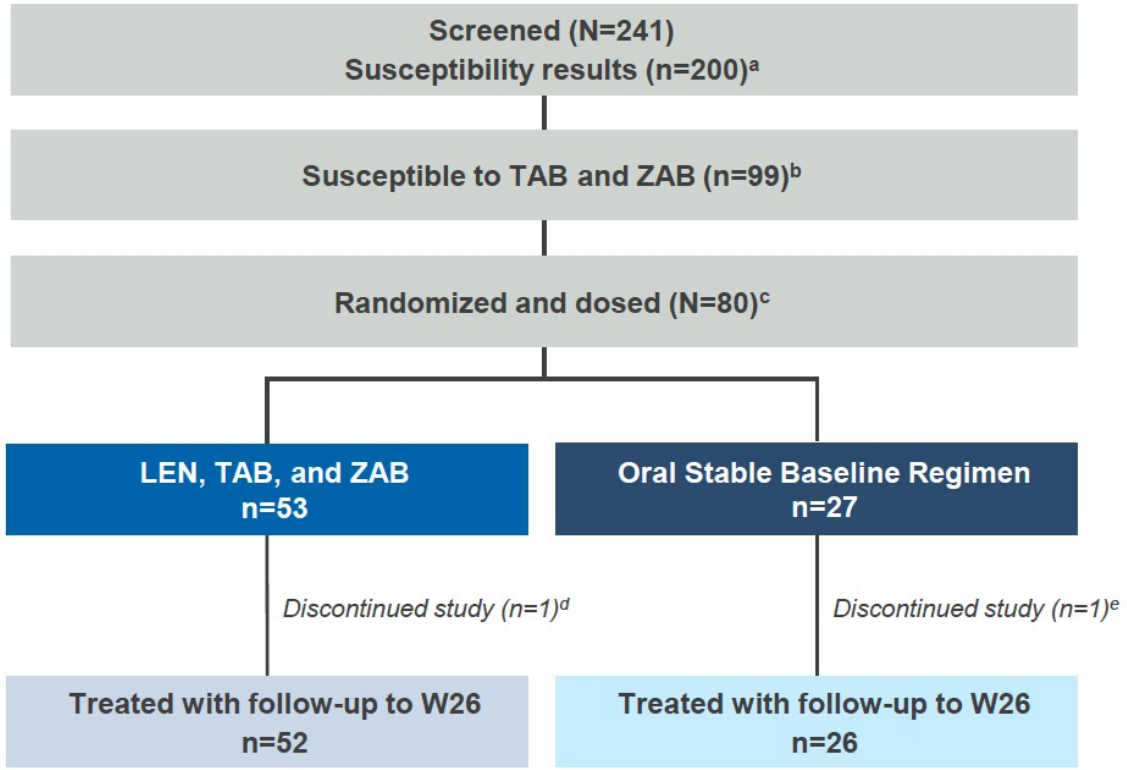
Secondary Outcomes: Safety (adverse events); change from baseline in CD4+ T-cell count, PK of LEN, TAB, and ZAB; anti-drug antibodies (ADAs) at Week 26

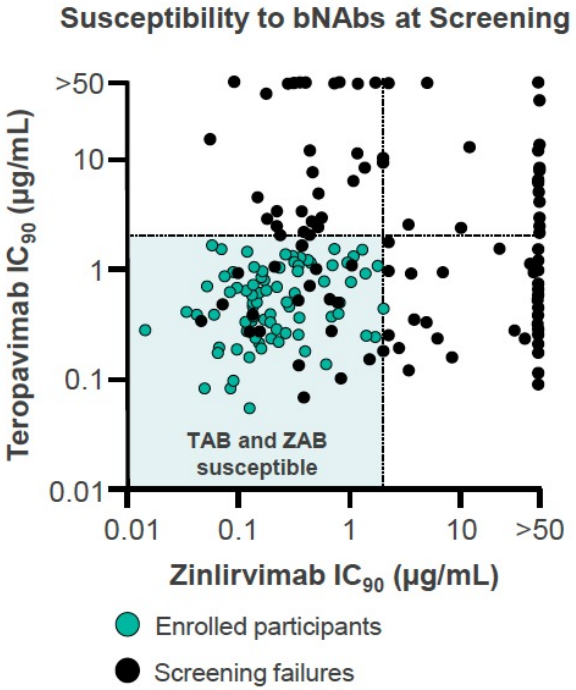
[a]NCT05729568. [b]By PhenoSense® mAb Assay (Monogram Biosciences).
ADAs, anti-drug antibodies; **ART,** antiretroviral therapy; **bNAb,** broadly neutralizing antibody; **HBV,** hepatitis B virus; **IC_{90},** 90% inhibitory concentration; **LEN,** lenacapavir; **PK,** pharmacokinetics; **Q6M,** every 6 months; **R,** randomized; **TAB,** teropavimab; **ZAB,** zinlirvimab.

Ogbuagu O, et al

HIV ART – bNAbs

Participant Disposition and bNAb Susceptibility





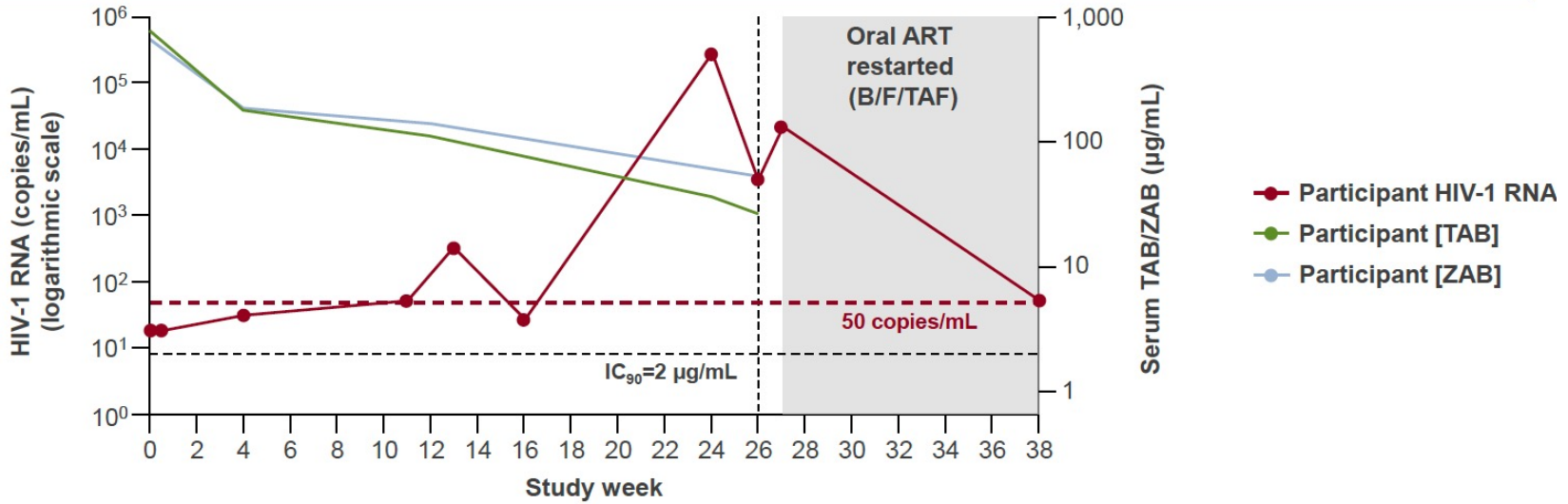
[a]41 with assay failure, 195 with screening data and 5 with results from the Phase 1b study; [b]TAB only: 47 (24%); ZAB only: 31 (16%); neither: 23 (12%). [c]84 participants met all eligibility criteria; 1 eligible but not randomized (participant decision); 3 randomized but not dosed (participant decision). [d]Discontinued study drug and study due to investigator's discretion (relocation). [e]Discontinued oral stable baseline regimen and study due to adverse event (metastatic pancreatic carcinoma).
bNAb, broadly neutralizing antibody; **IC_{90},** 90% inhibitory concentration; **LEN,** lenacapavir; **TAB,** teropavimab; **W,** week; **ZAB,** zinlirvimab.

Ogbuagu O, et al

HIV ART – bNAbs

- One virologic failure: in LEN+TAB+ZAB arm

Participant with Virologic Failure (TAB and ZAB PK)



Week 12: Resuppressed with no change in regimen.

Week 24: Resistance to LEN detected (Q67H in capsid); loss of ZAB susceptibility; TAB susceptibility unchanged from baseline.

— No ADAs detected

— TAB and ZAB concentrations similar to mean concentrations through Week 26

ADAs, anti-drug antibodies; **ART,** antiretroviral therapy; **B/F/TAF,** bictegravir/emtricitabine/tenofovir alafenamide; **IC_{90},** 90% inhibitory concentration; **LEN,** lenacapavir; **PK,** pharmacokinetics; **TAB,** teropavimab; **ZAB,** zinlirvimab.

Ogbuagu O, et al

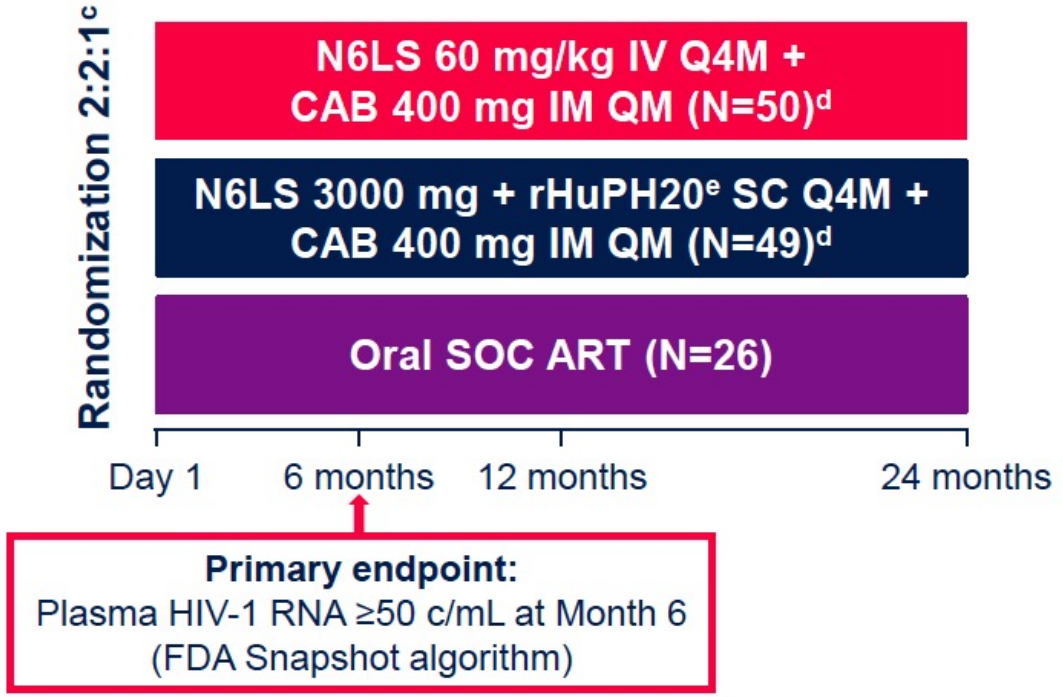
HIV ART – bNAbs

- **EMBRACE Trial** of bNAb N6LS (IV or SQ with hyaluronidase) plus CAB IM every month

Randomized, open-label, multicenter, phase 2b study conducted at 45 sites in the United States and Puerto Rico

Key inclusion/exclusion criteria

- Aged 18-70 years
- ≥2 HIV-1 RNA measurements <50 c/mL in the 12 months before screening
- No prior ART switch due to VF
- CD4+ cell count ≥350 cells/mm^3
- On stable ART for ≥6 months
- No active HBV co-infection[a]
- Phenotypic sensitivity to N6LS (IC_{90} ≤2.0 µg/mL and MPI >98%)[b]



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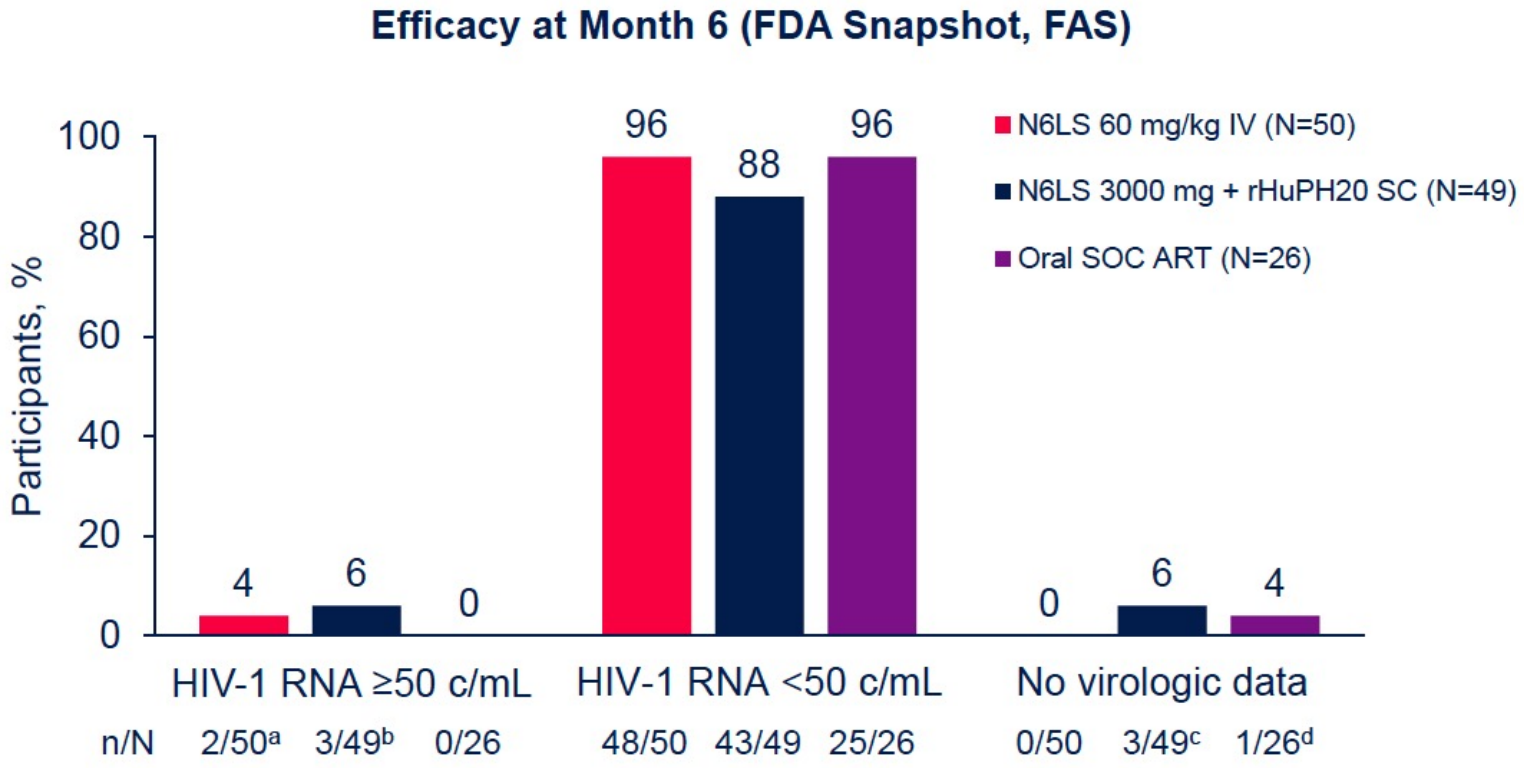
HIV ART – bNAbs



- CVF was defined as 2 consecutive HIV-1 RNA measurements ≥200 c/mL
- Of the 5 participants with Snapshot HIV-1 RNA ≥50 c/mL, 4 (n=2 in each N6LS group) met CVF criteria and 1 did not meet CVF criteria
- All participants with CVF re-suppressed on SOC ART[a]

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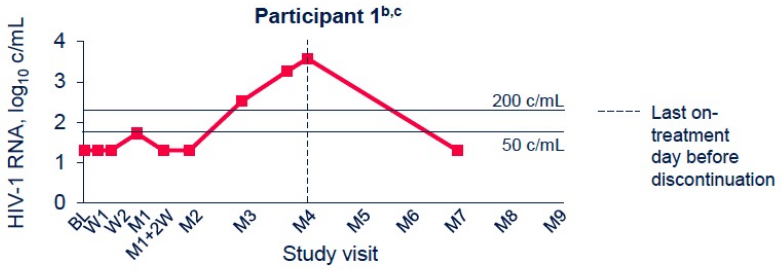
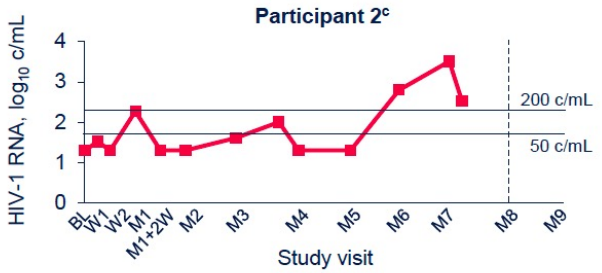
HIV ART – bNAbs

- Among the 2 participants receiving N6LS IV who met CVF criteria,[a] both had N6LS IC_{90} >2 µg/mL and none had INSTI RAMs

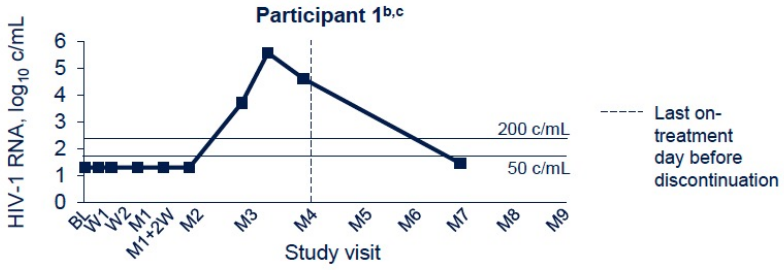


	N6LS IC_{90}, µg/mL	INSTI RAMs
BL (PBMC)	1.26	None
SVF (plasma)	>50	None
CVF (plasma)	>50	None

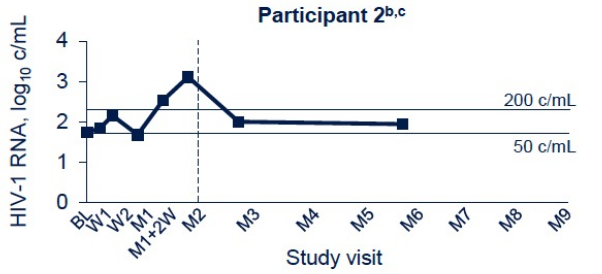


	N6LS IC_{90}, µg/mL	INSTI RAMs
BL (PBMC)	0.60	None
CVF (plasma)	3.34	None

- Among the 2 participants receiving N6LS SC who met CVF criteria,[a] neither had N6LS IC_{90} >2 µg/mL and 1 had an INSTI RAM



	N6LS IC_{90}, µg/mL	INSTI RAMs
BL (PBMC)	0.80	None
SVF (plasma)	1.08	None
Post-CVF (plasma)	—	Q148R[d]



	N6LS IC_{90}, µg/mL	INSTI RAMs
BL (PBMC)	0.94	None
SVF (plasma)	0.66	None
CVF (plasma)	—	None

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HIV ART – Other new ARVs

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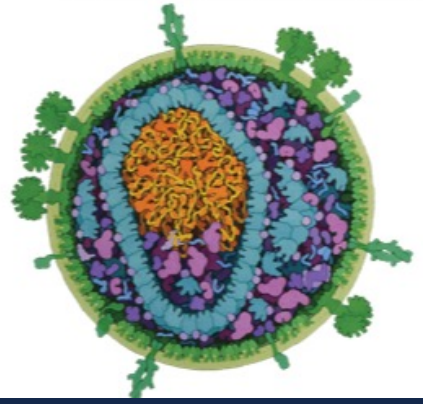
- MK-8527
  - Long acting NRTTI being studied as once a month oral PrEP and also as ART for PWH
- VH-184
  - Next generation INSTI with activity against resistant virus
- Others



CROI

Conference on Retroviruses and Opportunistic Infections

Complications/ Aging/ Co-morbidities

Complications – Weight

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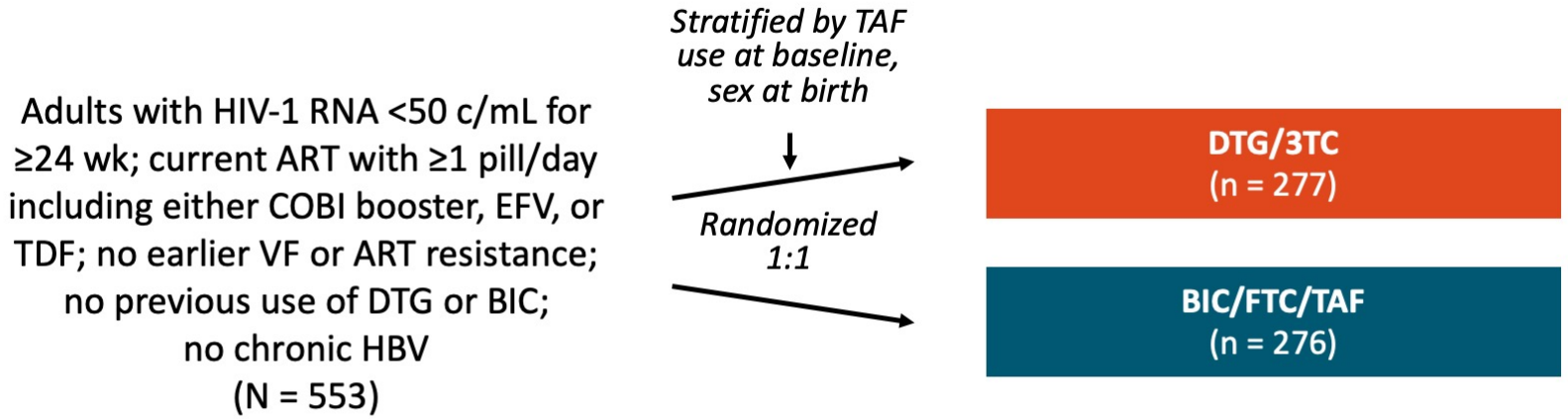
- What we know for sure:
  - TDF and EFV lead to attenuation of weight gain.
    - Switch from or stopping of these agents leads to a jump in weight
  - PWH starting ART often gain weight
    - Especially if CD4 cell count is low, HIV RNA is high
    - PWH starting BFTAF or ISL/DOR experienced similar weight gain

- What we don’t know:
  - Does TAF cause weight gain
  - Do INSTI cause weight gain

Complications – Weight

- **PASO DOBLE**
- Switch in people with suppressed VL
- On different ARV regimens but no current or prior INSTI
- TDF at entry:
  - 33% in DTG/3TC arm
  - 37% in BFTAF arm
- ~50% in each arm on NNRTI (EFV)

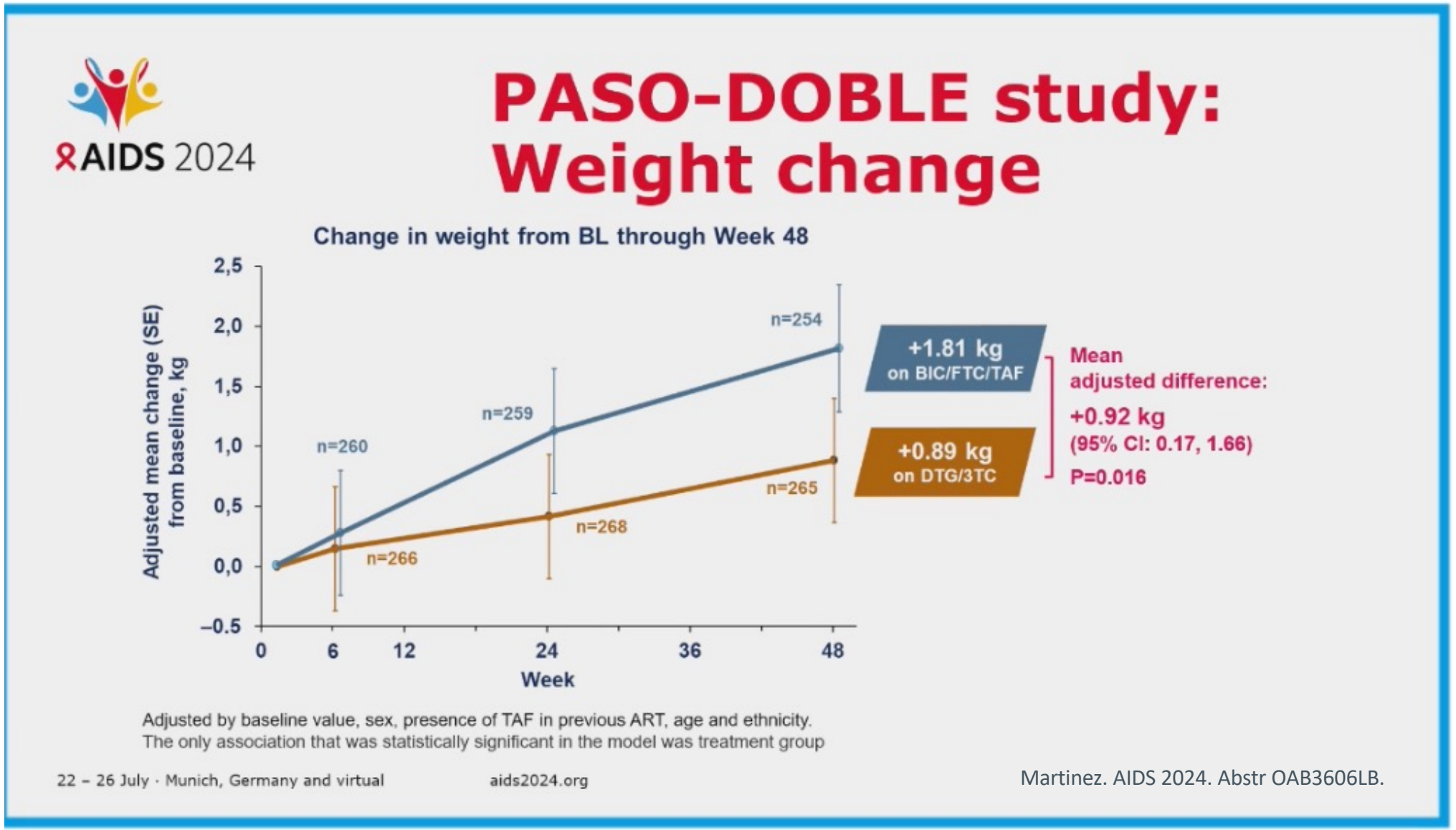
- Multicenter, randomized, open-label phase IV trial in Spain



- Primary endpoint: plasma HIV-1 RNA ≥50 c/mL at Wk 48 by FDA Snapshot with noninferiority margin of 4%
- Key secondary endpoints: efficacy, safety, tolerability, weight change

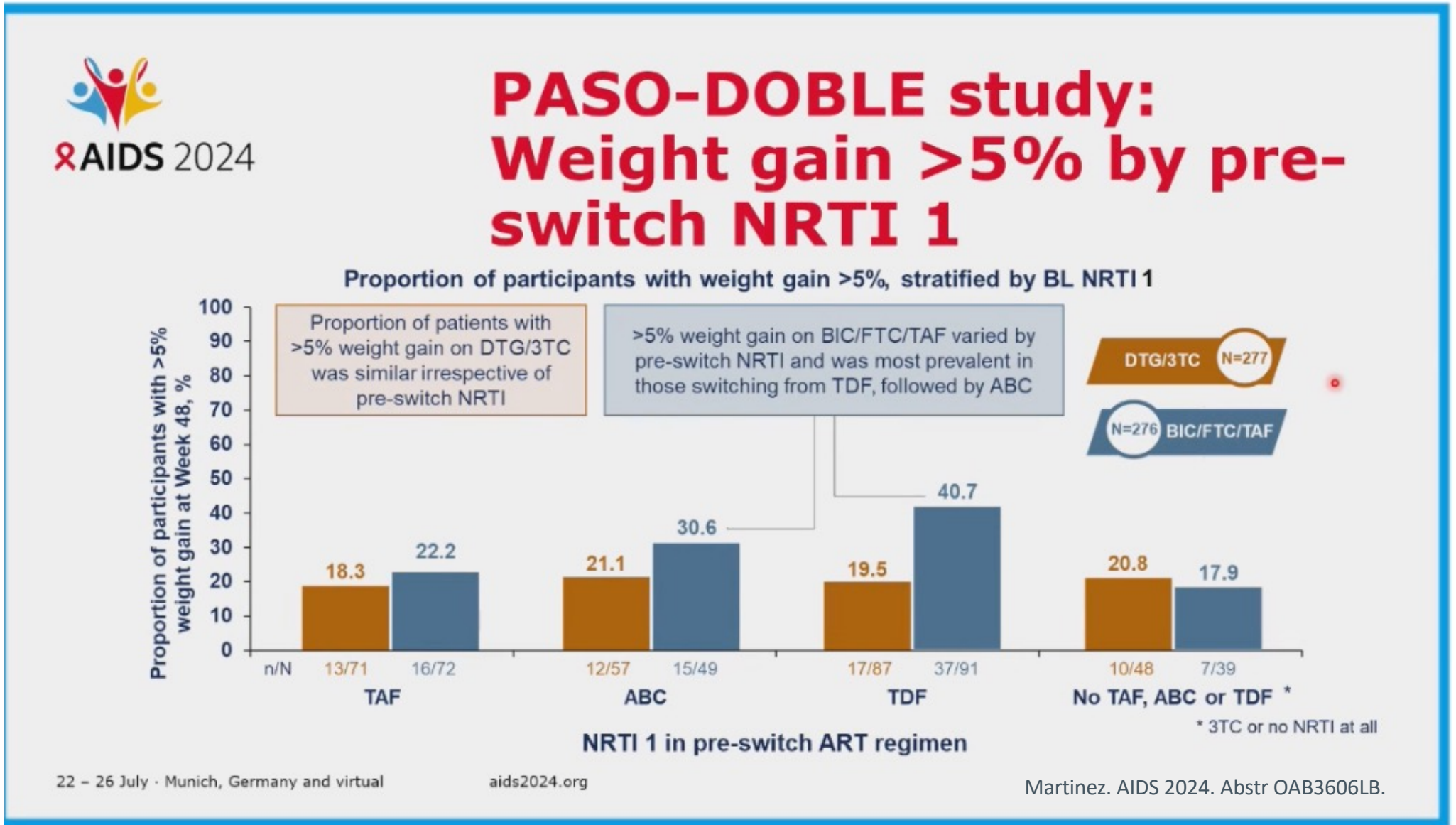
Martinez. AIDS 2024. Abstr OAB3606LB.

Complications – Weight



Martinez. AIDS 2024. Abstr OAB3606LB.

Complications – Weight



Martinez. AIDS 2024. Abstr OAB3606LB.

Complications – Weight

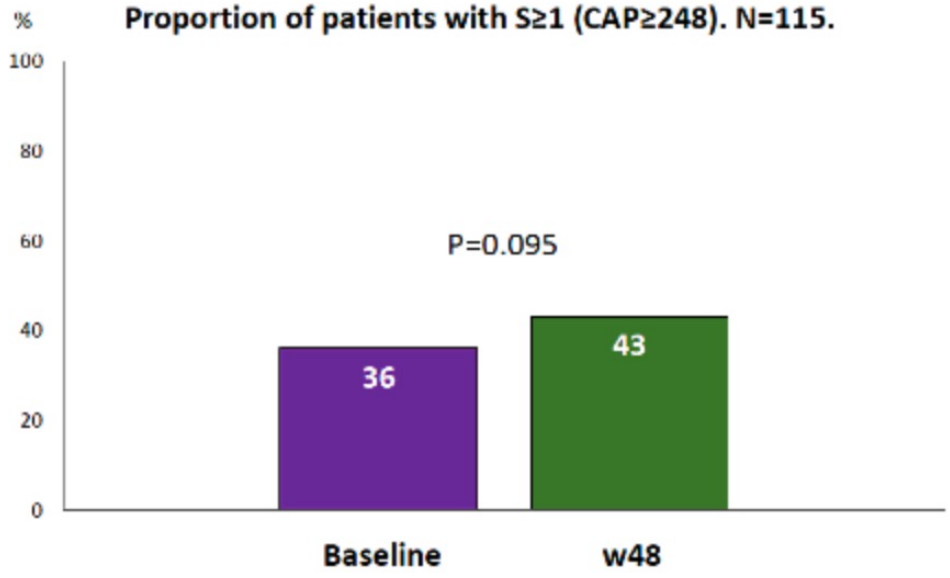
- PASO DOBLE at CROI 2025
- Two analyses:
  - Body Compartment Fat using DXA and CT[ABD]
  - Liver Fat Sub-study

Table. DXA-derived and abdomen CT-derived body composition compartments at baseline and mean changes from baseline in persons assigned to DTG/3TC (DOV) or BIC/FTC/TAF (BIK), and adjusted mean treatment differences (95% CI) in changes from baseline BIK minus DOV.

	Baseline DOV	Baseline BIK	Change from baseline DOV	Change from baseline BIK	Adjusted mean difference BIK minus DOV (95% CI)*
DXA Total Mass (TM) (kg)	73.70 (15.40)	74.46 (16.06)	0.34 (3.77)	1.06 (3.63)	0.80 (0.12 to 1.49)
DXA Total Fat Mass (FM) (kg)	21.12 (9.95)	21.32 (10.61)	2.00 (4.44)	2.33(4.31)	0.46 (-0.31 to 1.23)
DXA Appendicular Fat (LFM) (kg)	8.09 (4.34)	8.22 (4.31)	0.77 (2.02)	1.02 (1.75)	0.32 (0.00 to 0.65)
DXA Abdominal Fat (ABFM) (kg)	2.03 (1.21)	2.04 (1.34)	0.19 (0.51)	0.21 (0.50)	0.02 (-0.7 to 0.12)
DXA Visceral Fat (VFM) (kg)	1.04(0.84)	1.01 (0.89)	0.10 (0.36)	0.11 (0.33)	0.01 (-0.06 to 0.07)
DXA Total Lean Mass (LM) (kg)	50.01 (10.57)	50.54 (9.83)	-1.67 (3.74)	-1.26 (3.47)	0.43 (-0.19 to 1.04)
DXA Appendicular Lean Mass (ALM) (kg)	22.90 (5.65)	23.04 (5.24)	-0.88 (2.04)	-0.63 (1.87)	0.25 (-0.08 to 0.59)
Abdomen CT Subcutaneous Fat (SAT) (cm^2)	624.14 (172.60)	626.99(196.96)	-2.66 (93.93)	-4.21 (90.66)	-0.60 (-18.18 to 16.98)
Abdomen CT Visceral Fat (VAT) (cm^2)	125.64 (93.06)	118.46 (97.13)	6.00 (39.03)	10.32 (36.38)	3.59 (-3.48 to 10.66)

Data are mean (SD) unless otherwise stated
* Results from linear regression to assess treatments differences adjusted by sex, presence of TAF at baseline, age and race

Fig 5. Changes in proportion of PLWH with SLD (≥S1) along the follow-up



Gregorio S, et al; Pineda J, et al

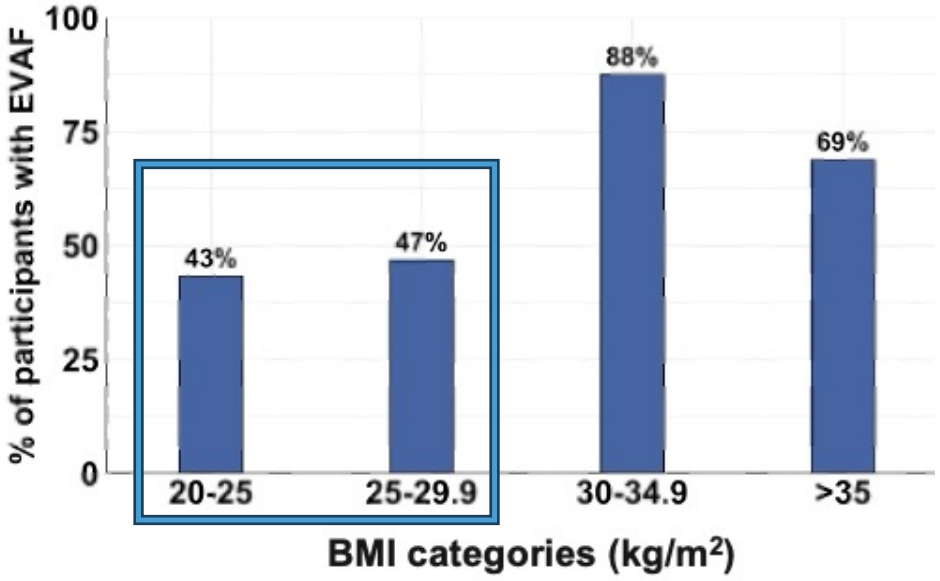
Complications – Weight

UNC SCHOOL OF MEDICINE

Visceral Adiposity Measurement and Observations Study (VAMOS):

- How CVD risk differs by BMI and Excess Visceral Abdominal Fat (EVAF)
  - N=170 PWH on ART with suppressed VL
  - BMI 20-40 kg/m^2
  - CT scan
  - RESULTS:
    While individuals with BMI 30-34.9 kg/m^2 had the highest prevalence of EVAF (88%), EVAF was still present in 47% and 43% of participants with overweight and normal BMI, respectively.

Figure 1: Prevalence of EVAF across BMI categories for participants.



Mounzer K, et al

Complications – Weight

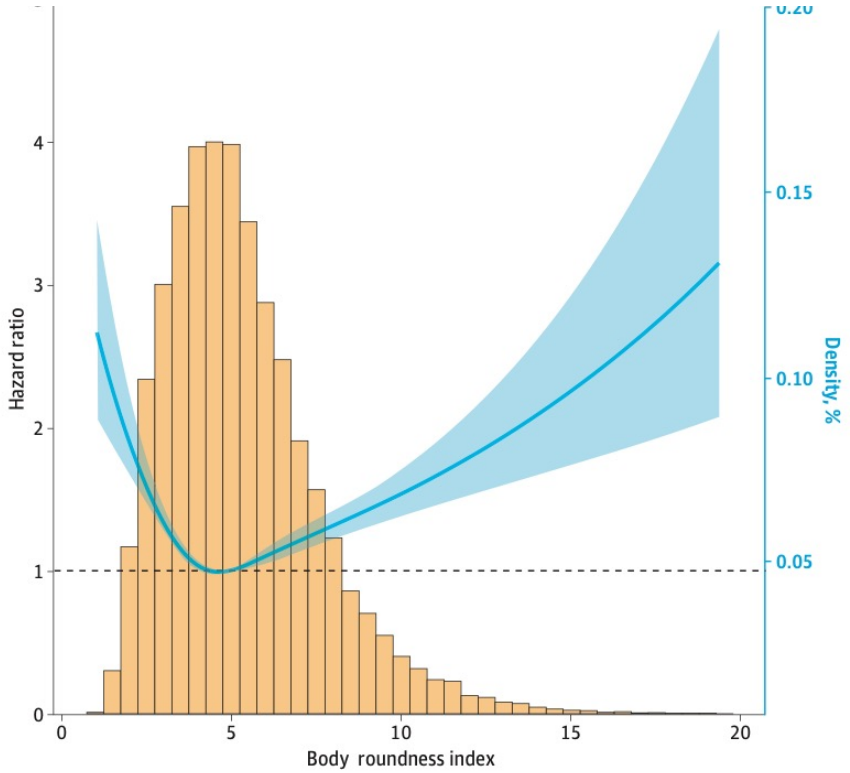
UNC SCHOOL OF MEDICINE

JAMA Network | Open

Original Investigation | Nutrition, Obesity, and Exercise

Body Roundness Index and All-Cause Mortality Among US Adults

Xiaoqian Zhang, MD; Ning Ma, MD; Qiushi Lin, MD, PhD; Kening Chen, MD; Fangjieyi Zheng, MD; Jing Wu, PhD; Xiaoqun Dong, MD, PhD; Wenquan Niu, PhD



- BRI associated with all cause mortality (Very low and very high BRI associated with increased risk vs middle range)
- Better than BMI in assessing VAT

Complications – Hypertension

- **OPERA Cohort** – Among ~10,000 PWH who initiated or switched ART with BP <140 SBP and <90 DBP, ART regimen was **not** associated with incident hypertension

Figure 2. Association between ART regimen and incident HTN in the ART-naïve population

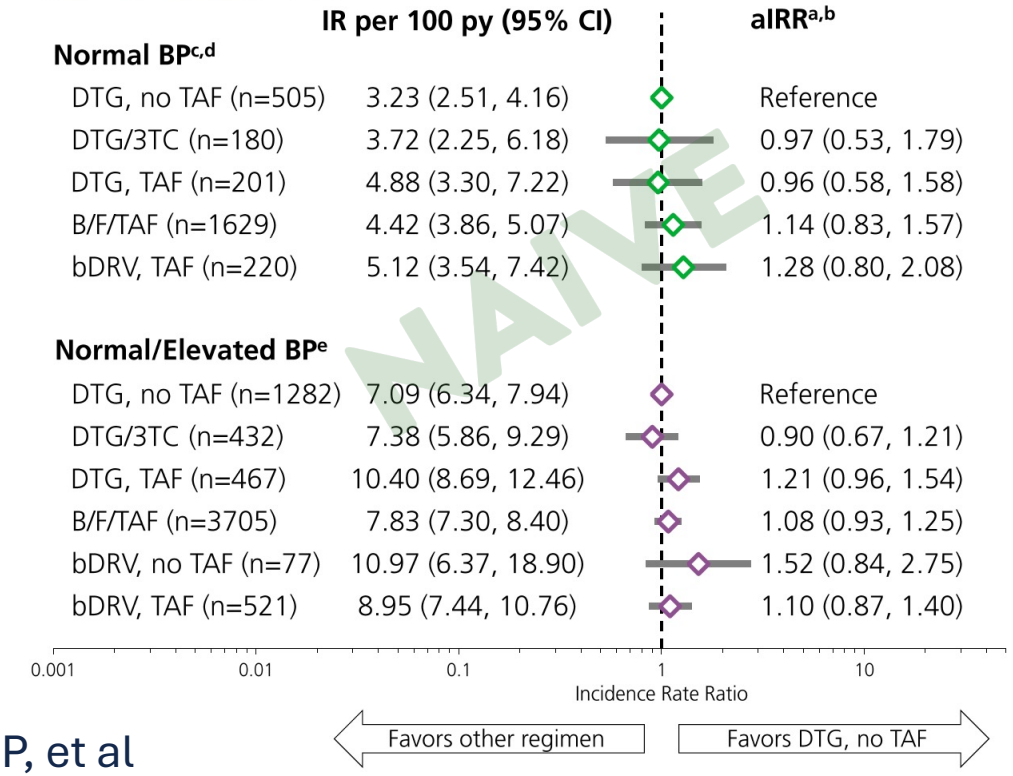
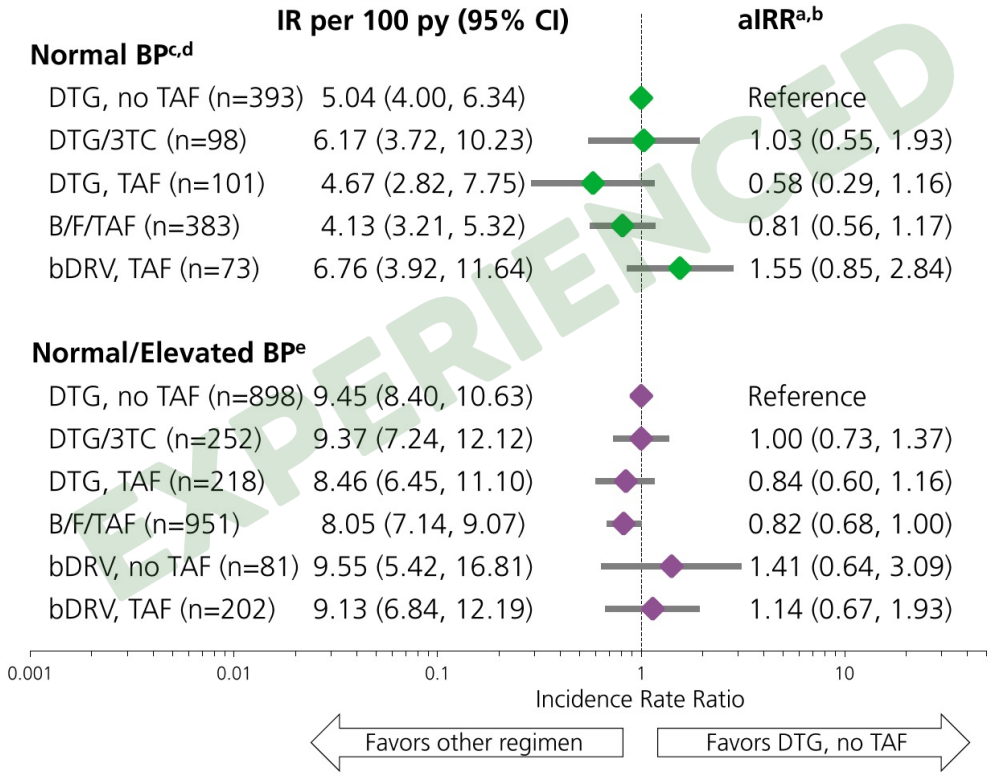


Figure 4. Association between ART regimen and incident HTN in the ART-experienced population



Lackey P, et al

Complications – Diabetes Mellitus (DM)

- **NA-ACCORD/IeDEA Cohorts**
- Incident DM among people switching from NNRTI- or PI-based regimens compared to people not switching

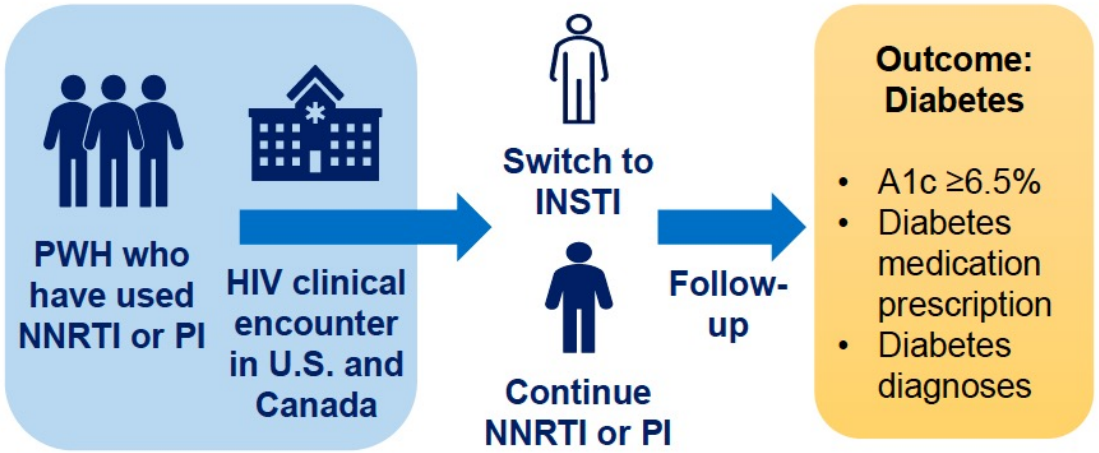


Figure 1. Adjusted cumulative incidence of diabetes after switching to INSTI compared to continuing NNRTI or PI

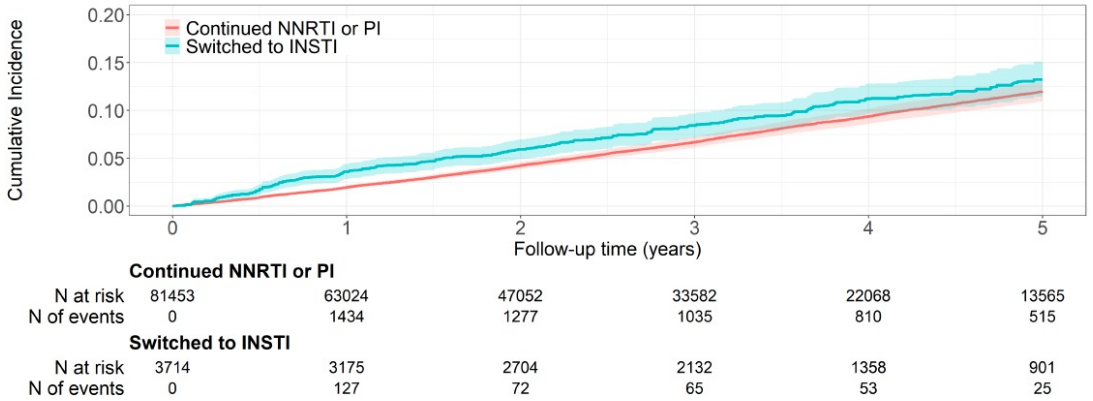


Table 1. The risk of incident diabetes associated with switching from NNRTI or PI to INSTI between 2016 and 2022

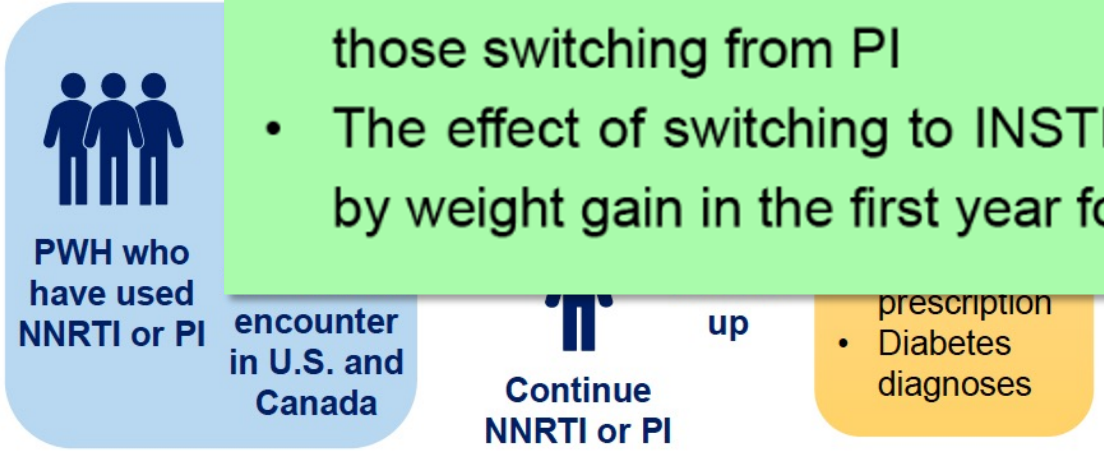
Comparison groups	N of events/ N of encounters (%)	Adjusted incidence rate, per 1,000 PY (95% CI)	Adjusted hazard ratio (95% CI)
Continued NNRTI or PI	5,041/81,365 (6.2)	23.9 (23.2–24.5)	Reference
Switched to any INSTI	400/4,416 (9.1)	29.3 (26.3–32.5)	1.22 (1.03–1.45)
Specific INSTI			
Bictegravir	87/1,097 (7.9)	29.6 (18.9–44.0)	1.13 (0.79–1.62)
Dolutegravir	182/1,953 (9.3)	27.8 (23.6–32.7)	1.11 (0.87–1.41)
Elvitegravir	127/1,322 (9.6)	30.4 (23.1–39.3)	1.22 (0.85–1.77)
Raltegravir	4/44 (9.1)	21.6 (5.9–55.4)	1.05 (0.26–4.17)

Hwang J, et al

Complications – Diabetes Mellitus (DM)

- **NA-ACCORD/IeDEA Cohorts**
- Incid… swit… base… peop…

- Switching to INSTI from NNRTI or PI was associated with a modest, but statistically significant risk of incident diabetes in multi-site cohorts of PWH across the U.S. and Canada
- Diabetes risk was concentrated in the the first two years after switch and those switching from PI
- The effect of switching to INSTI on diabetes was not meaningfully mediated by weight gain in the first year following the switch



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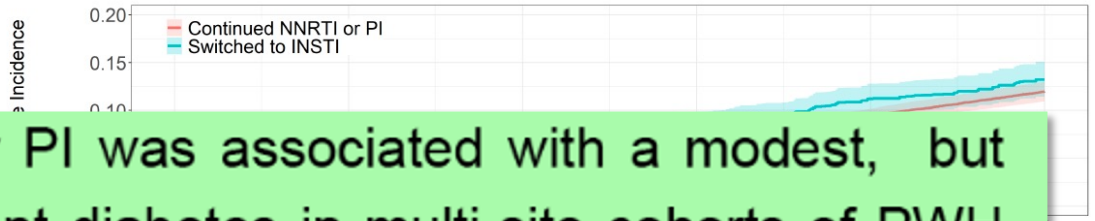

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Hwang J, et al

Complications – REPRIEVE Trial

UNC SCHOOL OF MEDICINE

- REPRIEVE Trial [NIH funded, ACTG sponsored] – landmark study that found statin in PWH with predicted low to moderate risk of CVD prevented **CVD and death** and progression of **non-calcified coronary plaque**

- Multiple analyses derived from the trial presented at CROI:
  - Biomarkers and plaque
  - Risk for functional decline
  - Cognition

Complications – REPRIEVE Trial

UNC SCHOOL OF MEDICINE

REPRIEVE Mechanistic Substudy

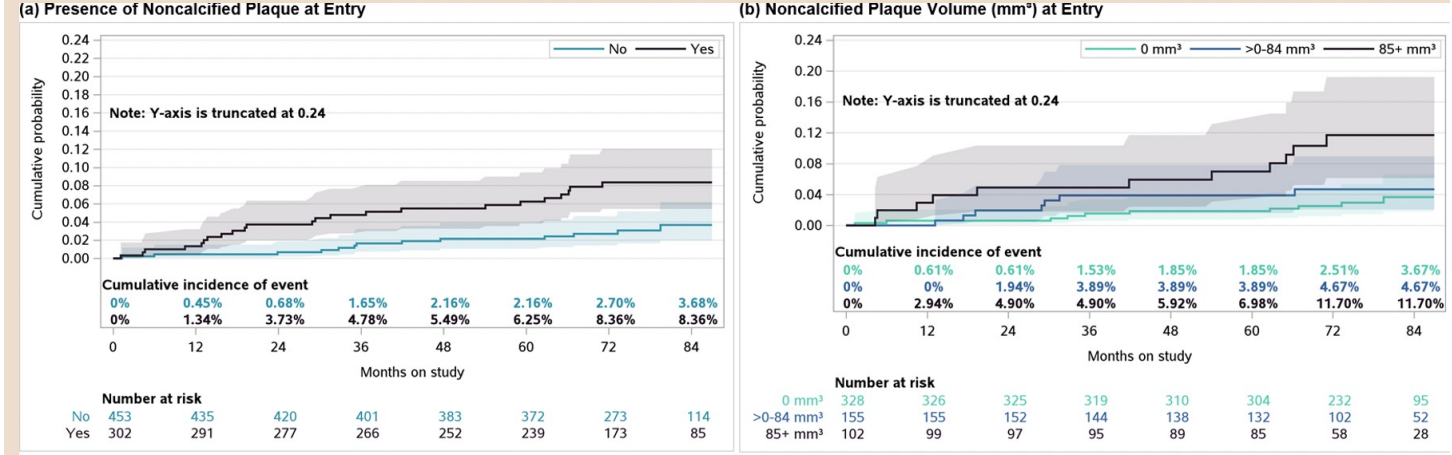
Lu M, et al

- Assess the relationship of coronary plaque and indices of inflammation and subclinical myocardial injury with Major Adverse CV Events (MACE) and the effects of pitavastatin on MACE.
- 38 participants with MACE and 766 without over 6 years of follow-up

Baseline Characteristics

			With MACE* (N=38)	Without MACE* (N=766)
Demographics	Male		31 (82%)	634 (83%)
	Female		7 (18%)	132 (17%)
	White		17 (45%)	408 (53%)
	Non-White		21 (55%)	358 (47%)
	Age (yrs)		54 (50, 57)	50 (46, 55)
	ASCVD risk %		6.5 (3.6, 9.9)	4.5 (2.6, 6.8)
	LDL mg/dL		93 (87, 113)	106 (89, 127)
Biomarkers	hsCRP (mg/L)	< 1.0	7 (19%)	222 (30%)
		1.0 - 3.0	11 (30%)	308 (41%)
		3.1 - 10.0	14 (38%)	160 (21%)
		> 10	5 (14%)	61 (8%)
	IL-6 (pg/mL)		2.3 (1.4, 2.9)	1.6 (1.0, 2.7)
	hs-cTNT (ng/L)	< 6	5 (16%)	291 (41%)
		6 - 7.52	3 (9%)	142 (20%)
		7.53 - 9.63	10 (31%)	143 (20%)
		> 9.64	14 (44%)	142 (20%)
Plaque	Any Plaque		26 (70%)	342 (48%)
	Any NCP Plaque		23 (62%)	279 (39%)

Cumulative Incidence of MACE Over Time, By Baseline Noncalcified Plaque



- Statin therapy reduced noncalcified plaque progression in REPRIEVE (Lu JAMA Cards 2024), suggesting a possible mechanism of MACE prevention

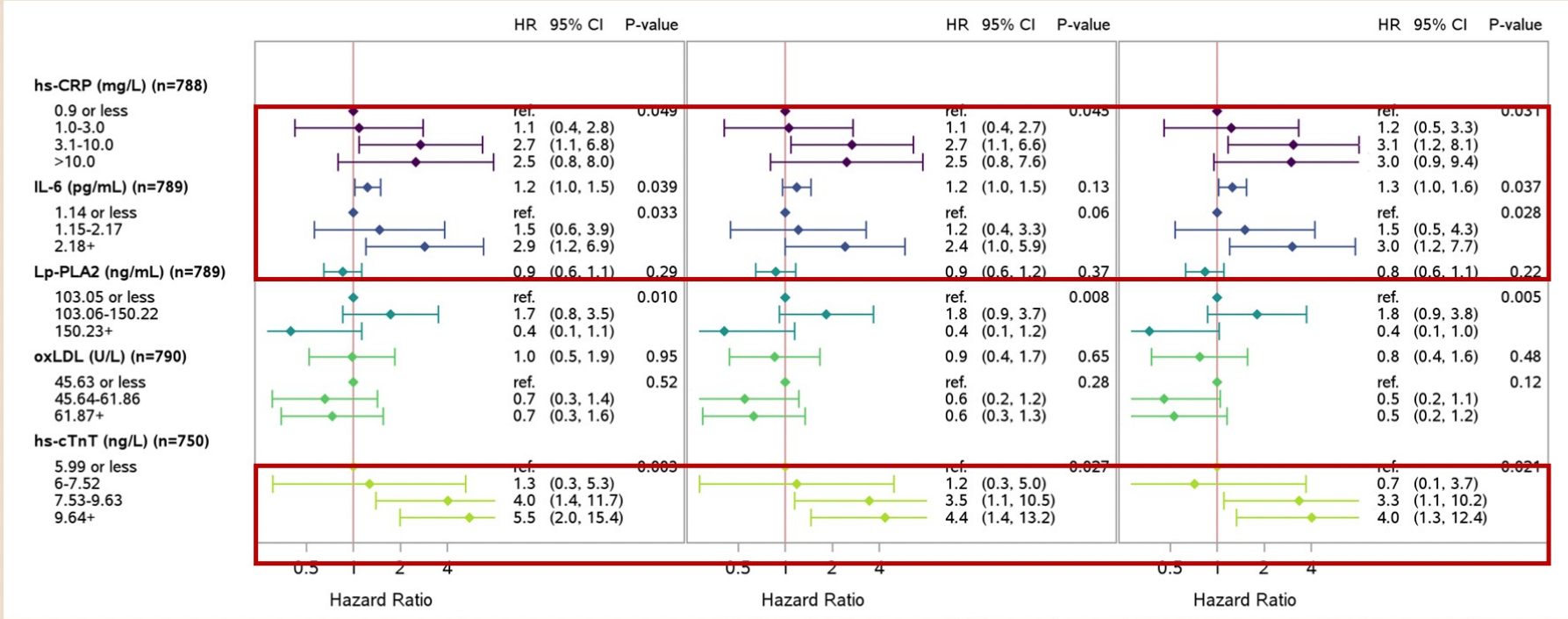
Complications – REPRIEVE Trial

UNC SCHOOL OF MEDICINE

- REPRIEVE Mechanistic Substudy

Lu M, et al

Estimated Baseline Biomarker Effect on Hazard of MACE



- In substudy, statin had limited effects on IL-6 but tended to reduce CRP (-11% vs. +6%, statin vs placebo, Lu JAMA Cards 2024). Future analyses relating statin effects to biomarkers and MACE are planned for full REPRIEVE cohort.

CROI 2025

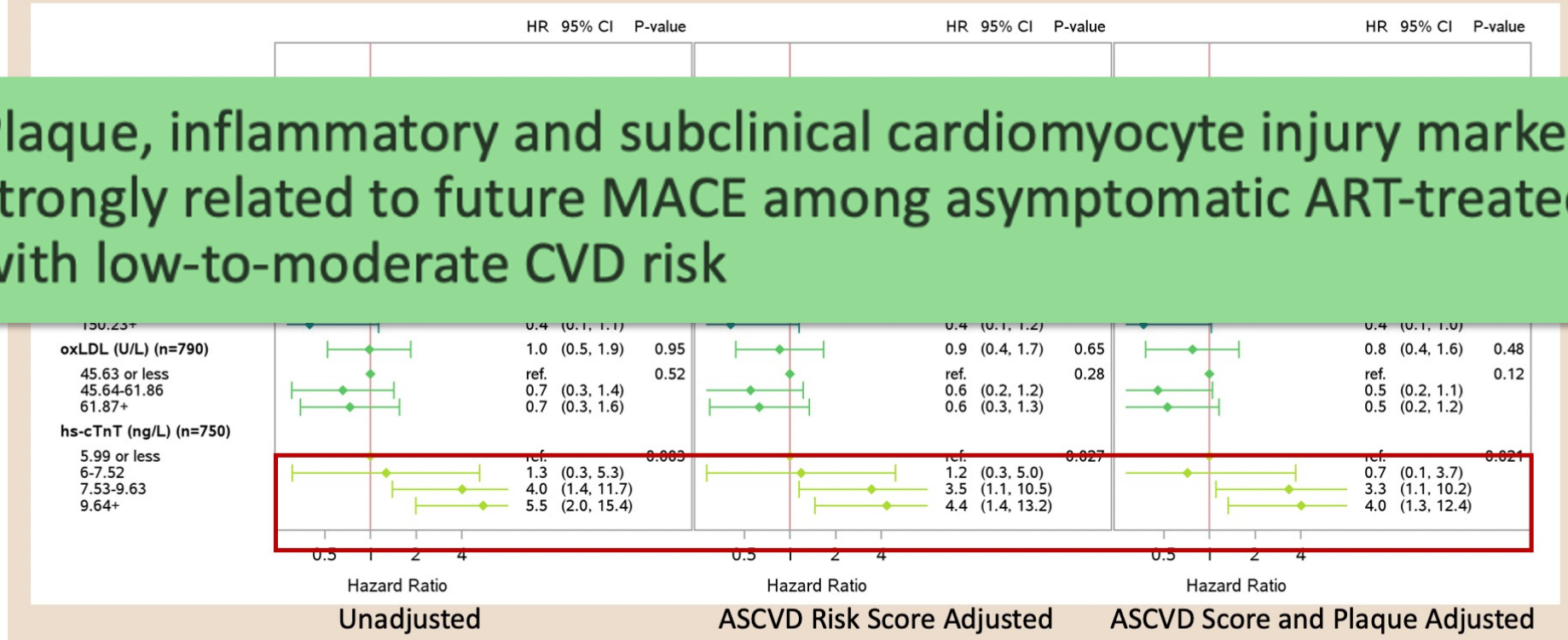
Complications – REPRIEVE Trial

UNC SCHOOL OF MEDICINE

- REPRIEVE Mechanistic Substudy

Lu M, et al

Estimated Baseline Biomarker Effect on Hazard of MACE



- Plaque, inflammatory and subclinical cardiomyocyte injury markers are strongly related to future MACE among asymptomatic ART-treated PWH with low-to-moderate CVD risk

- In substudy, statin had limited effects on IL-6 but tended to reduce CRP (-11% vs. +6%, statin vs placebo, Lu JAMA Cards 2024). Future analyses relating statin effects to biomarkers and MACE are planned for full REPRIEVE cohort.

CROI 2025

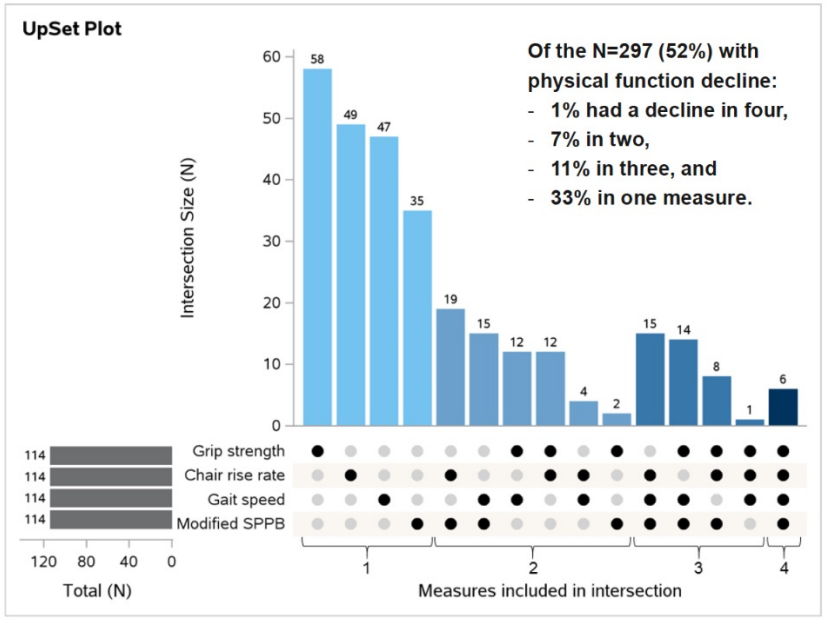
Complications – REPRIEVE Trial

UNC SCHOOL OF MEDICINE

Physical Function Impairment and Frailty Substudy

- Of 569 participants (81% male, 52% white), the median age was 51 (Q1-Q3: 47-55) years.
- There was a greater risk physical function decline among females, non-whites, and a trend of higher risk with increasing age (Figure 3).
- The sex difference was attenuated in models adjusted for BMI, history of depression treatment, and inflammatory markers, which were higher/more prevalent among females (RR: 1.16, 95%CI: 0.98-1.38 in females vs. males, when adjusted for hs-CRP).

Figure 2: Details on Participants Classified as Having Physical Function Decline



In models adjusted for age, sex, and race, risk of decline was greater among those with history of depression treatment, higher BMI, pre-existing functional impairment or frailty, and higher baseline hs-CRP and IL-6 levels.

Kulik G, et al

Complications – REPRIEVE Trial

UNC SCHOOL OF MEDICINE

- Statin effects on cognition in REPREIVE Trial participants co-enrolled in HAILO (ACTG neurocognitive study)
  - N=181: 88 on pitavastatin and 93 on placebo

- Participants were followed for a median of 2.9 (Q1-Q3 1.7-4.4), and up to 6 years prior to REPRIEVE randomization, and a median of 2.3 (Q1-Q3 1.1-3.7) and up to 6.5 years after REPRIEVE randomization.

	Pre-REPRIEVE	Post-REPRIEVE Randomization		
Outcome	Combined Arms	Placebo	Pitavastatin	P-value
NPZ4	0.050 (0.034, 0.065)	-0.006 (-0.030, 0.017)	-0.007 (-0.033, 0.020)	0.97
TrA	0.076 (0.053, 0.099)	-0.020 (-0.065, 0.024)	0.019 (-0.020, 0.058)	0.18
TrB	0.064 (0.039, 0.089)	0.033 (-0.006, 0.073)	0.014 (-0.026, 0.054)	0.46
DSY	0.041 (0.018, 0.064)	-0.003 (-0.043, 0.037)	-0.001 (-0.047, 0.045)	0.94
HVLT	0.017 (-0.011, 0.046)	-0.029 (-0.066, 0.008)	-0.062 (-0.115, -0.009)	0.27

We found no evidence suggesting a detrimental effect of pitavastatin use on a battery of neurocognitive assessments among PWH. These results provide reassurance to PWH and to providers who may have concerns about statin-related side effects.

Erlandson K, et al

Complications – Semgalutide

UNC SCHOOL OF MEDICINE

What Semaglutide makes better in PWH:

- Cardiometabolic Health [Lake J, et al]
  - SLIM-LIVER (ACTG A5371): 51 PWH on ART with MASLD.
    - Range of inflammatory markers decreased.
    - 25% reduction of risk of metabolic syndrome and reduced VAT and superficial abdominal fat.
    - Some benefits persisted after cessation of the drug.
- Cognition [Atieh O, et al]
  - RCT among 108 PWH with lipohypertrophy.
    - Significant improvement in visuospatial score
    - Markers of inflammation (C-reactive protein and sCD163) were mediators of effects on visuospatial score.
- Alcohol abstinence [Crane H, et al]
  - CNICS Cohort: 443 PWH who drank.
    - AUDIT-C scores dropped.

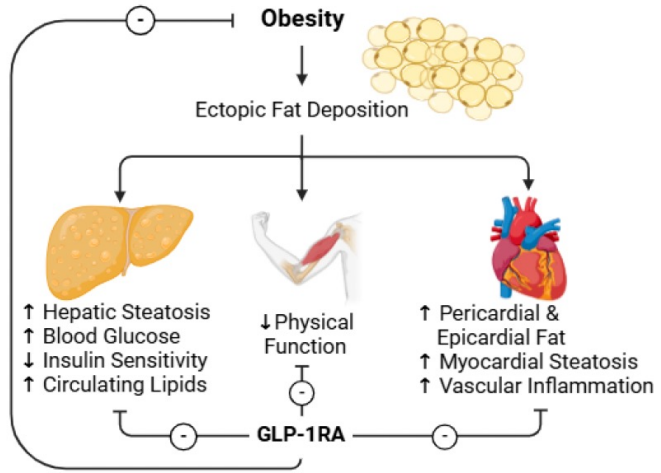


Fig. 1. Therapeutic actions of GLP-1RA

Complications – Semgalutide

UNC SCHOOL OF MEDICINE

But there is an innovation lag in semaglutide prescribing

- CNICS Cohort: PWH with ≥1 in timeframe and eligible for semaglutide therapy by BMI ≥30 kg/m^2 or HbA1c ≥6.5%

N=11,617

Overall:
- Median age: 53 (IQR: 42-61)
- 74% male; 26% female
- 48% Black, 35% White

774 PWH (7%) received semaglutide
- 75% male, 25% female
- 36% Black, 41% White

Table 1. Association (Prevalence Ratio, PR) between race/ethnicity and receiving semaglutide among eligible PWH, adjusted for maximum BMI, age, sex, and CNICS site

Model	Race/ethnicity	N on semaglutide	PR (95% CI)	p-value
Everyone	White	315	Ref	
	Black	279	**0.80** (0.67-0.95)	0.01
	Hispanic	136	**0.84** (0.69-1.02)	0.08
	Other	44	**1.05** (0.78-1.41)	0.7
BMI ≥ 30 kg/m^2	White	287	Ref	
	Black	259	**0.82** (0.69-0.99)	0.03
	Hispanic	124	**0.81** (0.66-1.00)	0.049
	Other	39	**1.09** (0.80-1.49)	0.6
HbA1c ≥ 6.5%	White	187	Ref	
	Black	198	**0.65** (0.53-0.79)	<0.001
	Hispanic	76	**0.75** (0.58-0.96)	0.02
	Other	20	**0.63** (0.41-0.97)	0.04

Hahn A, et al

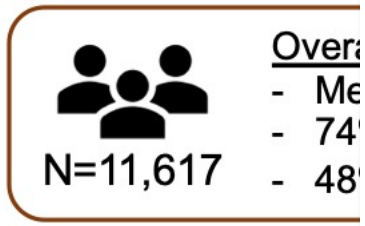
Complications – Semgalutide

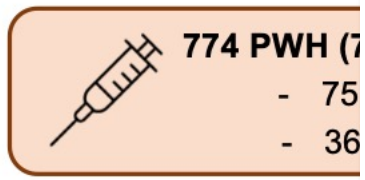
But there is an innovation lag in semaglutide prescribing

- CNICS C … for semaglut … %

Black PWH were *20% less likely to receive semaglutide* versus **White** PWH, despite greater indication for use

This was more pronounced among those with high HbA1c





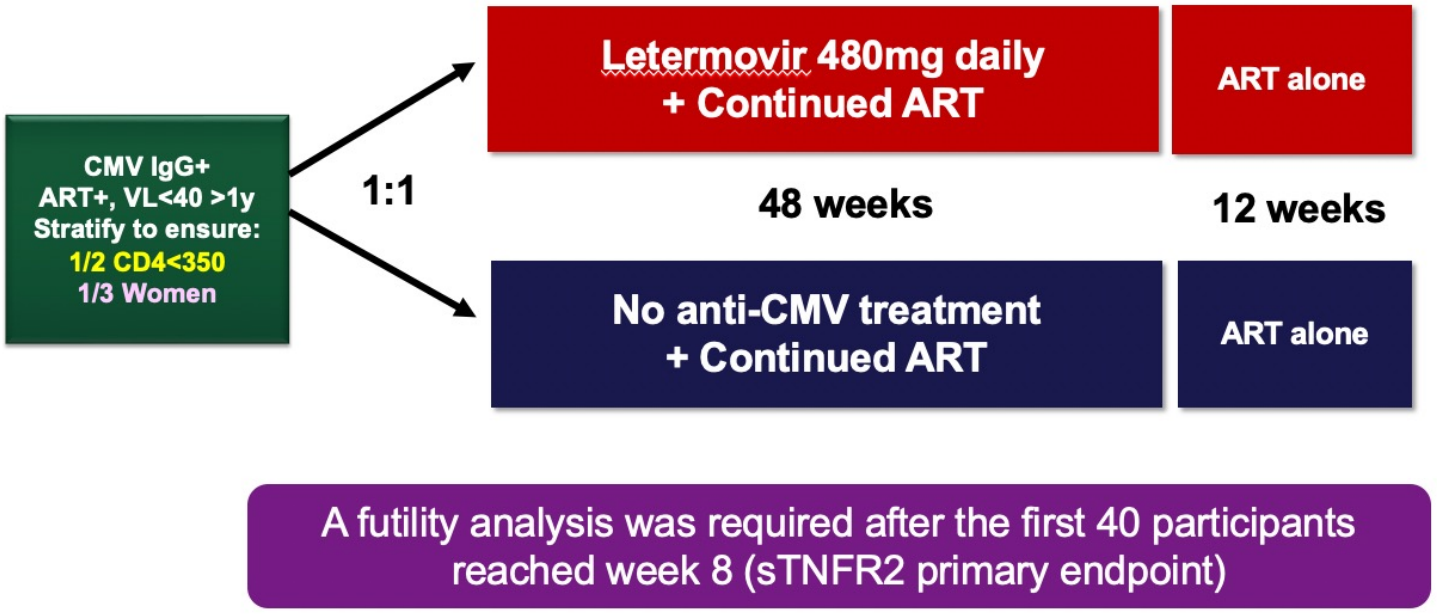
…ity and receiving …ge, sex, and CNICS site

		% CI)	p-value
		67-0.95)	0.01
		69-1.02)	0.08
		78-1.41)	0.7
		69-0.99)	0.03
		66-1.00)	0.049
		80-1.49)	0.6
		53-0.79)	<0.001
Hispanic	76	**0.75** (0.58-0.96)	0.02
Other	20	**0.63** (0.41-0.97)	0.04

Hahn A, et al

Complications – Letermovir

- CMV co-infection is common in PWH and may be a driver of inflammation
- Letermovir is a CMV terminase inhibitor used to prevent CMV, mostly in transplant recipients
- ACTG A5383: RCT (N=180) of Letermovir to reduce markers of inflammation



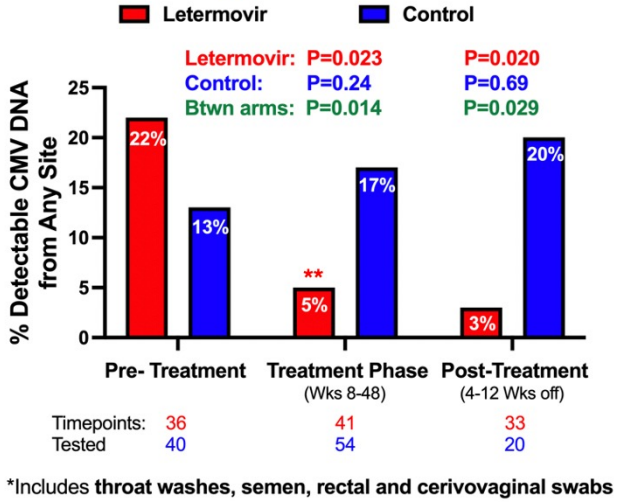
https://clinicaltrials.gov/ct2/show/NCT0

Gianella S, et al

Complications – Letermovir

UNC SCHOOL OF MEDICINE

Letermovir Suppresses Mucosal* CMV Shedding



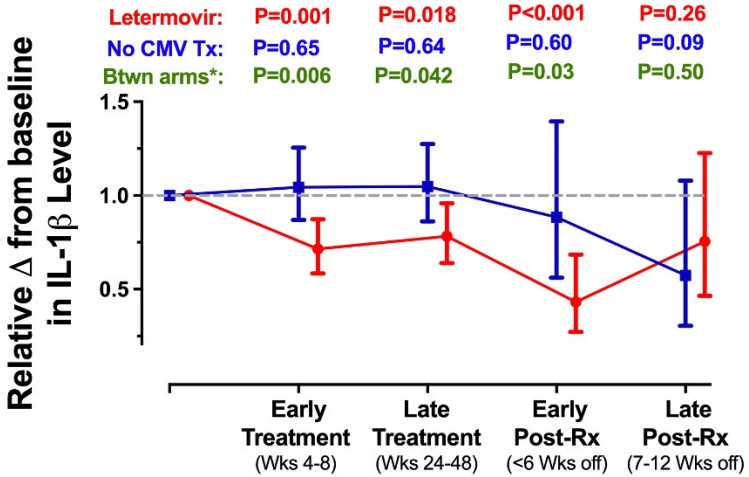
*Includes **throat washes, semen, rectal and cerivovaginal swabs**

P values test change from baseline using repeated measures logistic regression modeling

***During treatment, there were only 2 detectable CMV DNA levels in the letermovir arm (both in semen and at week 8), and both had declined from baseline:
10,645 c/ml->51 c/ml
1,805 c/ml-> 460 c/ml*

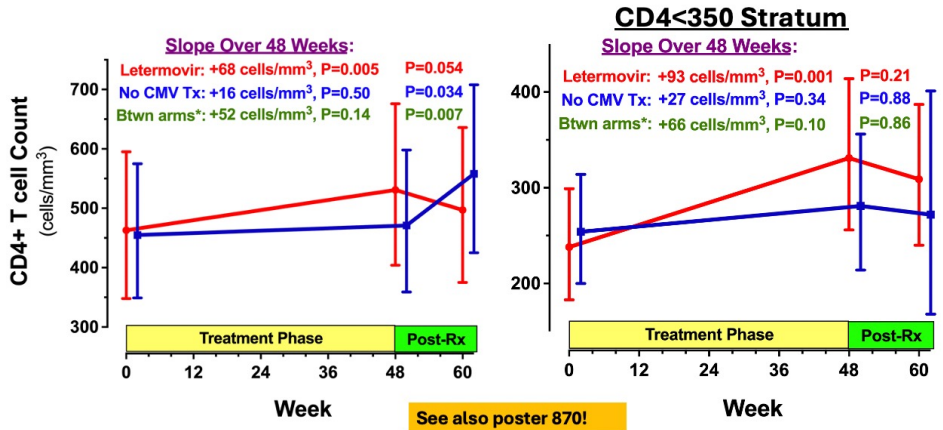
All plasma CMV DNA levels tested in the study were undetectable

Letermovir Caused Early and Sustained Reductions in Plasma IL-1β Levels



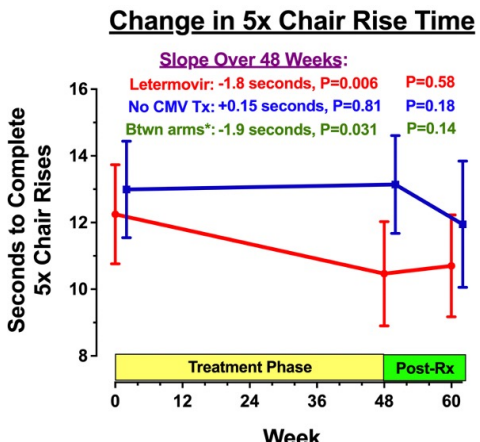
IL-1β is causally associated with CVD and cancer mortality in the general population (CANTOS trial)

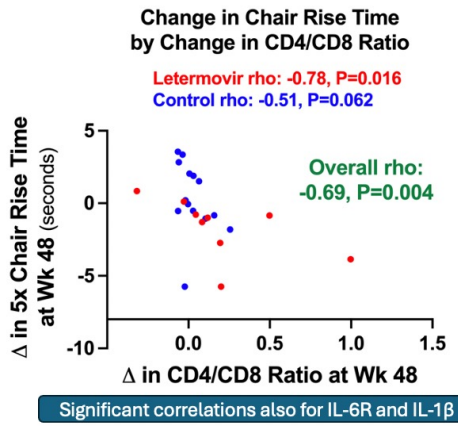
CD4 Count Increased in the Letermovir Arm Particularly Among Those with CD4<350



See also poster 870!

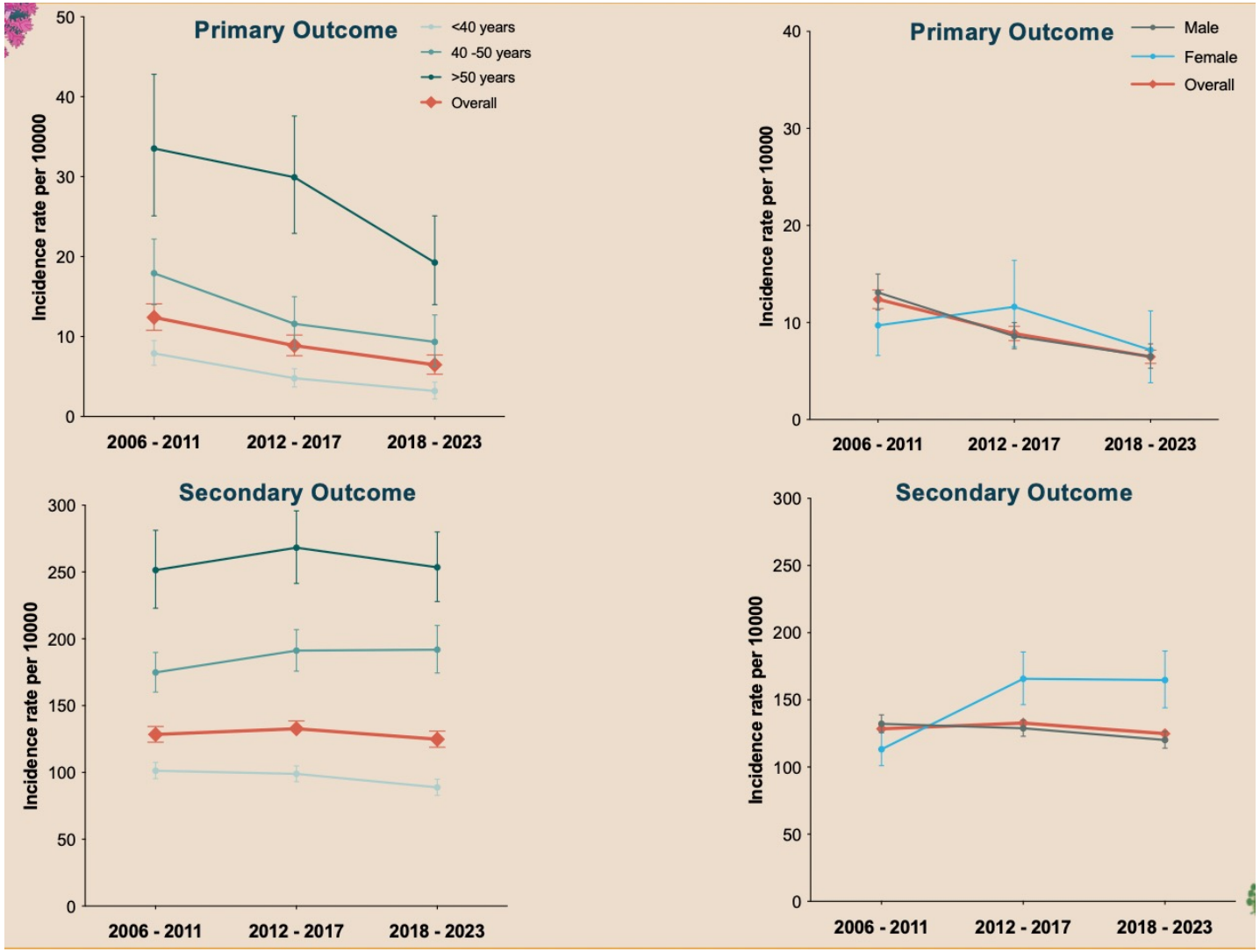
Letermovir Improved physical function, which Correlated with Immunologic Improvement



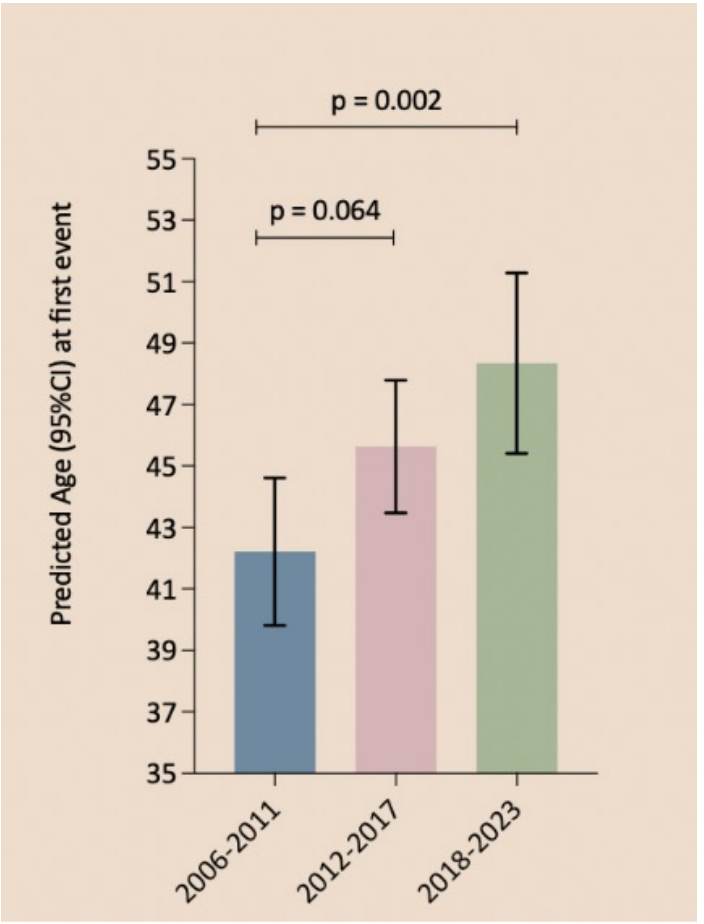


Significant correlations also for IL-6R and IL-1β

Complications – CoRIS Cohort



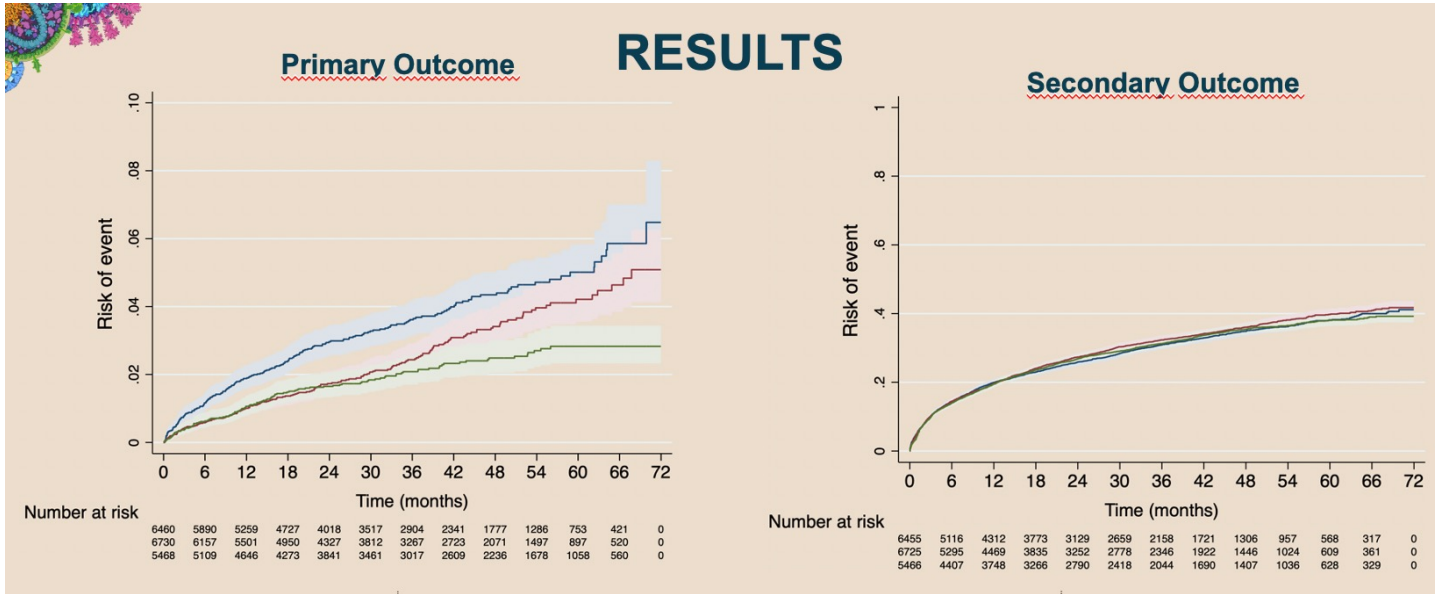
Age at onset of first SNAE

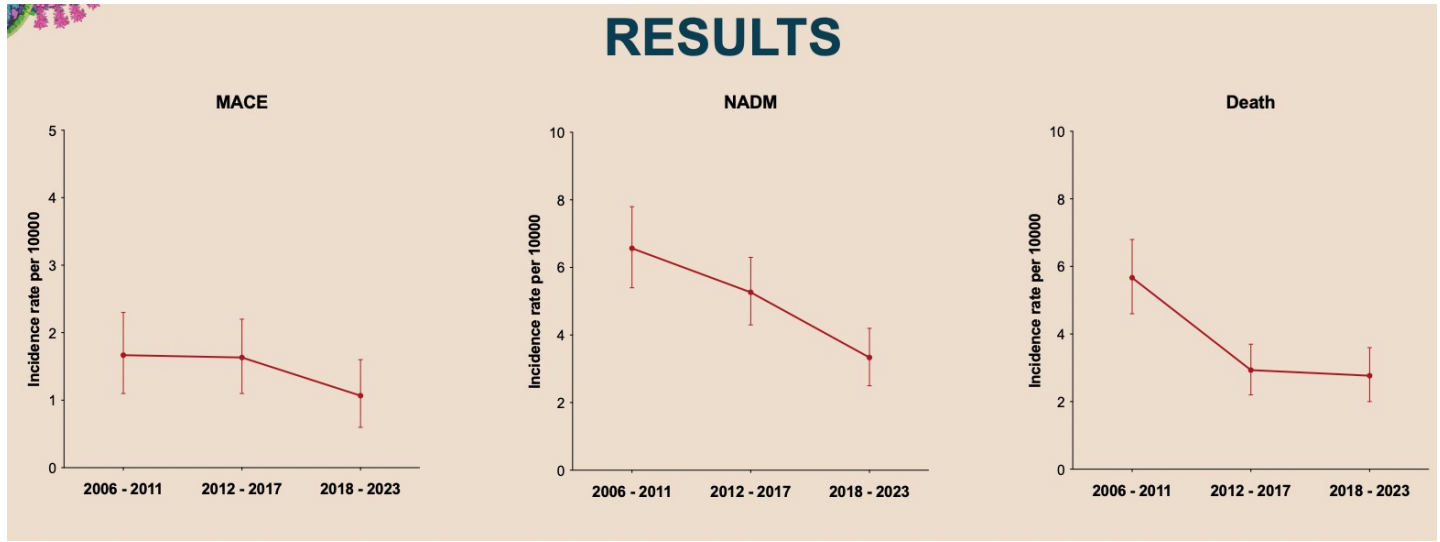


Complications – CoRIS Cohort

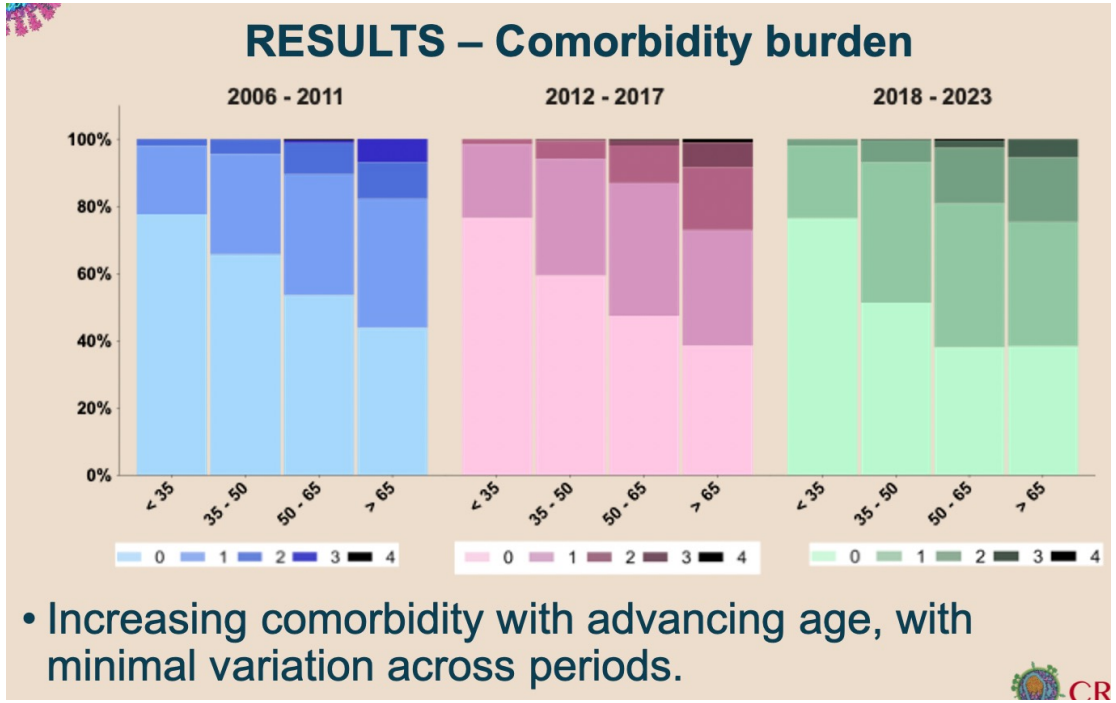
- Spanish cohort study of >20,000 PWH with 18 years of follow-up
- Analysis for:
  - Primary: Severe Non-AIDS Events (SNAEs) like CVD, Cancer, non-AIDS/accidental deaths
  - Secondary: Other comorbidities

García-Ruiz de Morales A, et al

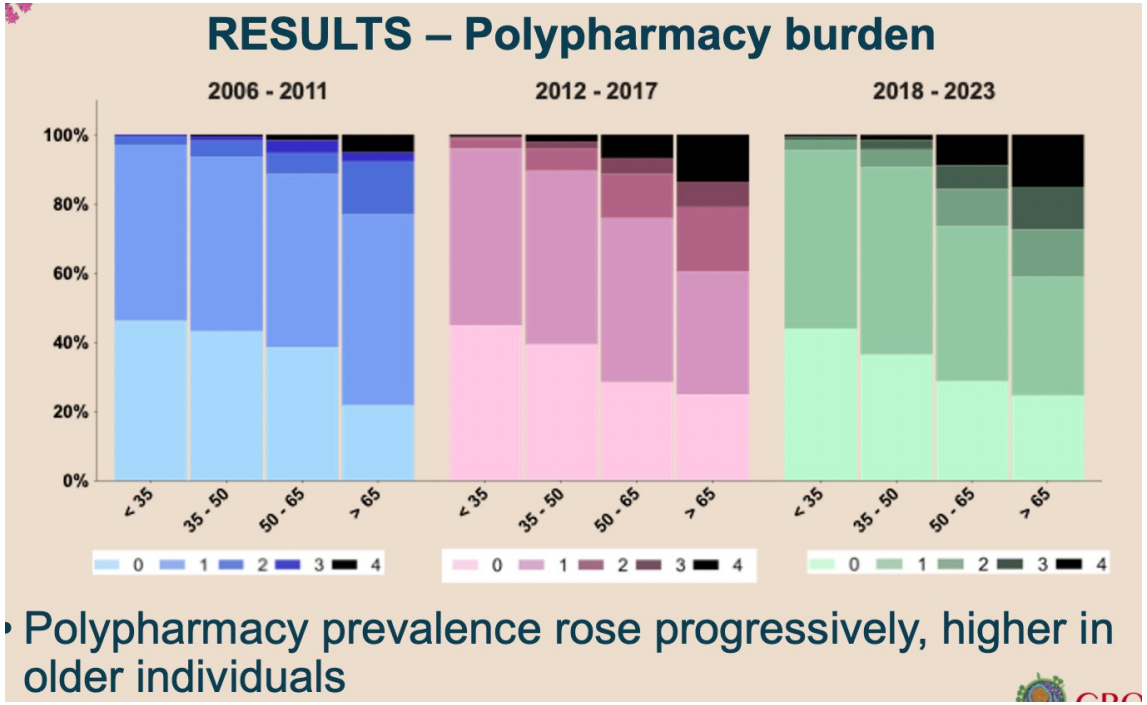




Complications – CoRIS Cohort

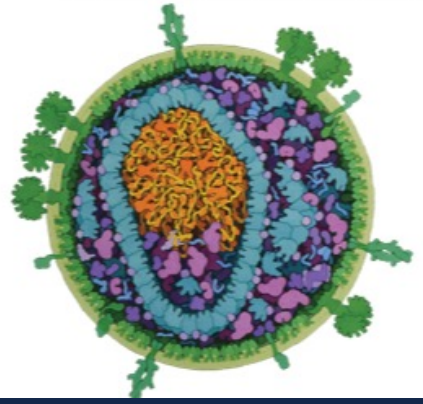


- Increasing comorbidity with advancing age, with minimal variation across periods.



- Polypharmacy prevalence rose progressively, higher in older individuals

García-Ruiz de Morales A, et al



CROI

Conference on Retroviruses and Opportunistic Infections

mpox

MPOX

UNC SCHOOL OF MEDICINE

The New York Times

W.H.O. Declares Global Emergency Over New Mpox Outbreak

The epidemic is concentrated in the Democratic Republic of Congo, but the virus has now appeared in a dozen other African countries.

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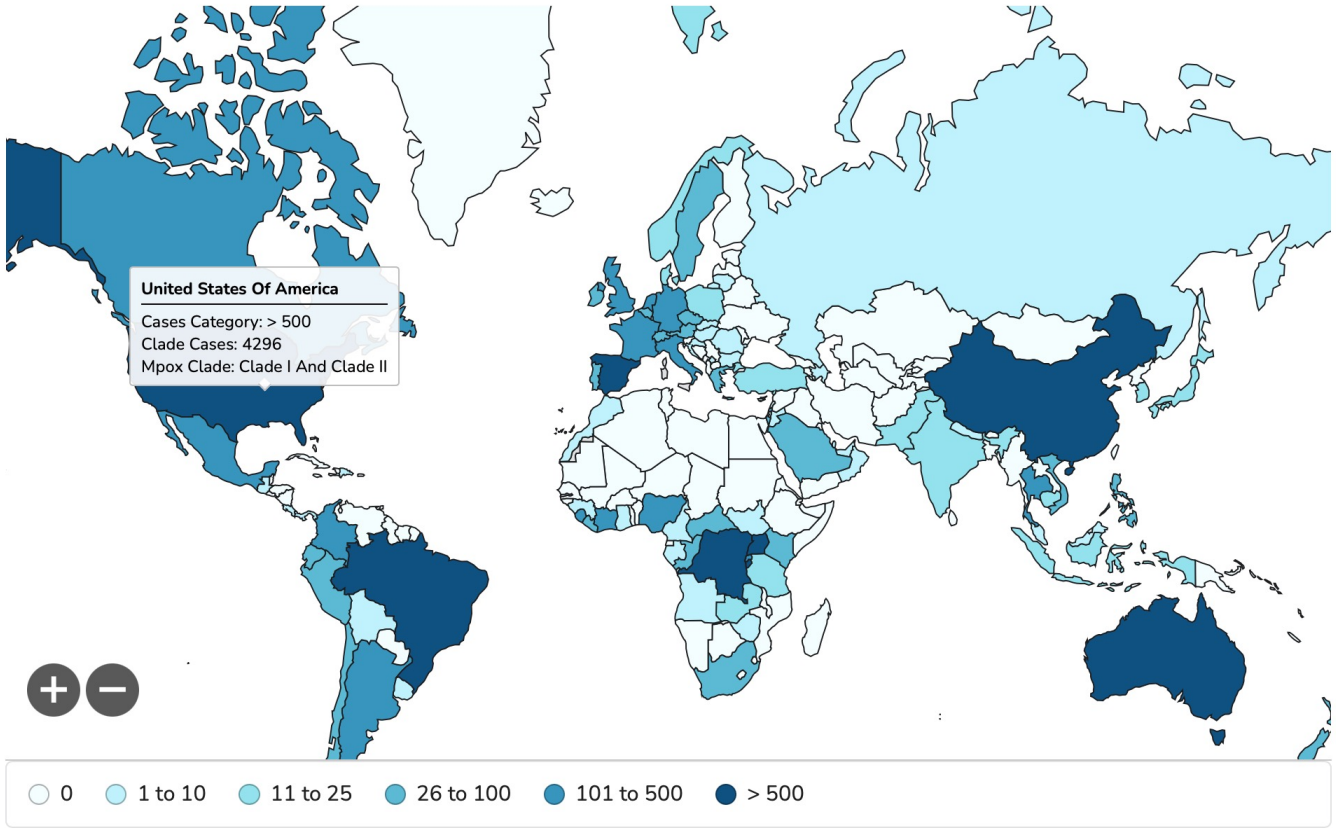
A laboratory nurse, with samples taken from a patient with a suspected case of mpox near Goma, Democratic Republic of Congo. Arlette Bashizi/Reuters

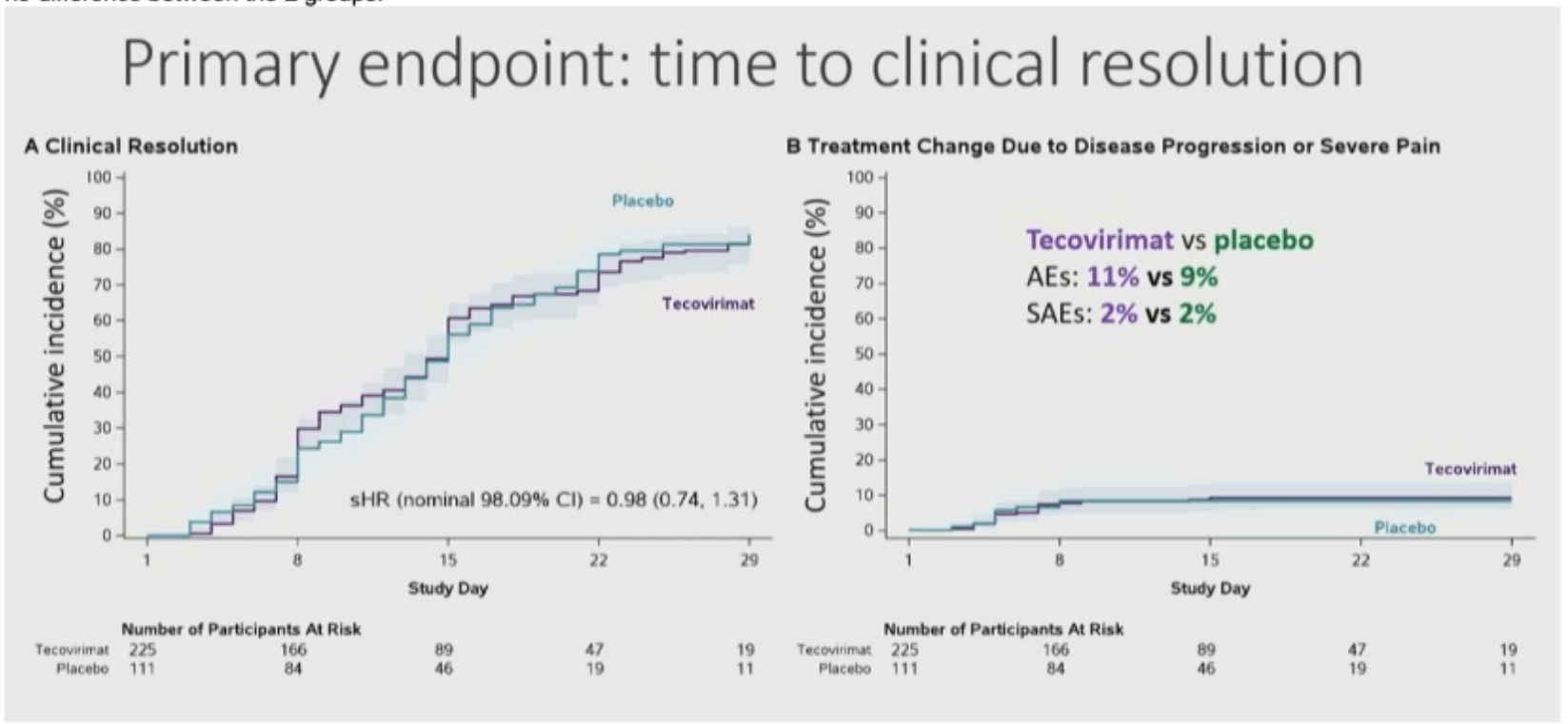
U.S. Cases	U.S. Deaths	Global Cases
Total Cases	Total Deaths	Total Cases
32,063	58	99,518



MPOX

- ACTG A5418
  - RCT of tecovirimat for mpox clade II
  - Primary outcome: time to lesion resolution

no difference between the 2 groups.



Wilkin T, et al

MPOX

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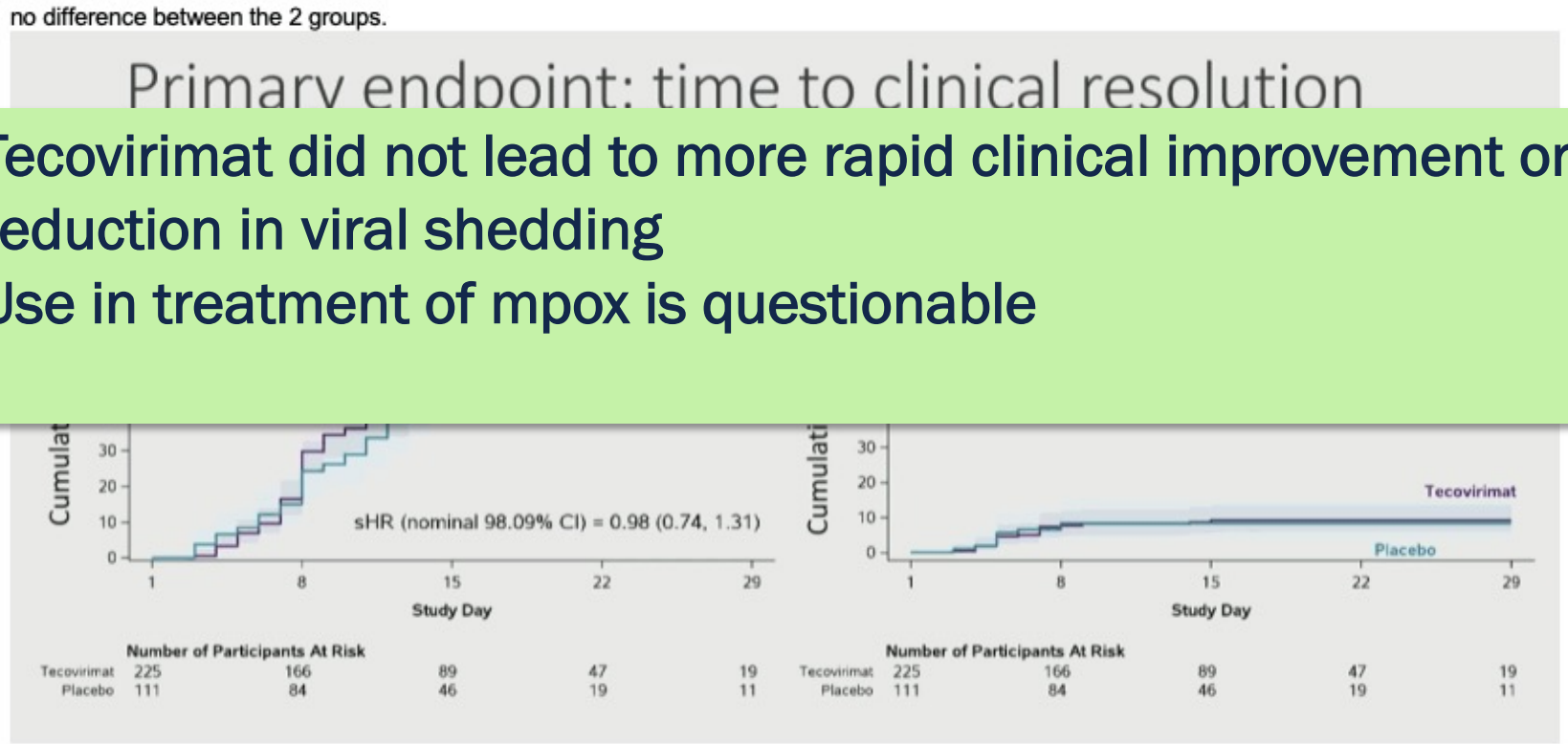
  - Primary outcome: time to lesion resolution

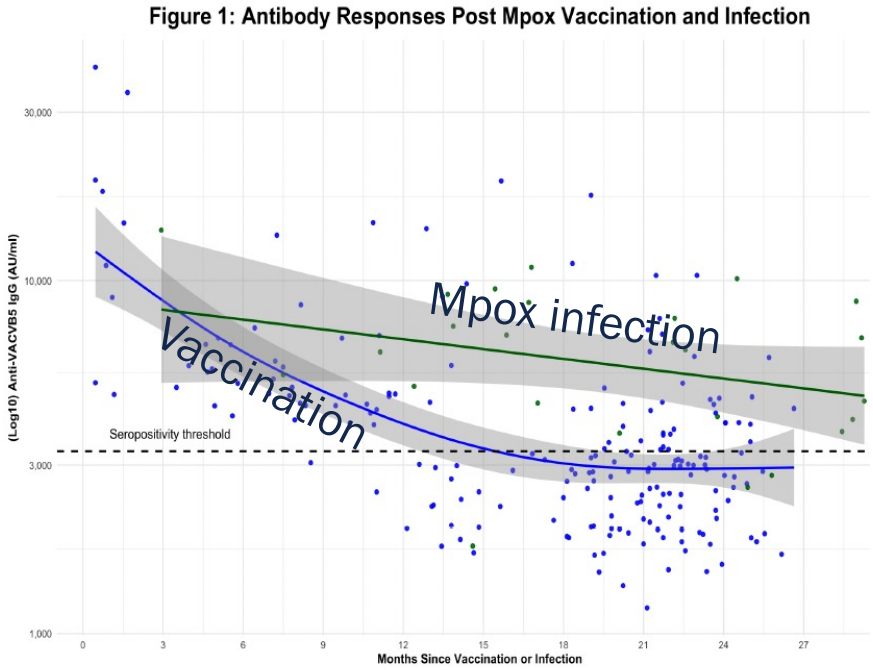


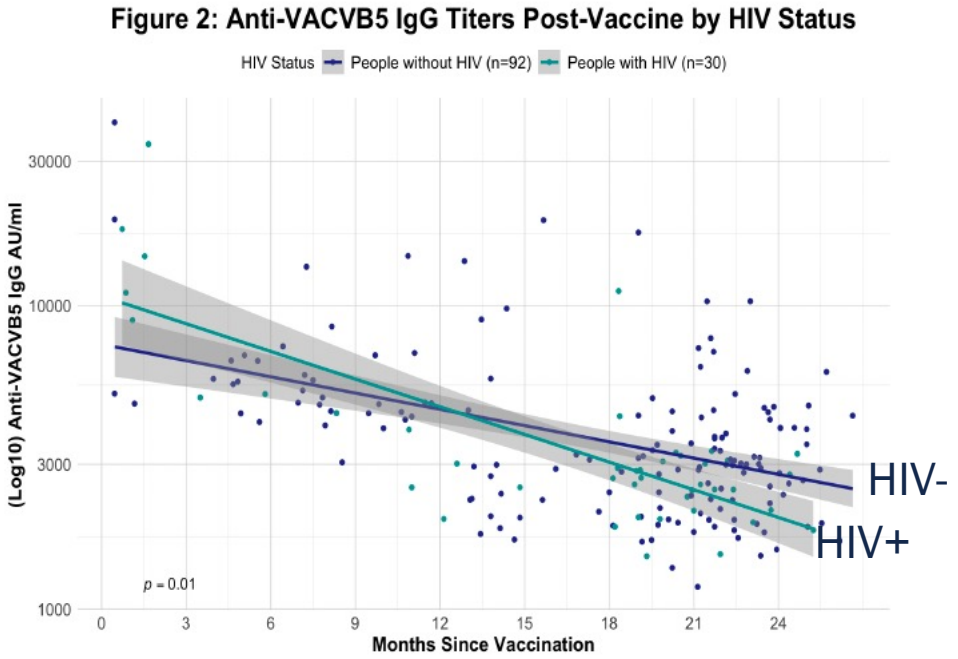
- Tecovirimat did not lead to more rapid clinical improvement or reduction in viral shedding
- Use in treatment of mpox is questionable

Wilkin T, et al

MPOX

- JYNNEOS smallpox vaccine used to prevent mpox
  - Concerns regarding duration of protection
  - Whether PWH have less of a response to the vaccine
- All Ireland Infectious Diseases Cohort Study:
  - 122 vaccinated people
  - 13 people who had mpox (no prior vaccination)



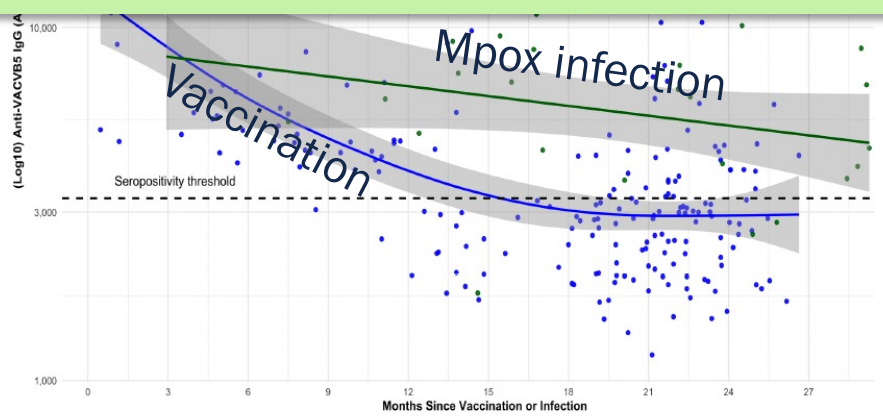


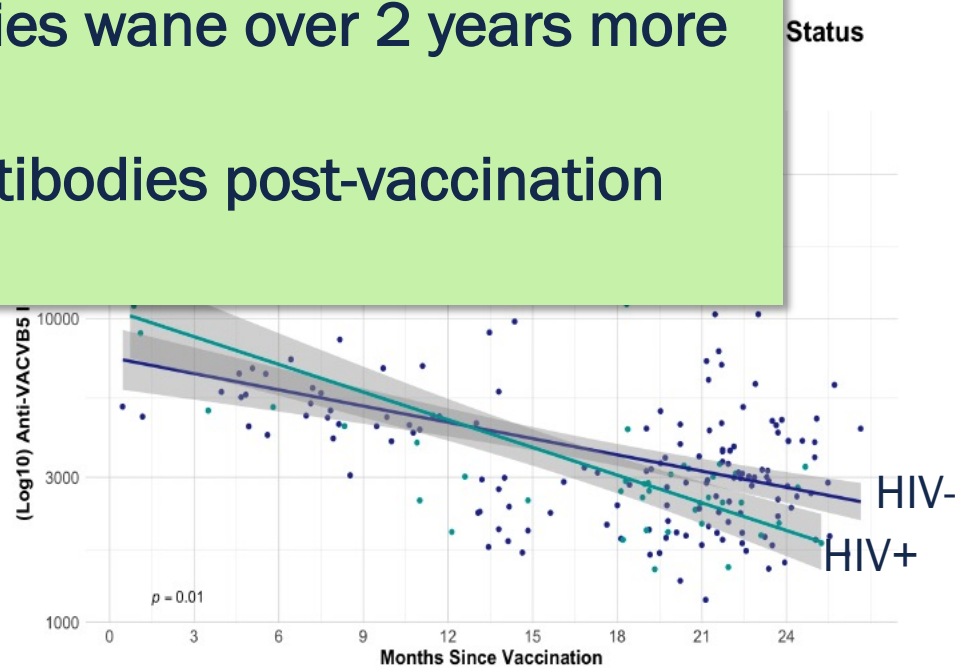
Byrne J, et al

MPOX

- JYNNEOS smallpox vaccine used to prevent mpox and has been found to be protective and attenuate disease when breakthrough occurs
  - Concerns regarding duration of protection
  - Whether PWH have less of a response to the vaccine
- All Ireland Infectious Diseases Cohort Study:
  - 122 vaccinated people
  - 13 peop

- **After JYNNEOS vaccination antibodies wane over 2 years more quickly compared to infection**
- **PWH have more rapid decline in antibodies post-vaccination**





Byrne J, et al