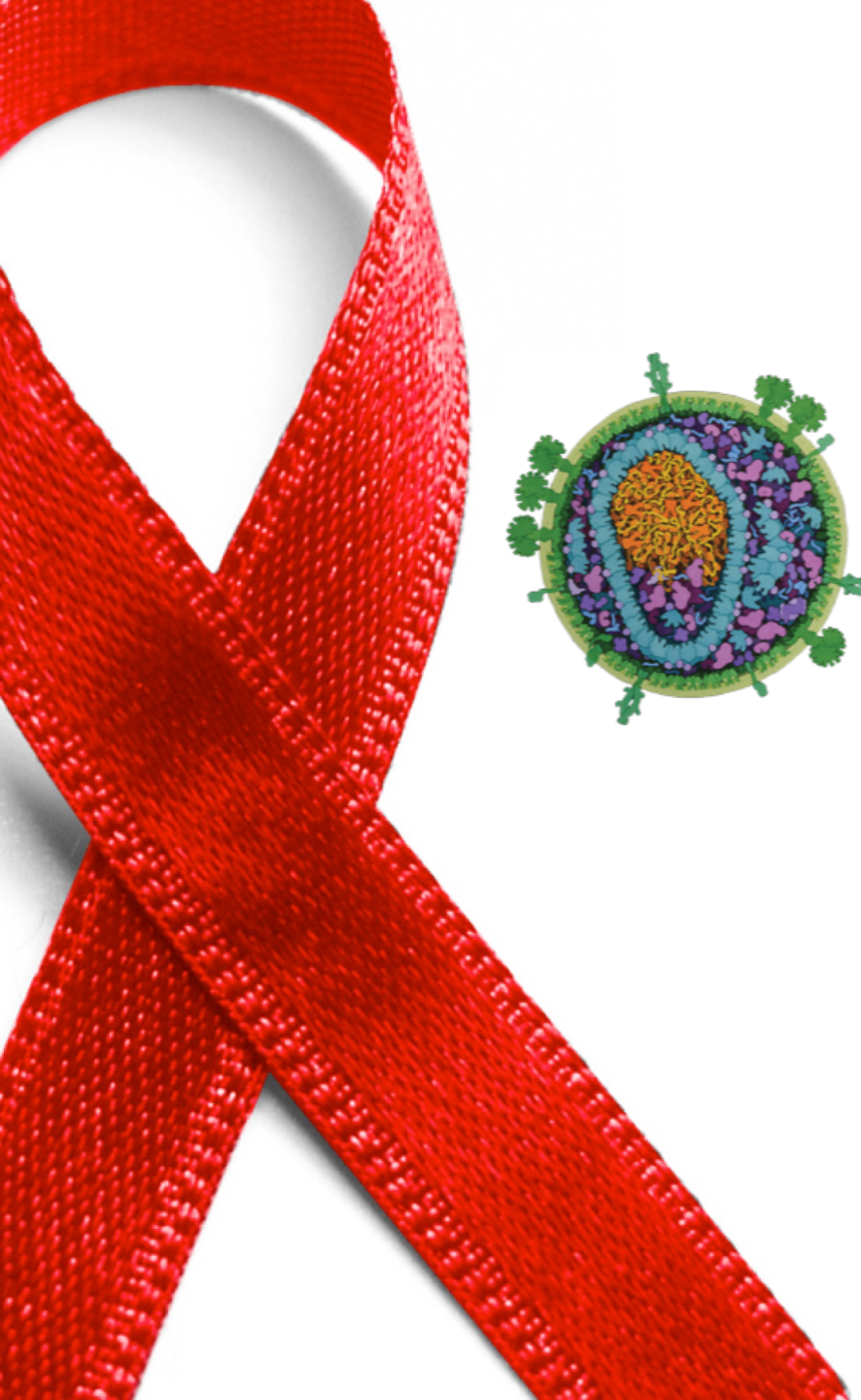


UNC
INSTITUTE FOR GLOBAL HEALTH
& INFECTIOUS DISEASES

CROI 2024
Conference on Retroviruses
and Opportunistic Infections

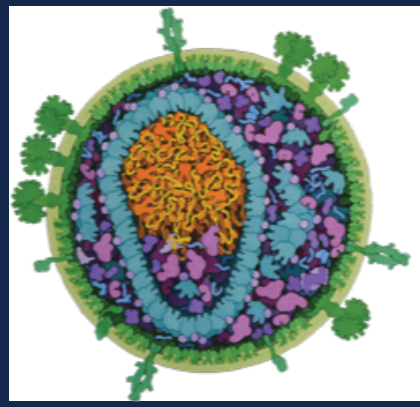
A NATAP UPDATE

David Alain Wohl, MD
Professor of Medicine
Co-PI, Infectious Diseases Clinical Trials Unit
Institute of Global Health and Infectious Diseases
The University of North Carolina at Chapel Hill

CROI 2024: What Matters Most

UNC SCHOOL OF MEDICINE

- Pipeline HIV Therapies
  - ISL + LEN weekly oral ART
  - MK8527
  - bnAbs
    - VRC07 – A5357
    - Len + bnAbs
    - CAB/RPV ultra long acting
    - N6LS – BANNER
  - Other early-stage agents
    - GS9770
    - GS1720
    - Q6M BIC IM
- Current HIV Therapies
  - LATTITUDE Trial (A5359)
  - CARES Trial
  - Real-er world use of LA-ART
  - Creative combos
    - LEN + BIC
    - LEN + CAB
- Comorbidities/Clinical Events
  - Trends
    - Mortality
    - Cardiovascular disease
  - REPRIEVE updates
    - Number needed to treat
    - Relative benefits
    - AHA Calculator performance
    - Statin tolerability
  - Weight gain on ART
  - Semaglutide
    - Weight
    - Liver fat
    - Effect on lean mass
- Co-Infections
  - HBV
    - Bee-HIVe Trial (A5379): Heplisav vs Engerix in prior non-responders to HBV vaccination
    - Reactivation of HBV with switch off of TFV
  - More DoxyPEP data
- Prevention
  - Insurance coverage and PrEP use
  - LA-PrEP in real-er world
    - Trio
    - Opera
  - Preferences among key population
  - Where is my CAB?



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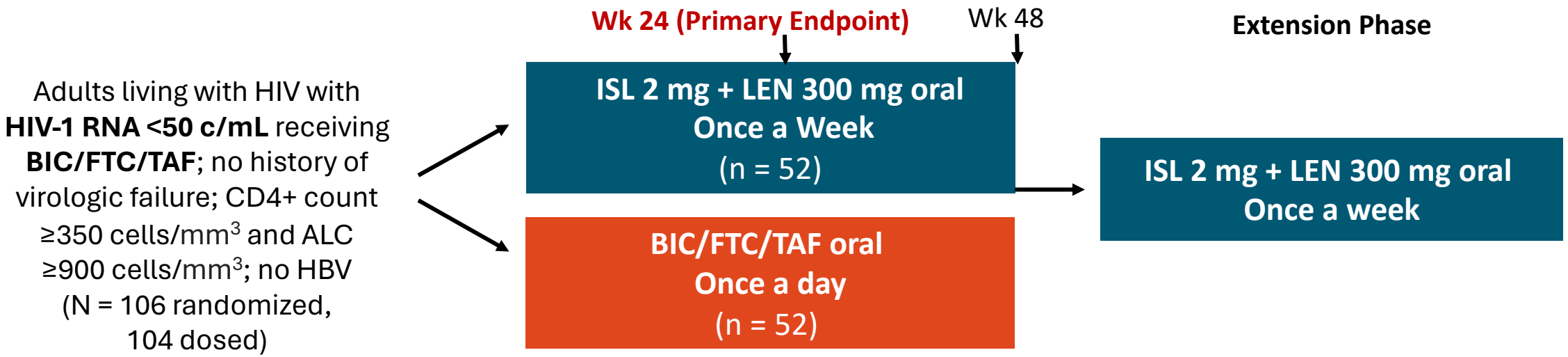
Pipeline ART

Phase II Trial of Oral Weekly Islatravir (ISL) + Lenacapavir (LEN):

- Open-label, active-controlled phase II trial

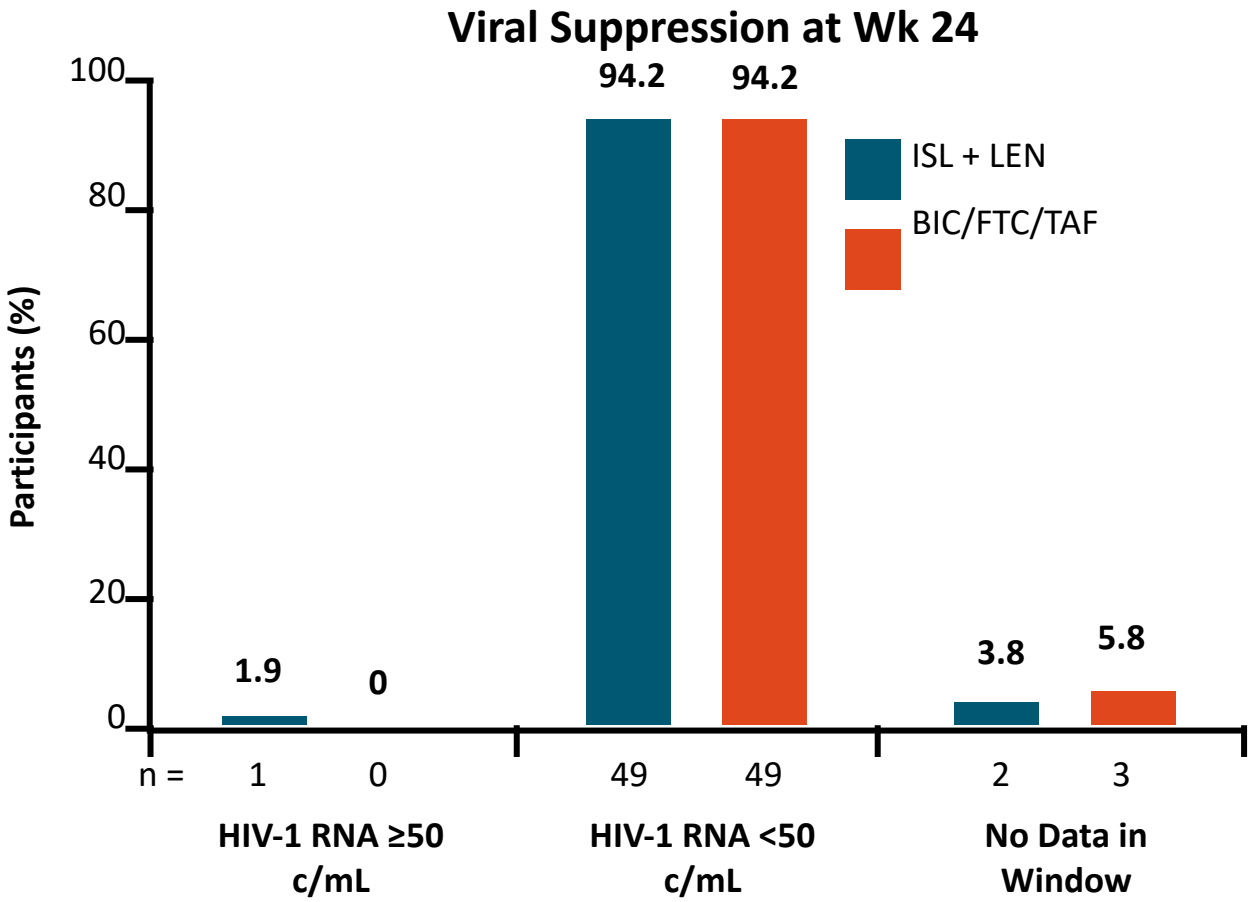


Primary endpoint: proportion of participants with HIV-1 RNA ≥50 c/mL at **Week 24** by FDA Snapshot algorithm

Colson. CROI 2024. Abstr 208.

Phase II Trial of Oral Weekly ISL + LEN: Efficacy at Wk 24

- **High rates of virologic suppression maintained in both treatment arms**



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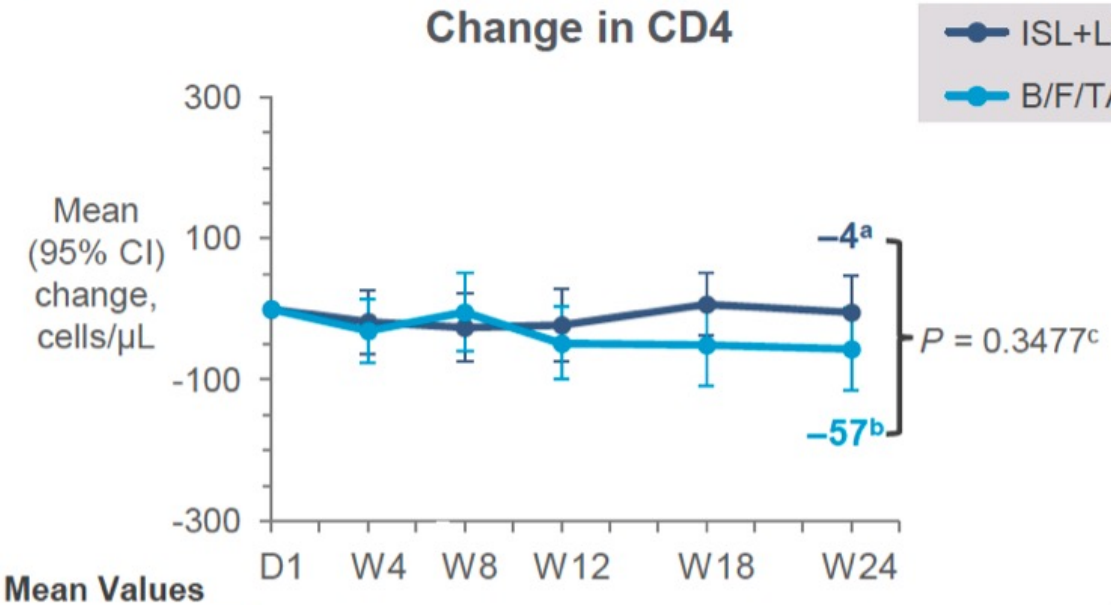
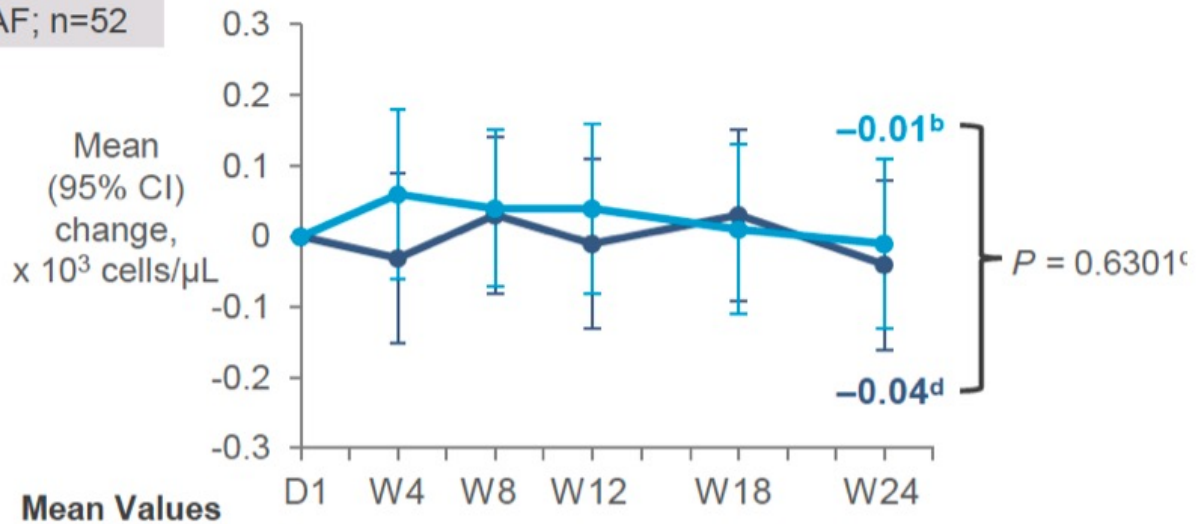
CD4 and Absolute Lymphocyte Count Changes Through Week 24

Change in CD4



Mean Values	D1	W4	W8	W12	W18	W24
ISL + LEN	755	738	729	732	766	755
B/F/TAF	818	787	813	758	767	761

Change in Absolute Lymphocyte Counts



Mean Values	D1	W4	W8	W12	W18	W24
ISL + LEN	1.94	1.93	1.97	1.94	1.98	1.92
B/F/TAF	1.95	1.97	1.99	1.99	1.97	1.96

- No between-group differences in CD4 and absolute lymphocyte count changes at Week 24
- No participants discontinued due to CD4 or absolute lymphocyte count decreases

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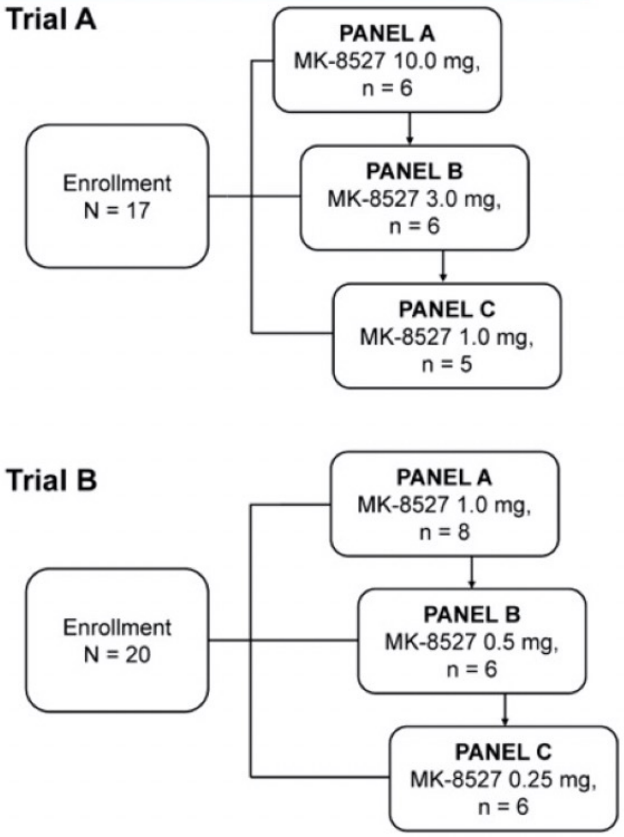
MK-8527 – New NRTTI

MK-8527 is a novel oral nucleoside reverse transcriptase translocation inhibitor (NRTTI) that is phosphorylated intracellularly to its active triphosphate (TP) form

Study design for trial A and trial B

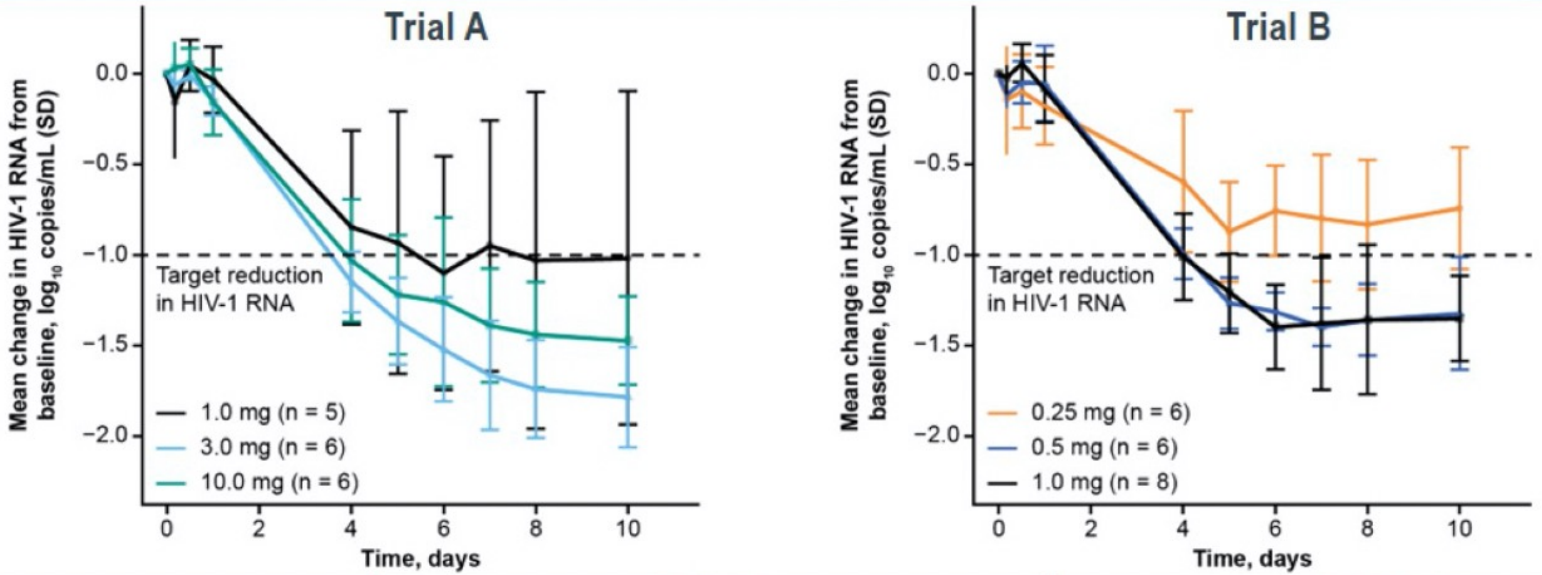
- In these open-label, single-dose, multi-panel studies, participants received single oral doses of MK-8527 (1.0, 3.0, or 10.0 mg; fasted) for trial A (NCT03615183; single site) and MK-8527 (0.25, 0.5, or 1.0 mg; fasted) for trial B (NCT05494736; multiple sites)
- **Key inclusion criteria:**
  - Adults (18-60 years of age) with HIV-1
  - Plasma HIV-1 RNA ≥5000 copies/mL and CD4+ T-cell count ≥200 cells/mm^3 at screening
  - Treatment naive
  - No virologic resistance to nucleos(t)ide reverse transcriptase inhibitors (NRTIs)
- **Key exclusion criteria:**
  - Creatinine clearance ≤90 mL/min (trial A: Cockcroft-Gault equation) or ≤80 mL/min (trial B: CKD-EPI equation)
  - Positivity for hepatitis B virus (HBV) surface antigen, history of chronic hepatitis C virus (HCV) infection



Carstens. CROI 2024

MK-8527 – New NRTTI

Change in HIV-1 RNA following single doses of MK-8527



	Trial A			Trial B		
Dose	**Panel A** 10.0 mg, n = 6	**Panel B** 3.0 mg, n = 6	**Panel C** 1.0 mg, n = 5	**Panel A** 1.0 mg, n = 8	**Panel B** 0.5 mg, n = 6	**Panel C** 0.25 mg, n = 6
Change in plasma HIV-1 RNA at Day 7, mean (range), log_{10} copies/mL	−1.39 (−0.87 to −1.67)	−1.66 (−1.23 to −2.02)	−0.95 (0.03 to −1.60)	−1.38 (−0.98 to −2.10)	−1.40 (−1.24 to −1.54)	−0.80 (−0.37 to −1.21)

- Combined trial results for 1-mg dose show a mean reduction in plasma HIV-1 RNA at 1.21 log_{10} copies/mL at Day 7 postdose
- Following single doses of MK-8527 (0.5-10.0 mg), the mean decrease in HIV-1 RNA at Day 7 postdose was ≥1.0 log_{10} copies/mL

Carstens. CROI 2024

bnAbs: VRC07-523LS + CAB

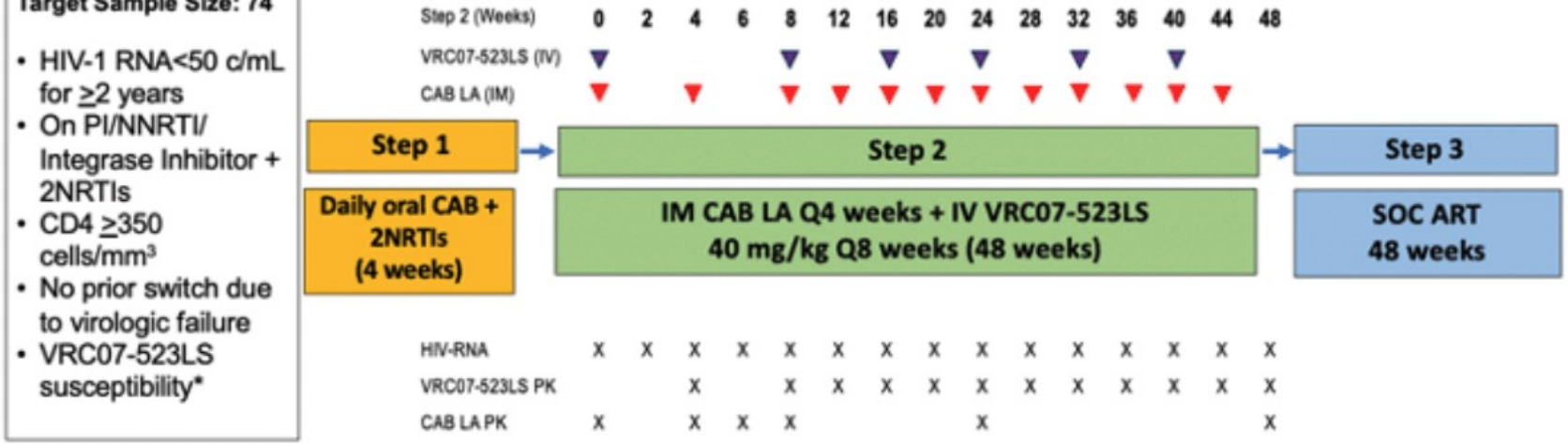
VRC07-523LS binds CD4 with 38-day half-life.

A5357 is a phase 2 study of VRC07 + CAB

Study Schema

Target Sample Size: 74

- HIV-1 RNA<50 c/mL for ≥2 years
- On PI/NNRTI/ Integrase Inhibitor + 2NRTIs
- CD4 ≥350 cells/mm^3
- No prior switch due to virologic failure
- VRC07-523LS susceptibility*



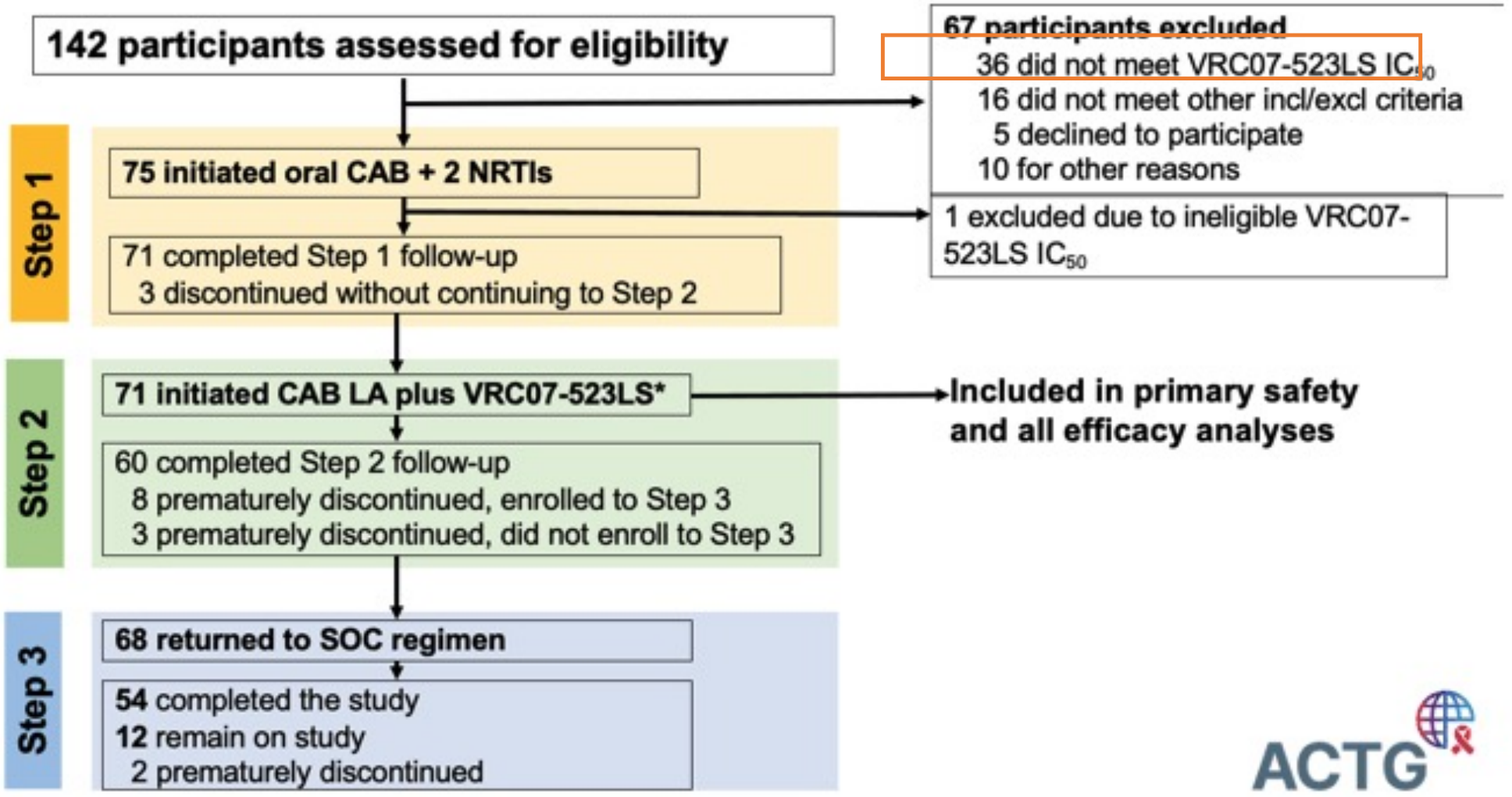
*Half-maximal inhibitory concentration (IC_{50}) ≤ 0.25 µg/mL and a maximum percent inhibition (MPI) > 98% on the Monogram PhenoSense mAb Assay (Labcorp-Monogram Biosciences) using PBMCs collected at screening.

▼ VRC07-523LS Infusion
▼ CAB LA Injection

ACTG

Taiwo. CROI 2024

bnAbs: VRC07-523LS + CAB



ACTG

Taiwo. CROI 2024

bnAbs: VRC07-523LS + CAB

Primary Outcome 1: Safety (Preliminary)

Outcome Measure: AE of Grade 3 or 4, or of any grade if it led to treatment discontinuation, judged as at least possibly related to VRC07-523LS or CAB LA.

- 16.9% (12/71, 95% CI [9.9%, 27.3%]) experienced the outcome measure.

Any AE leading to treatment discontinuation (N = 1, 1.4%, 1 event)

- **Grade 1** Infusion related reaction (non-productive cough, "head pressure", feeling flushed/warm in the head and right forearm) starting and resolving on the day of the 3rd infusion of VRC07-523LS

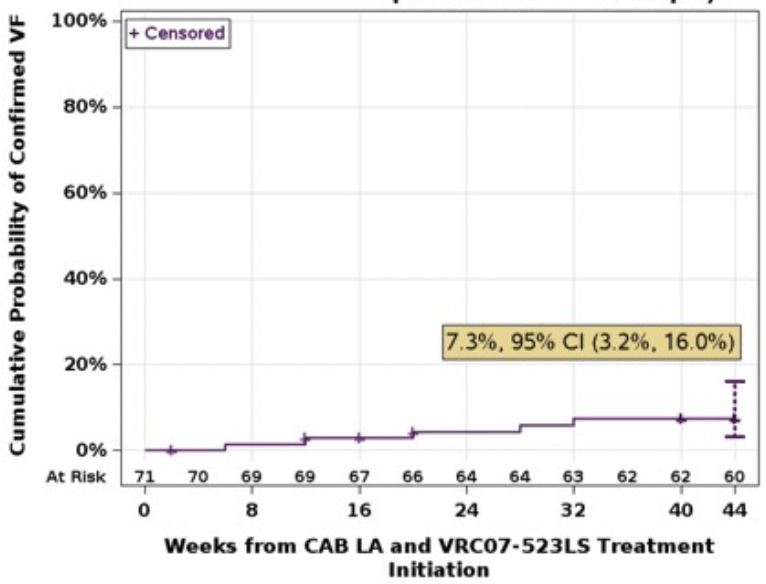
Grade 3 Events (N = 11, 16 events)

- 12 events at least possibly related to VRC07-523LS
  - Chills (x4), feeling unwell, fatigue (x2), generalized aching, vasospasm, hypotension, myalgia, headache
- 2 events at least possibly related to CAB LA
  - Muscle pain, decreased CrCl
- 2 events at least possibly related to both VRC07-523LS and CAB LA
  - Increased ALT (x2, one participant)

Grade 4 Events – None

Primary Outcome 2: Virologic Failure

Cumulative Probability of Confirmed Virologic Failure (confirmed viral load ≥200 copies/mL at or prior to week 44 of Step 2).



5 Virologic Failure Events

- 2 resuppressed on LA regimen
- 1 had low-level viremia after switching to oral SOC
- 2 within 14 days of Mpox vaccine

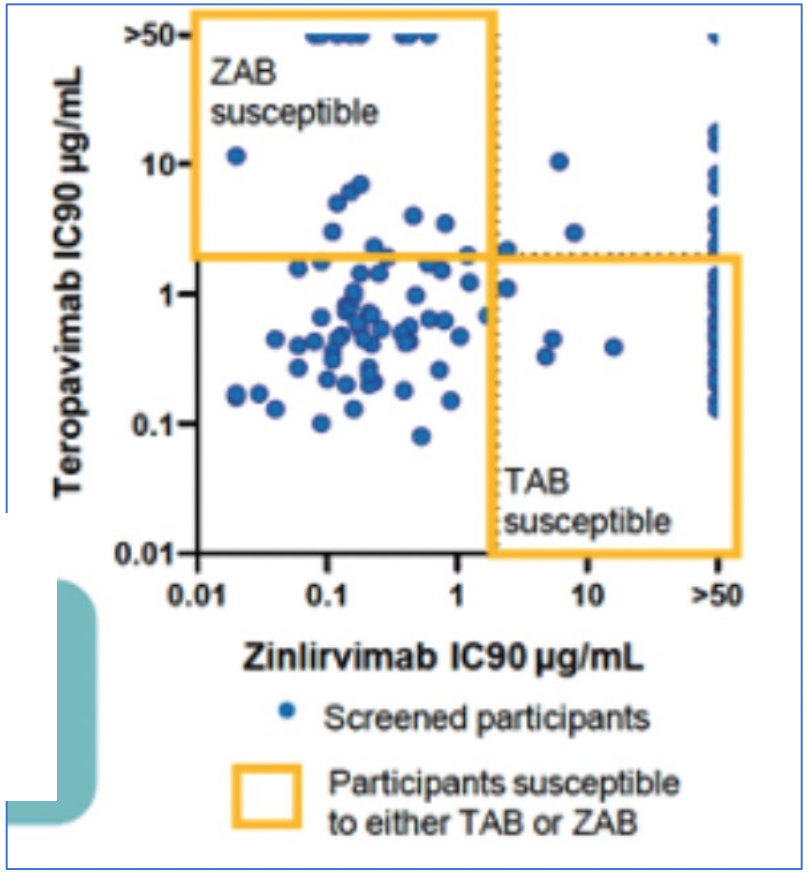
ACTG

- Two of the five participants who met virologic failure criteria resuppressed on the investigational LA regimen; one other participant continued to have low-level viremia after switching to oral SOC.
- The R263K integrase mutation emerged in one participant with a relatively high baseline VRC07-523LS IC50 and possible functional CAB LA monotherapy.

Taiwo. CROI 2024

bnAbs: Teropavimab or Zinlirvimab + LEN

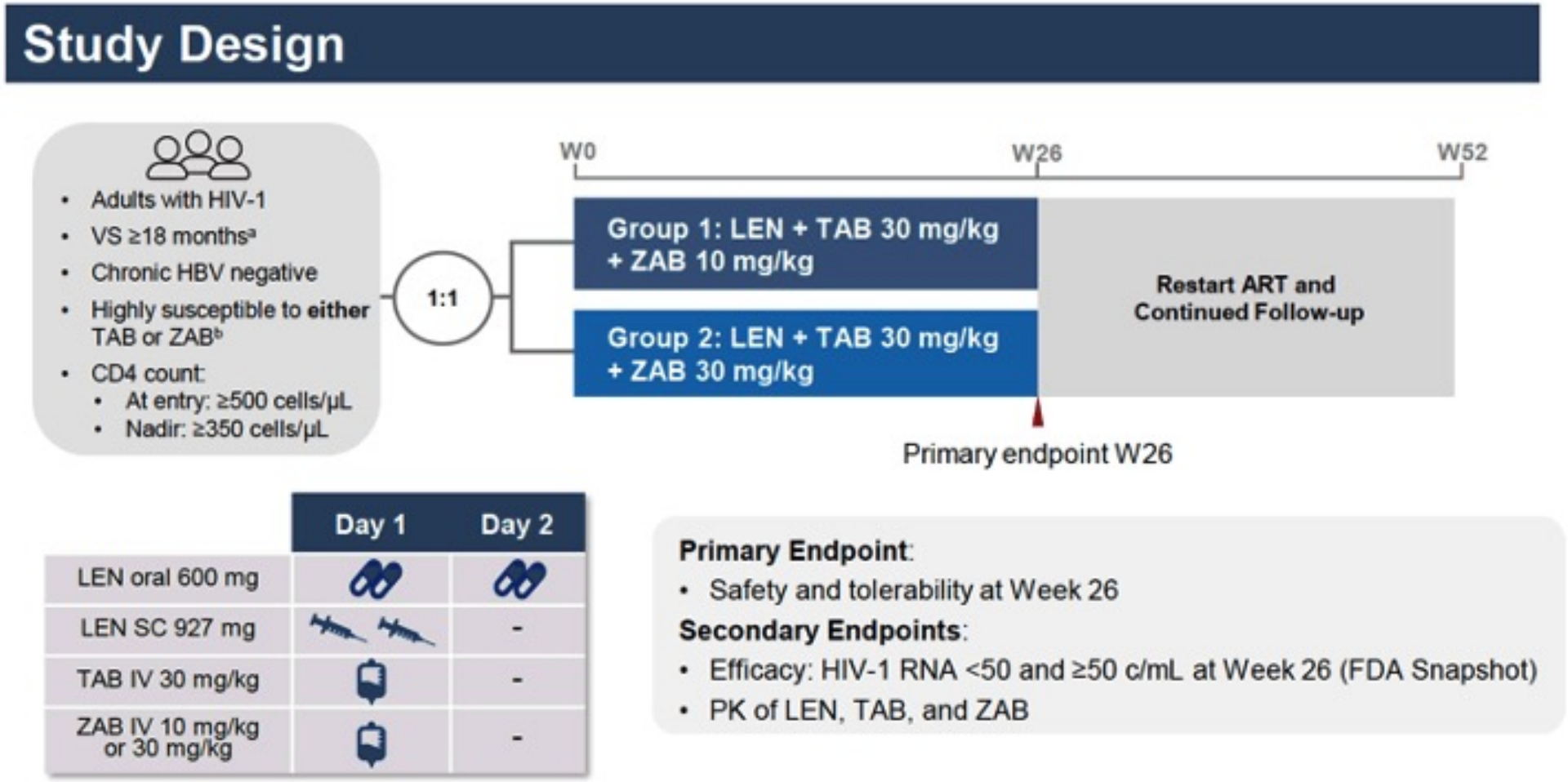
- Teropavimab (TAB) and zinlirvimab (ZAB) are broadly neutralizing antibodies (bNAbs) against the CD4-binding site of gp120 and a non-overlapping epitope on the V3 glycan of HIV-1 Env, respectively[1]
- Approximately 50% of clade B viruses are highly susceptible to both TAB and ZAB with a 90% inhibitory concentration (IC90) ≤2 µg/mL, while over 90% are highly susceptible to either TAB or ZAB[2]
- TAB and ZAB have extended half-lives that allow for dosi every 6 months[1]
- Lenacapavir (LEN) is a first-in-class, small molecule caps inhibitor with high potency and a long half-life that can be administered subcutaneously every 6 months and is indicated in heavily treatment-experienced people with HIV-1 (PWH)[3]



1. Gautam R, et al. *Nat Med* 2016; 24(5): 610-6. 2. Selzer L, et al. Presented at CROI 2023. Poster 580. 3. Sunlenca® Prescribing Information, available at https://www.gilead.com/-/media/files/pdfs/medicines/hiv/sunlenca/sunlenca_pi.pdf (accessed February 2024). 4. Estimated coverage given predicted IC90 closely resembles coverage given IC80 shown here. Data from CATNAP CombiNAber (Yoon H, et al. *Nucleic Acid Res.* 2015;43:W213-9, Wagh K, et al. *PLoS Pathog.* 2016 Mar30;12(3)) using 479 Clade B viruses.

Eron. CROI 2024

bnAbs: Teropavimab or Zinlirvimab + LEN



Eron. CROI 2024

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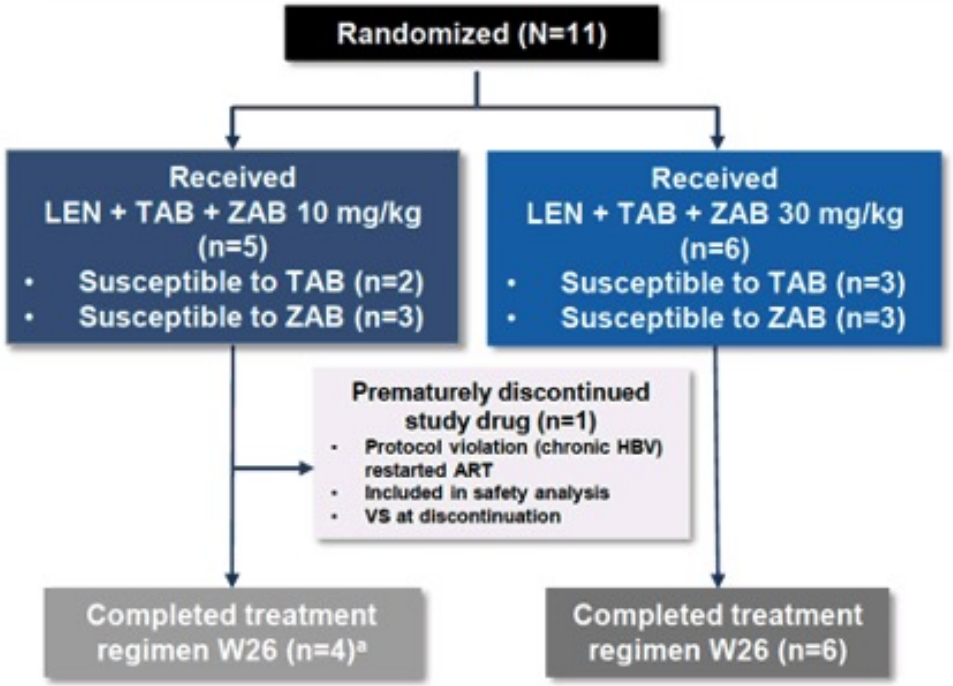


Viral Suppression at Week 26

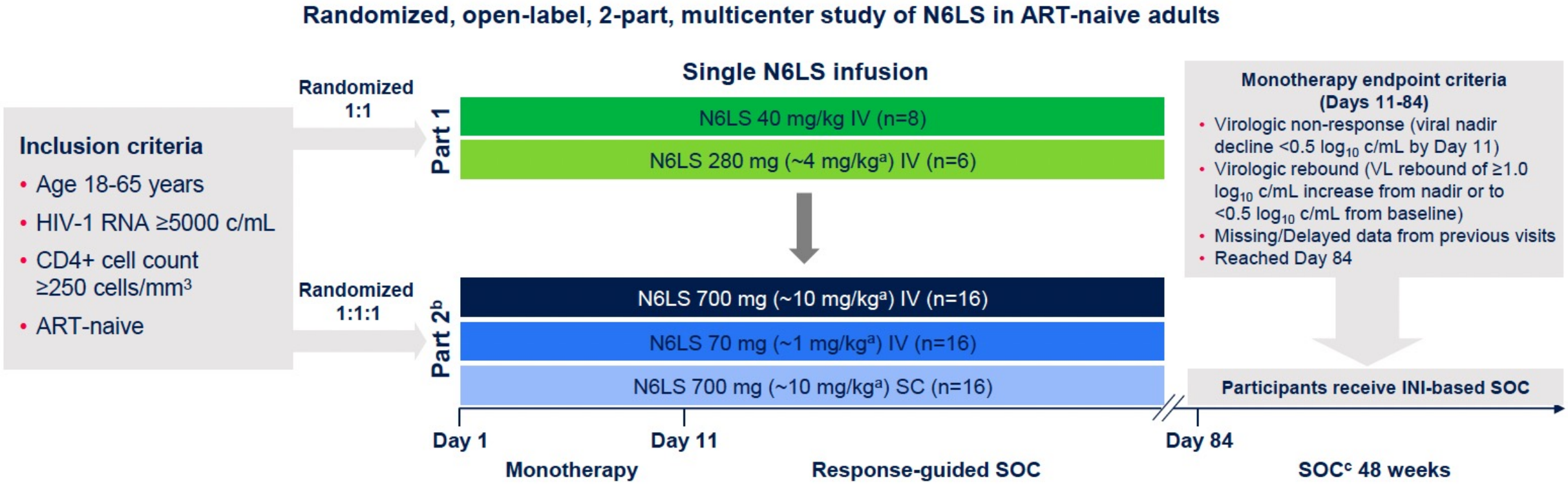
	LEN + TAB + ZAB 10 mg/kg (n=4)[a]	LEN + TAB + ZAB 30 mg/kg (n=6)	Total (N=10)
HIV-1 RNA ≥50 copies/mL, **n** (%; [95% CI])	**2** (50; [7, 93])	**0** (0; [0, 46])	**2** (20; [3, 56])
HIV-1 RNA <50 copies/mL, **n** (%; [95% CI])	**2** (50; [7, 93])	**6** (100; [54, 100])	**8** (80; [44, 98])

- Eight out of 10 participants remained virologically suppressed with HIV-1 RNA <50 copies/mL 6 months after dosing
- All participants in the higher dose group (n=6; ZAB 30 mg/kg) remained suppressed at Week 26
- 5 participants had treatment related AEs – all were Grade 1 injection site reactions related to LEN administration
- No infusion-related reactions occurred with bNAb administration
- There were no Grade ≥3 treatment-emergent laboratory abnormalities

- One dose of the long-acting combination of LEN + TAB + ZAB maintained virologic suppression for 6 months in 8 out of 10 participants with HIV-1 highly susceptible to either TAB or ZAB, but not both
  - Two participants in the low dose ZAB (10 mg/kg) group had HIV-1 RNA between 50 – 100 copies/mL in the Week 26 snapshot window; no treatment-emergent resistance was detected
  - Other than a lower ZAB dose, no risk factors for virologic rebound were observed in participants with virologic rebound
  - All 6 participants in the higher dose group remained suppressed for 6 months after dosing

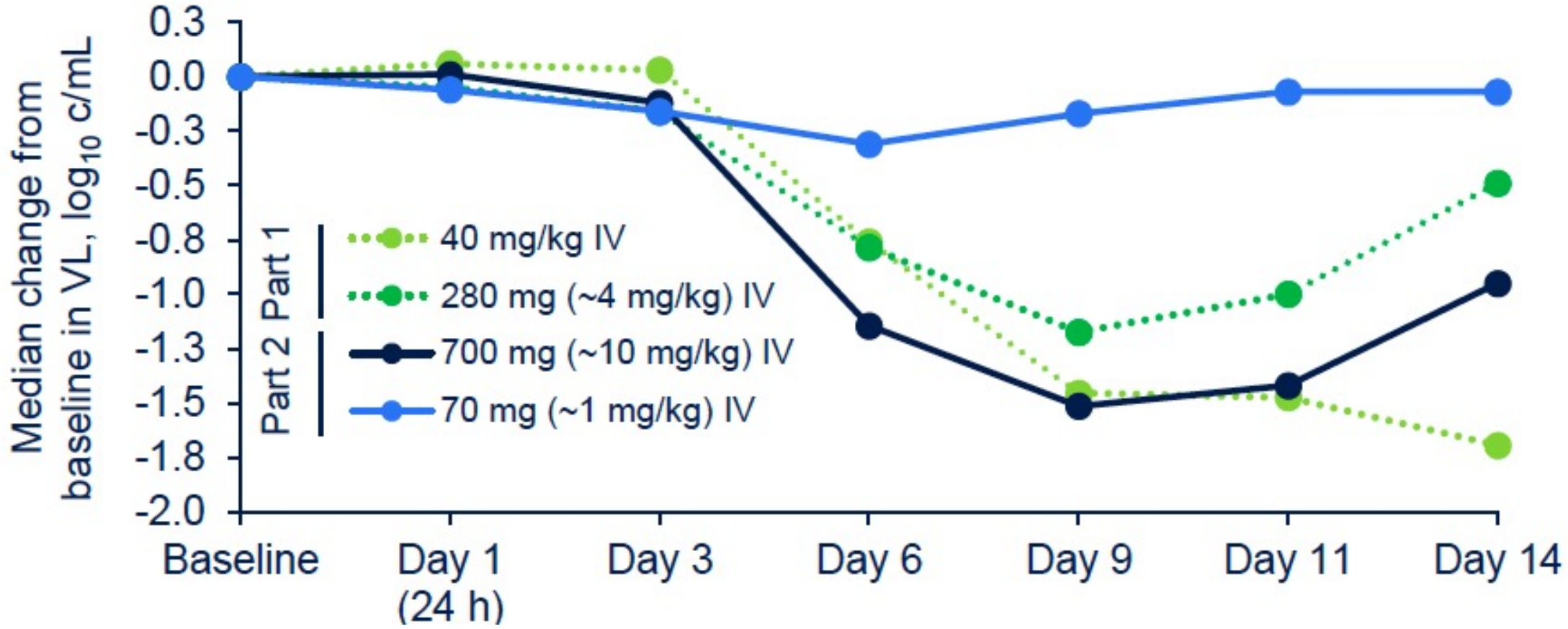
Eron. CROI 2024

bnAbs: N6LS



- N6LS antibody susceptibility screening was not performed; instead, N6LS susceptibility was determined retrospectively using the PhenoSense® monoclonal antibody assay (Monogram Biosciences, South San Francisco, CA)

bnAbs: N6LS



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Ultra-Long-Acting Cabotegravir IM

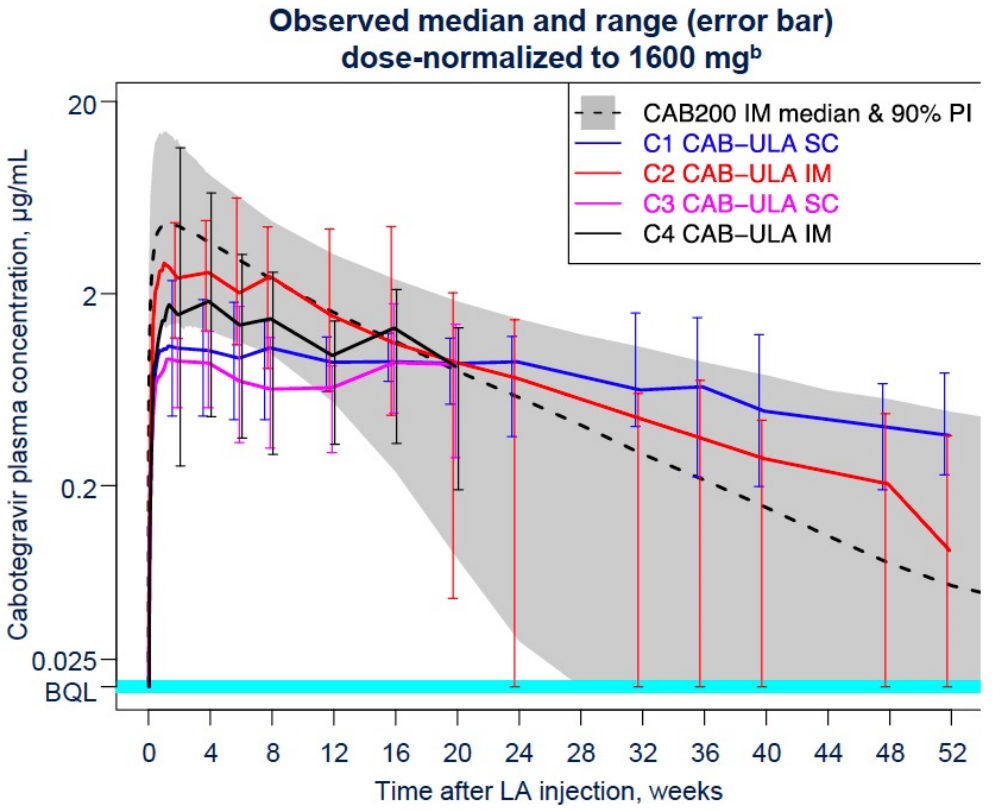
Formulation of cabotegravir that is more slowly absorbed

Part C: CAB-ULA

Parameter, geometric mean (%CVb)	SC C1 800 mg (2 mL) (n=8)	SC C3 1200 mg (3 mL) (n=8)	IM C2 800 mg (2 mL) (n=8)	IM C4 1200 mg (3 mL) (n=8)
Cmax, µg/mL	0.7 (35.5)	0.8 (39.0)	1.8 (53.5)	1.8 (148)
tmax, hours	570 (158)	349 (147)	298 (136)	383 (107)

CAB-ULA has slower absorption and longer $t_{1/2}$ than CAB200 IM

- PK profiles were flatter than CAB200 IM
- CAB-ULA Cmax was lower with SC than IM; both were lower than CAB200 IM[1]
- tmax was longer than CAB200 IM[1]
- **CAB-ULA $t_{1/2}$ for SC and IM was predicted to be >6x and >2x the $t_{1/2}$ of CAB200 IM, respectively[1,a]**



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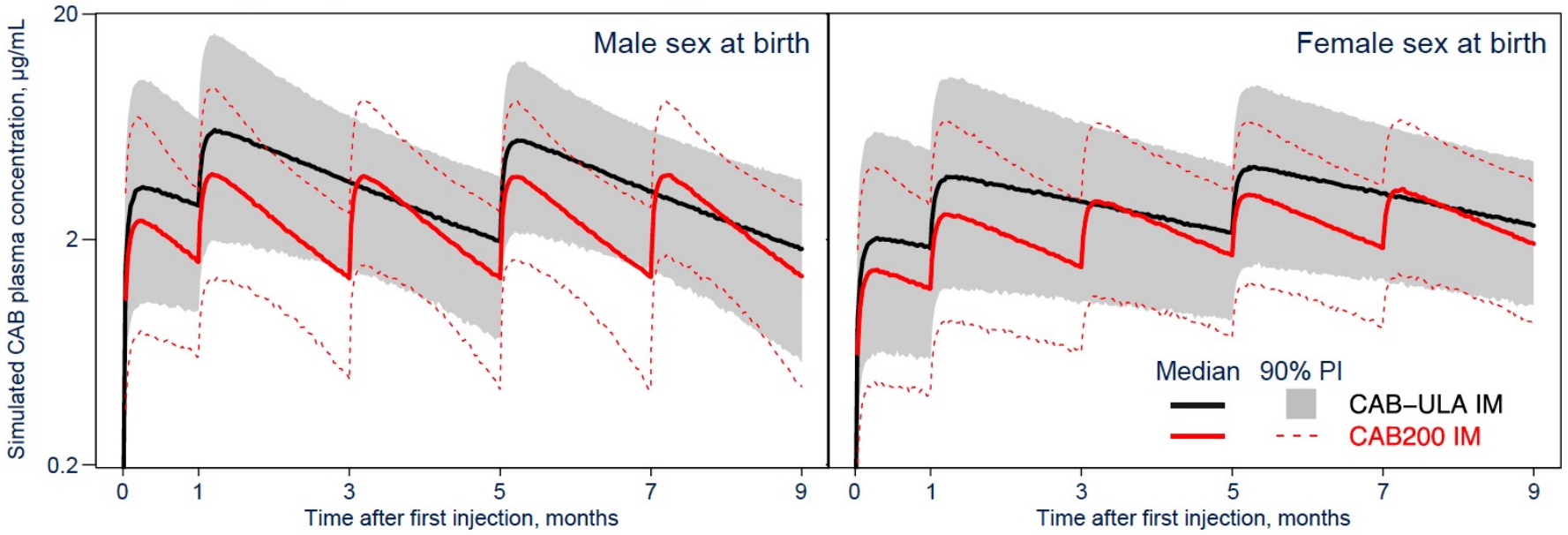
Ultra-Long-Acting Cabotegravir IM

Pharmacokinetic Simulations of CAB-ULA Q4M Dosing

- PK simulations[a] predict a CAB-ULA IM dose interval of ≥4 months achieves higher exposure than approved CAB200 IM at intervals of 2 months
- CAB-ULA IM $t_{1/2}$ was predicted to be >2x the $t_{1/2}$ of CAB200 IM



CAB, cabotegravir; IM, intramuscular; PI, prediction interval; PK, pharmacokinetics; Q4M, every 4 months; SC, subcutaneous; $t_{1/2}$, terminal half-life; ULA, ultra-long-acting. [a]1600-mg (3-mL) CAB-ULA per injection.

Data support every 4-month IM administration

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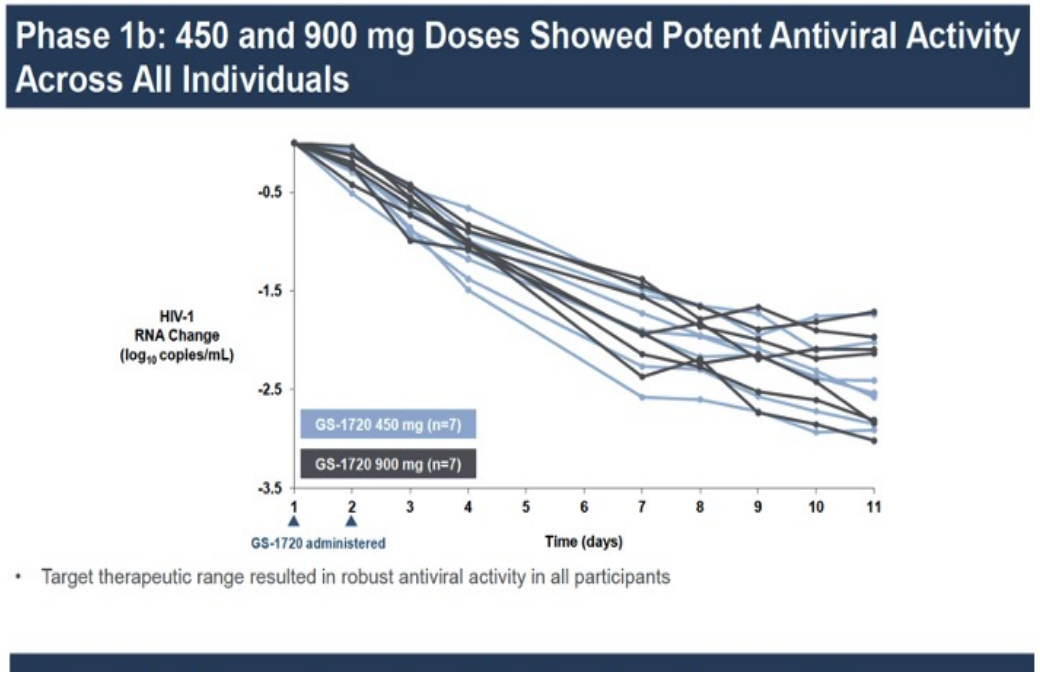
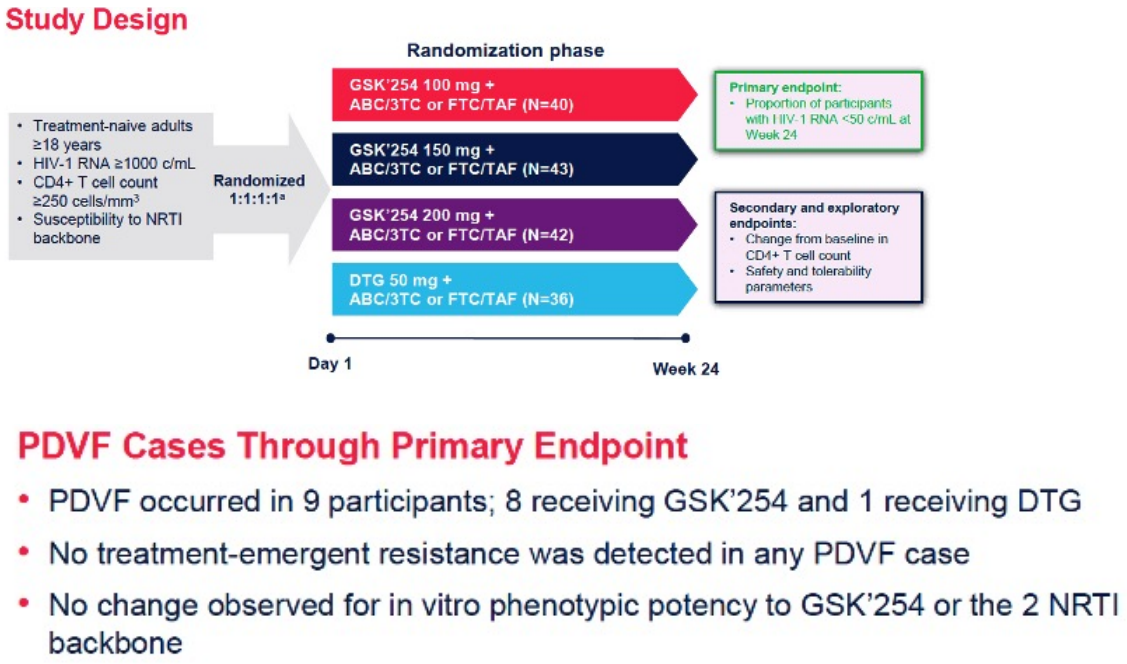
Other new ART in the pipeline

- GS-1720: Once weekly oral INSTI



- GSK'254: Oral Maturation Inhibitor
  - Active even vs virus with polymorphisms at gag active site



PDVF Cases Through Primary Endpoint

- PDVF occurred in 9 participants; 8 receiving GSK'254 and 1 receiving DTG
- No treatment-emergent resistance was detected in any PDVF case
- No change observed for in vitro phenotypic potency to GSK'254 or the 2 NRTI backbone

Fichtebaum. CROI 2024

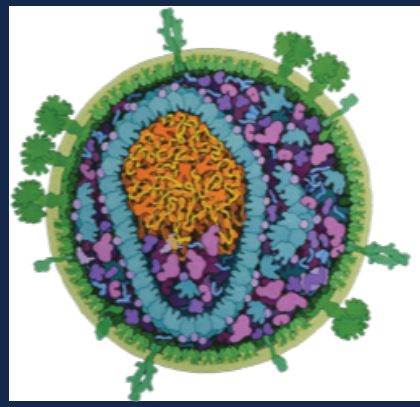
Jeffrey. CROI 2024

NEW HIV Drug & Therapy Pipeline at CROI

Isatravir+ Lenacapavir	Oral weekly	NRTTI+capsid	phase 2	new ART classes	Merck-Gilead
GS-1720	oral weekly	INSTi	phase 1a	potent	Gilead
GS-5894	Oral Once-Weekly	NNRTI	Preclinical	Favorable Resistance	Gilead
Bicetegravir +Lenacapavir	Daily oral	INSTi+capsid	phase 2	nuk-sparing	Gilead
MK-8527	LA prevention	NRTTI	phase 1	treatment, LA	Merck
LEN+bNAbs	LA treatment	capsid+2 bNAbs	phase 1b	new	Gilead
Cabotegravir	4-months LA	INSTi	HIV-nega.	extra LA	ViiV
N6LS	LA	bNAb	SC	potent, extra LA	ViiV
VH3739937	LA ?	Maturation inhibitor	early	new class, preclinical	ViiV
GSK-254	New	Maturation inhibitor	early	phase 1 HIV+	ViiV
GS-9770	new once daily	unboosted Protease inh.	early	Preclinical	Gilead
Trispecifuc bNAb SAR441236	new IV Treatment/prevention	3 bNAbs	early	single dose PK/safety/tolerability/low activity	ACTG
ABBV-382	new, 'viral control'	PD-1 inhibitor Anti-a4b7 Ab	early clinical		Abbvie

Why does this matter? New HIV Therapies

- HIV therapy is shifting away from daily oral medications
- Less frequent regimens provide options to fit individual **preference**
- **Novel mechanisms of action** reduce the significance of viral resistance to existing ARVs
- What to expect:
  - Islatravir likely next -> Weekly ART! More people will prefer this than many providers think.
  - bnAbs after?
    - Susceptibility and need for screening an issue
  - Longer lasting formulation of CAB/RPV will help



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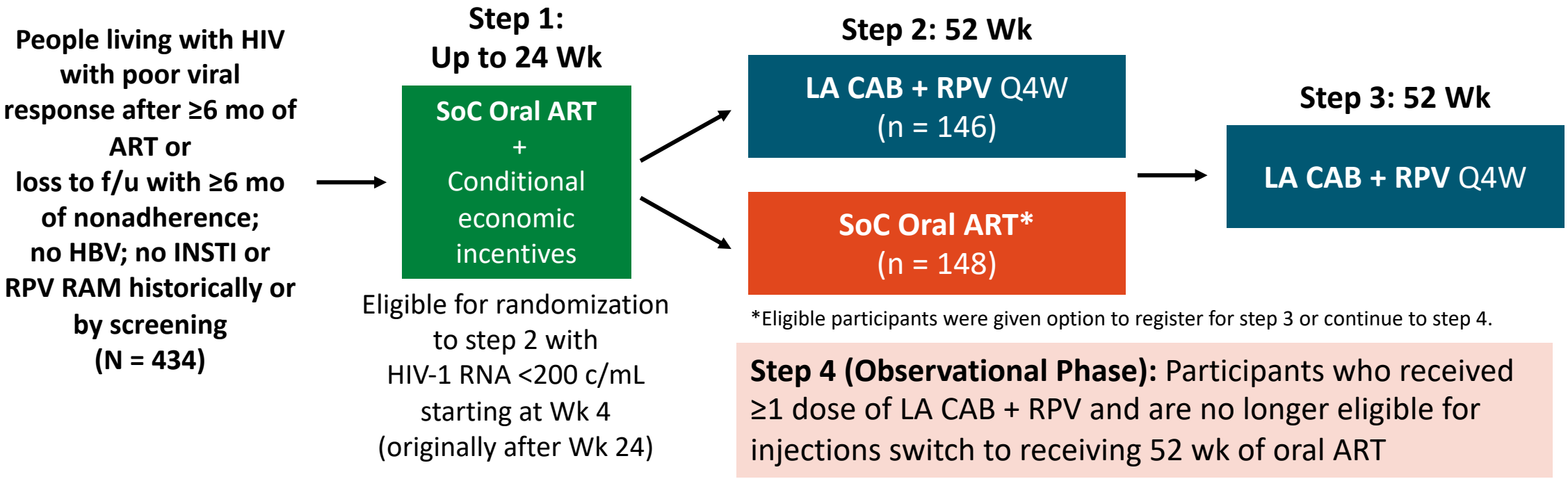
Current ART

ACTG A5359 LATITUDE: Study Design

- Prospective, randomized, open-label phase III trial in the United States



*Eligible participants were given option to register for step 3 or continue to step 4.

Step 4 (Observational Phase): Participants who received ≥1 dose of LA CAB + RPV and are no longer eligible for injections switch to receiving 52 wk of oral ART

- **Primary endpoint:** regimen failure defined as earliest confirmed virologic failure or discontinuation during step 2
- **Key secondary endpoints:** virologic failure, treatment-related failure, permanent treatment discontinuation

Rana. CROI 2024. Abstr 212.

ACTG A5359 LATITUDE: Baseline Characteristics

Characteristic, n (%)	Step 1 Total (N = 434)
Median age, yr (Q1, Q3) ▪ ≤30 yr ▪ 31-50 yr ▪ ≥51 yr	40 (32, 51) 88 (20) 232 (53) 114 (26)
Female sex at birth	129 (30)
Transgender spectrum	21 (5)
Race ▪ Black ▪ White ▪ Other/multiple/unknown	 277 (64) 117 (27) 40 (9)
Hispanic or Latino/a ethnicity	75 (17)
Current or previous injection drug use	61 (14)
Nonadherence criteria ▪ Lost to follow-up ▪ Poor response ▪ Both	 87 (20) 283 (65) 64 (15)
Median time since HIV diagnosis, yr (Q1, Q3)	13 (7, 21)

Step 1

Characteristic	Step 1 Total (N = 434)
BL HIV-1 RNA, n (%) ▪ <200 c/mL ▪ 201-10,000 c/mL ▪ 10,001-100,000 c/mL ▪ >100,000 c/mL	 141 (32) 110 (25) 121 (28) 62 (14)
Median BL CD4 count, cells/mm^3 (Q1, Q3)	270 (116, 498)

Step 2

Characteristic	LA CAB + RPV (n = 146)	SoC Oral ART (n = 148)
BL HIV-1 RNA >200 c/mL, n (%)	24* (17)	10 (7)
Median BL CD4 count, cells/mm^3 (Q1, Q3)	417 (198, 688)	374 (198, 605)

*Includes 8 participants with HIV-1 RNA >10,000 c/mL.

Rana. CROI 2024. Abstr 212.

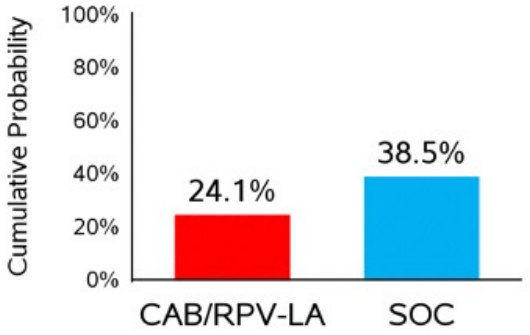
Slide credit: clinicaloptions.com

ACTG A5359 LATITUDE: Results

Primary Outcome

Regimen Failure

Difference	Nominal 98.75% CI
-14.5%	(-29.8%, 0.8%)

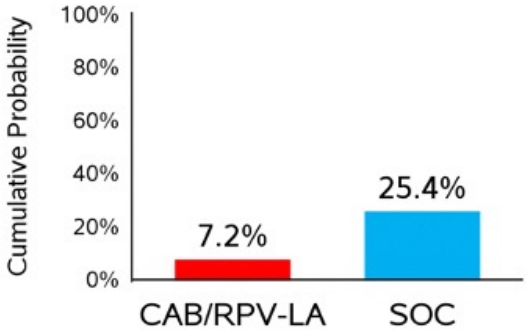


Number of participants	CAB/RPV-LA	SOC
Regimen Failure	28	47
VF	5	28
TRT-DISC	23	19

Secondary Outcomes

Virologic Failure

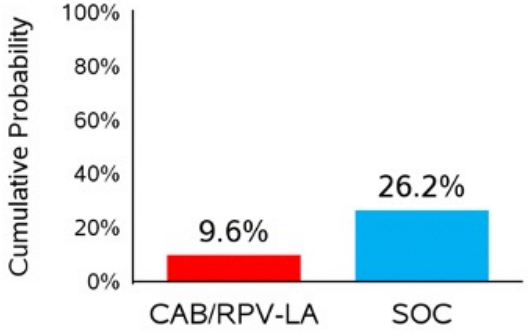
Difference	Nominal 98.75% CI
-18.2%	**(-31.1%, -5.4%)**



Number of participants	CAB/RPV-LA	SOC
Virologic Failure	6	28

Treatment-related Failure

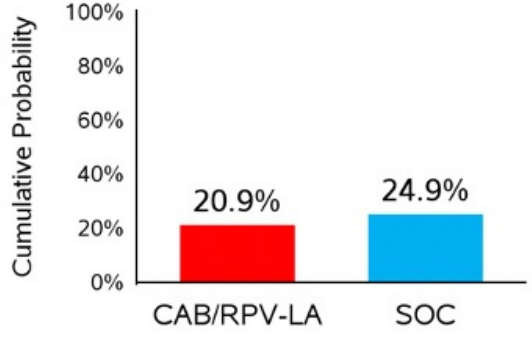
Difference	Nominal 98.75% CI
-16.6%	**(-29.9%, -3.3%)**



Number of participants	CAB/RPV-LA	SOC
Treatment-related Failure	9	29
VF	6	28
TRT-DISC (AE)	3	1

Permanent Treatment Discontinuation

Difference	Nominal 98.75% CI
-4.1%	(-18.0%, 9.8%)



Number of participants	CAB/RPV-LA	SOC
Permanent TRT-DISC	25	30

- Study stopped early by DSMB due to **superior efficacy of LA CAB + RPV** in secondary outcomes

Rana. CROI 2024. Abstr 212.

ACTG A5359 LATITUDE: Confirmed Virologic Failure in Step 2

RAM Evaluation, n	LA CAB + RPV (n = 6)	SoC Oral ART (n = 28)
With new RAM Mutation signature by Wk	**2** Wk 18: *E138EK; G140GS; Q148K; K103R* Wk 49: *E138K; Q148K; K20KR; M230ML*	**2** Wk 37: *A71V; V77I; V106I* Wk 48: *M184I*
Without new RAM	3	19
Discontinued without confirmation sample	0	2
HIV-1 RNA <400 c/mL	1	3
Sample not collected	0	2

Rana. CROI 2024. Abstr 212.

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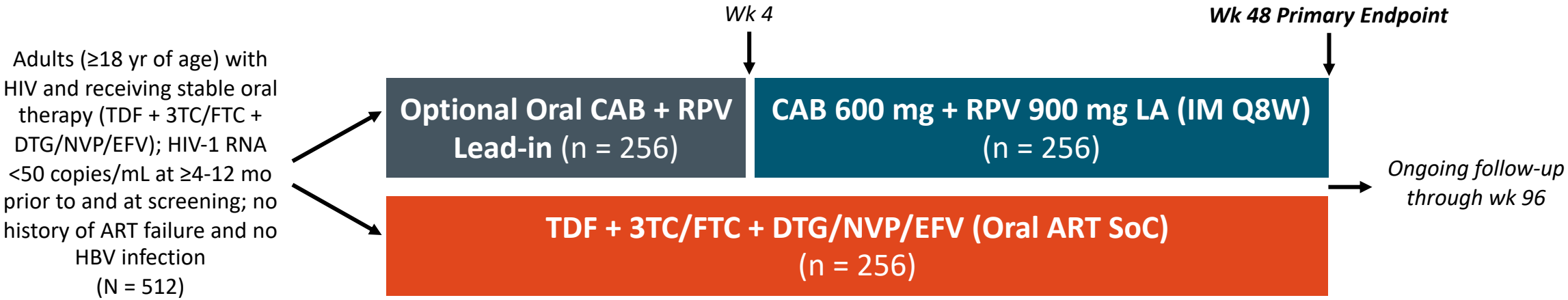
CARES: Study Design

- Multicenter, randomized, active controlled, open-label, phase IIIb study in **Uganda, Kenya, and S Africa**



- HIV-1 RNA assessed Q24W; safety monitoring at Wks 4, 8 (LA ART), 12 (SoC), 24, and Q24W onward
- **Primary endpoint:** proportion of patients with HIV-1 RNA <50 copies/mL by FDA snapshot analysis in ITT population at Wk 48; 10% noninferiority analysis; sensitivity analysis in per-protocol population
- **Secondary endpoints:** proportion of patients with HIV-1 RNA ≥50 copies/mL by FDA snapshot analysis in ITT population at Wk 48; 4% noninferiority analysis; proportion of patients with CFV (2 consecutive HIV-1 RNA ≥200 copies/mL); safety; treatment satisfaction per HIVTSQc

Kityo. CROI 2024. Abstr 122.

CARES: Baseline Characteristics

Parameter	LA CAB + RPV (n = 255)	Oral ART (SoC) (n = 257)
Female sex, n (%)	146 (57.2)	149 (58.0)
Median age, yr (IQR)	43 (36-51)	42 (35-49)
Black race, n (%)	254 (99.6)	256 (99.6)
Median time on first-line ART, yr (IQR)	8 (4-13)	7 (4 – 13)
Prior exposure to NNRTI, n (%)	189 (73.7)	191 (74.3)
NNRTI regimen at screening, n (%)	24 (9.4)	17 (6.6)
INSTI regimen at screening, n (%)	231 (90.6)	240 (93.4)

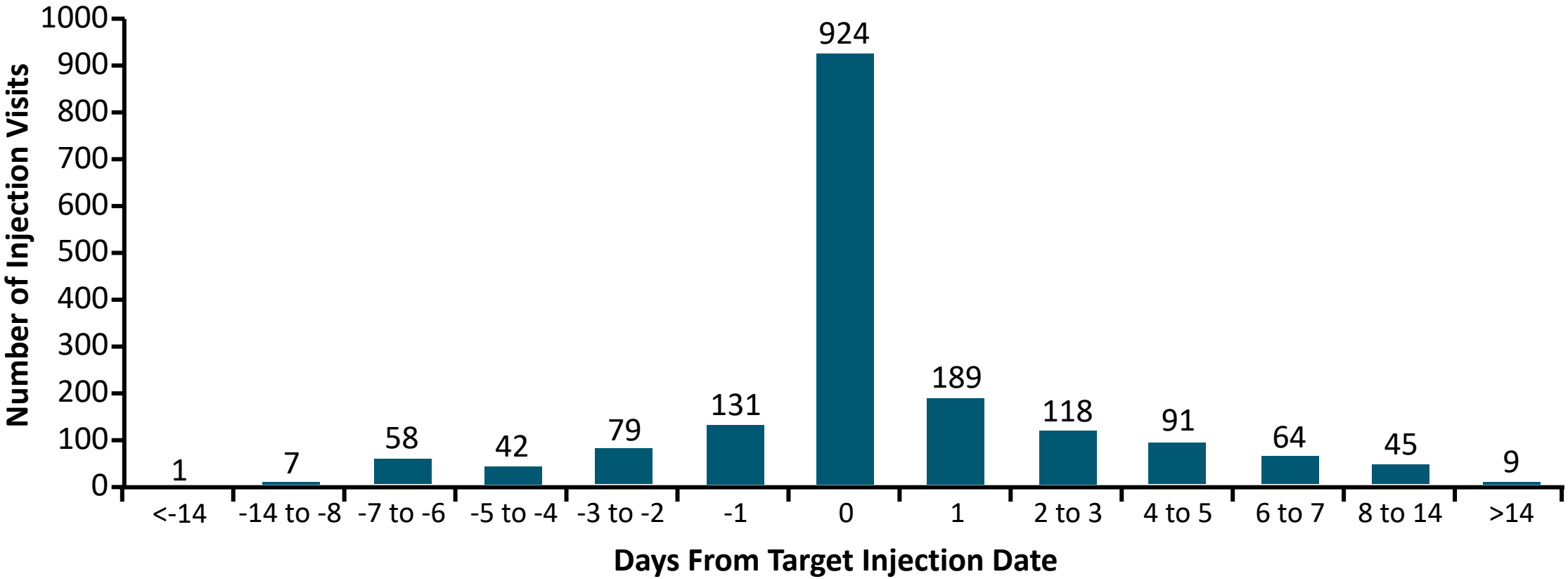
Parameter	LA CAB + RPV (n = 255)	Oral ART (SoC) (n = 257)
BMI ≥30 kg/m^2, n (%)	57 (22.4)	51 (19.8)
Archived DNA analysis*†		
▪ **Viral subtype A1, n/N (%)**	**119/213 (55.9)**	**115/201 (57.2)**
▪ **CAB resistance mutations, n/N (%)**	**15/95 (15.8)**	**14/85 (16.5)**
▪ **CAB intermediate/high-level resistance, n/N (%)**	**10/95 (10.5)**	**5/85 (5.9)**
▪ **RPV resistance mutations, n/N (%)**	**25/200 (12.5)**	**26/177 (14.7)**
▪ **RPV intermediate/high-level resistance, n/N (%)**	**17/200 (8.5)**	**21/177 (11.9)**

*Retrospective, batched sequencing performed on archived DNA from PBMCs at baseline. †Viral subtype, resistance mutations, and drug susceptibility were determined with Los Alamos National Laboratory Panel, and Stanford algorithm, respectively.

- Resistance analysis of baseline samples was performed at Wk 48 (not at baseline) due to the public health approach to enrollment

Kityo. CROI 2024. Abstr 122.

CARES: Timing of LA CAB + RPV Injections and Adherence



- 82.7% of patients received all scheduled injections during the 7-day period required per study protocol; 96% of scheduled injections occurred within the 7-day period

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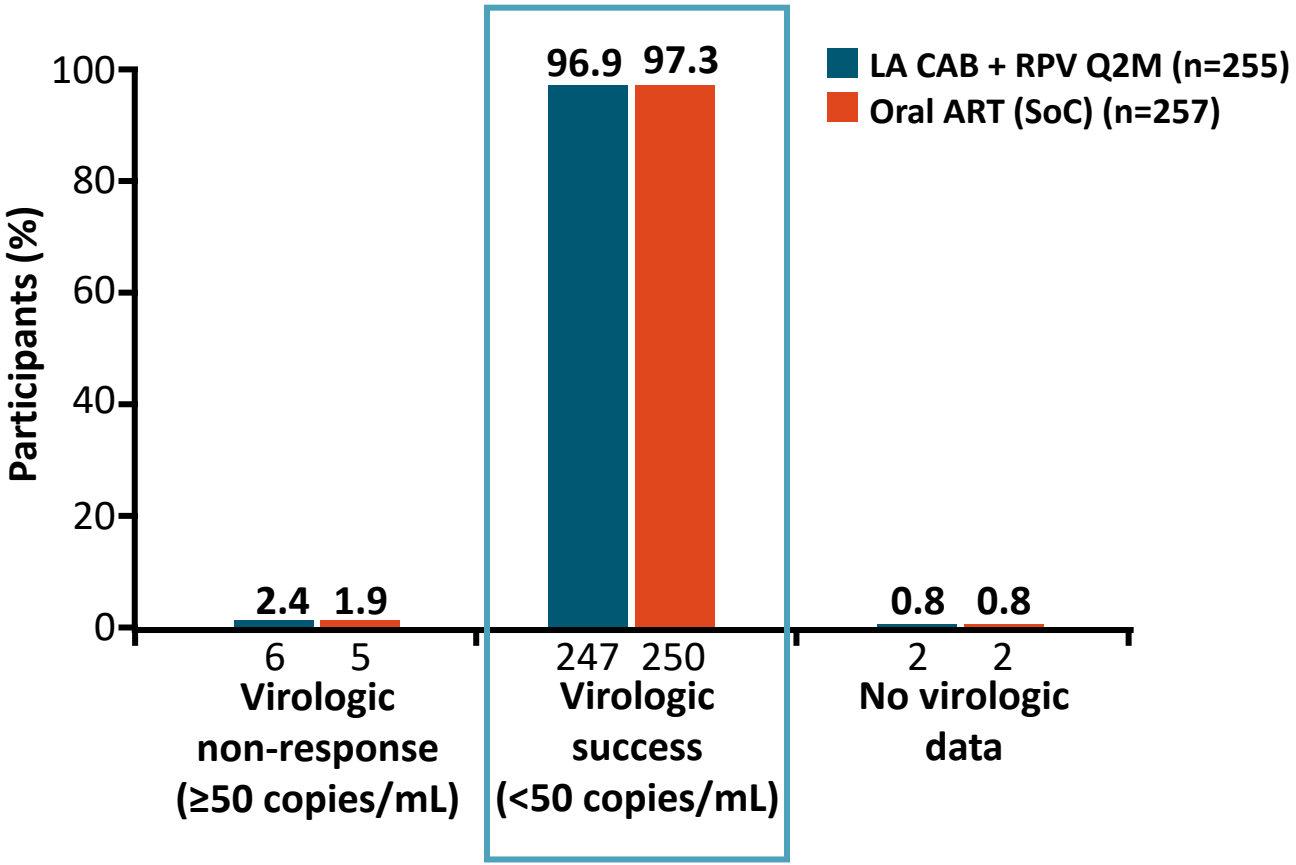
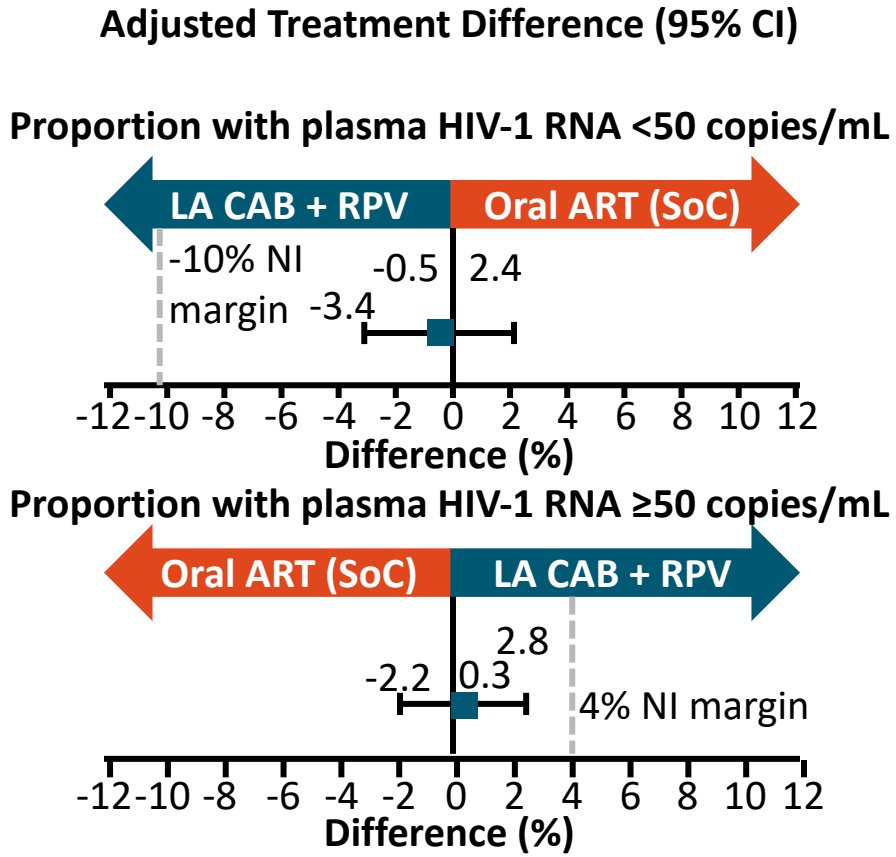
CARES: Primary Outcomes at 48 Wk





- LA CAB + RPV demonstrated noninferior virologic efficacy to oral ART (SoC) at 48 wk

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CARES: Virological Failure at Wk 48

Outcome	LA CAB + RPV (n = 255)	Oral ART (SoC) (n = 257)	Difference (95% CI)
Confirmed virologic failure, n (%)	1 (0.4)*	0	0.4 (-0.4 to 1.2)

*1 additional virologic failure (unconfirmed) in LA CAB + RPV arm.

Confirmed Virologic Failure: Patient Characteristics

- HIV-1 RNA 8608 copies/mL
- No delayed injections
- Sex and location: female from Uganda
- Baseline BMI 25.9 kg/m^2
- Subtype A1
  - Resistance mutations at baseline: no NNRTI or INSTI
  - Failure mutations: V108I, E138K, V179L (RPV high); E92E/V, N155H, L74M (CAB intermediate; DTG nil)
- Resuppressed on TDF/3TC/DTG once daily

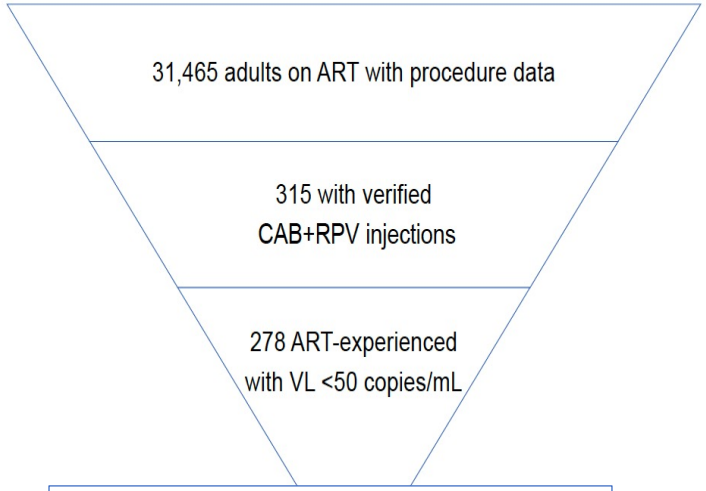
Unconfirmed Virologic Failure: Patient Characteristics

- HIV-1 RNA 44,984 copies/mL
- No delayed injections
- Sex and location: male from Uganda
- Baseline BMI 22.0 kg/m^2
- Subtype D
  - Resistance mutations at baseline: K103N/S, E138A (RPV low); no INSTI mutations
  - Failure mutations: K103N/S, V106V/A, E138A (RPV low), G118R (CAB high; DTG intermediate)

Kityo. CROI 2024. Abstr 122.

Real(er) World US Data: CAB/RPV

TRIO Health Cohort



- Median follow-up 10M
- 80% on q2M injections
- 89% got injections on time

Table 1. Study population characteristics

Characteristic		PWH with CAB+RPV Injections N = 278 n (%) unless specified
Age	Age, median (IQR)	44 (35, 55)
Gender	Female	47 (17)
	Male	221 (79)
	Unknown	10 (4)
Race/Ethnicity	White	137 (49)
	Black or African American	99 (36)
	Hispanic or Latino	20 (7)
	Another Race	6 (2)
	Unknown Race	16 (6)
Payer Type	Commercial	176 (63)
	Medicare/Medicaid	11 (4)
	Other/Self Pay	88 (32)
	Unknown Payer	3 (1)

Figure 2. PWH on CAB+RPV regimen at the end of follow up, n = 278

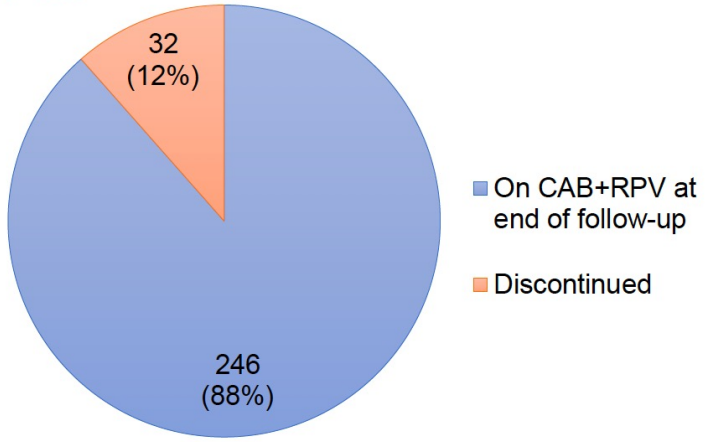
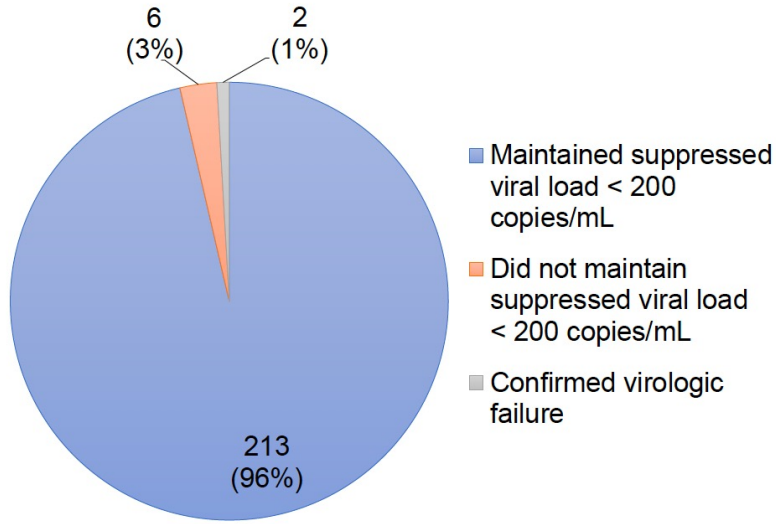


Figure 3. PWH on CAB+RPV LA at last VL, n = 221



Eron. CROI 2024

Real(er) World US Data: CAB/RPV

Opera Cohort

- Prospectively captured, routine clinical data from electronic health records in the US (101 clinics, 23 US states/territories), representing ~14% of people with HIV (PWH) in the US
- **Inclusion criteria**
  - ART-experienced PWH aged ≥18 years
  - Virologically suppressed (VL <50 copies/mL)
  - Switched to CAB+RPV LA or a new oral ART regimen between 21JAN2021 and 31DEC2022

Table 1. Baseline characteristics

	CAB+RPV LA N = 1,362	Oral ART N = 2,783
Age, median years (IQR)	39 (32, 52)	45 (34, 56)
Female sex, n (%)	237 (17)	514 (18)
Black race, n (%)[a]	557 (41)	1,198 (43)
Hispanic ethnicity, n (%)[a]	390 (29)	678 (24)
Care in Southern USA, n (%)	752 (55)	1,742 (63)
Viral load, median c/mL (IQR)	19 (19, 20)	19 (19, 19)
CD4 cell count, median cells/μL (IQR)[a]	686 (496, 902)	700 (524, 913)
Prior core agent class, n (%)		
INSTI-based	1,003 (74)	1,880 (68)
NNRTI-based	106 (8)	474 (17)
PI-based	42 (3)	203 (7)
More than one core agent	211 (16)	226 (8)
Months on prior ARV regimen, median (IQR)	20 (7, 38)	37 (20, 55)

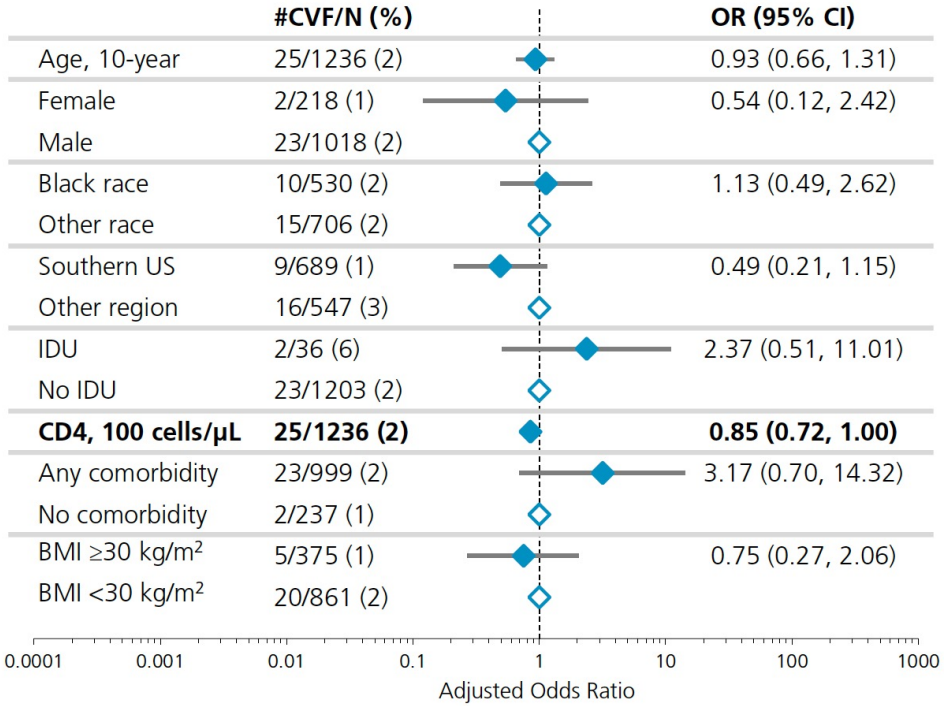
c/mL, copies/milliliter; IQR, interquartile range; INSTI, integrase inhibitor; N, number; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor

[a] N missing = 133 (race), 132 (ethnicity), 35 (CD4 cell count)

Table 2. Virologic outcomes among those with follow-up VL

		CAB+RPV LA N = 1,293	Oral ART N = 2,523
Last VL	<200 c/mL, n (%)	1,281 (99)	2,431 (96)
	<50 c/mL, n (%)	1,229 (95)	2,298 (91)

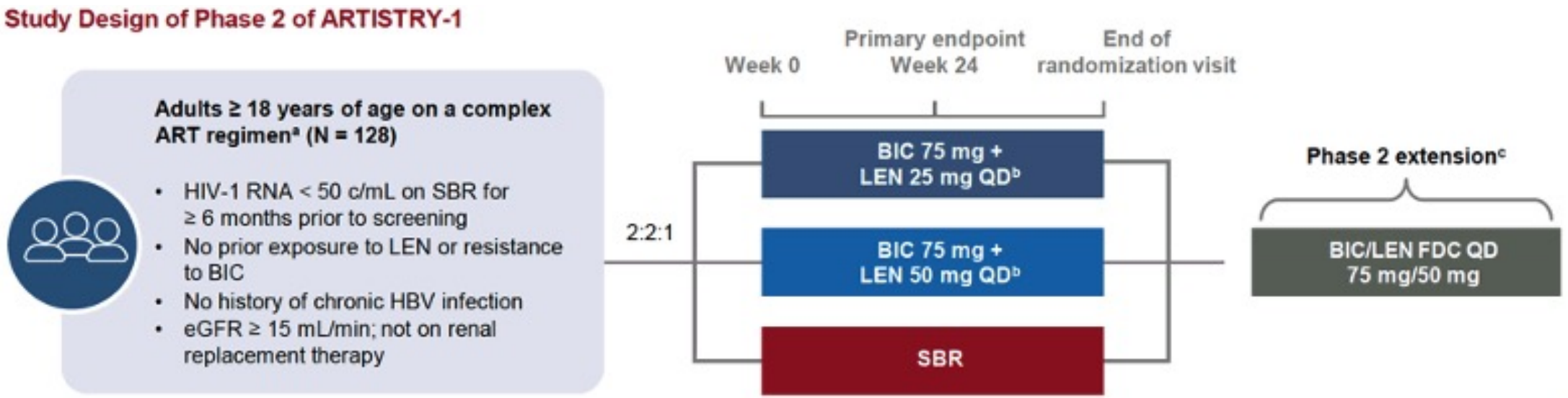
Figure 3. Predictors of confirmed virologic failure among people switching to CAB+RPV LA with ≥1 follow-up viral load (N=1,236)[a]



◊ reference

[a] Excluding 57 individuals without race or baseline CD4 cell count

BIC + LEN (oral) Switch in those on a complex regimen



- A complex regimen was defined as:
  - A regimen containing a boosted protease inhibitor or a non-nucleoside reverse transcriptase inhibitor plus ≥ 1 other third agent from a class other than nucleos(t)ide reverse transcriptase inhibitors, or
  - A regimen of ≥ 2 pills/day, or a regimen requiring dosing more than once daily, or
  - A regimen containing parenteral agent(s) (excluding a complete long-acting injectable regimen) as well as oral agents

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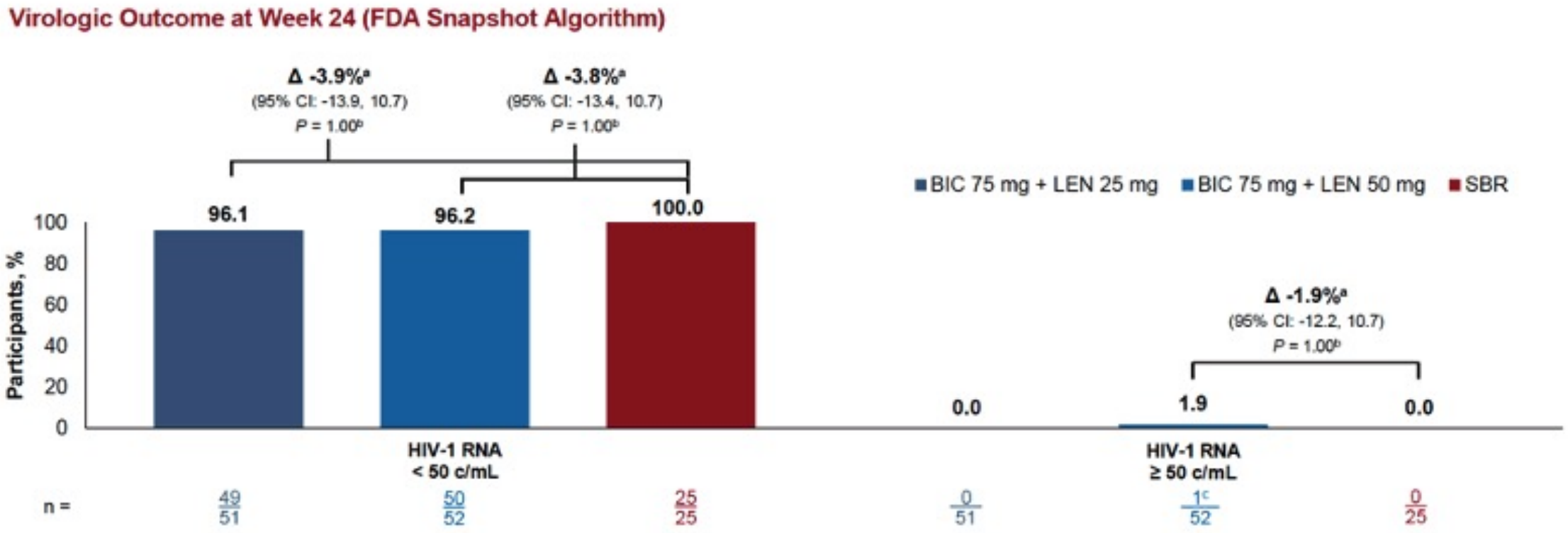
BIC + LEN (oral) Switch in those on a complex regimen



Two participants (3.9%) in the BIC 75 mg + LEN 25 mg group and one (1.9%) in the BIC 75 mg + LEN 50 mg group had no virologic data in the Week 24 window; reasons: one participant (2.0%) in the BIC 75 mg + LEN 25 mg group and one (1.9%) in the BIC 75 mg + LEN 50 mg group discontinued study drug due to an AE/death and last available HIV-1 RNA < 50 c/mL, and one participant (2.0%) in the BIC 75 mg + LEN 25 mg group discontinued study drug due to other reasons and last available HIV-1 RNA < 50 c/mL.

[a]Difference in % (95% CI): BIC + LEN – SBR calculated based on an unconditional exact method using two inverted one-sided tests.

[b]Based on Fisher exact test.

[c]HIV-1 RNA ≥ 50 c/mL in Week 24 window (later suppressed to < 50 c/mL without regimen change). No genotype/phenotype was performed as virologic failure did not reach threshold as per protocol (> 200 c/mL).

AE, adverse event; BIC, bictegravir; c, copies; FDA, Food and Drug Administration; LEN, lenacapavir; SBR, stable baseline regimen.

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Case Series Examining the Long-Acting Combination of Lenacapavir and Cabotegravir: Call for a Trial

Monica Gandhi;[1] Lucas Hill;[2] Janet Grochowski;[1] Alexander Nelson;[3] Katerina Christopoulos;[1] Diane Havlir;[1] Catherine A. Koss;[1] Francis Mayorga-Munoz;[1] Jon Oskarsson;[1] John Szumowski;[1] Ann Avery;[3] Laura Bamford;[2] Jillian Baron;[4] William R. Short;[4] Corrilynn O. Hileman[3]

[1]University of California, San Francisco (UCSF), SF, CA; [2]University of California, San Diego (UCSD), San Diego, CA; [3]Metrohealth Medical Center and Case Western University, Cleveland, OH; [4]University of Pennsylvania (UPenn), Philadelphia, PA

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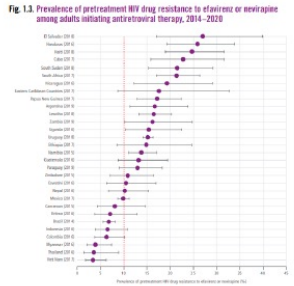
Background

- Injectable cabotegravir (CAB)/rilpivirine (RPV) is the only combination long-acting (LA) antiretroviral treatment (ART) regimen approved for HIV
- RPV is not effective among individuals with nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance (when the mutations are RPV resistance associated mutations, RAMs), which has >10% prevalence in many countries (Figure)
- Lenacapavir (LEN) is a LA capsid inhibitor given every six months but has not been studied in combination with other LA agents

Methods

- Four clinics where providers are using either LA CAB/RPV or LA CAB paired with LA LEN for selected patients with adherence challenges off-label were identified (UCSF Ward 86, UCSD Owen Clinic, MetroHealth's HIV Clinic, UPenn Clinic) and a case series assembled
- All patients in this series experienced challenges to taking oral ART which is why LA ART was prescribed
- Variables, including sex; gender; age; race; ethnicity; current housing status; substance use; viral load (VL) prior to starting LEN/CAB; duration between CAB doses (every 4 or 8 weeks); whether injectable RPV was also given; viral mutations in the NNRTI or INSTI class; BMI; time on the regimen; and LEN injection site reaction garnered from medical record
- IRB approval in clinics to present data if no patient identifiers

Figure: Rates of NNRTI resistance across countries as of WHO report 2021 (RPV 2.7-18.7%)



HIV DRUG RESISTANCE REPORT 2021

World Health Organization

In this case series of 34 patients on LEN/CAB from four U.S. academic medical centers, high rates of virologic suppression (94%) were seen (up from 47% at baseline). Clinicians used LEN/CAB for adherence challenges and NNRTI resistance. These data support a clinical trial of LEN/CAB as CAB/RPV cannot be used in LMICs with high rates of NNRTI resistance

Table: Details of patients (n=34) of LEN/CAB in this case series

Reason for LEN	Patient number	Age/Sex/ Gender/ Race-ethnicity/ substance use and/or housing insecurity/BMI (kg/m²)/ viral subtype	VL prior to LEN/CAB, copies/mL	NNRTI or minor INSTI mutations for patients 28-32	Regimen prior to LEN/CAB	Weeks between CAB doses/ RPV included/ ISR*	VS <75 after LEN/CAB start/ time to VS
NNRTI mutations- virologically suppressed when started LEN	1	55/M/M/Latino/yes/29.1	UD	A98G, K103N, V179E, G190A	DRV/c/FTC/TAF	4 weeks/ no/ no	Yes/ NA
	2	32/M/M/Latino/no/33.8	UD	K103N, G190A	DRV/c/FTC/TAF + DTG	8 weeks/ yes/ no	Yes/ NA
	3	28/M/M/Latino/no	UD	K103R, V179D	DRV/c + DTG	4 weeks/ yes/ grade 1	Yes/ NA
	4	47/F/F/Latina/no/28.1	UD	L100I, K103N	DRV/c + DTG	8 weeks/ no/ no	Yes/ NA
	5	75/F/F/Black/no/23.1/B	UD	L100I, K103N, V179I, Y181C	DTG + 3TC + DRV/r	8 weeks/ no/ no	Yes/ NA
	6	41/M/M/Black/yes/23.57/B	UD	V108I, V179D	EVG/c/FTC/TAF + DRV	8 weeks/ no/ grade 1	Yes/ NA
	7	55/M/M/White/no/21.7/B	UD	V90I, E138G	BIC/TAF/FTC	8 weeks/ yes/ no	Yes/ NA
	8	29/F/F/Black/no/30.9/AG	UD	Y181C	DTG/ABC/3TC	8 weeks/ yes/ grade 1	Yes/ NA
NNRTI mutations - viremic when started LEN	9	58/F/F/Latina/yes/29.2/B	329	K101K/Q, K103R, V179I	BIC/TAF/FTC+ DOR	4 weeks/ yes/ grade 2	Yes/ 4 wks
	10	48/M/F/Black/yes/26.7/B	815	V90I, V106I, Y181C, H221Y	DTG + TAF/FTC	4 weeks/ no/ grade 1	Yes/ 12 wks
	11	41/M/M/Black/no/46.22/B	5,280	Y181C, Y188L K103V	DRV/c/FTC/TAF + DTG	8 weeks/ yes/ grade 1	Yes/ 4 wks
	12	54/M/M/Black/yes/22.1/B	9,760	L100I, K103N, Y181Y/C, H221H/Y	EVG/c/FTC/TAF + DRV	8 weeks/ yes/ grade 1	Yes/ 16 wks
	13	50/M/M/Latino/yes/23/B	36,342	L100I, V179I, Y181I	DRV/c/FTC/TAF	4 weeks/ no/ grade 2	Yes/ 4 wks
	14	51/M/M/White/yes/28.2/B	239,000	L100I, K103N	DRV/c/FTC/TAF+DTG	4 weeks/ no/ grade 1	Yes/ 4 wks
	15	59/M/M/Latino/no/19.9/B	1,271,051	V106I, G190S, V179T, F227L	DRV/c/FTC/TAF + DTG	4 weeks/ no/ no	Yes/ 8 wks
Suspected archived NNRTI mutations	16	31/M/M/Black/no/25.18/B	7,740	None	BIC/TAF/FTC + DRV/c	8 weeks/ yes/ no	Yes/ 8 wks
	17	54/M/M/Black/yes/21.8/B	229,000	None	DRV/r/TAF/FTC	8 weeks/ yes/ no	Yes/ 16 wks
High VL within 3 months prior to starting LA ART (+/- NNRTI mutations)	18	57/M/M/Black/yes/22.0	UD	K103N, V108I, P225H	LA CAB/RPV	8 weeks/ yes/ no	Yes/ NA
	19	43/M/M/Black/no/24.9/B	UD	K103N, V108I, P225H	DRV/c/FTC/ TAF+DTG	8 weeks/ yes/ no	Yes/ NA
	20	42/M/M/White/yes/19.4/B	UD	None	LA CAB/RPV	8 weeks/ no/ grade 2	Yes/ NA
	21	28/M/M/Latino/no/30.5	UD	None	LA CAB/RPV	8 weeks/ no/ no	Yes/ NA
	22	60/M/M/White/yes/28.2/B	190	None	BIC/TAF/FTC	8 weeks/ yes/ no	Yes/ 12 wks
	23	39/M/M/Latino/yes/21.2/B	194,000	None	BIC/TAF/FTC	8 weeks/ yes/ no	Yes/ 5 wks
Low level viremia on CAB/RPV (+/- NNRTI mutations)	24	39/M/M/Latino/no/36.0/B	UD	K103R	LA CAB/RPV	8 weeks/ yes/ no	Yes/ NA
	25	35/M/M/Black/yes/34.7/B	95	None	LA CAB/RPV	8 weeks/ yes/ no	Yes/ 3 wks
	26	38/M/M/Latino/yes/23/B	145	None	LA CAB/RPV	4 weeks/ yes/ grade 2	No/ no VS
	27	42/M/M/White/yes/26.5/B	165	K103N, V106I	LA CAB/RPV	8 weeks/ yes/ no	Yes/ 16 wks
INSTI mutations	28	34/M/M/Latino/yes/22/B	UD	V90I, T66T/I	BIC/TAF/FTC	4 weeks/ yes/ grade 1	Yes/ NA
	29	52/M/M/White/yes/22.2/B	105	E92Q	DTG/RPV + DRV/c	8 weeks/ yes/ no	Yes/ 16 wks
	30	44/F/F/Black/no/25.5/B	228	T97A	BIC/TAF/FTC	8 weeks/ yes/ no	No/ no VS
	31	40/F/F/Latina/no/24.8/B	290	E92Q	DRV/c/FTC/TAF + DOR	8 weeks/ yes/ grade 1	Yes/ 9 wks
	32	72/M/M/Black/yes/17.7/B	50,900	T97A	BIC/TAF/FTC + DRV/c	8 weeks/ yes/ no	Yes/5 wks
Other	33[1]	47/F/F/Black/no/41.2/B	UD	None	BIC/TAF/FTC	8 weeks/ yes/ grade 1	Yes/ NA
	34[2]	57/M/M/White/yes/22.7/B	UD	None	LA CAB/RPV	4 weeks/ no/ grade 1	Yes/ NA

M-male; F-female; UD-undetectable; DRV/c-darunavir/cobicistat; BIC-bictegravir; TAF-tenofovir alafenamide; FTC-emtricitabine; DTG-dolutegravir; 3TC-lamivudine; EVG-elvitegravir; DOR-doravirine; [1]High BMI > 40 kg/m²; [2]Intolerance to LA-RPV; *ISR injection site reaction; K103(X) mutations not counted as RPV associated mutations

Results

- All patients (n=34: 76% male; 24% cis/trans female; 41% Black; 38% Latino/a; median age 47 [range 28-75] years; 29% and 71% on CAB every 4 or 8 weeks) reported challenges adhering to oral ART (**Table**)
- Reason(s) for using LEN/CAB with or without RPV were: either documented or suspected NNRTI mutations (n= 21, 59%), integrase mutations (n=5, 15%), high VL (n=6, 18%), or continued viremia on CAB/RPV alone (n=4, 12%)
- Injection site reactions on LA-LEN were reported in 44% (32% grade I, 12% grade 2).
- All patients but two (32/34; 94%) suppressed (VL< 75 copies/mL) after starting LEN at a median of 8 (4-16) weeks, with 16/34 (47%) suppressed at baseline.

Conclusion

- First case series of patients on a novel combination of long-acting ART with LEN (subcutaneous every 6 months) and CAB (intramuscular every 4-8 weeks) with or without RPV
- All experienced adherence challenges with oral ART
- Most common reason for use of this off-label combination was NNRTI mutations
- Overall, viral suppression doubled from 47% at baseline to 94% on LEN/CAB
- Patients with documented or suspected NNRTI mutations all achieved suppression on LEN/CAB
- Due to prevalence of NNRTI mutations worldwide (**Figure**), CAB/RPV not approved as LA ART by WHO in low-and-middle-income countries (LMICs)
- Therefore, in 2024, disparities exist in availability of LA ART between high and LMICs
- Trial needed to study LEN/CAB in patients with NNRTI resistance worldwide given this disparity; this case series serves as a call for this trial

Acknowledgements: Funded by NIAID/NIH 5R37AI098472

UCSF Penn University of Pennsylvania Case Western Reserve University

UC San Diego MetroHealth Devoted to Hope, Health, and Humanity

Case Series Examining the Long-Acting Combination of Lenacapavir and Cabotegravir: Call for a Trial

Monica Gandhi;[1] Lucas Hill;[2] Janet Grochowski;[1] Alexander Nelson;[3] Katerina Christopoulos;[1] Diane Havlir;[1] Catherine A. Koss;[1] Francis Mayorga-Munoz;[1] Jon Oskarsson;[1] John Szumowski;[1] Ann Avery;[3] Laura Bamford;[2] Jillian Baron;[4] William R. Short;[4] Corrilynn O. Hileman[3]

[1]University of Califor ... versity, Cleveland,

629

Background

- Injectable cabotegravir (CAB)/rilpivirine (only combination long-acting (LA) antiret treatment (ART) regimen approved for H
- RPV is not effective among individuals w nonnucleoside reverse transcriptase inhi (NNRTI) resistance (when the mutations resistance associated mutations, RAMs) >10% prevalence in many countries (Fig
- Lenacapavir (LEN) is a LA capsid inhibit every six months but has not been studie combination with other LA agents

Methods

- Four clinics where providers are using ei CAB/RPV or LA CAB paired with LA LEN patients with adherence challenges off-la identified (UCSF Ward 86, UCSD Owen MetroHealth's HIV Clinic, UPenn Clinic) series assembled
- All patients in this series experienced ch taking oral ART which is why LA ART wa
- Variables, including sex; gender; age; ra current housing status; substance use; v prior to starting LEN/CAB; duration betw doses (every 4 or 8 weeks); whether inje was also given; viral mutations in the NN INSTI class; BMI; time on the regimen; a injection site reaction garnered from mec
- IRB approval in clinics to present data if identifiers

Figure: Rates of NNRTI resistance across co of WHO report 2021 (RPV 2.7-18.7

HIV DR RESIST REPORT 2021

World Health Organization

Results

- All patients (n=34: 76% male; 24% cis/trans female; 41% Black; 38% Latino/a; median age 47 [range 28-75] years; 29% and 71% on CAB every 4 or 8 weeks) reported challenges adhering to oral ART (**Table**)
- Reason(s) for using LEN/CAB with or without RPV were: either documented or suspected NNRTI mutations (n= 21, 59%), integrase mutations (n=5, 15%), high VL (n=6, 18%), or continued viremia on CAB/RPV alone (n=4, 12%)
- Injection site reactions on LA-LEN were reported in 44% (32% grade I, 12% grade 2).
- All patients but two (32/34; 94%) suppressed (VL< 75 copies/mL) after starting LEN at a median of 8 (4-16) weeks, with 16/34 (47%) suppressed at baseline.

INSTI mutations	28	34/M/M/Latino/yes/22/B	UD	V90I, T66T/I	BIC/TAF/FTC	4 weeks/ yes/ grade 1	Yes/ NA
	29	52/M/M/White/yes/22.2/B	105	E92Q	DTG/RPV + DRV/c	8 weeks/ yes/ no	Yes/ 16 wks
	30	44/F/F/Black/no/25.5/B	228	T97A	BIC/TAF/FTC	8 weeks/ yes/ no	No/ no VS
	31	40/F/F/Latina/no/24.8/B	290	E92Q	DRV/c/FTC/TAF + DOR	8 weeks/ yes/ grade 1	Yes/ 9 wks
	32	72/M/M/Black/yes/17.7/B	50,900	T97A	BIC/TAF/FTC + DRV/c	8 weeks/ yes/ no	Yes/5 wks
Other	33[1]	47/F/F/Black/no/41.2/B	UD	None	BIC/TAF/FTC	8 weeks/ yes/ grade 1	Yes/ NA
	34[2]	57/M/M/White/yes/22.7/B	UD	None	LA CAB/RPV	4 weeks/ no/ grade 1	Yes/ NA

M-male; F-female; UD-undetectable; DRV/c-darunavir/cobicistat; BIC-bictegravir; TAF-tenofovir alafenamide; FTC-emtricitabine; DTG-dolutegravir; 3TC-lamivudine; EVG-elvitegravir; DOR-doravirine; [1]High BMI > 40 kg/m²; [2]Intolerance to LA-RPV; *ISR injection site reaction; K103(X) mutations not counted as RPV associated mutations

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Conclusion

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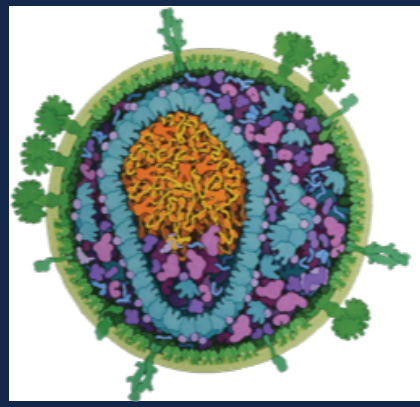
Acknowledgements: Funded by NIAID/NIH 5R37AI098472

UCSF Penn CASE WESTERN RESERVE UNIVERSITY

UC San Diego MetroHealth Devoted to Hope, Health, and Humanity

Why does this matter? Current HIV therapies

- Current HIV therapy is remarkably good, but we can make **existing HIV therapies better**
- CAB/RPV has had a slow start, but use is growing
- Expanded use of **CAB/RPV** was expected and makes sense PRACTICE CHANGER
  - Offers option to those for whom oral therapies are not a good fit
  - Provides more **equitable** use of this innovation
- **Creative combinations** give some options where there we few or none PRACTICE CHANGER



CROI
Conference on Retroviruses
and Opportunistic Infections

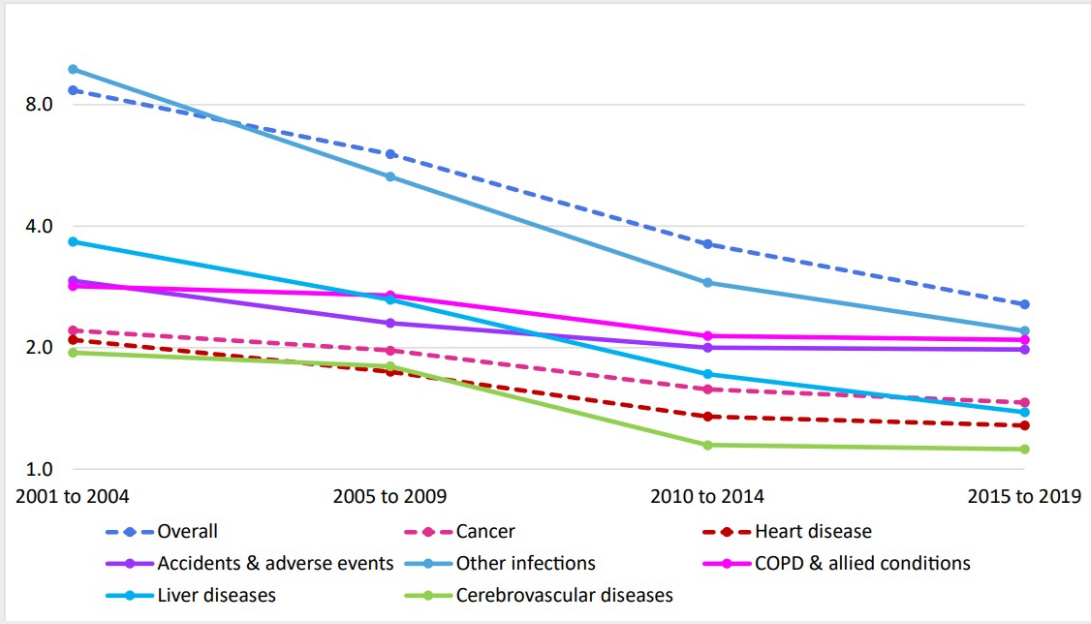
Comorbidities/ Clinical Events

Mortality Trends PWH 2001-2019

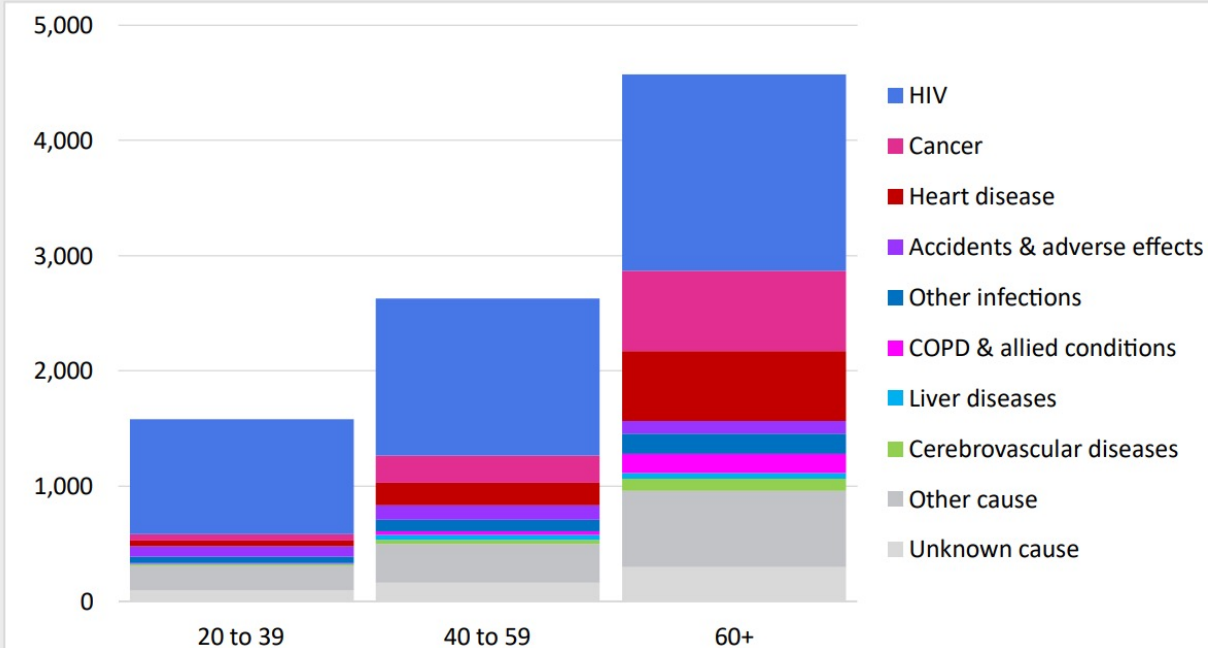
- Analysis of mortality recorded in the HIV/AIDS Cancer Match database from 12 states, DC, and PR
- During 2001–2019, there were 176,051 deaths among PWH over 7.3 million person-years of follow-up.
  - Among decedents, 71.6% were male, 61.6% were aged 40–59 years, and 49.0% were non-Hispanic Black.
  - The leading cause of death was HIV, accounting for 37.1% of deaths, followed by cancer (7.5% of deaths) and heart disease (6.1% of deaths)
- Other data reported at CROI from California found age-adjusted mortality rates 2018-19 versus 2020-21:
  - Increased due to **COVID-19** and **overdoses** (64%), especially in people of color
  - HIV-associated mortality declined

Volesky-Avellaneda. CROI 2024; Stainken. CROI 2024

SMRs overall and for leading causes of death among PWH, by calendar period



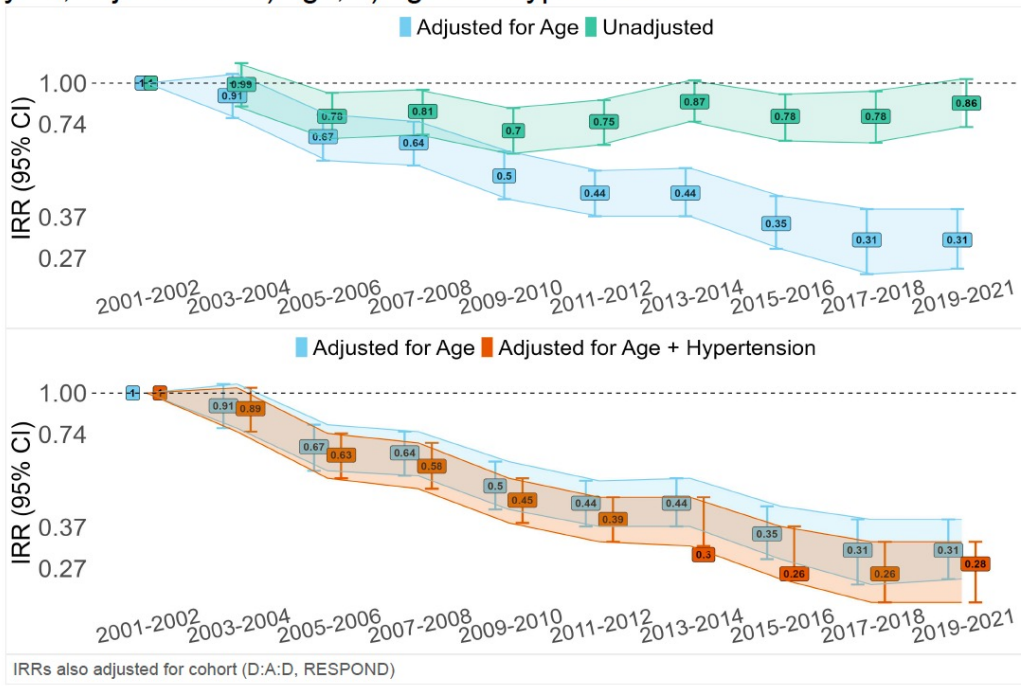
Mortality rates per 100,000 per years among PWH by age group, 2001–2019



Cardiovascular Disease (CVD) Trends over 20 years 2001-2021

- CVD is leading cause of death in the world, people with HIV included
- While CVD is a concern, data have shown a decrease in CVD rates in people with HIV as a consequence of better control of viremia and CVD prevention measures.
- 20-year trend in CVD examined in **D:A:D and RESPOND** cohorts in Europe
  - **66,680 i**ncluded individuals, 18% were age >50 (median 40, interquartile range [IQR] 33–47) at baseline, 74% were male, **38% current smokers**, 45% had dyslipidemia, 8% hypertension, 3% diabetes, and 1% prior CVD

Figure 3. Change in CVD incidence per two-year increase in calendar year, adjusted for a) age, b) age and hypertension



IRRs also adjusted for cohort (D:A:D, RESPOND)

- After adjusting for age, the CVD IR declined over time; additional adjustment for hypertension strengthened the declining estimates (Figure 3). Adjustment for changes in other CVD risk factors did not affect the temporal trends
- The declining CVD incidence per two years time was independent of sex/gender, recent virological failure (viral load of >200 copies/mL), smoking status, diabetes, and multimorbidity burden (all interaction P>0.1)

Jaschinski. CROI 2024

Cardiovascular Disease (CVD) Trends over 20 years (2001-2021)

Figure 1. Age-standardised IRs over time for all CVD events and MIs, strokes and ICPs

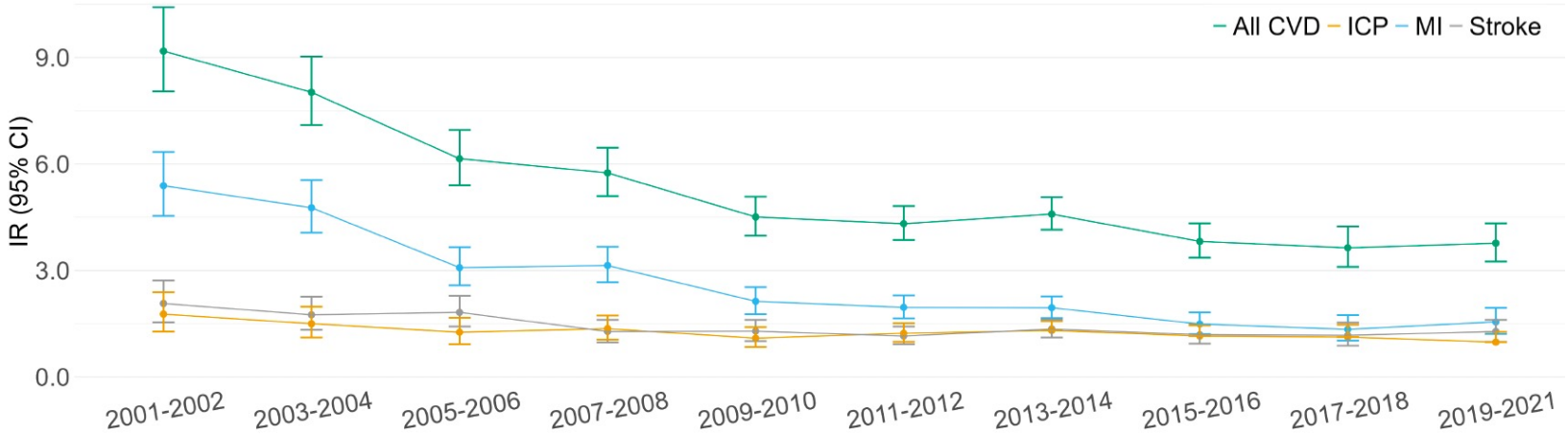
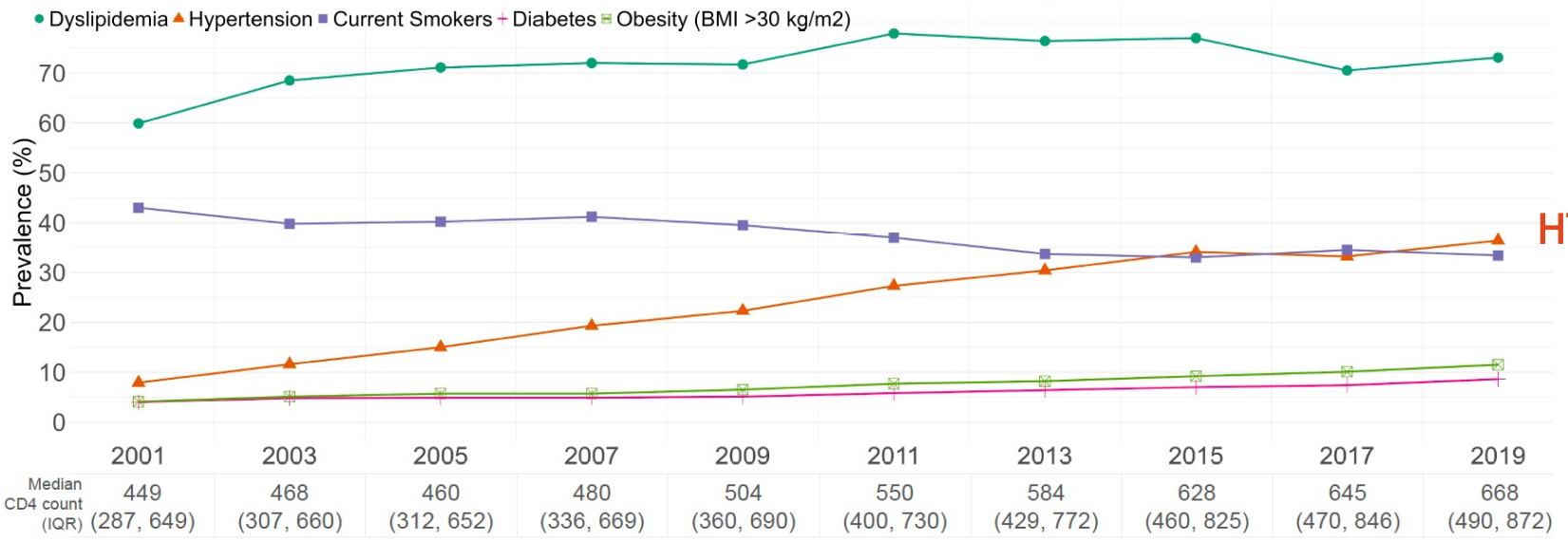
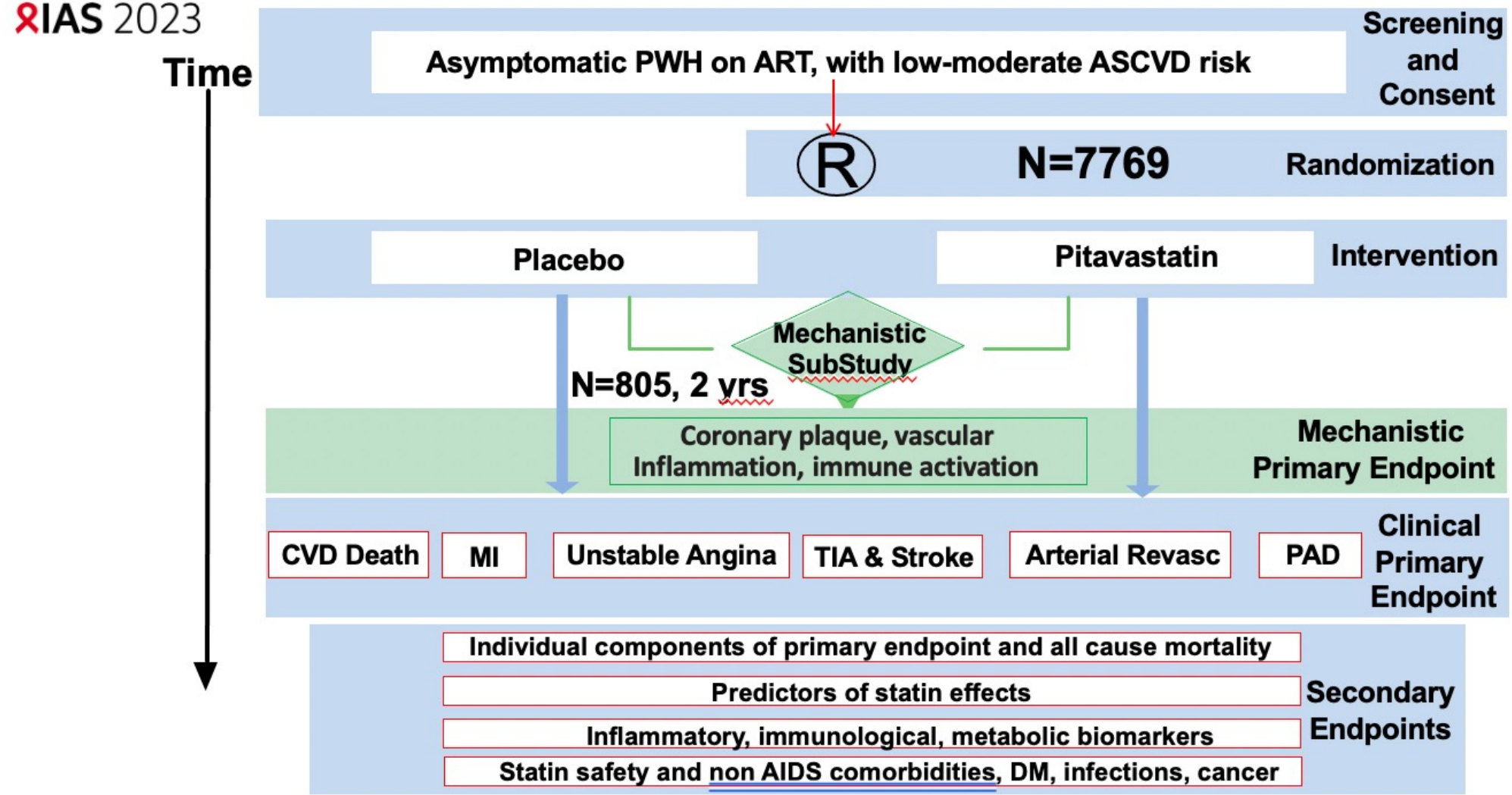


Figure 2. Distribution of traditional CVD risk factors in individuals under follow-up over time



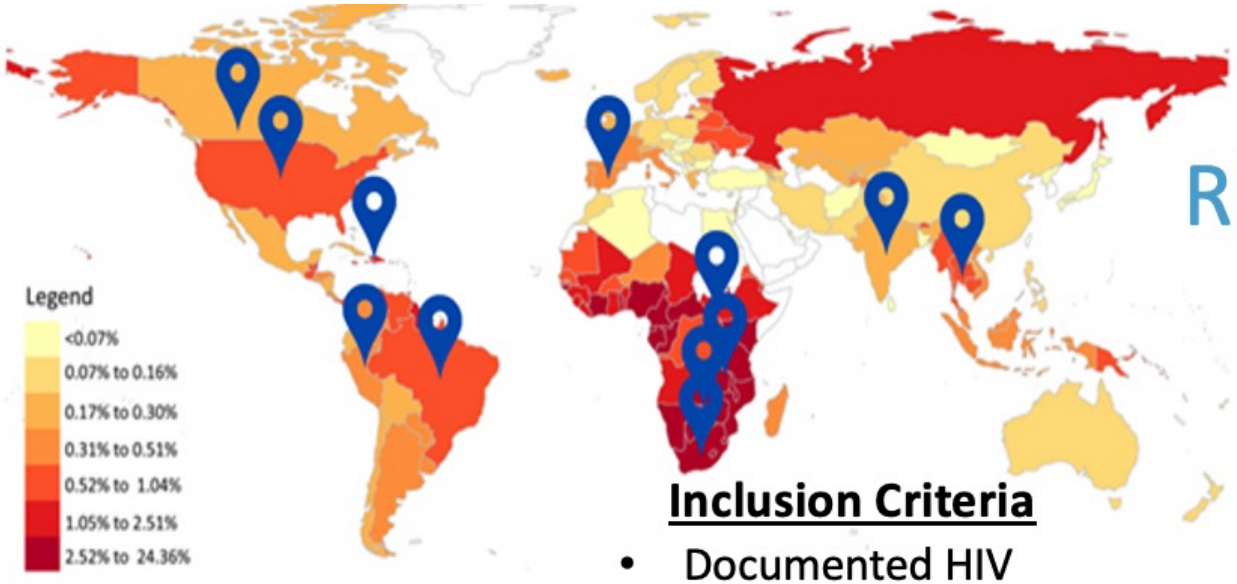
Jaschinski. CROI 2024

REPRIEVE Trial Schema



Grinspoon S. IAS 2023, NEJM 2023

REPRIEVE Study Population



Inclusion Criteria

- Documented HIV
- Receiving stable ART
- CD4+ > 100 cells/mm3
- Age ≥ 40 years, ≤ 75 years
- No known atherosclerotic cardiovascular disease (ASCVD)
- 10-yr ASCVD risk score
  - <7.5% LDL < 190 mg/dL
  - ≥7.5% and ≤ 10% LDL, < 160 mg/dL
  - >10% and ≤15%, LDL < 130 mg/dL
- Certain laboratory parameters

Exclusion Criteria

- Current use of statins, gemfibrozil, or PCSK9 inhibitors
- Known decompensated cirrhosis

Note: For LDL, to convert from mg/dL to SI (in mmol/L) multiply by 0.02586

IAS 2023

Grinspoon S. IAS 2023, NEJM 2023

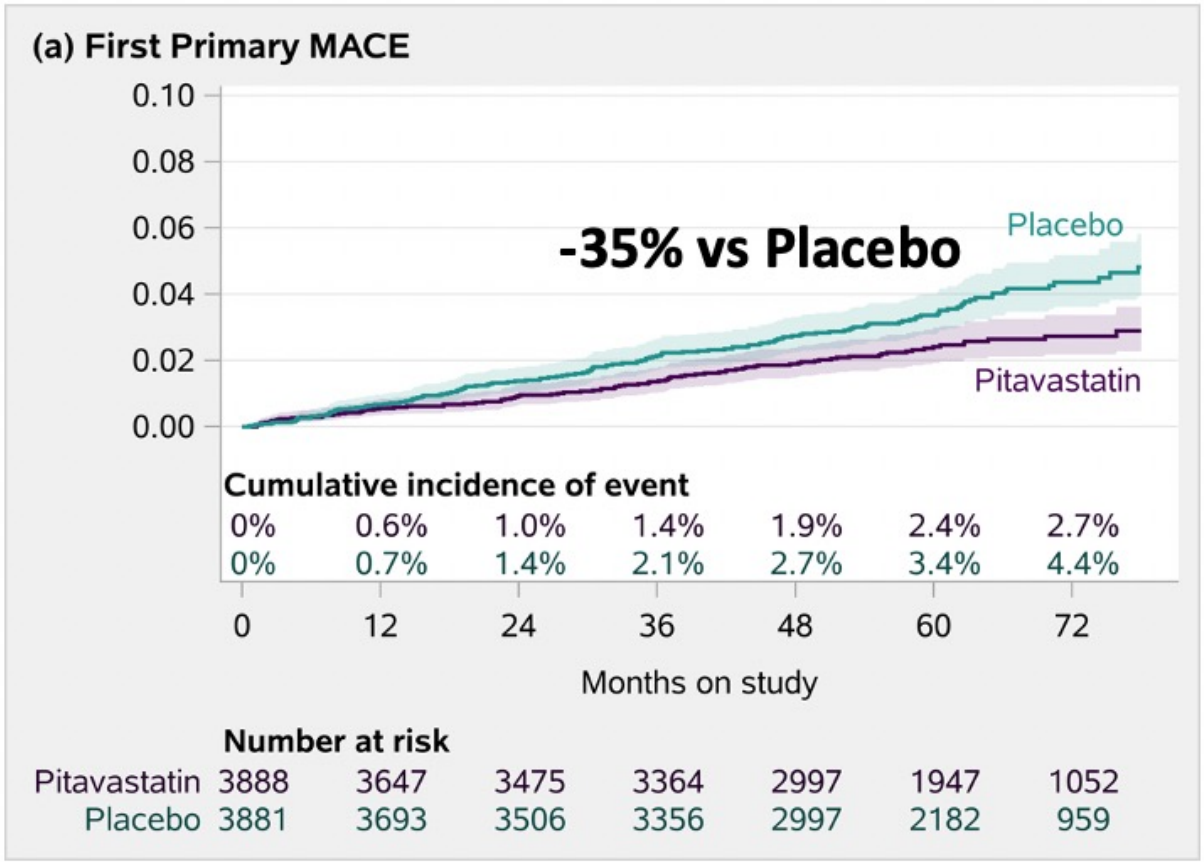
	High Income (N=118)	Latin America and Caribbean (N=15)	S. East/East Asia (N=2)	South Asia (N=2)	Sub-Saharan Africa (N=8)	Total (N=145)
Overall Statistics						
Total number screened	5,539	1,953	824	634	1,915	10,865
Total number enrolled	4,095	1,423	590	504	1,157	7,769
Percent of total enrollment	53%	18%	7.6%	6.5%	15%	100%

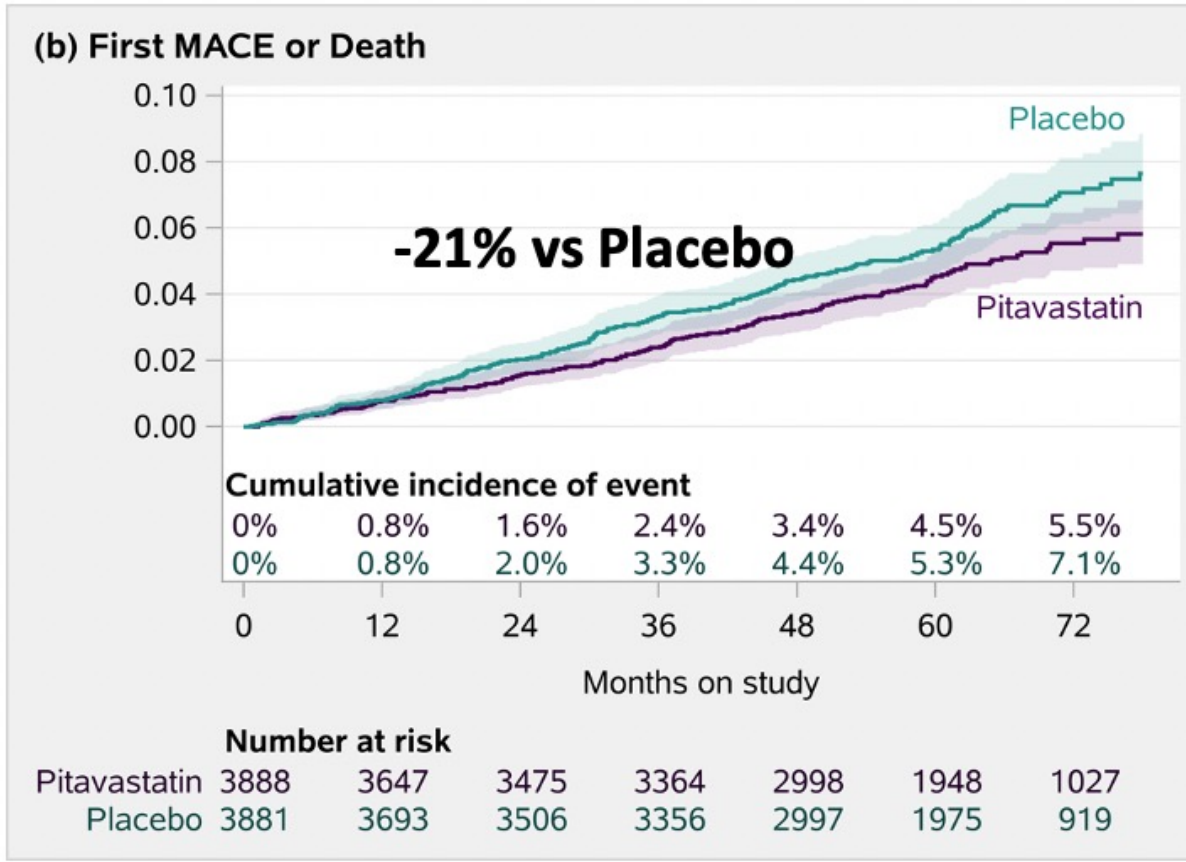
Baseline Characteristics		**Total (N=7769)**	**Pitavastatin (N=3888)**	**Placebo (N=3881)**
Age (years)	Median (Q1 – Q3)	50 (45-55)	50 (45-55)	50 (45-55)
Natal sex	Male	5350 (69%)	2677 (69%)	2673 (69%)
	Female	2419 (31%)	1211 (31%)	1208 (31%)
Gender identity	Cisgender	7367 (95%)	3687 (95%)	3680 (95%)
	Transgender spectrum	127 (2%)	63 (2%)	64 (2%)
	Not reported	275 (4%)	138 (4%)	137 (4%)
Race	White	2704 (35%)	1634 (35%)	1340 (35%)
	Black/African American	3208 (41%)	1569 (40%)	1639 (42%)
	Asian	1138 (15%)	571 (15%)	567 (15%)
CD4 count (cells/mm3)	Median (Q1 – Q3)	621 (448-827)	620 (449-832)	622 (445-824)
Nadir CD4 count (cells/mm3)	< 50 50-199 ≥ 200	1409 (18%) 2392 (31%) 3706 (48%)	688 (18%) 1202 (31%) 1859 (49%)	721 (19%) 1190 (31%) 1847 (47%)
HIV RNA (Copies/mL)	< LLQ LLQ - < 400 400+ Missing	5250 (88%) 617 (10%) 130 (2%) 1772	2641 (88%) 305 (10%) 63 (2%) 879	2609 (87%) 312 (10%) 67 (2%) 893
ASCVD risk score, (%)	Median (Q1 – Q3)	4.5 (2.1-7.0)	4.5 (2.1-7.0)	4.5 (2.2-7.0)
LDL-C (mg/dL)	Median (Q1 – Q3)	108 (87-128)	109 (87-128)	108 (87-127)

Grinspoon S. IAS 2023, NEJM 2023

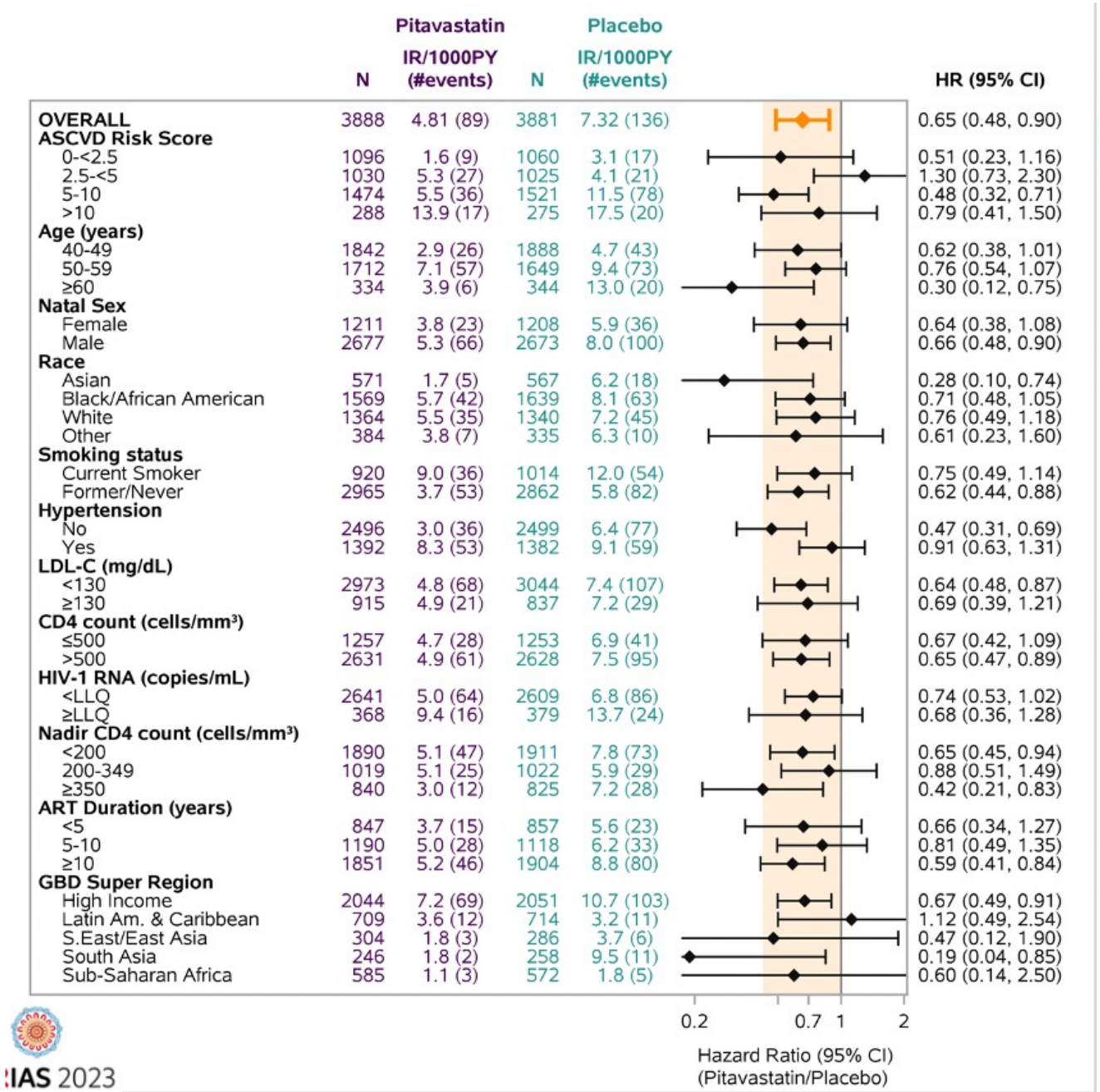
IAS 2023

Primary and Key Secondary Endpoints





Grinspoon S. IAS 2023, NEJM 2023



Effects on Key Subgroup

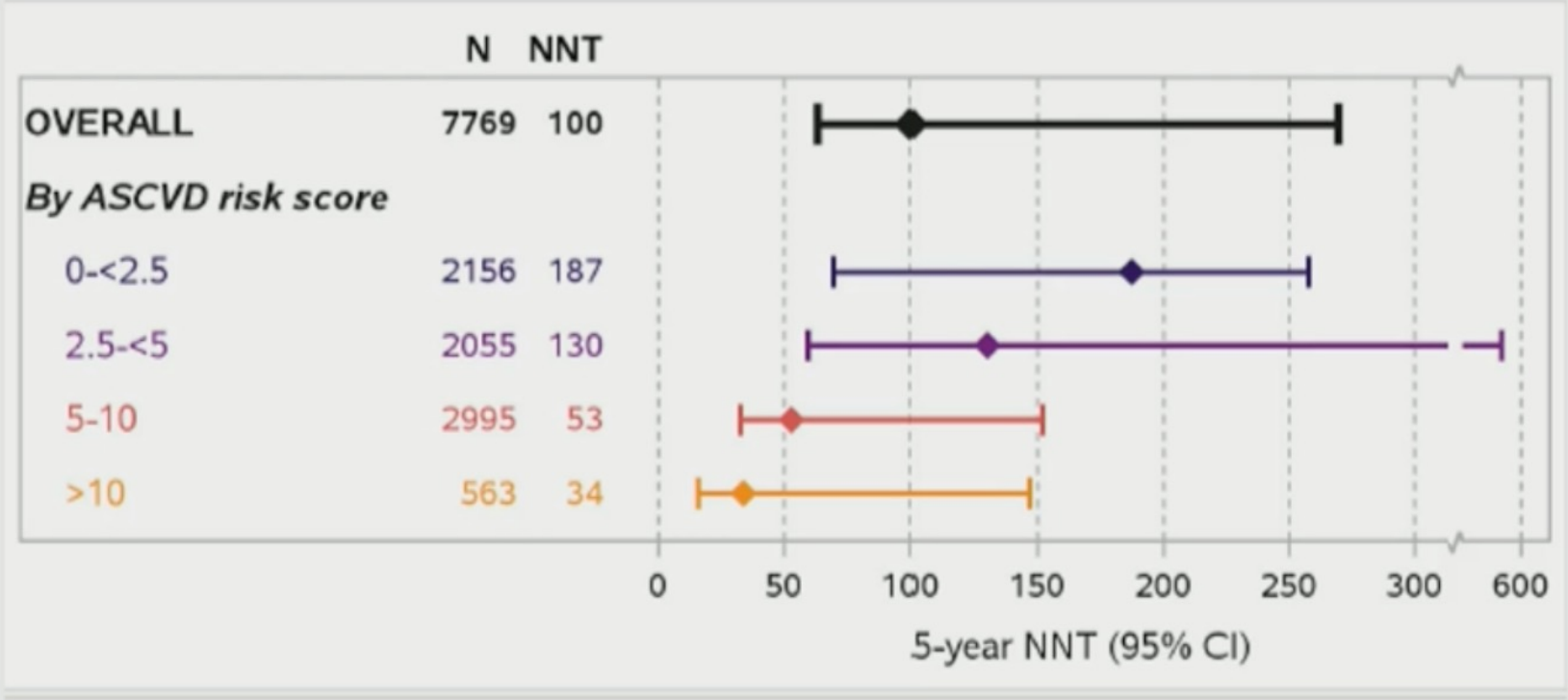
- Very consistent affect across major subgroups
- No treatment modification based on LDL, age, sex
- Generally consistent effects across race and GBD regions
- No treatment modification based on CD4, nadir CD4, HIV RNA, ART Duration

GBD = global burden of disease

Grinspoon S. IAS 2023, NEJM 2023

30% reduction in LDL cholesterol in pitavastatin arm. None in placebo arm.

5-Yr Number Needed To Treat (NNT) to Prevent One MACE Event



Decreasing NNT with increasing ASCVD risk score

CROI 2024

Grinspoon NEJM 2023; updated with final REPRIEVE data

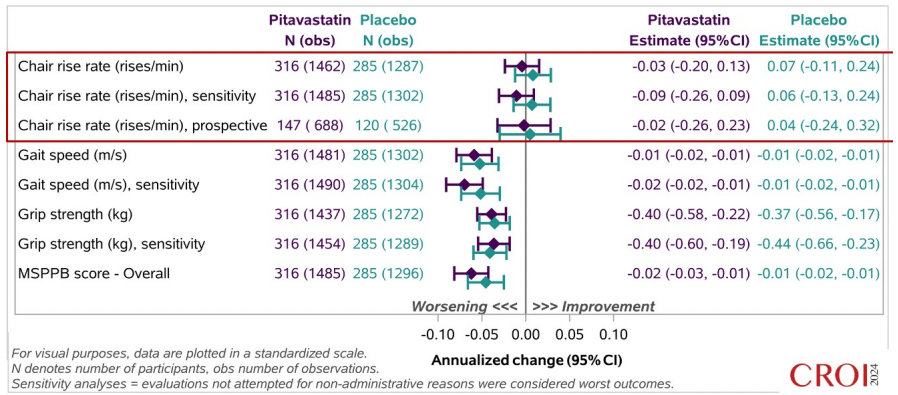
REPRIVE Updates at CROI

- Female sex was not protective against CVD (unlike non-HIV)
- Smoking, hypertension, and detectable HIV viral load associated with CVD
- No impact of statin on physical function among subset of participants
  - 4-meter gait, balance, grip strength, rising from a chair 10 times, and the manual short physical performance battery

Results

Minimal changes in rise change in either group
- Similar results seen when restricted to prospective only group
- Smaller change than anticipated 0.58 rise/min/year

	Pitavastatin N (obs)	Placebo N (obs)	Pitavastatin Estimate (95%CI)	Placebo Estimate (95%CI)
Chair rise rate (rises/min)	316 (1462)	285 (1287)	-0.03 (-0.20, 0.13)	0.07 (-0.11, 0.24)
Chair rise rate (rises/min), sensitivity	316 (1485)	285 (1302)	-0.09 (-0.26, 0.09)	0.06 (-0.13, 0.24)
Chair rise rate (rises/min), prospective	147 (688)	120 (526)	-0.02 (-0.26, 0.23)	0.04 (-0.24, 0.32)
Gait speed (m/s)	316 (1481)	285 (1302)	-0.01 (-0.02, -0.01)	-0.01 (-0.02, -0.01)
Gait speed (m/s), sensitivity	316 (1490)	285 (1304)	-0.02 (-0.02, -0.01)	-0.01 (-0.02, -0.01)
Grip strength (kg)	316 (1437)	285 (1272)	-0.40 (-0.58, -0.22)	-0.37 (-0.56, -0.17)
Grip strength (kg), sensitivity	316 (1454)	285 (1289)	-0.40 (-0.60, -0.19)	-0.44 (-0.66, -0.23)
MSPPB score - Overall	316 (1485)	285 (1296)	-0.02 (-0.03, -0.01)	-0.01 (-0.02, -0.01)

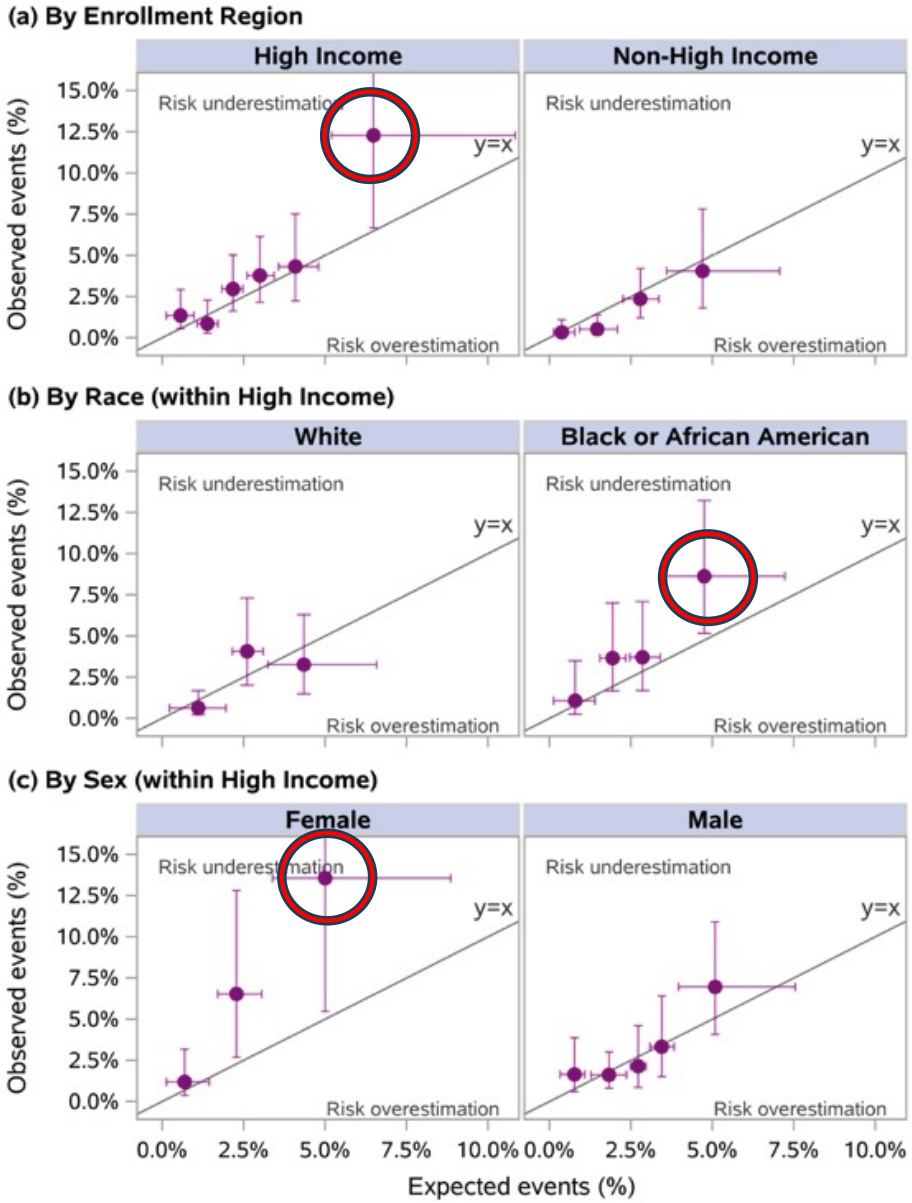


For visual purposes, data are plotted in a standardized scale.
N denotes number of participants, obs number of observations.
Sensitivity analyses = evaluations not attempted for non-administrative reasons were considered worst outcomes.

CROI 2024

- ACC/AHA CVD risk calculator performance varied by high- vs low-income country and demographics

Figure 1. Calibration plots showing observed versus expected CV death, MI, stroke events. Error bars show the 95% CI for observed events and the 10th and 90th percentile predicted risk score per decile.



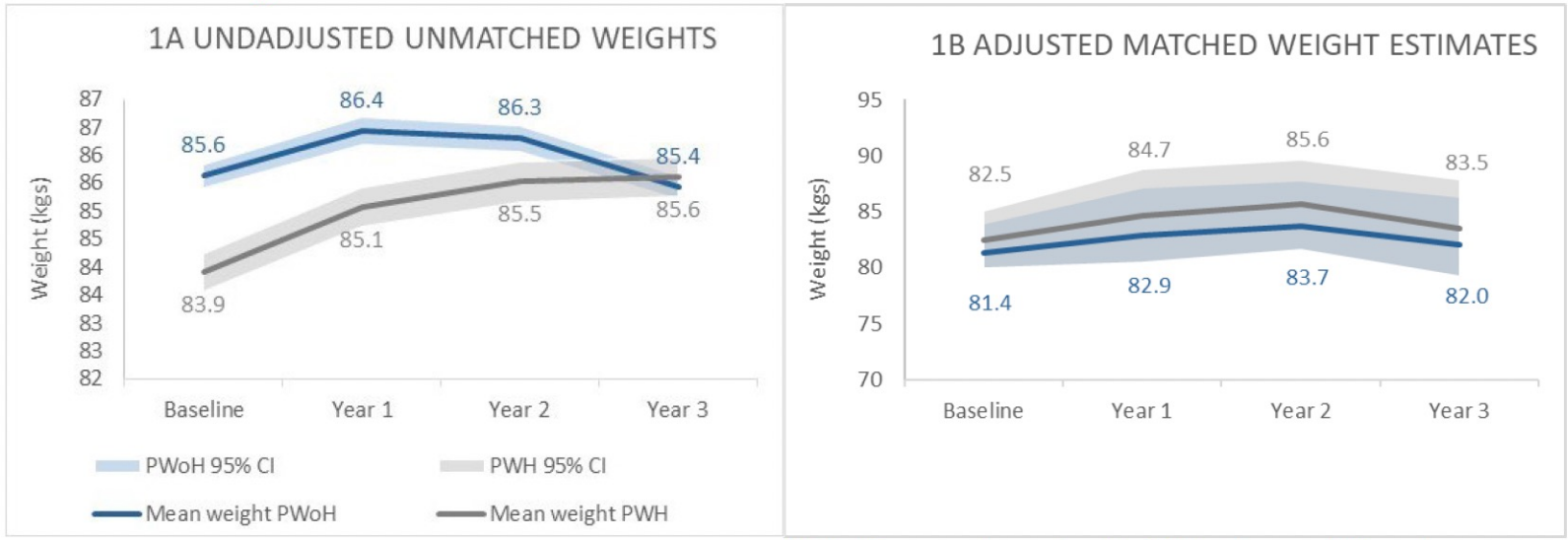
Zanni. CROI 2024, Erlandson. CROI 2024, Grinspoon. CROI 2024

Weight Change Data at CROI: Comparing PWH and PWoH

TRIO Health Cohort

- Retrospective review of weight and BMI at 3 years among PWH and PWoH (2015-23):
  - PWH: 1) treatment-experienced virally suppressed at baseline and 3 years, or 2) stable on 1st ART, ≥ 12 months since regimen start and virally suppressed ≥ 6 months (i.e., most PWH in care)
  - PWoH: matched to PWH
- 68,856 qualified individuals, 11,888 (17%) were PWH (902 [8%] suppressed on 1st ART).

Figures 1a-b: Weight change over time: unadjusted unmatched and adjusted matched weight estimates



Adjusted for race, gender, age, baseline BMI, baseline comorbidities and concomitant medications different based on baseline characteristics analysis.

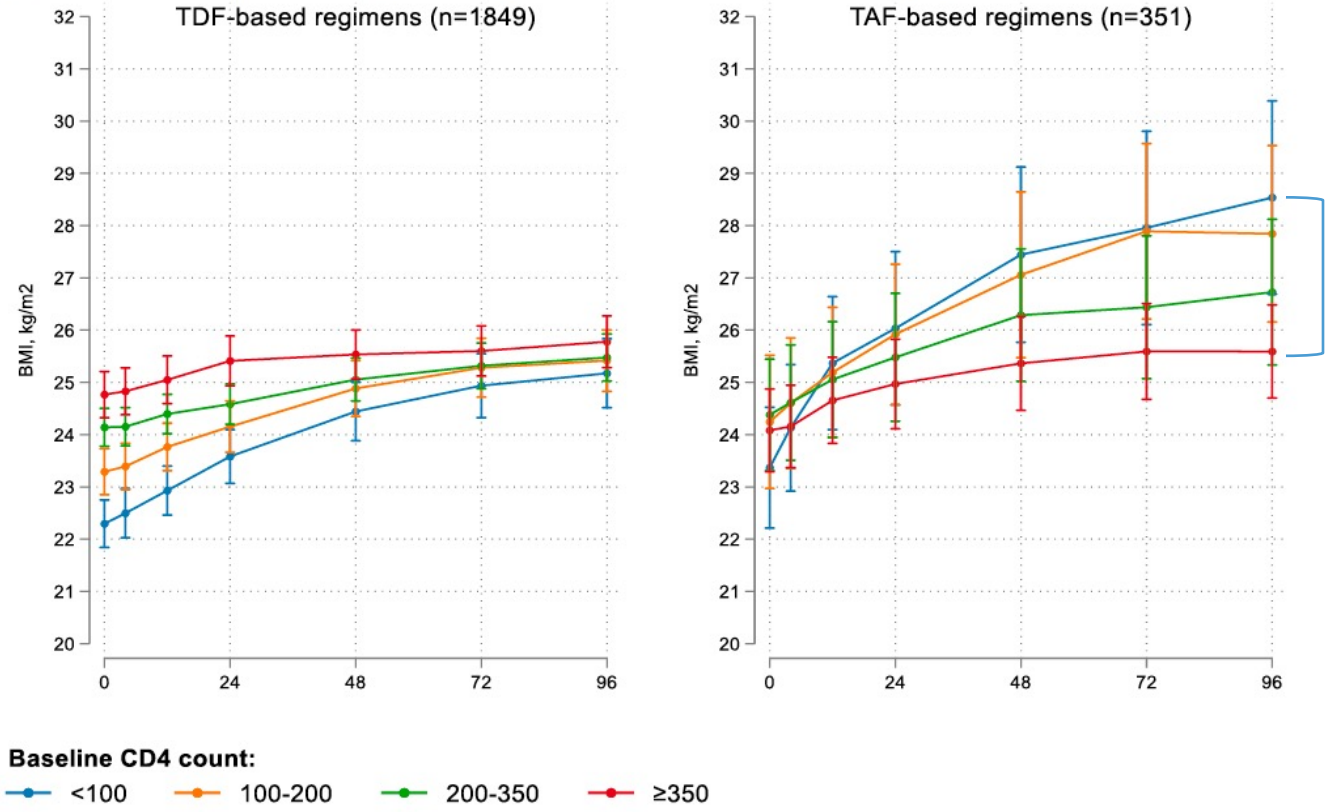
Elion. CROI 2024

Weight Change Data at CROI: Baseline CD4 and weight gain after ART initiation

- Data were pooled from 3 clinical trials: ADVANCE (n=1053), NAMSAL (n=613), and WHRI001 (n=536).
- The trials used **first-line ARV regimens** (TAF/XTC/DTG, TDF/XTC/DTG, and TDF/XTC/EFV) and enrolled **in Cameroon, India, Uganda and South Africa.**
- BMI over 96 weeks was assessed, stratified by baseline CD4 count as a marker for disease stage (<100, 100-200, 200-350, ≥350 cells/mm3).
- Multivariate models at week 96 assessed factors associated with BMI and clinical obesity (BMI ≥30), adjusting for baseline CD4 category, age, sex, TDF, EFV and trial. Models were assessed with/without interactions between baseline CD4 category and TDF/EFV use

ADVANCE, NAMSAL, WRHI Trials

Figure 1 – Pooled analysis showing BMI change for those on TAF vs TDF containing regimens across the three studies



Hill. CROI 2024

Weight Change Data at CROI: Sex differences in weight gain after switch to Integrase Inhibitors

Study AIM: Assess differences in body weight change by sex up to 6 years following switch to INSTIs

METHODS

MWCCS
MACS/WIHS COMBINED COHORT STUDY

We used data collected between 2007-2020 from men and women enrolled in the MACS/WIHS Combined Cohort Study (MWCCS):

1) **INSTI group:** on ART ≥ 2 years, HIV VL <200 cop/mL and switched to INSTI-ART
2) **Non-INSTI Control**: on ART ≥ 2 years, HIV VL <200 cop/mL and remained on non-INSTI ART
3) **HIV seronegative Control**

*Excluded study visits where pregnant/within 2 years postpartum, active malignancy or TB, receiving chemotherapy/radiation or PrEP

RESULTS

Table 1. Baseline (pre-switch) cohort characteristics, n=3466

Median (Q1, Q3) or n(%)	INSTI N=634			Non-INSTI N=1123			HIV seronegative N=1709		
	Men N=223	Women N=411	P value	Men N=412	Women N=711	P value	Men N=891	Women N=818	P value
Age, years	55 (49, 62)	51 (45, 57)	<0.001	52 (45, 58)	48 (41, 53)	<0.001	58 (50, 64)	46 (37, 53)	<0.001
Black race	50 (22)	270 (66)	<0.001	121 (29)	428 (60)	<0.001	183 (21)	561 (69)	<0.001
<HS Education	9 (4)	153 (37)	<0.001	34 (8)	247 (35)	<0.001	33 (4)	292 (36)	<0.001
BMI, kg/m²	25 (23, 29)	29 (25, 35)	<0.001	26 (23, 28)	29 (25, 35)	<0.001	27 (24, 30)	31 (26, 37)	<0.001
CD4, cells/mm³	610 (476, 841)	701 (519, 874)	0.010	648 (483, 855)	602 (446, 792)	0.004	*n/a*	*n/a*	*n/a*
Undetectable HIV RNA	197 (88)	349 (85)	ns	369 (90)	615 (87)	ns	*n/a*	*n/a*	*n/a*
TAF use	12 (5)	16 (4)	ns	14 (3)	5 (1)	0.002	*n/a*	*n/a*	*n/a*
NNRTI use	117 (53)	180 (44)	0.045	243 (59)	363 (51)	0.012	*n/a*	*n/a*	*n/a*
Time on ART, years	16 (11, 20)	13 (7, 18)	<0.001	13 (5, 18)	12 (6, 15)	<0.001	*n/a*	*n/a*	*n/a*

- PWH had lower BMI than PWoH
- Few were on TAF pre-switch, meaning likely most on TFV, which suppresses weight

Lahiri. CROI 2024

Weight Change Data at CROI: Sex differences in weight gain after switch to Integrase Inhibitors

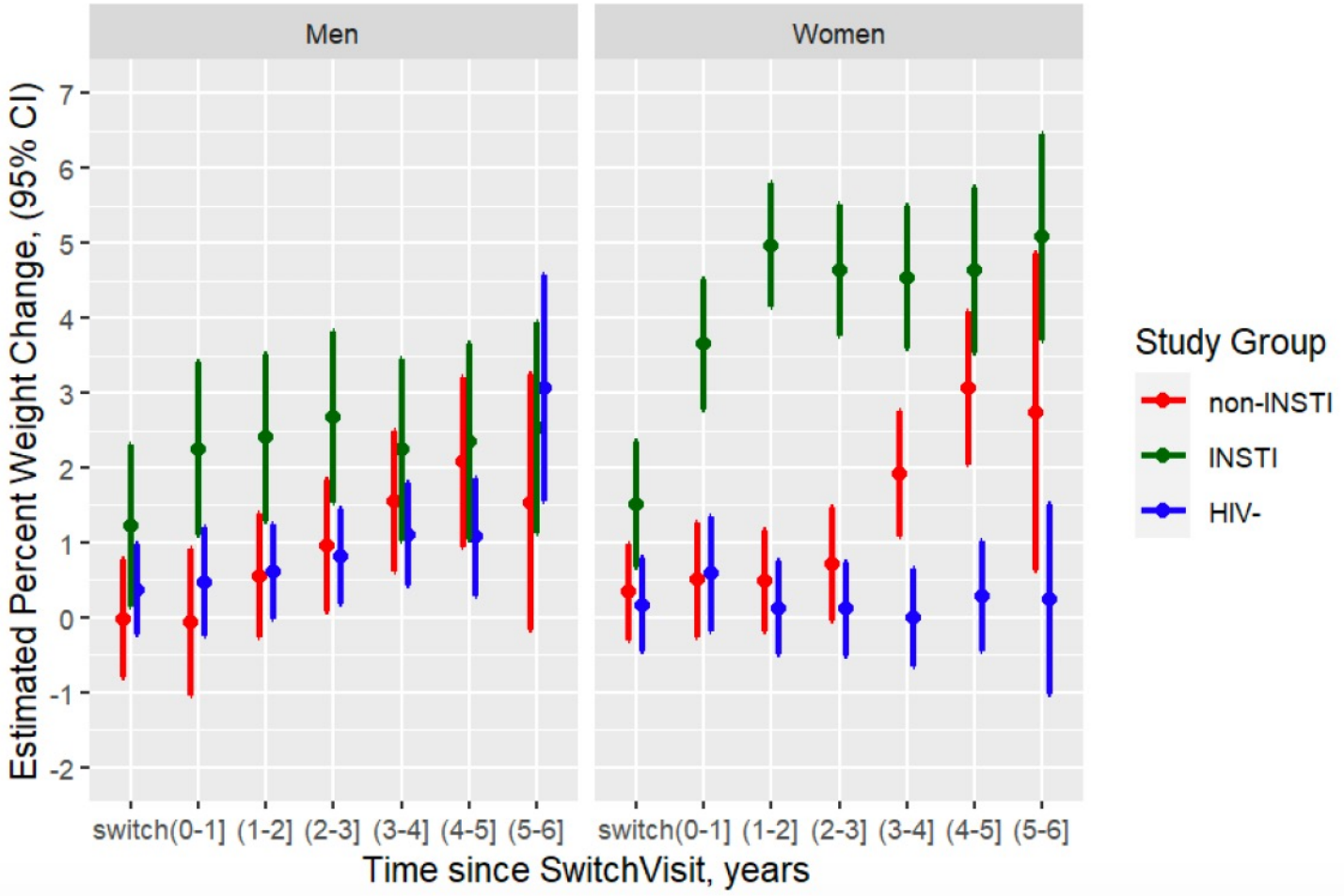
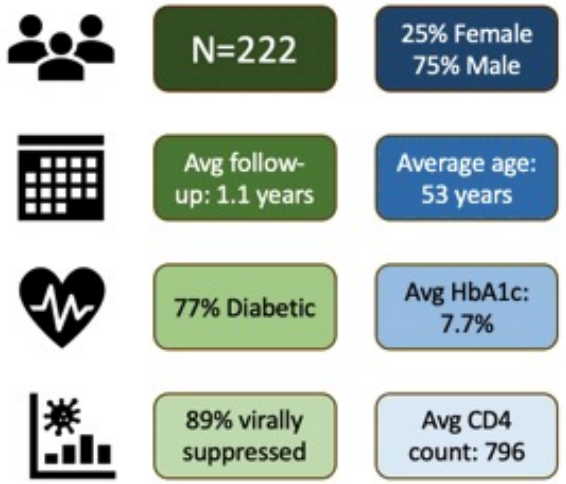


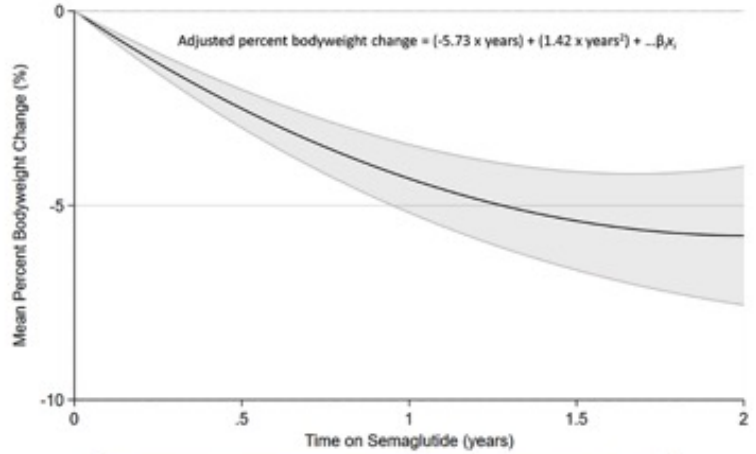
Figure 2. Model-estimated mean percent weight change among men and women with and without HIV in the MWCCS, stratified by study group and years since switch. Models adjusted for age, race/ethnicity, socioeconomic status, diabetes. Sex*group*years interaction term, p<0.0001

Weight Change Data at CROI: Semaglutide

- CINCS cohort study (2018-2022; n=222)
  - Initiated injectable or oral semaglutide and had ≥2 weight measurements
  - Baseline characteristics
    - Age (53 years), virologically suppressed (89%), diabetic (77%), female (25%), HbA1c (7.7%)

- Semaglutide results at 1 year:
  - Associated with significant weight loss (**6.5 kg [5.7% of bodyweight]**)
  - Those who weighed more at start, lost more





On average, PWH lost 5.7% of bodyweight (95% CI: -6.9, -4.5)

On average, PWH lost 6.5kg (95% CI: -7.7, -5.2)

CINCS: Centers for AIDS Research Network of Integrated Clinical Systems.

Crane HM, et al. CROI 2024. Abstract 797.

Impact of Semaglutide on Inflammation and Immune Activation in HIV-Associated Lipohypertrophy

- Randomized, double-blind study (n=108)
  - Stable ART, HIV-associated hypertrophy, BMI ≥25 kg/m^2, waist circumference (male/female ≥95/≥94 cm)
  - Baseline characteristics
    - Age (53 years), HbA1c (5.6%), INSTI (82%)
- Groups
  - Semaglutide versus placebo
- Semaglutide had significant effects on several key biomarkers associated with CVD in HIV

Key Findings at Week 32

	Changes With Semaglutide (%)
Visceral adipose tissue	-31
Subcutaneous adipose tissue	-11
Body weight	-10
Lean body mass	-6
hsCRP	-40
IL-6	-19
sCD163	-12

Eckard AR, et al. CROI 2024. Abstract 798.

ACTG A5371 (SLIM LIVER): Impact of Semaglutide on metabolic dysfunction-associated steatotic liver disease MASLD in PWH

- Open label study (N=49) of PWH on suppressive ART, elevated waist circumference, and evidence of MASLD
- Clinically significant reductions in Intra-Hepatic Triglyceride (IHTG) as measured by MRI scan with semaglutide (*P*<0.001)
  - ≥30% relative reduction in 58%
  - Complete resolution
  - Greater reductions in women, white/Hispanic, and >60 years of age
- Mean weight loss: 7.8 kg
  - Greatest losses in women, white/Hispanic, and ≥40 years of age
- Significant improvements in fasting plasma glucose, HOMA-IR, HbA1c, and triglycerides
- Semaglutide was well tolerated

Outcomes at Week 24

	Result
Change in IHTG by MRI-PDFF (%)	-31*
Complete resolution of MASLD (%)	**29***
Change in:	
Waist circumference (cm)	-6.7*
Glucose (mg/dL)	-9.9*
HOMA-IR	-1.5*
HbA1c (%)	-0.3*
Triglycerides (mg/dL)	-27†

*P<0.001 and †P<0.01 versus baseline.

Lake JE, et al. CROI 2024. Abstract 159.

ACTG A5371 (SLIM LIVER):

Methods

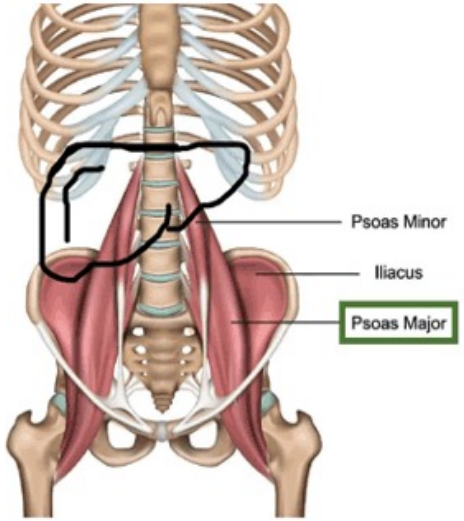
CROI 2024

Outcomes (baseline → week 24)

- Psoas volume/fat fraction: captured from th liver magnetic resonance imaging proton-density fat fraction (MRI-PDFF)
- Physical function: timed chair rise test & 4-meter gait speed

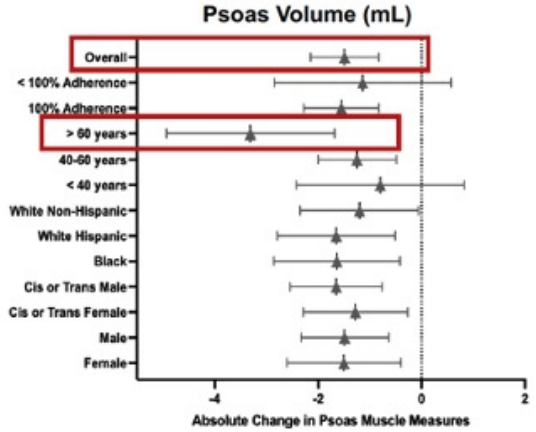
Statistical Analysis

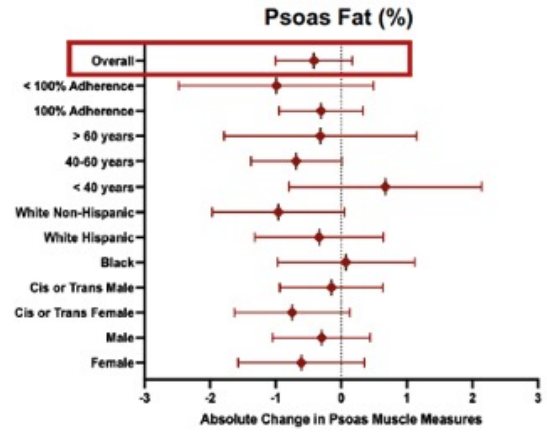
- Mean change from baseline estimated with linear regression models
- Spearman's correlations used to examine associations between MASLD markers and muscle measures



Results: Change in muscle volume & fat

CROI 2024





Overall psoas muscle volume **declined**, but psoas muscle fat content did not significantly change. PWH >60 years had the greatest decline in muscle volume.

Results: Change in physical function

CROI 2024

Parameter	Baseline	Week 24	Change, Baseline to Week 24 (estimate, 95% CI)	P-value
5x Chair Rise (seconds)	12.5 (3.6)	11.9 (3.3)	-0.66 (-1.4, 0.07)	0.077
10x Chair Rise (seconds)	26.2 (7.0)	25.0 (6.8)	-1.27 (-2.7, 0.10)	0.069
Gait speed (meters/second)	0.93 (0.23)	0.98 (0.24)	0.05 (-0.01, 0.10)	0.078
Presence of slow gait speed (<1 meters/second)	No: 18 (37%) Yes: 31 (63%)	No: 26 (54%) Yes: 22 (46%)	RR: 0.73 (0.55, 0.97)	0.029

Chair rise time and gait speed were **preserved** despite loss of psoas muscle volume. These changes in function were not correlated with change in overall weight or BMI.

Grace. CROI 2024

Routine Collection of Patient-Reported Outcomes in HIV Clinics: Findings After >100,000 Assessments

Mindy Dai[1], Lydia N Drumright[1], Rob Fredericksen[1], Joseph AC Delaney[1], L Sarah Mixson[1], Bridget M Whitney[1], William B Lober[1], Mari M Kitahata[1], Kenneth H Mayer[2], Jeffrey Jacobson[3], Edward Cachay[4], Laura Bamford[4], Katerina Christopoulos[5], Heidi M Crane[1] , for the CNICS Cohort

[1] University of Washington, Seattle, WA, USA; [2] The Fenway Institute, Boston, MA; [3] Case Western Reserve University, Cleveland, OH; [4] University of California, San Diego, San Diego, CA; [5] University of California, San Francisco, San Francisco, CA;

CNICS CFAR Network Of Integrated Clinical Systems

BACKGROUND

- Patient-reported measures and outcomes (PROs) provide important information to supplement routine clinical care and facilitate research.
- The CFAR Network of Integrated Clinical Systems (CNICS), a network of multi-provider, outpatient HIV clinics, has integrated PRO collection into routine care to improve clinical care and facilitate research.
- The routine collection of PROs was initiated at the University of Washington in 2009 and has since been expanded to 8 sites across the United States.

METHODS

- People living with HIV (PWH) presenting for care completed touch-screen-based assessments at routine clinic visits every 3-6 months using a web-based application.
- The length and number of instruments are optimized based on prior responses, skip patterns, time since the last PRO, and other factors.
- Assessments are available in English and Spanish, and more recently Amharic, Haitian Creole, and Brazilian Portuguese.
- The assessment includes validated instruments on antiretroviral medication adherence, mental health, substance use, quality of life, symptom burden, HIV stigma, social support, sexual risk behavior, intimate partner violence (IPV), and other clinically relevant domains.

RESULTS

- **20,455** unique PWH patients with an average of **5.7 PROs** completed
- **65% of patients** have 3 or more PROs completed
- CNICS PROs have been utilized in **80+ research papers** to date

Figure: PROS (n=116, 895) by Site and Region

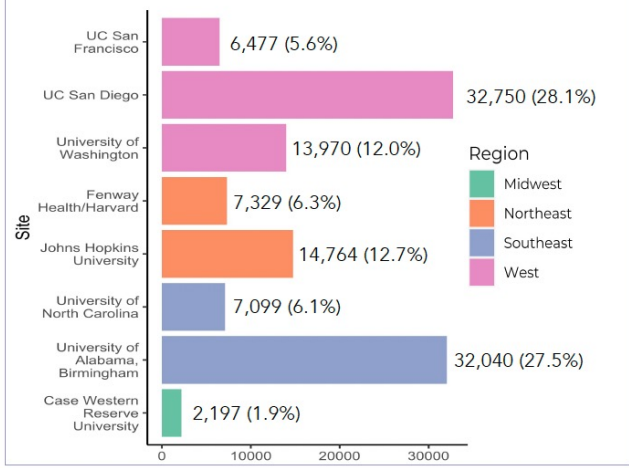


Table 1: Demographic Characteristics of PWH

	All Individuals (N=20455)
Age at Assessment	
Mean (SD)	43.9 (11.5)
Median [Range]	44 [18, 93]
Female Sex	3435 (16.8%)
Transgender	338 (1.7%)
Race	
White	8800 (43.0%)
Black	7508 (36.7%)
Hispanic	3046 (14.9%)
Other/Unknown	1101 (5.4%)

Table 2: Proportion of PWH Reporting Actionable Patient Reported Outcomes and Measures at first and last PRO and mean number of times reported

	Initial PRO % (95%CI)	Last PRO % (95%CI)	PROs per Person Mean (±SD)		Initial PRO % (95%CI)	Last PRO % (95%CI)	PROs per Person Mean (±SD)
Moderate-severe depression	25 (24, 26)	22 (21, 22)	5.3 (±4.4)	Current cocaine use	9 (8, 9)	8 (7, 8)	5.1 (±4.3)
Suicidal Ideation	4 (2, 4)	5 (5, 5)	5.0 (±4.3)	Current methamphetamine use	11(10, 11)	11 (10, 11)	5.1 (±4.3)
Anxiety/Panic Attack	28 (27, 29)	27 (25, 27)	5.3 (±4.5)	Current opioid use	4 (3, 4)	4 (3, 4)	5.1 (±4.3)
At-risk/Hazardous Alcohol use	19 (18, 19)	17 (16,17)	5.2 (±4.4)	Any current meth, cocaine, opioid use	18 (18, 19)	17 (17,18)	5.1 (±4.3)
Current Binge Alcohol use	35 (35, 36)	32 (31, 33)	5.3 (±4.5)	Intimate Partner Violence	11 (10,12)	10 (9, 10)	2.7 (±1.9)
Current Cigarette use	39 (38, 40)	36 (35, 37)	4.3 (±3.5)	Concern for STI	18 (18, 20)	18 (17, 19)	2.5 (±1.8)

CONCLUSIONS

- PRO collection can be efficiently and effectively implemented in the daily workflow of busy HIV primary care clinics.
- PROs provide insight into behavioral health challenges that may otherwise be unobserved.
- Key example: PROs identified a high prevalence of depression, anxiety, substance use, and intimate partner violence.

1 in 5 reported moderate-severe depression

1 in 3 reported binge drinking

More than **1 in 6** reported recreational cocaine, opioid, or methamphetamine use

1 in 10 reported concern for intimate partner violence

Acknowledgments

Patients, providers, and staff of the CNICS Cohort. This work was supported by NIAAA: U24AA020801, U01AA020793, U01AA020802; CNICS R24AI067039; NIAID: UW CFAR P30AI027757, UAB CFAR P30AI027767, UNC CFAR P30AI050410, UCSF CFAR P30AI027763, K24AI167805, JHU CFAR P30AI094189; NIDA: R01DA047045, R01DA058938, R01DA044112, U24DA058307; NIA: R33AG067069; NIMH: P30MH062246.

UNIVERSITY of WASHINGTON

CFAR UNIVERSITY OF WASHINGTON/FRED HUTCH CENTER FOR AIDS RESEARCH

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RESULT

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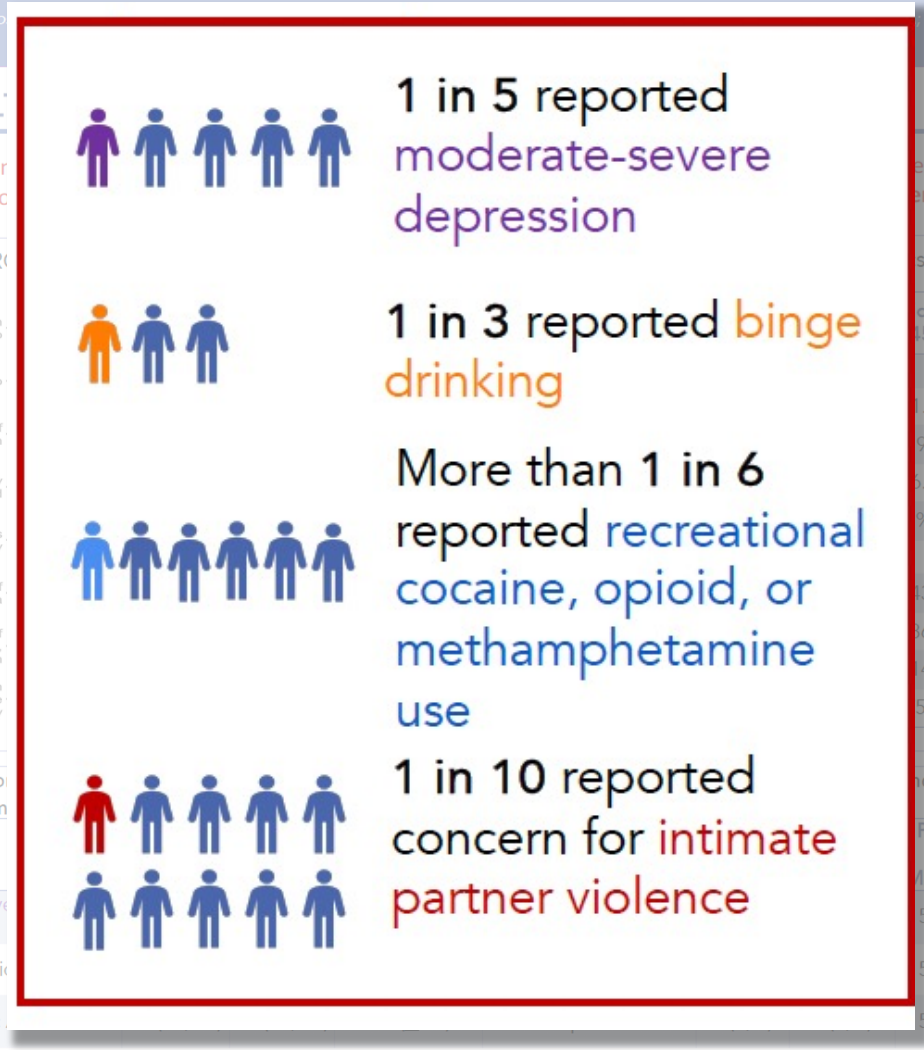
Figure: PR…



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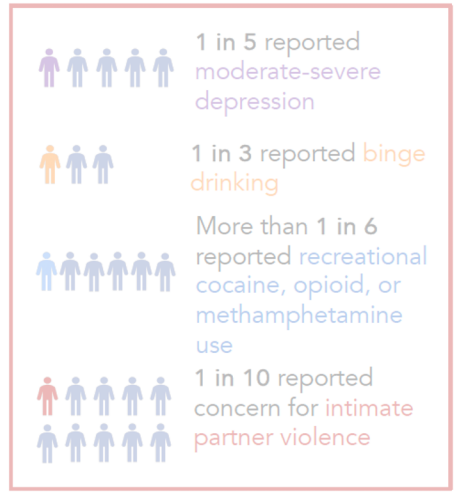

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UNIVERSITY of WASHINGTON

CFAR

Frailty and Health-Related Quality of Life in an Aging Cohort of People with HIV 2012-2022

0840

Lydia N Drumright[1], Bridget M Whitney[1], Crystal Chapman Lambert[2], Amanda L Willig[2], Robin M Nance[1], Stephanie A Ruderman[1], Sonia Napravnik[3], Katerina Christopoulos[4], Edward Cachay[5], Lara Haidar[6], Jimmy Ma[1], Mari M Kitahata[1], Joseph AC Delaney[1], Allison R Webel[1], Heidi M Crane[1]

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KEY FINDINGS

- Overall, quality of life (QoL) increased over time among people with HIV (PWH) in care in the USA
- PWH who were frail had a 24% lower QoL than those who were robust and prefrail had a 10% lower QoL
- Minimizing and preventing frailty among PWH are realistic targets that could increase QoL among PWH

BACKGROUND

- People with HIV (PWH) are now living near normal lifespans, due to advancements in antiretroviral therapy.
- However, PWH experience accelerated aging and frailty at earlier ages than the general population.
- We examined the impact of frailty on quality of life (QoL) over time among PWH.

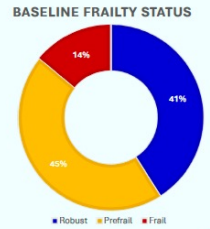
METHODS

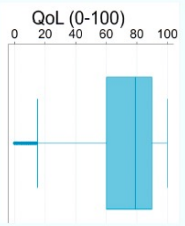
- Participants included PWH from 6 CFAR Network of Integrated Clinical Systems (CNICS) sites between 2012-2022.
- QoL was measured using EQ-5D visual analog scale (0-100).
- Frailty was assessed using a validated, modified frailty phenotype based on 4/5 Fried frailty components.
- Measures were collected by computer-based patient report outcomes, collected on a tablet in clinic every 4-6 months.
- Linear mixed models were used to assess individual level associations between frailty and QoL over time adjusting for age, sex, race/ethnicity, year, and post-March 2020 vs before.
- Linear regression of mean QoL by frailty category adjusted by year and March 2020 was used to assess population changes.

CONCLUSIONS

- QoL among PWH in care appears to be slowly increasing over time, however frailty can have a significant impact on QoL.
- PWH who were frail reported 24% lower QoL and those that were prefrail reported 10% lower QoL than robust PWH.
- Minimizing and preventing frailty among PWH, including addressing comorbidities that contribute to frailty, could increase QoL significantly among PWH in care.

RESULTS





- 23,397 PWH with 38,830 frailty assessments were included:
  - Mean age was 44.7 years (±11.4).
  - 13% were female at birth.
  - 48% reported White, 27% Black/African American, 18% Latine/Hispanic, and 7% other race/ethnicity.
- Left Figures: At baseline: 41% were robust, 45% prefrail, 14% frail; mean QoL: 73 (± 21.5)
- Table: QoL increased annually, by 0.4%, but decreased by 2% following March 2020. QoL was 24% lower among frail and 10% lower among prefrail PWH than robust PWH.
- Right Figure: Population-level trends in QoL with respect to frailty were similar to individual-level results, including a 13% lower in prefrail and 31% lower in frail QoL compared to robust PWH.

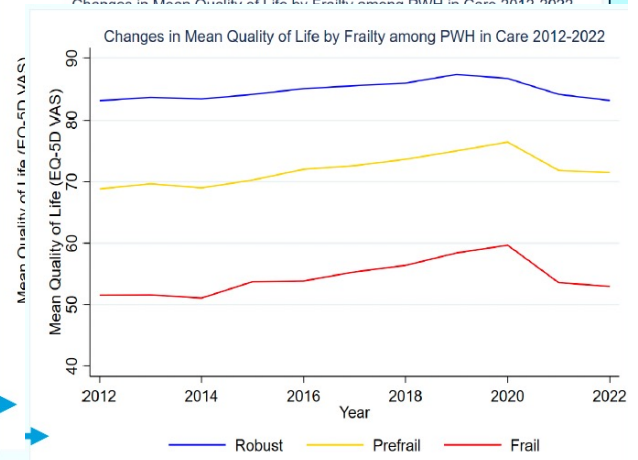


Table 1: Adjusted Associations between Frailty Status and QoL among PWH in Care 2012-2022 (N=12,397)

		Coefficient	95% CI	p-value
Frailty Status:	**Robust**	REF		
	Prefrail	-10.03	-10.42, -9.64	<0.001
	Frail	-23.76	-24.35, -23.17	<0.001
Age (per year)		-0.01	-0.04, 0.01	0.271
Male vs Female Sex		-0.34	-1.15, 0.48	0.413
Race/ Ethnicity:	**White**	REF		
	Black/ African American	4.66	3.99, 5.32	<0.001
	Latine/ Hispanic	3.48	2.74, 4.21	<0.001
	Other	2.52	1.39, 3.65	<0.001
March 2020 or later (vs before)		-2.06	-2.66, -1.46	<0.001
Year (per year)		0.37	0.31, 0.43	<0.001

ADDITION INFORMATION

We thank the participants, providers, and staff who made this study possible.

Funding was provided by NIAAA: U24AA020801, U01AA020793, U01AA020802; CNICS R24AI067039; NIAID: UW CFAR P30AI027757, UAB CFAR P30AI027767, UNC CFAR P30AI050410, UCSF CFAR P30AI027763, K24AI167805, JHU CFAR P30AI094189; NIDA: R01DA047045, R01DA058938, R01DA044112, U24DA058307; NIA: R33AG067069; NIMH: P30MH062246; and NHLBI: R01HL126538.

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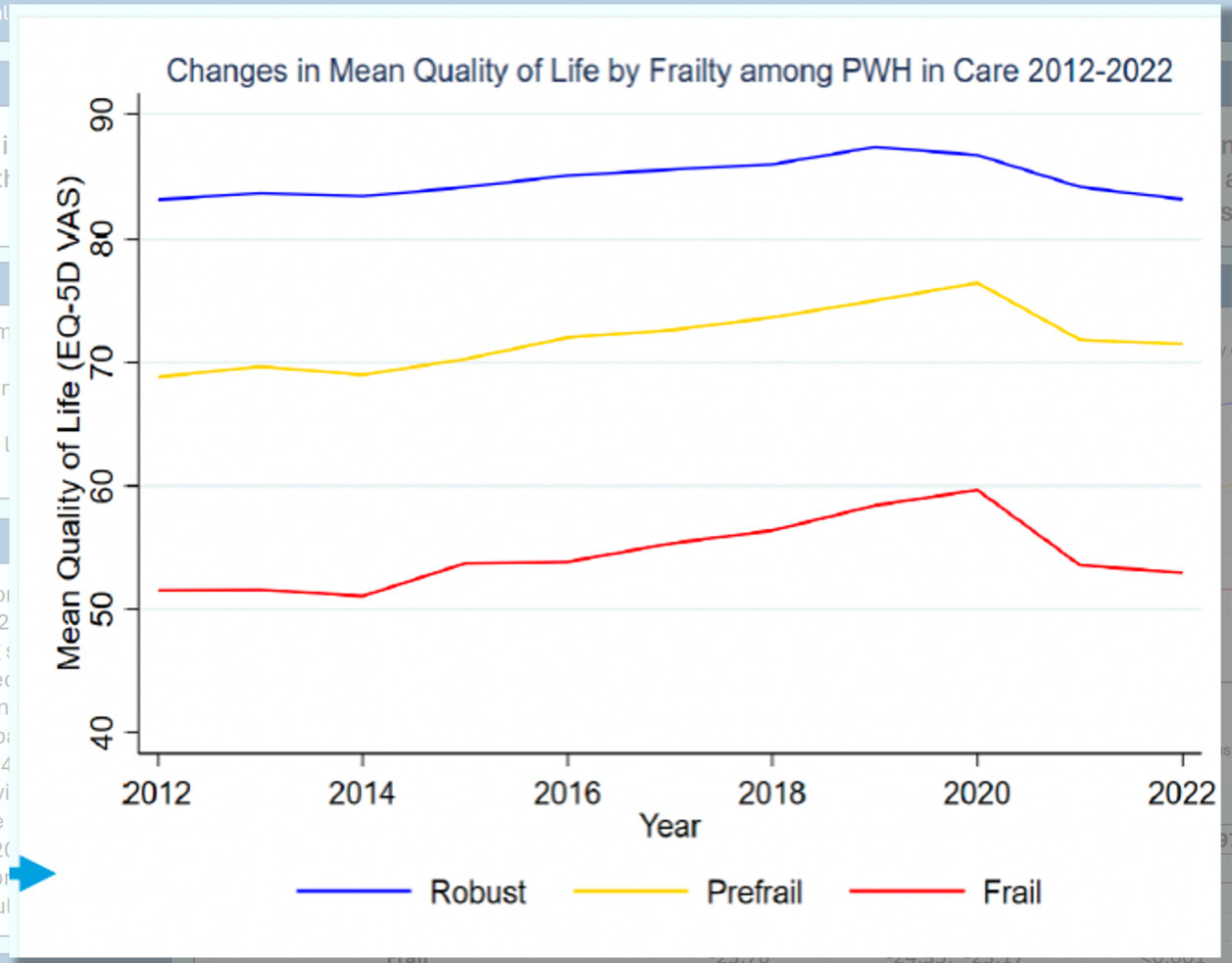

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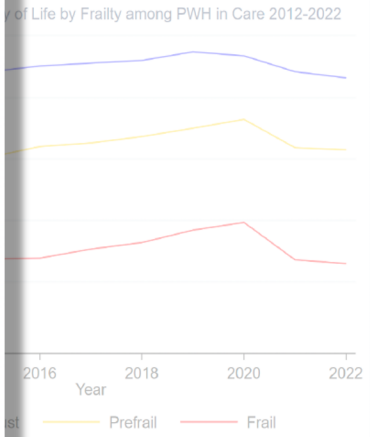

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Male vs Female Sex		-0.34	-1.15, 0.48	0.413
Race/ Ethnicity:	White	REF		
	Black/ African American	4.66	3.99, 5.32	<0.001
	Latine/ Hispanic	3.48	2.74, 4.21	<0.001
	Other	2.52	1.39, 3.65	<0.001
March 2020 or later (vs before)		-2.06	-2.66, -1.46	<0.001
Year (per year)		0.37	0.31, 0.43	<0.001

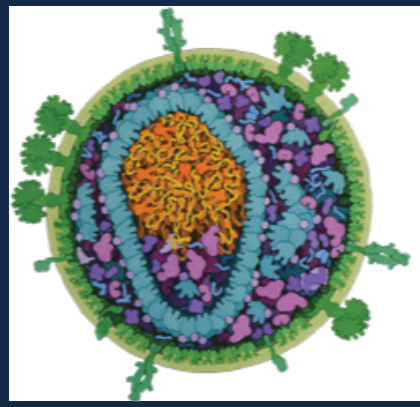
ADDITION INFORMATION

We thank the participants, providers, and staff who made this study possible.

Funding was provided by NIAAA: U24AA020801, U01AA020793, U01AA020802; CNICS R24AI067039; NIAID: UW CFAR P30AI027757, UAB CFAR P30AI027767, UNC CFAR P30AI050410, UCSF CFAR P30AI027763, K24AI167805, JHU CFAR P30AI094189; NIDA: R01DA047045, R01DA058938, R01DA044112, U24DA058307; NIA: R33AG067069; NIMH: P30MH062246; and NHLBI: R01HL126538.

Why does this matter? Comorbidities

- Comorbid conditions continue to be more common in people with HIV
  - But for CVD differences between people with and without HIV are **narrowing**
- Statin treatment reduces the risk of CVD in people with HIV, is well tolerated, and is a **biomedical approach** that can help further reduce comorbidity burden among people with HIV. PRACTICE CHANGER
- Weight changes on ART are complex with several factors at play in different people
- Semaglutide reduces weight, inflammatory markers, and liver fat and is a **biomedical approach** to further reduce comorbidity burden among people with HIV. PRACTICE CHANGER
- Heavy burden of mental health disorders and social stressors in people with HIV in clinical care. Demonstrates the value of **patient reported outcomes.** PRACTICE CHANGER



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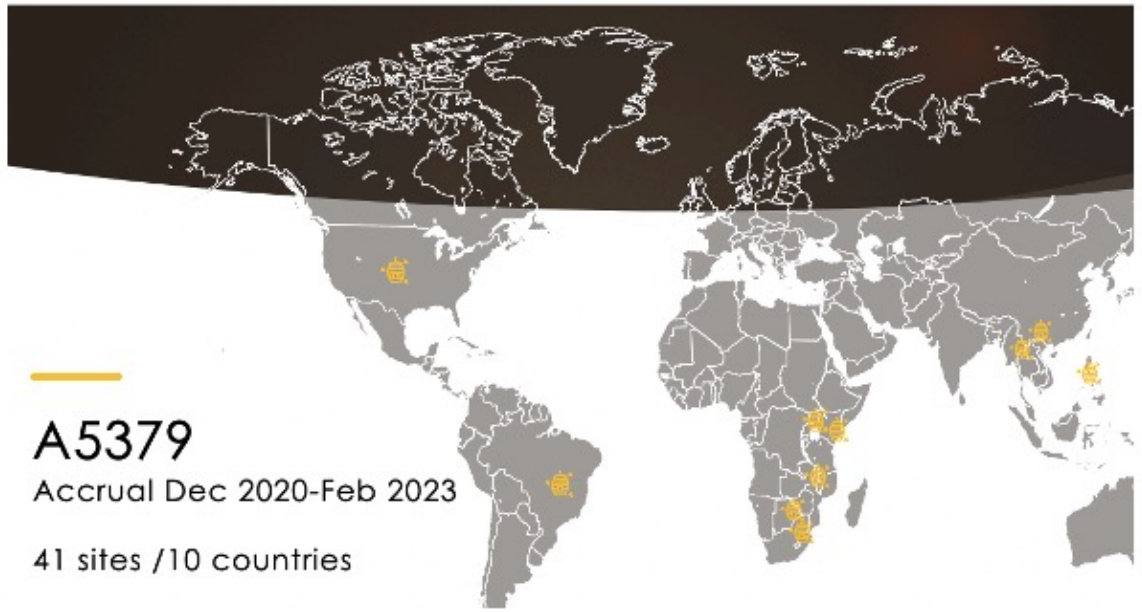
Co-Infections

Heplisav HBV re-vaccination in non-responders to prior vaccine



A5379 (BEeHIVe) Study Design

Phase III, prospective, open-label, interventional, two group study being conducted at US and non-US sites

Group B – No prior HBV vaccination (n=73)

- Participants receive HepB-CpG 3 doses at entry and at weeks 4 and 24.

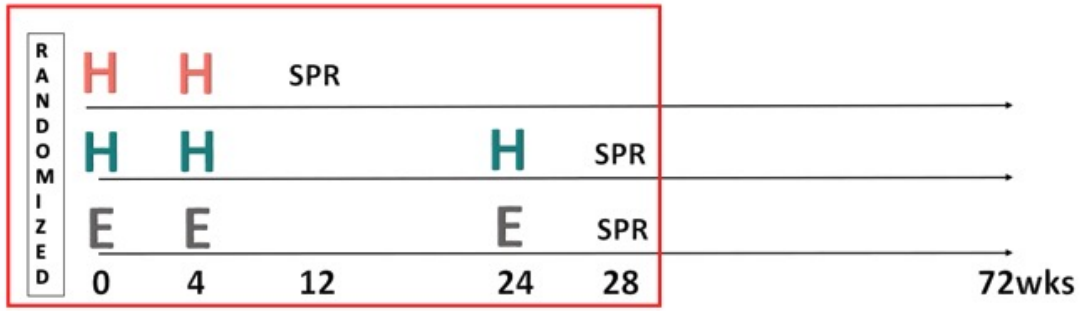
Group A – Non-response to conventional vaccine (n=561)

- Participants randomized 1:1:1 to receive
  - HepB-CpG 2 doses at entry and week 4 (n=187)
  - HepB-CpG 3 doses at entry and at weeks 4 and 24 (n=187)
  - HepB-alum (Engerix®) 3 doses at entry and at weeks 4 and 24 (n=187).
- Group A stratified by sex at birth and diabetes
- Participants on study for 72 weeks

HepB-CpG administered IM as 0.5 mL dose (contains 20 mcg of HBsAg and 3000 mcg CpG 1018® adjuvant)
HepB-alum administered as 1.0 ml dose (contains 20 mcg of HBsAg)

Primary Objectives – Non-responders

- **To compare the seroprotection response (SPR) of 2-dose HepB-CpG to 3-dose HepB-alum (non-inferiority)**
- **To compare SPR of 3-dose HepB-CpG to 3-dose HepB-alum (superiority)**
- **To describe safety**



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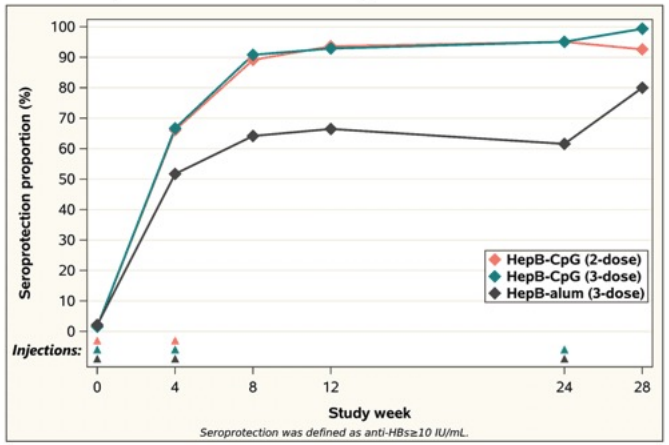
Statistical Considerations

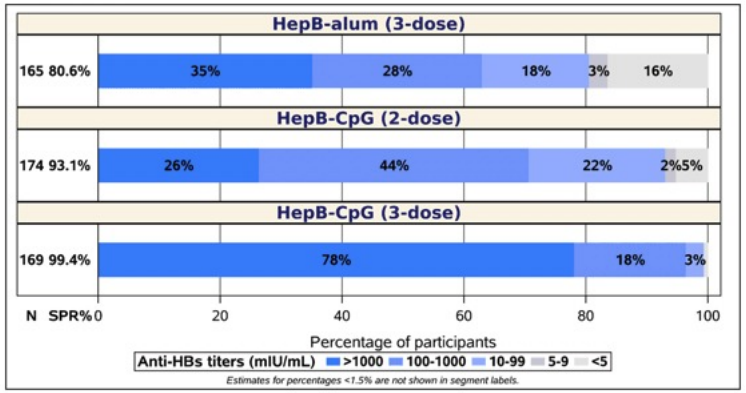
Primary SPR Endpoint

Seroprotection response (SPR) defined as anti-HBs ≥10 mIU/mL at Week 28 in 3-dose arm and Week 12 in 2-dose arm

SPR Proportion at Study Visits

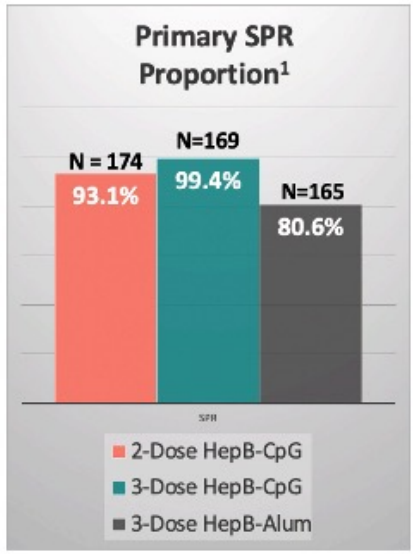


Distribution of Anti-HBs titers*



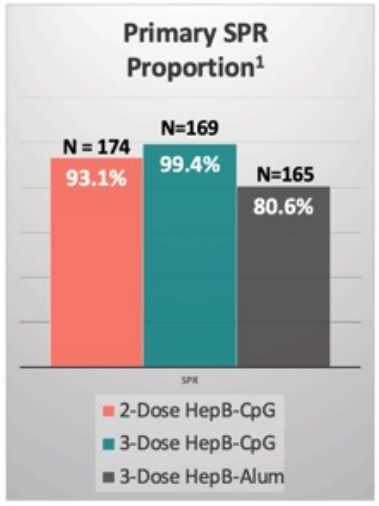
*Anti-HBs titers corresponding to the primary endpoint timepoint

Primary Results

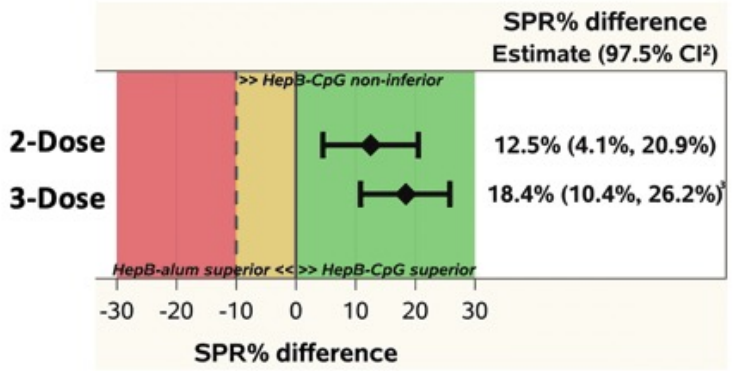


A sensitivity analysis that included participants with imputed results showed SPR:
92.3% (n=182), 99.4% (n=181), and 77.8% (n=180).

Primary Results



HepB-CpG SPR Comparison to HepB-Alum



[1] N denotes the number of participant in the Analysis Set
[2] 97.5% Newcombe CI
[3] Repeated CI adjusted for group sequential monitoring

ACTG

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HBV reactivation after switching from tenofovir (TFV)

- TDF and TAF both are highly effective against HBV as well as HIV
- When switching HIV regimens to 2-drug regimens like DTG/3TC, DTG, RPV, and CAB/RPV, there is risk of HBV reactivation in those with occult HBV infection
- Report of 41 patients who switched from TFV to non-TFV regimen:
  - 34 with anti-HBc + anti-HBsAg
  - **7 with isolated anti-HBc**
- **1 reactivation after switch in patient with isolated anti-HBc**

Of 7 PLWH with **isolated antiHBc**, 1 (14.3%) experienced **HBV reactivation** 3 months after switching to **CAB/RPVLA**

Figure 2. Trend of transaminases in the participant with HBV reactivation

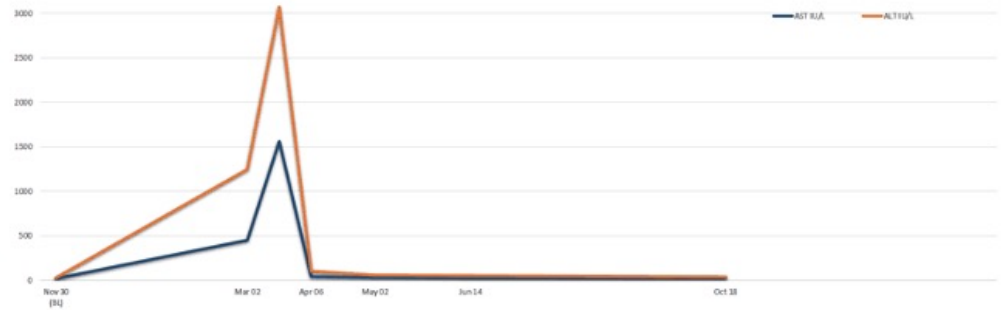
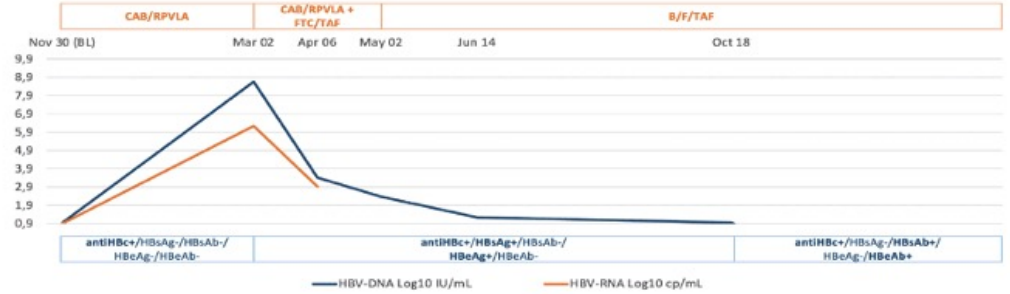


Figure 3. Trend of HBV-DNA, -RNA and serology in the participant with HBV reactivation. Alignment of the partial HBsAg before any ART and during HBV reactivation in the bottom



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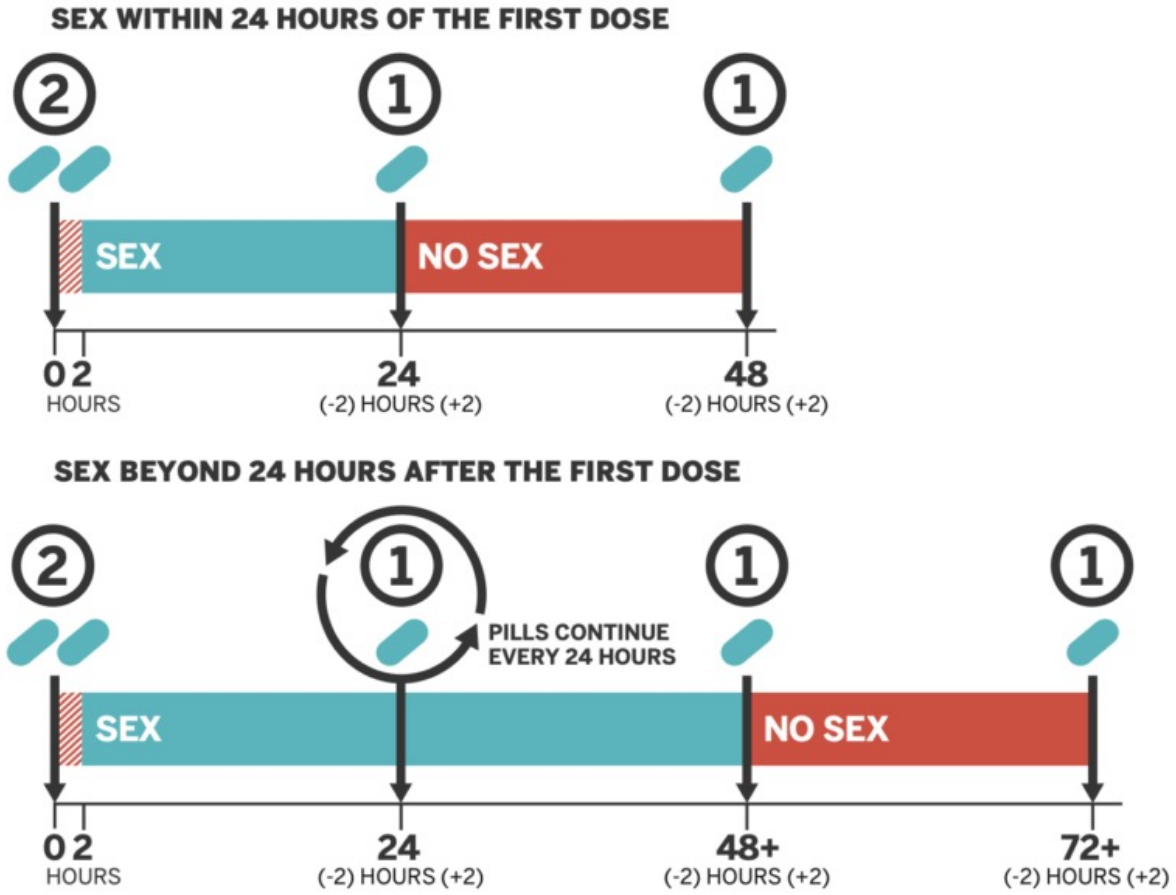
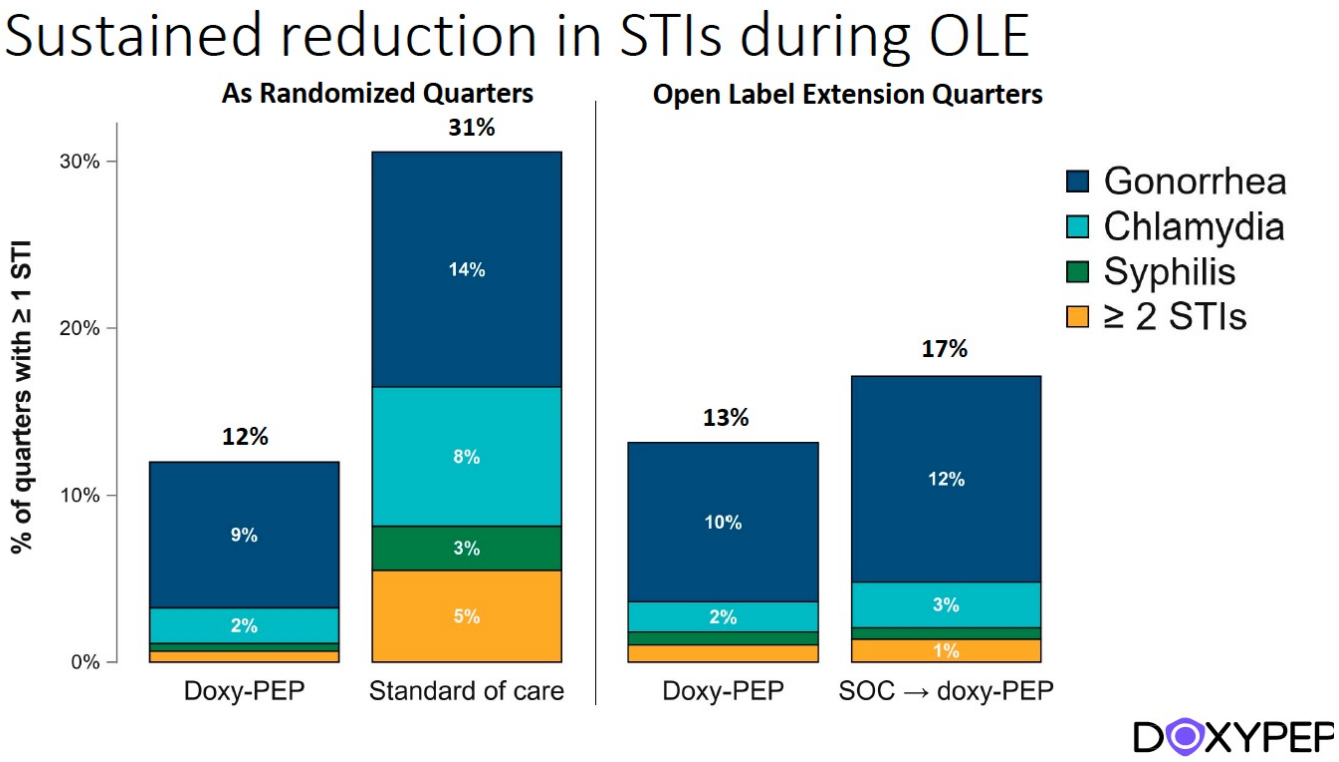
DoxyPEP at CROI



- DoxyPEP Trial
- ANRS DOXYVAC Trial
- SF Experience

DoxyPEP at CROI

- DoxyPEP Trial (Seattle, SF)
  - Open label extension (N=289)
  - **Sustained reduction in STIs** with Doxy PEP
  - Even as risk increased
  - Median doses per month = 6
  - Only 2 people stopped Doxy PEP (rash, preference)



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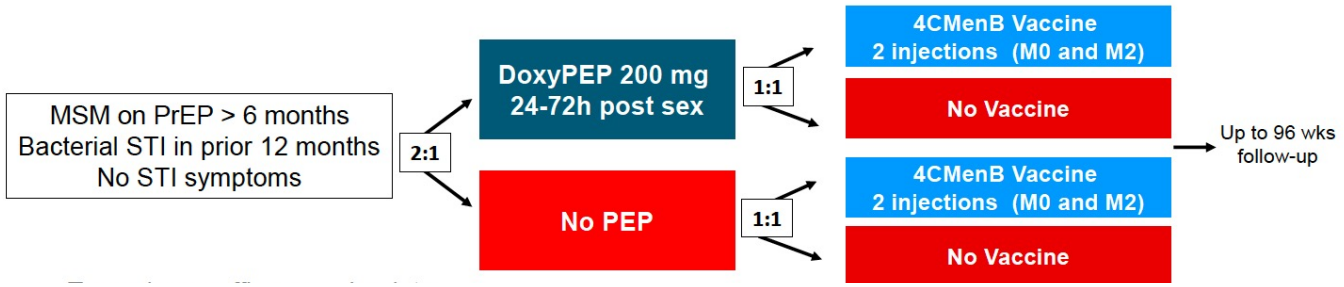
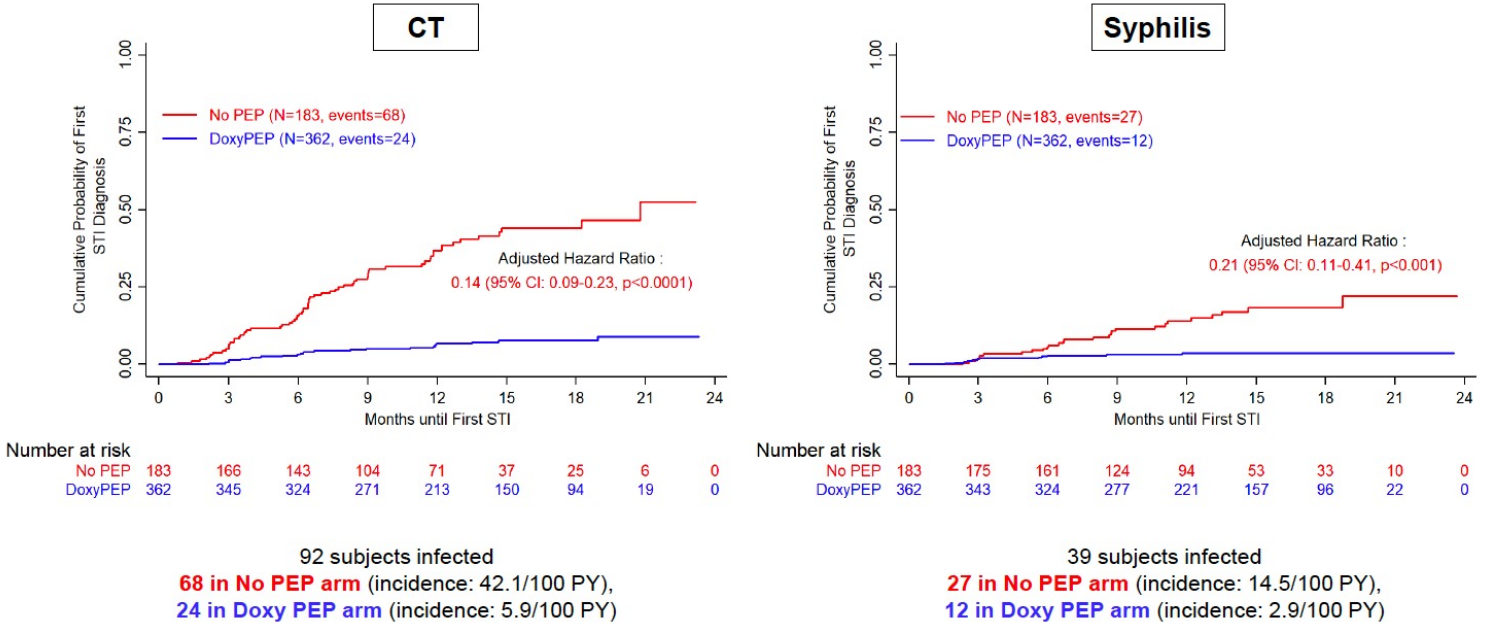
DoxyPEP at CROI

- ANRS DOXYVAC Trial (Paris)
  - N=556
  - **Doxy reduced chlamydia, syphilis and gonorrhea infections**
  - More resistant gonorrhea infections over time
  - MenB vax marginal benefit

- Multicenter, 2 x 2 factorial randomized, open-label, superiority, phase III trial (NCT04597424)



Doxycycline PEP
Time to First CT and Syphilis Infection



92 subjects infected
68 in No PEP arm (incidence: 42.1/100 PY),
24 in Doxy PEP arm (incidence: 5.9/100 PY)

39 subjects infected
27 in No PEP arm (incidence: 14.5/100 PY),
12 in Doxy PEP arm (incidence: 2.9/100 PY)

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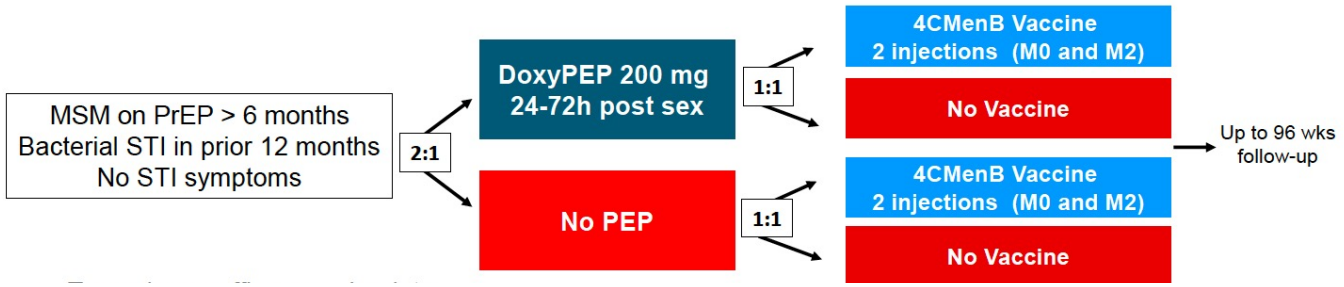
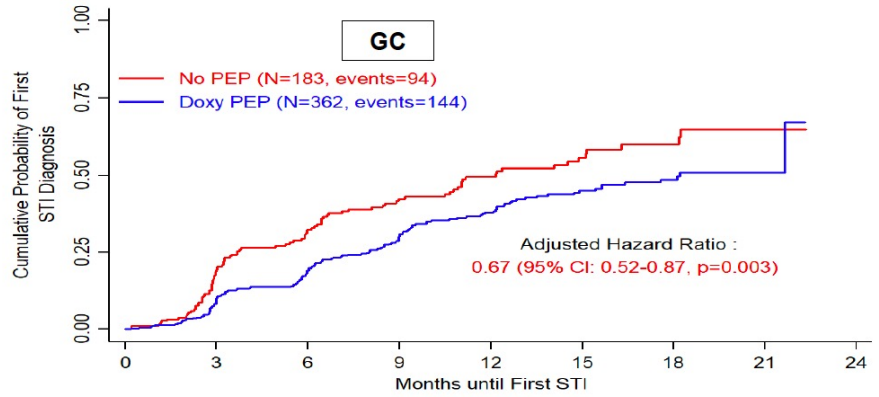
DoxyPEP at CROI

- Multicenter, 2 x 2 factorial randomized, open-label, superiority, phase III trial (NCT04597424)



Doxycycline PEP
Time to First GC



Number at risk

No PEP	183	143	117	82	57	32	18	4	0
DoxyPEP	362	317	270	196	134	88	47	6	0

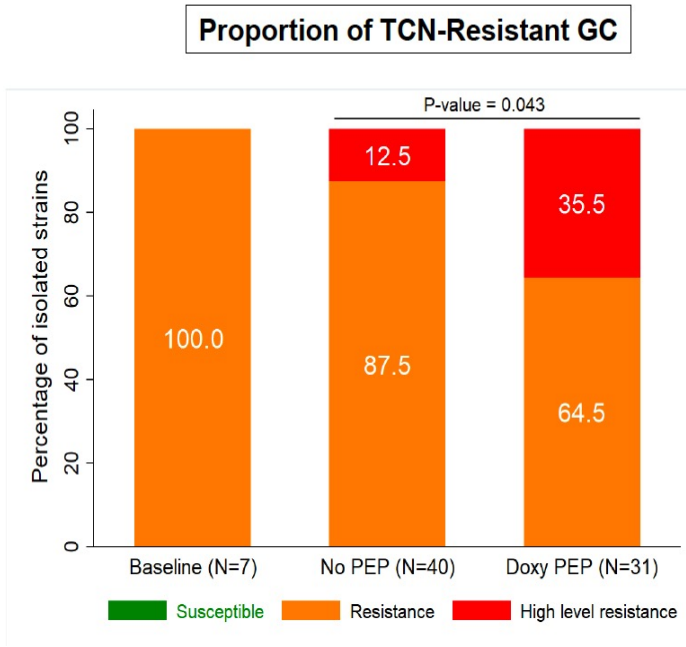
Interim analyis:
84 subjects infected, aHR: 0.49

238 subjects infected
94 in No PEP arm (incidence: **68.4/100** PY)
144 in Doxy PEP arm (incidence: 45.5 /100 PY)

GC multi-sites infection = 1 sin

Tetracycline (TCN) Resistance for GC and CT

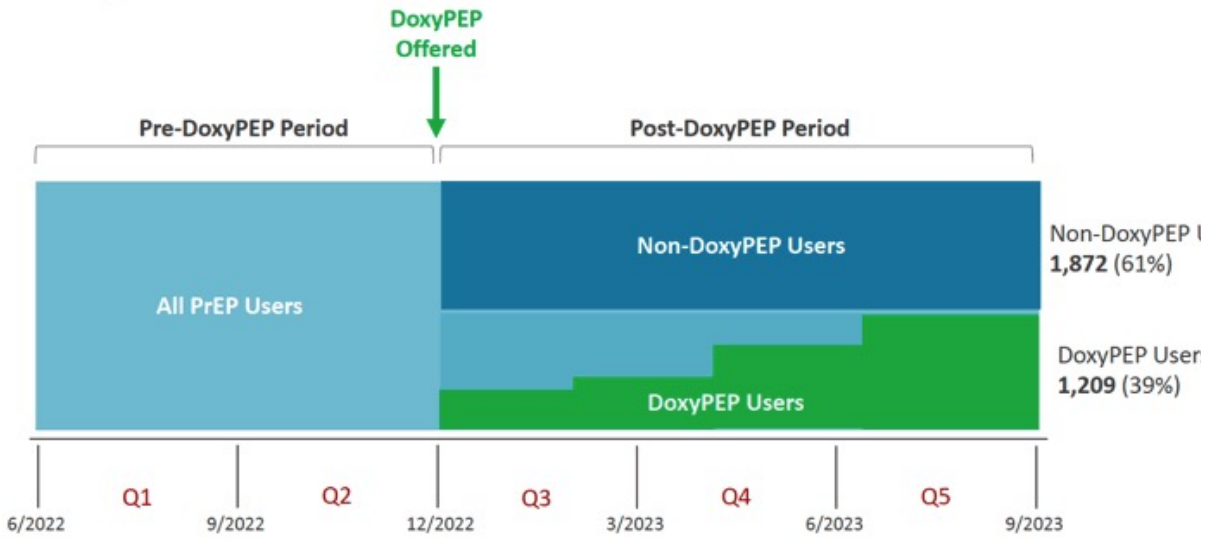
- **GC:**
  - 78 cultures available for resistance testing (17% of PCR positive events)
  - Tetracycline MICs determined by Etest
  - Resistance using EUCAST 2023 breakpoints
    - Resistance: MIC > 0.5 mg/L
    - High level resistance: MIC > 8 mg/L
- **CT**:
  - 4/23 swabs tested for TCN-R in culture: no resistance (but none from PEP arm)
  - 68/126 PCR+ swabs with16S rRNA sequences: no TCN-R mutation (only 8 from PEP arm)



DoxyPEP at CROI

- SF Dept of Public Health
  - Castro district sexual health clinic
  - Compared STI incidence between DoxyPep users to non-users

DoxyPEP Timeline



Race/Ethnicity

Race /Ethnicity	Total PrEP Clients N=3,081 n	DoxyPEP Uptake n=1,209 %
American Indian or Alaska Native	9	56%
Asian	509	37%
Black or African American	126	37%
Hispanic or Latinx	723	43%
Multi-Racial	408	41%
Native Hawaiian or Pacific Islander	16	25%
White	1,095	37%
Declined/Other/Unknown	195	45%

Age

Age (years)	Total PrEP Clients N=3,081 n	DoxyPEP Uptake n=1,209 %
18-24	223	38%
25-29	636	40%
30-39	1,299	43%
40-49	535	36%
50-59	256	34%
60+	132	27%

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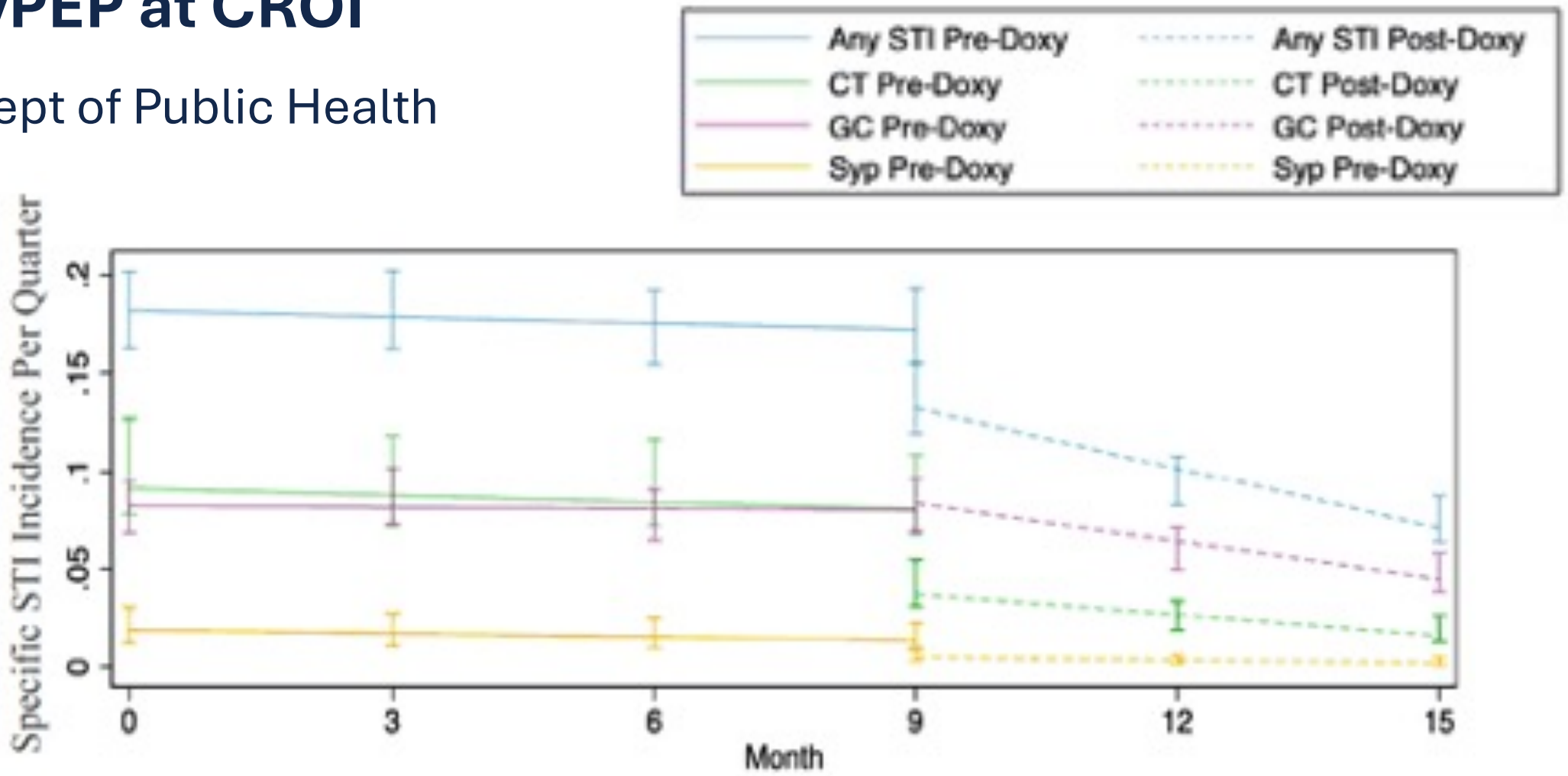
DoxyPEP at CROI

- SF Dept of Public Health



ITS: Any STI: p=0.32; Chlamydia: p=0.021; Gonorrhea: p=0.003; Syphilis: p=0.360

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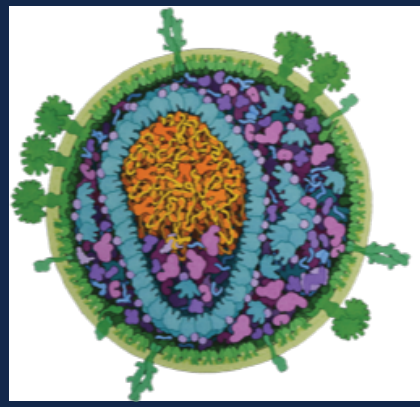
Why does this matter? Co-infections

- HBV re-vaccination with **Heplisav** was better than with Engerix and should now be the standard. PRACTICE CHANGER
- People with isolated **HBV core antibody** may be at risk of HBV reactivation when switching to a non-TFV containing regimen. If such a switch made, monitoring for HBV viral load and transaminase elevations would be a good idea. PRACTICE CHANGER
- **DoxyPEP** works in trials and in real(er) world. As syphilis, including congenital syphilis, is a growing public health issue, more potential users and primary care clinicians should be made aware of this option.
  - The **CDC** has issued only preliminary guidance about DoxyPEP and needs to make a definitive guidance available with strong support to promoting DoxyPEP. PRACTICE CHANGER
  - Continued monitoring for drug resistance among gonorrhea important even if DoxyPEP does not contribute as impacts efficacy against this STI.



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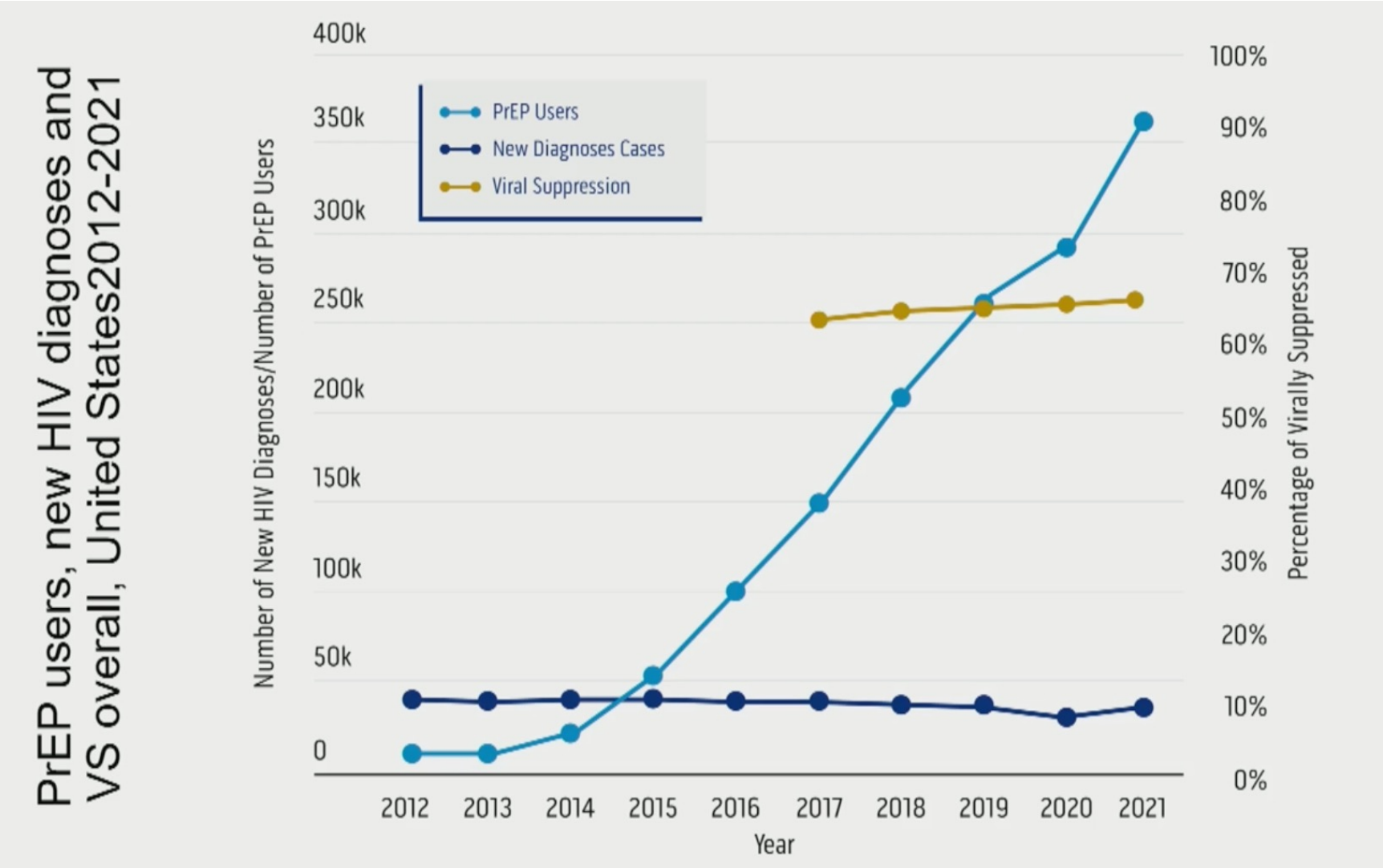
HIV Prevention

PrEP in the USA



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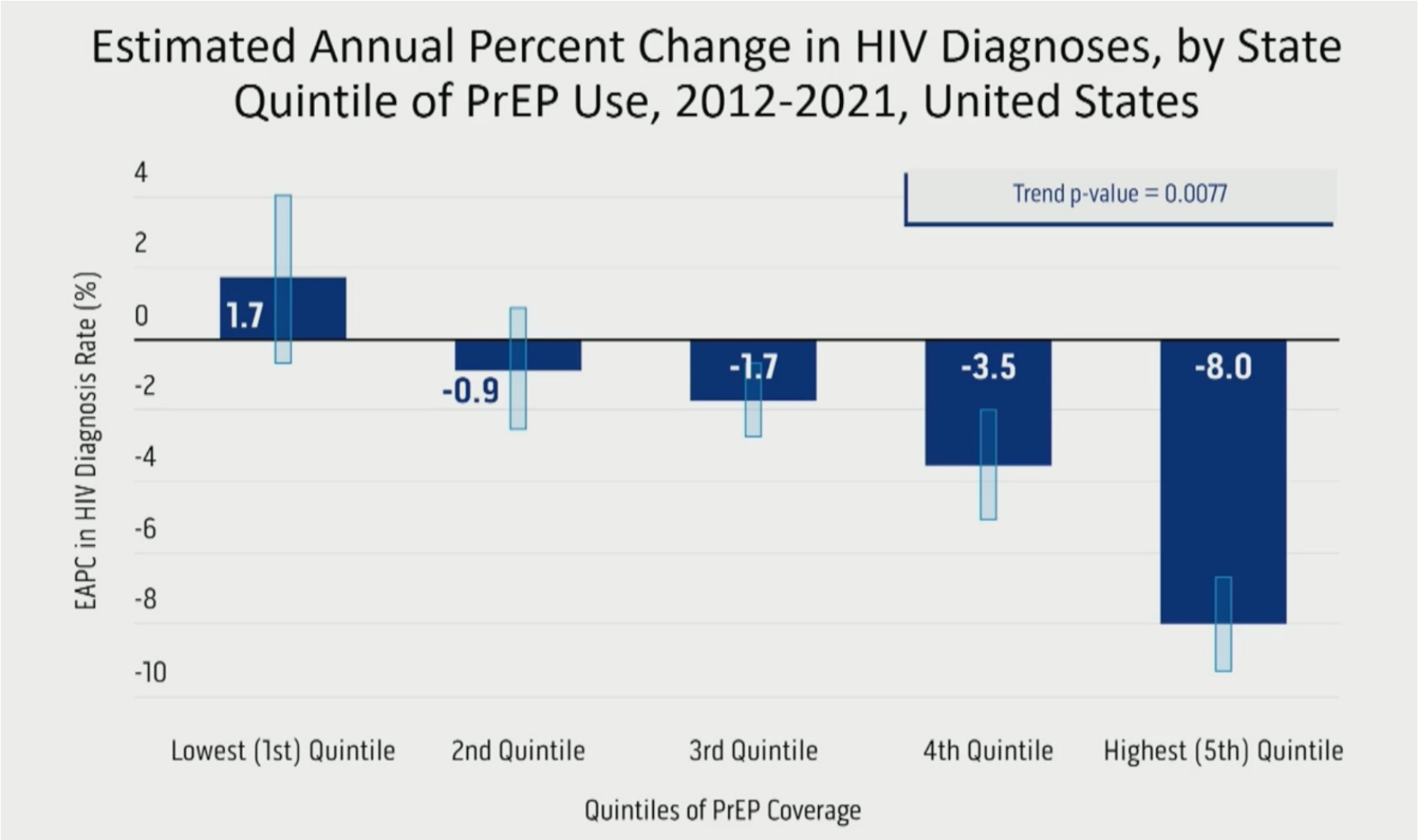
PrEP in the USA



The more PrEP coverage in a state, the greater the % change in new diagnoses of HIV

Sullivan. CROI 2024

PrEP in the USA

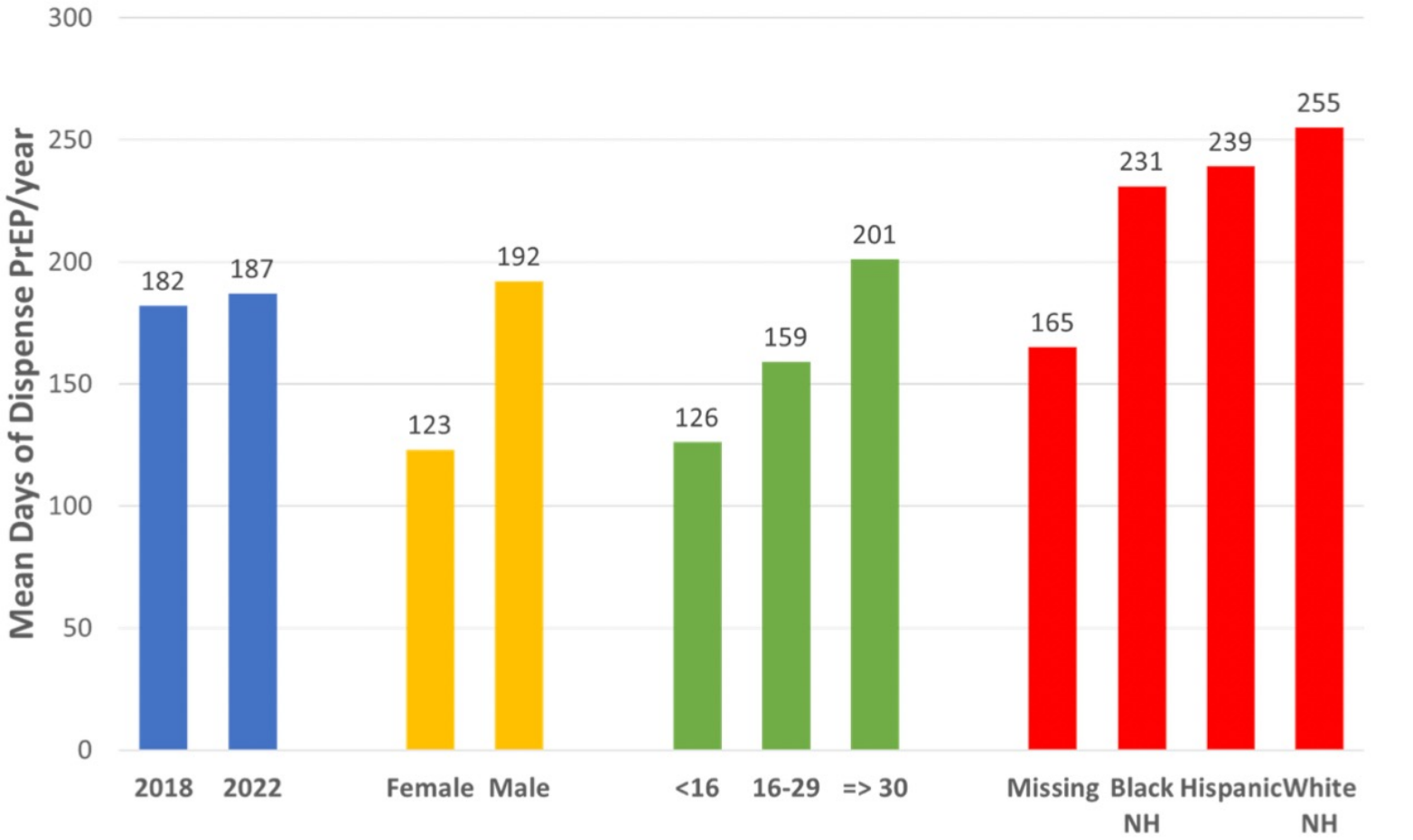


Figure 1. Mean number of days covered on oral pre-exposure prophylaxis, 2018 and 2022; and by sex, age and race/ethnicity, 2022

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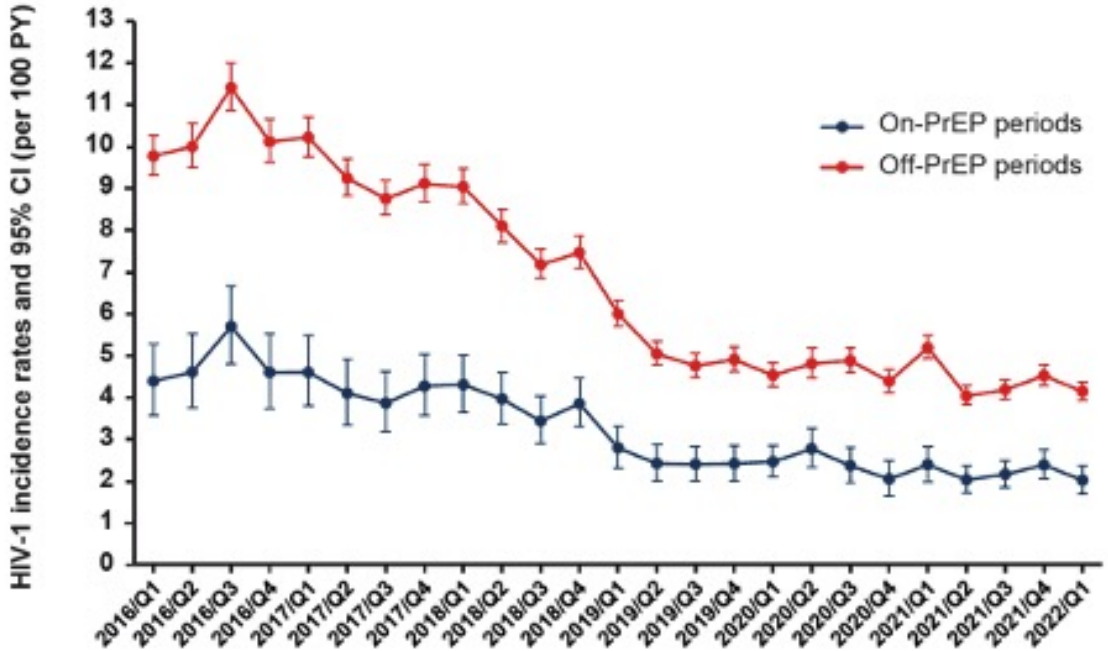
PrEP non-persistence and risk of HIV

- IQVIA claims data covering 93% of prescriptions in the US used to look at gaps and discontinuations in oral PrEP

		On-PrEP		Off-PrEP			
	Total N	HIV-1 Infections (n)	Person Time (years)	HIV-1 Infections (n)	Person Time (years)		IRR Off vs On PrEP (95% CI)
All	123,901	1343	62,525.5	2488	58,973.4		1.96 (1.84–2.10)

Figure 5. Trends of HIV-1 Incidence Rates of Individuals During On- and Off-PrEP Periods



PrEP, pre-exposure prophylaxis; PY, person-years; Q, quarter.

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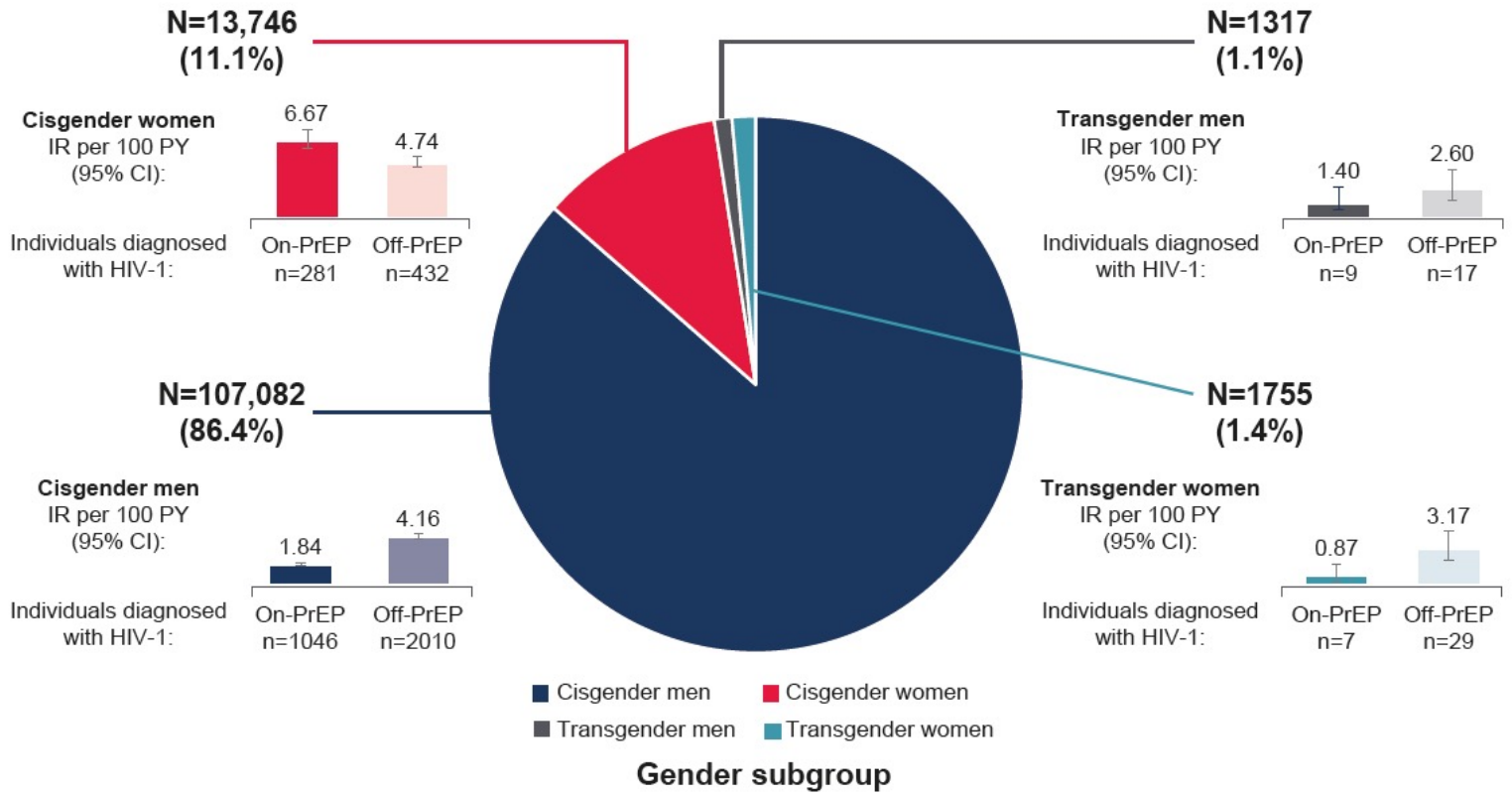
PrEP non-persistence and risk of HIV acquistion

Figure 1. Distribution of Individuals Included in This Analysis and HIV-1 Incidence Rates (per 100 PY) for On-PrEP Versus Off-PrEP Periods by Gender



CI, confidence interval; IR, incidence rate; PrEP, pre-exposure prophylaxis; PY, person-years.

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CAB PrEP Real(er) World Use OPERA Cohort

Results

Figure 2. CAB LA injection patterns

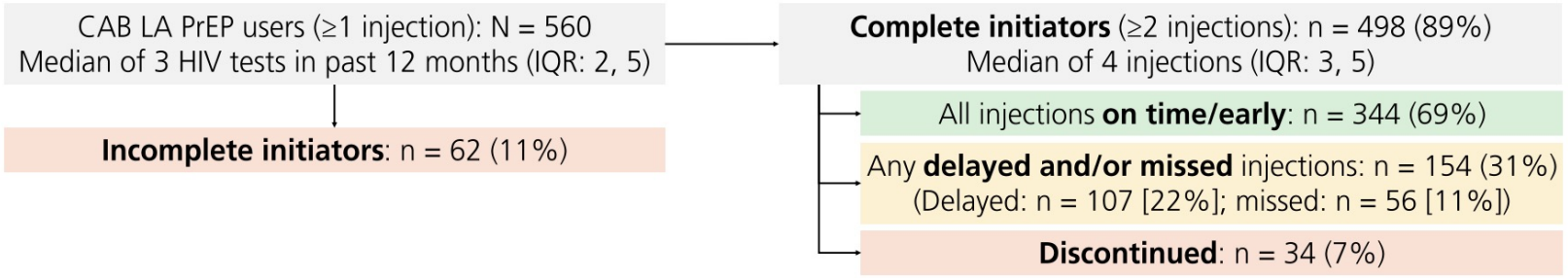

Figure 3. Timeline of the single HIV acquisition during follow-up

* No HIV tests were administered prior to switching from oral PrEP to CAB LA PrEP

Table 1. Baseline characteristics and likelihood of non-adherence to injection schedule among complete initiators

	No delayed or missed injection	Any delayed and/or missed injection	aOR (95% CI)
N	344	154	NA
Age	Median: 32 (IQR: 27, 40)	Median: 31 (IQR: 26, 40)	0.97 (0.78, 1.20)[a]
Female	43 (13%)	20 (13%)	0.61 (0.26, 1.39)
Black race[b]	109 (32%)	52 (34%)	1.03 (0.62, 1.70)
Hispanic ethnicity	103 (30%)	40 (26%)	0.75 (0.44, 1.30)
Southern US	106 (31%)	54 (35%)	1.28 (0.80, 2.06)
Married or in a domestic partnership[c]	41 (12%)	16 (10%)	0.87 (0.44, 1.71)
Any STI within 12 months prior to 1st injection	145 (42%)	66 (43%)	0.98 (0.62, 1.56)
Any history of PrEP use	299 (87%)	142 (92%)	1.72 (0.78, 3.77)

[a] Per 10-year increase.
[b] Missing race: n=29.
[c] Missing marital status: n=98.

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CAB PrEP Real(er) World Use

TRIO Health Cohort

- CAB PrEP Dec 2021-May 2023 (N=85)
- No HIV infections

Table 1. Study Population Characteristics

Study Population Characteristics, n (%)		Individuals with ≥1 Documented Injection N=85	Individuals with ≥2 Documented Injections N=64	Individuals with ≥3 Documented Injections N=43
Age	Age, median (IQR)	41 (33,48)	41 (34,48)	43 (38,52)
Gender	Female	5 (5.9%)	5 (7.8%)	2 (4.7%)
	Male	79 (92.9%)	58 (90.6%)	40 (93.0%)
	Unknown gender	1 (1.2%)	1 (1.6%)	1 (2.3%)
Race	White	51 (60.0%)	42 (65.6%)	30 (69.8%)
	Black or African American	8 (9.4%)	6 (9.4%)	3 (7.0%)
	Hispanic or Latino	16 (18.8%)	11 (17.2%)	7 (16.3%)
	Other Race	2 (2.4%)	1 (1.6%)	0 (0.0%)
	Unknown Race	8 (9.4%)	4 (6.2%)	3 (7.0%)
Payer Type	Commercial	55 (64.7%)	45 (70.3%)	33 (76.7%)
	Medicaid/Medicare	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Other/Self Pay	7 (8.2%)	7 (10.9%)	5 (11.6%)
	Unknown Payer	23 (27.1%)	12 (18.8%)	5 (11.6%)
Region	East	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Northeast	0 (0.0%)	0 (0.0%)	0 (0.0%)
	South	70 (82.4%)	59 (92.2%)	43 (100.0%)
	West	15 (17.6%)	5 (7.8%)	0 (0.0%)
PrEP History	Prior FTC/TAF	62 (72.9%)	47 (73.4%)	33 (76.7%)
	Prior FTC/TDF	46 (54.1%)	35 (54.7%)	25 (58.1%)
	Prior both FTC/TAF & FTC/TDF	35 (41.2%)	26 (40.6%)	22 (51.2%)
HIV Testing within 90 days prior to 1st injection	HIV Ag/Ab-	85 (100.0%)	64 (100.0%)	43 (100.0%)
	HIV Ag/Ab+	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Unknown HIV Ag/Ab	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Undetectable HIV RNA	65 (76.5%)	52 (81.2%)	37 (86.0%)
	Unknown HIV RNA	20 (23.5%)	12 (18.8%)	6 (14.0%)

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Figure 1. Proportion of CAB LA PrEP Initiators with all on time injections by Injection Period

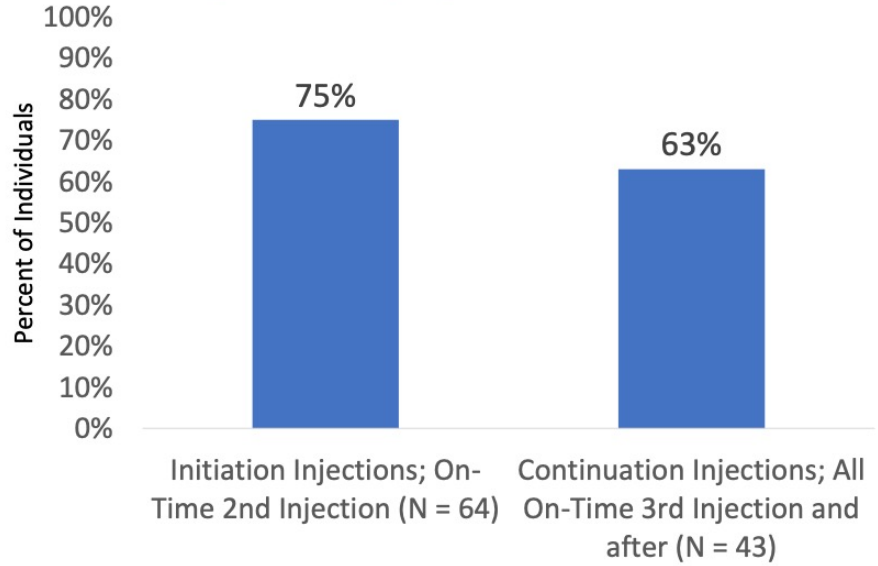
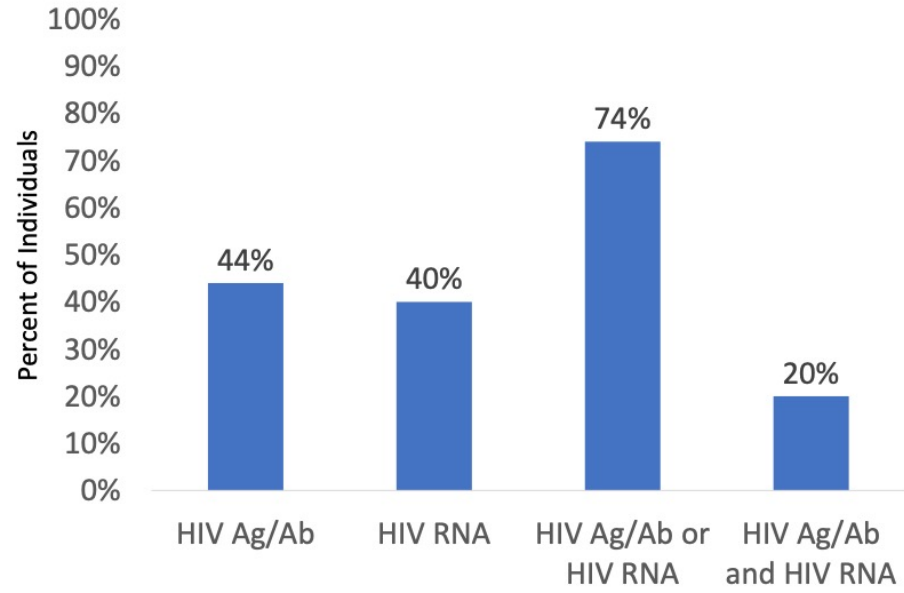
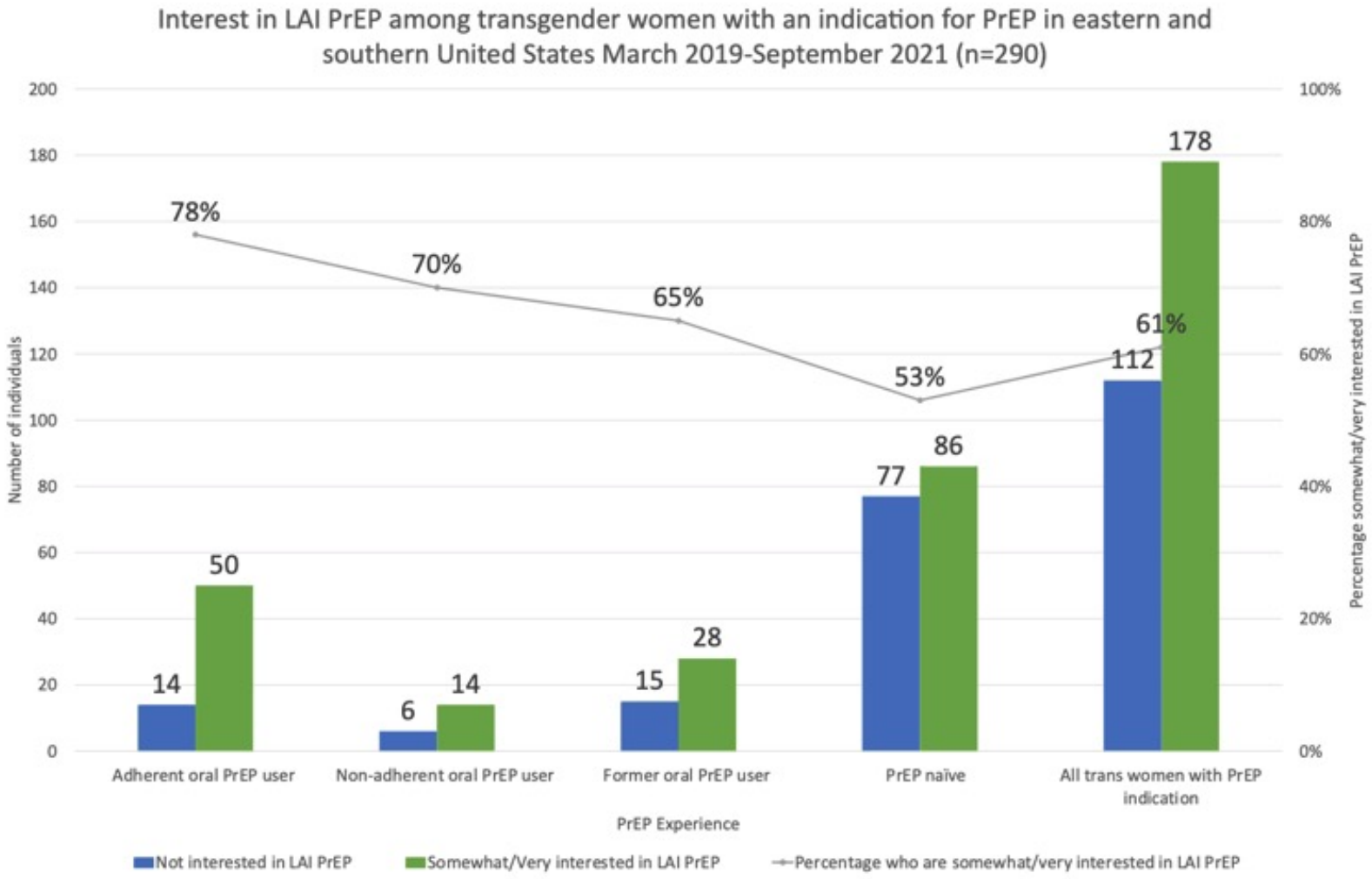


Figure 2. Proportion of CAB LA PrEP Initiators with HIV screening at all follow-up injections (N=64)



PrEP Preferences among Transgender Women (TW) in the US



Transgender women—particularly Black trans women, those who can benefit from PrEP, and those with oral PrEP experience—are interested in using Long-Acting Injectable PrEP.

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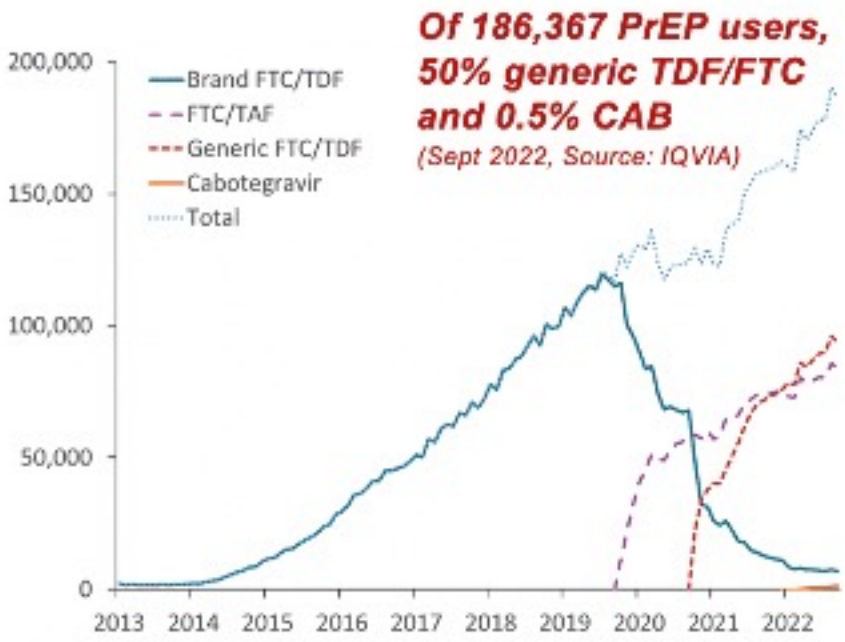
CAB PrEP – Slow Rollout

PrEP Prescribing in the United States



***186,367** persons were prescribed PrEP (Sept 2022):*

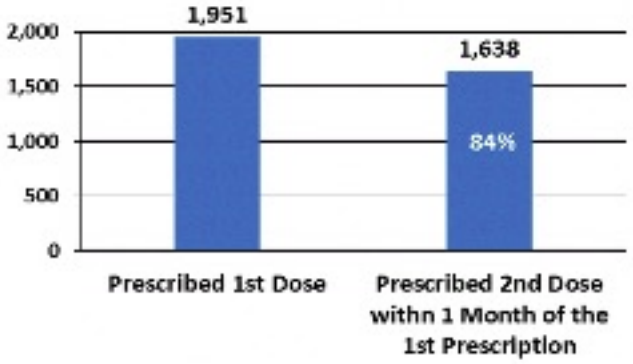
Generic FTC/TDF:	**93,808**	**(50.3%)**
FTC/TAF:	84,141	(45.1%)
Brand FTC/TDF:	7,065	(3.8%)
CAB-LA:	**1,353**	**(0.5%)**

Zhu W. et al. Oral and Injectable PrEP Use in the U.S., 2013-2022. CROI 2023 Abstract #980

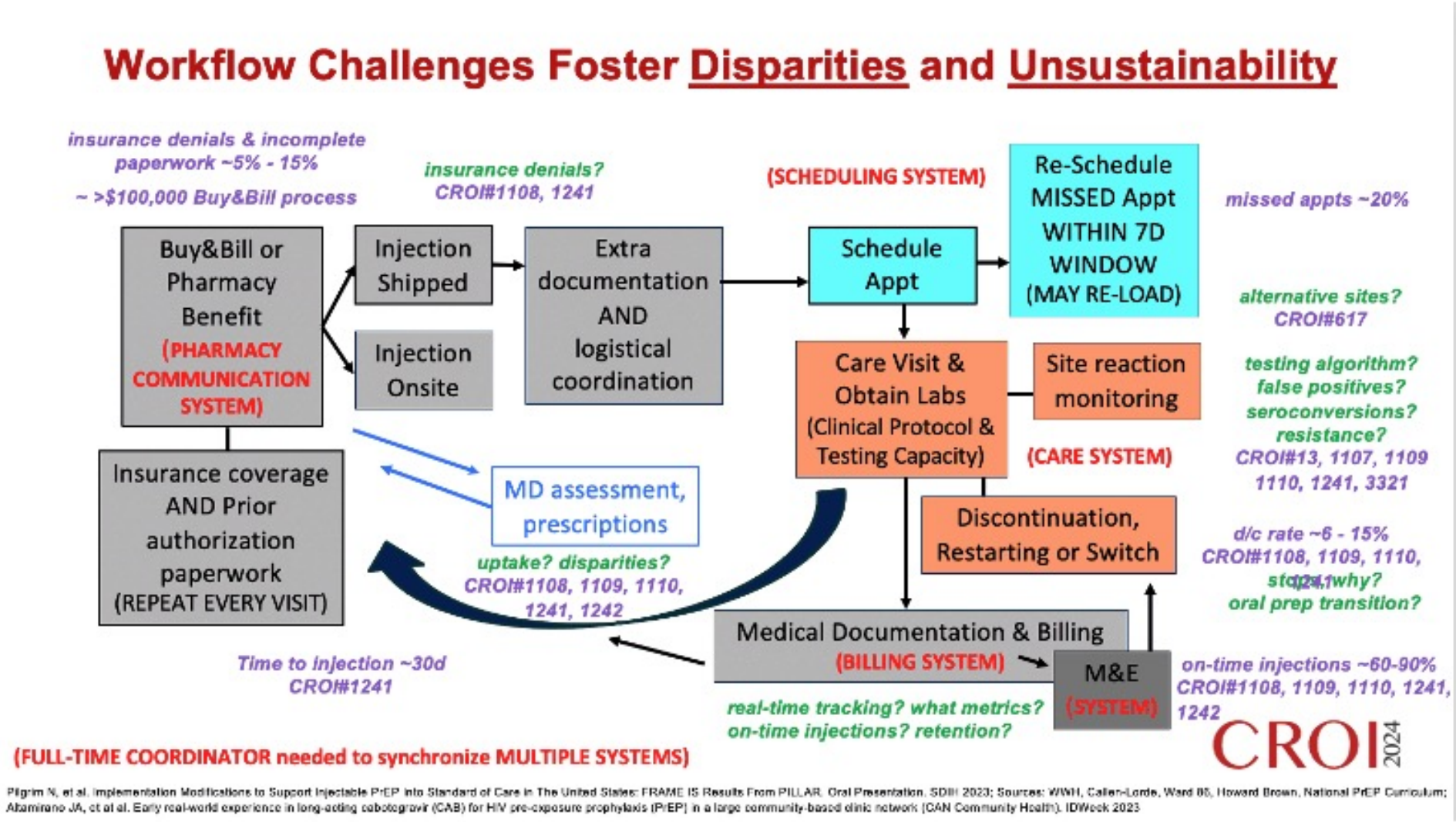
Table. Characteristics of persons prescribed long-acting cabotegravir, United States, January 2013 through September 2022

	Oral PrEP		Injectable PrEP	
	N	%	N	%
Total	**381,883**		**2,695**	
Sex				
Male	355,087	93.0	2,359	87.5
Female	26,697	7.0	336	12.5
Unknown	99	0.0	0	0.0
Age				
13-24	46,814	12.3	369	13.7
25-34	150,864	39.5	1,111	41.2
35-44	96,243	25.2	698	25.9
45-54	47,668	12.5	297	11.0
55-64	31,427	8.2	149	5.5
65+	8,867	2.3	71	2.6

Number of People Who Received a CAB-LA PrEP Prescription, Jan 2022 - Aug 2022



CAB PrEP – Slow Rollout



Pilgrim N, et al. Implementation Modifications to Support Injectable PrEP into Standard of Care in The United States: FRAME IS Results From PILLAR. Oral Presentation. SDBI 2023; Sources: WWH, Callen-Lorde, Ward 86, Howard Brown, National PrEP Curriculum; Altamirano JA, et al. Early real-world experience in long-acting cabotegravir (CAB) for HIV pre-exposure prophylaxis (PrEP) in a large community-based clinic network (CAN Community Health). IDWeek 2023

Patel. CROI 2024

Why does this matter? PrEP

- PrEP is an amazingly effective HIV prevention intervention that most people who can benefit from don't take, and those who do don't stay on. We need better PrEP.
- Current PrEP is not accessible to many who may be willing to take it. Easing access, increases use.
- **IM CAB** for PrEP effective in practice but has been slow to roll out. Multiple issues including lack of awareness, clinical resources, access due to cost and insurance barriers