WHAT IS NEW IN INFECTIOUS DISEASES?
DATA FROM 2024 CONGRESSES

Milano, 26 Settembre 2024
Centro Congressi StarHotels Ritz

PANDORA ID - 24
TIME TO WEBINAR IN INFECTIOUS DISEASES

TMT CONGRESS & EVENTS

Sistema Socio Sanitario
Regione Lombardia
ASST Ovest Milanese

UNIVERSITAS STUDIORUM MEDIOLANENSIS

CROI: novità in tema di terapia antiretrovirale

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COIs

GSK, Gilead, Janssen-Cilag, MSD, ViiV, Menarini, AstraZeneca

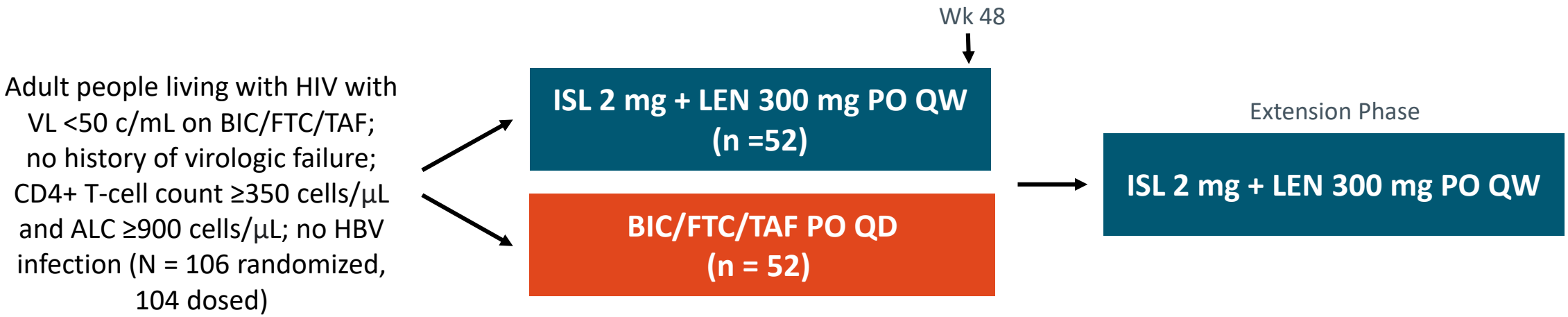
MEDICI CON L'AFRICA CUAMM

Outline

- Future strategie terapeutiche
- Terapie long-acting attuali
- PWH HTE
- Novità sulla PEP/PrEP

Phase II Trial of Oral Weekly ISL + LEN in People Living With HIV: Study Design

- Open-label, active-controlled phase II trial



- **Primary endpoint:** proportion of participants with HIV-1 RNA ≥50 c/mL at Wk 24 by FDA Snapshot algorithm
- **Secondary endpoints:** proportion of participants with HIV-1 RNA ≥50 c/mL by Wk 12 and 48; proportion with HIV-1 RNA <50 c/mL at Wk 12, 24, and 48; change from baseline in CD4+ T-cells, AEs leading to discontinuation of study drug; PK

Colson. CROI 2024. Abstr 208.

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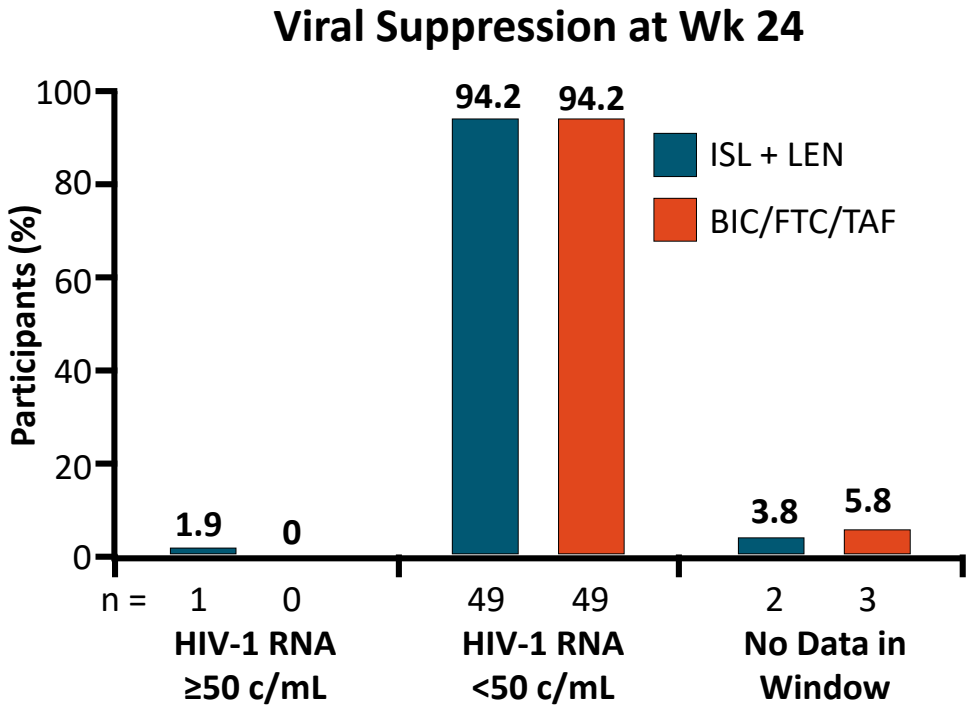
Phase II Trial of Oral Weekly ISL + LEN: Baseline Demographics and Efficacy

Characteristic, n (%)	ISL + LEN (n = 52)	BIC/FTC/TAF (n = 52)
Median age, yr (range)	40 (28-67)	40 (26-76)
Female at birth, n (%)	10 (19.2)	9 (17.3)
Race, n (%)		
▪ White	25 (48.1)	27 (51.9)
▪ Black	21 (40.4)	16 (30.8)
▪ Asian	2 (3.8)	1 (1.9)
▪ American/Alaska Native	1 (1.9)	2 (3.8)
▪ Hawaiian or Pacific Islander	0 (0)	1 (1.9)
▪ Other	3 (5.8)	5 (9.6)
Ethnicity, Hispanic or Latino/a, n (%)	13 (25.0)	17 (32.7)
Mean (SD) CD4+ T-cells/μL	755 (223.6)	818 (271.3)
▪ ≥500	46 (88.5)	50 (96.2)
Mean (SD) ALC x 10^3/μL	1.94 (0.445)	1.95 (0.652)



- 1 participant with HIV-1 RNA ≥50 c/mL:
  - Resuppressed at Wk 30 on ISL + LEN
  - No resistance and adequate PK

Colson. CROI 2024. Abstr 208.

Slide credit: clinicaloptions.com

Phase II Trial of Oral Weekly ISL + LEN: Safety

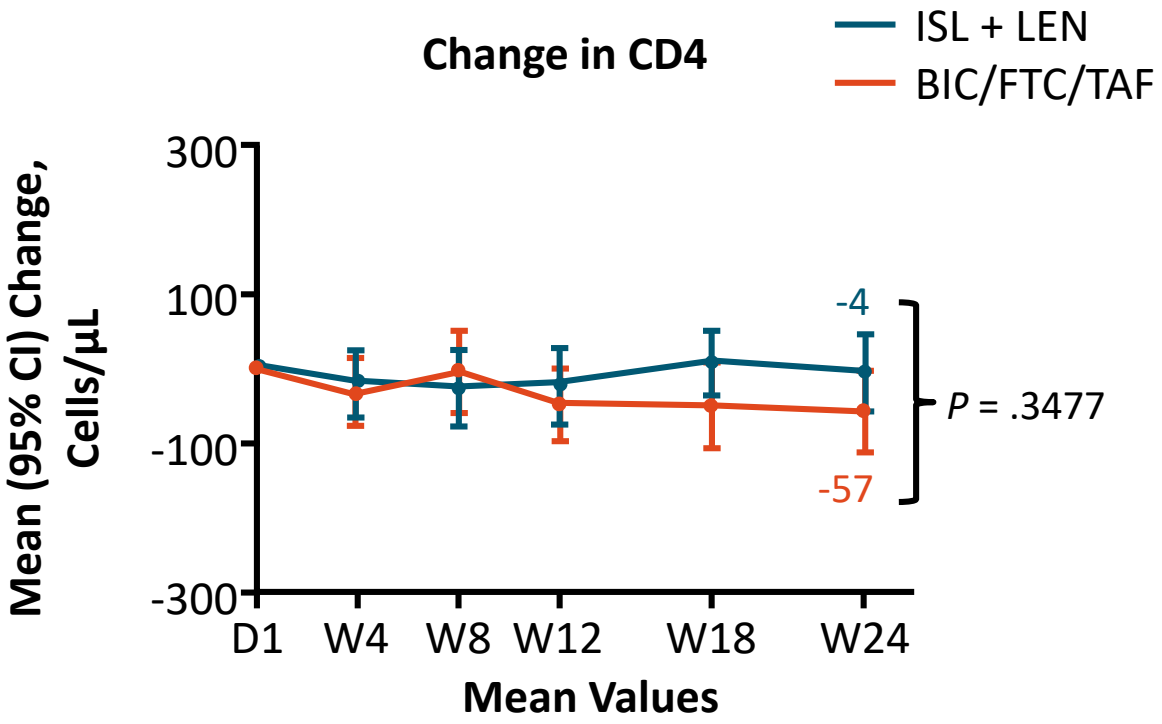
Patients With AE, n (%)	ISL + LEN (n = 52)	BIC/FTC/TAF (n = 52)
Any AE	40 (76.9)	38 (73.1)
Any TRAE	9 (17.3)	3 (5.8)
Grade 1/2 TRAEs in ≥2 on ISL + LEN	9 (17.3)	3 (5.8)
▪ Dry mouth	2 (3.8)	0
▪ Nausea	2 (3.8)	0
Grade 3/4 TRAEs	0 (0)	0 (0)
Serious AE	3 (5.8)	0
AE leading to d/c	2 (3.8)	0

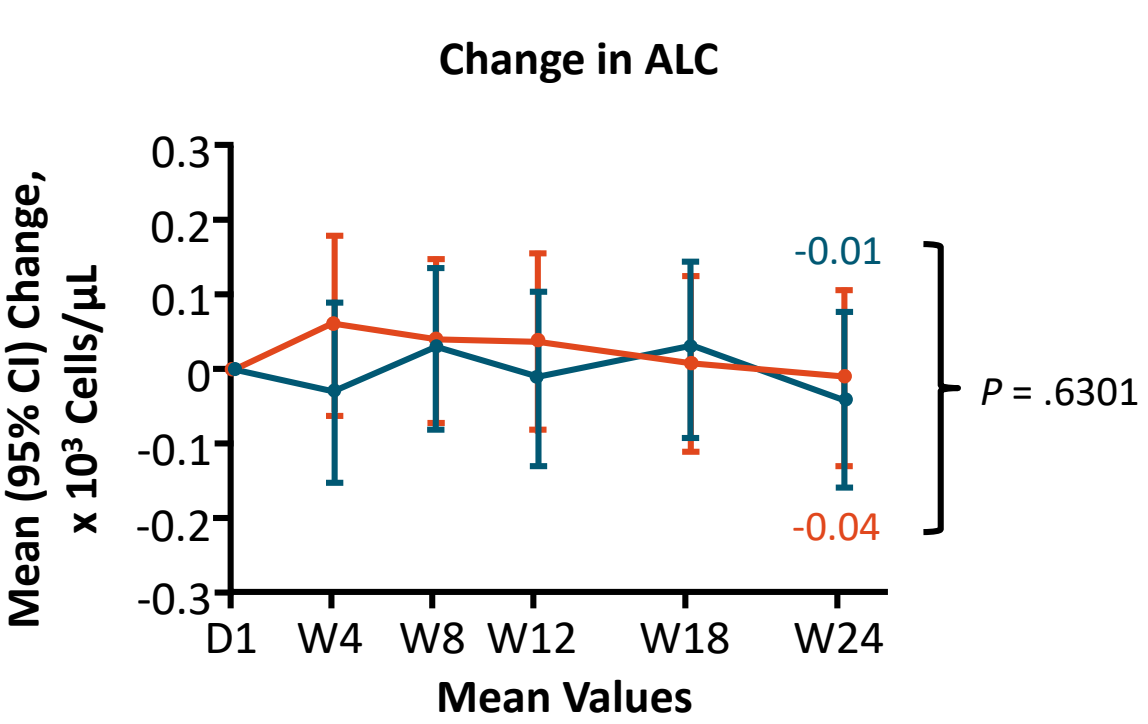
Patients With Grade 3/4 Lab Abnormality, n (%)	ISL + LEN (n = 52)	BIC/FTC/TAF (n = 52)
Grade 3	5 (9.6)	4 (7.8)
▪ Increased ALT	1 (1.9)	0
▪ Increased SCr	1 (1.9)	0
▪ Decreased CrCl	2 (3.8)	2 (3.9)
▪ Fasting hyperglycemia	0	1 (2.6)
▪ Non-fasting hyperglycemia	1 (2.5)	2 (4.9)
▪ Hyperkalemia	1 (1.9)	0
▪ Glycosuria	1 (1.9)	2 (3.9)
Grade 4	1 (1.9)	0
▪ Increased creatine kinase	1 (1.9)	0

- Only clinically significant grade 3/4 lab abnormality was elevated ALT in a person with acute hepatitis B

Colson. CROI 2024. Abstr 208.

Phase II Trial of Oral Weekly ISL + LEN: CD4 and ALC Changes Through Wk 24





- No between-group differences for change from baseline to Wk 24 for CD4+ T-cells (*P* = .3477) or ALC (*P* = .6301)

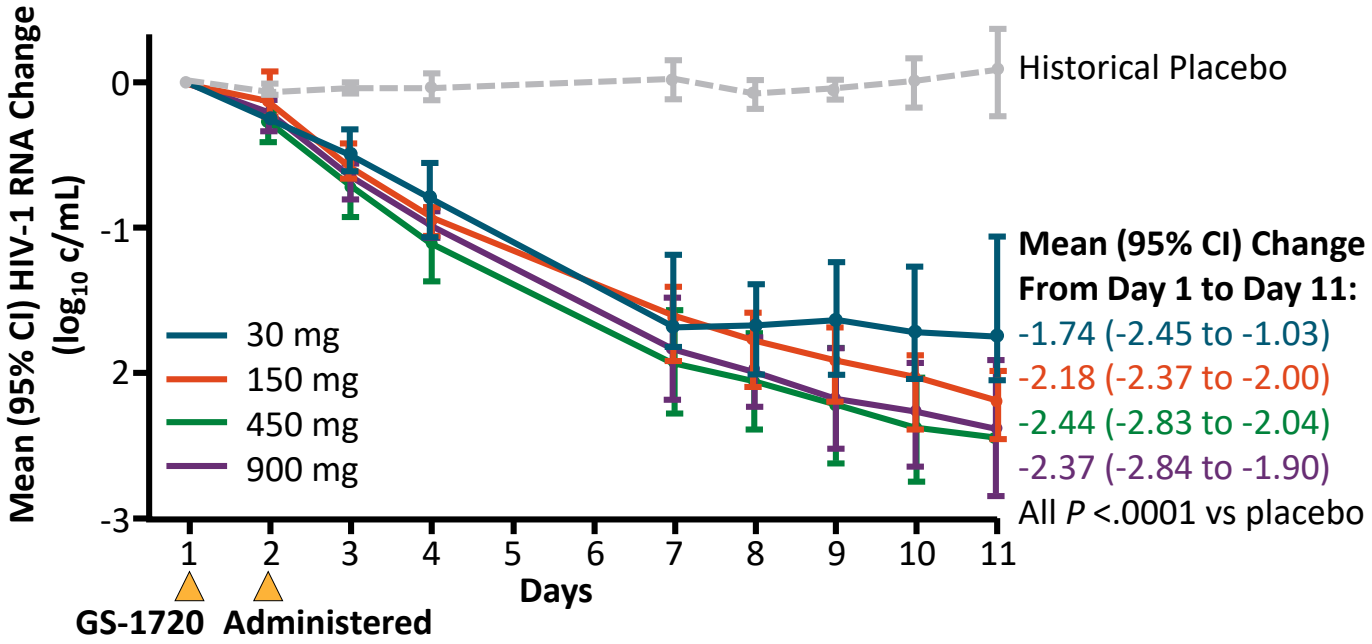
- No person discontinued treatment due to decline in CD4+ T-cells or ALC

Colson. CROI 2024. Abstr 208.

Slide credit: clinicaloptions.com

Additional Oral Weekly HIV Treatments in Development

- **GS-1720 INSTI** phase Ia/b results
  - Median $t_{1/2}$ = 9.4 days
  - Potent antiviral activity



- **MK-8527 NRTTI** phase I results
  - Following single oral doses of 0.5, 1, 3, and 10 mg, mean decrease in HIV-1 RNA at Day 7 was ≥1.0 $\log_{10}$ c/mL

$\log_{10}$ c/mL, Mean (Range)	Change in Plasma HIV-1 RNA at Day 7
Trial A	
▪ 10 mg (n = 6)	-1.39 (-0.87 to -1.67)
▪ 3 mg (n = 6)	-1.66 (-1.23 to -2.02)
▪ 1 mg (n = 5)	-0.95 (0.03 to -1.60)
Trial B	
▪ 1 mg (n = 8)	-1.38 (-0.98 to -2.10)
▪ 0.5 mg (n = 6)	-1.40 (-1.24 to -1.54)
▪ 0.25 mg (n = 6)	-0.80 (-0.37 to -1.21)

Fichtenbaum. CROI 2024. Abstr 116. Carstens. CROI 2024. Abstr 115.

Broadly Neutralizing Antibodies in HIV Treatment

Trial	Phase	N	Agents (Target)	Results
BANNER[1]	IIa	62	N6LS (CD4bs)*	▪ Exposure-dependent antiviral activity ▪ BL N6LS activity predicted concentration needed to achieve adequate antiviral effect ▪ Higher exposure with IV vs SC
ACTG A5357[2]	II	71†	VRC07-523LS (CD4bs) + LA CAB‡	▪ 5 cases of virologic failure, 2 resuppressed, no ADAs ▪ 1 developed R263K to CAB w/high BL VRC07-523LS IC50 ▪ 16.9% w/AEs, 1 grade 1 IRR leading to discontinuation
NCT04811040[3]	Ib	11	LEN + TAB (CD4bs) + ZAB (V3)§	▪ 8/10 maintained suppression at Wk 26 when highly susceptible to 1 of 2 bNAbs, 2 w/HIV-1 RNA ≥50 c/mL ▪ Most common AE: grade 1 ISR related to LEN
T003[4]	I/IIa	12‖	PGDM1400 (V2) + PGT121 (V3) + VRC07-523LS (CD4bs)¶	▪ 83% maintained suppression at Wk 28 ▪ 36% maintained suppression at Wk 44 w/bNAb decline ▪ 2 cases early rebound w/BL resistance, 5 late rebound

*Single infusion 1-40 mg/kg IV or 10 mg/kg SC. †Received VRC01-523LS (CD4-binding site) + LA CAB. ‡40 mg/kg VRC01-523LS IV Q8W + IM LA CAB Q4W. §LEN 600 mg D1, D2, LEN 927 SC mg D1 + single infusion 30 mg/kg TAB on D1 + single infusion 10 mg/kg IV or 30 mg/kg IV ZAB on D1. ‖In analysis set. ¶20 mg/kg PGDM1400 IV Q4W, 20 mg/kg IV PGT121 Q4W, 20 mg/kg VRC01-523LS IV Q4W.

1. Losos. CROI 2024. Abstr 117. 2. Taiwo. CROI 2024. Abstr 119. 3. Eron. CROI 2024. Abstr 120. 4. Juelg. CROI 2024. Abstr 121.

Take home messages new TARVs

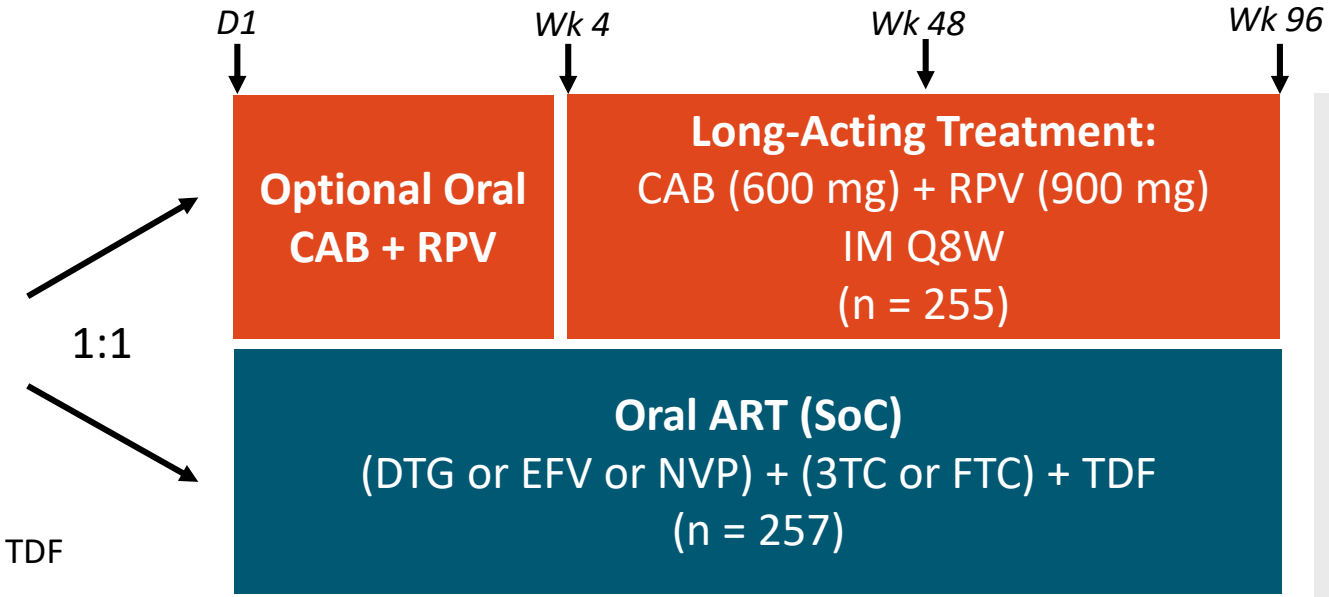
- Islatravir + lenacapavir QW orale: ottima risposta nel trial, ergo una valida strategia L-A orale;
- In corso trials di fase I con molecole ultra-long (GS e MK): anche la terapia si sta sempre più orientando verso l'approccio L-A;
- bnAbs in studio: non ancora maturi per largo uso.

CARES: LA CAB + RPV in a Sub-Saharan African Population (Uganda, Kenya, SA) Using a Public Health Approach

- Multicenter, randomized, parallel-group, active-controlled, open-label, noninferiority phase IIIb study; no resistance testing (although PBMCs stored)

Adults aged ≥18 yr; receiving stable oral ART*; HIV-1 RNA <50 c/mL at ≥4-12 mo before and at screening; no history of treatment failure; no HBV infection (N = 512)

*(DTG or EFV or NVP) + (3TC or FTC) + TDF



VL occurred every 24 wk; *safety monitoring at Wk 4, 8 (LA), Wk 12 (SoC), and Wk 24 then every 24 wk*

- **Primary endpoint:** proportion of individuals with Wk 48 VL <50 c/mL by FDA snapshot algorithm (noninferiority margin of 10%) in ITT population, sensitivity analysis in per-protocol population
- **Secondary endpoints:** proportion of individuals with VL ≥50 c/mL (noninferiority margin of 4%), CVF, safety and tolerability, treatment satisfaction

Kityo. CROI 2024. Abstr 122.

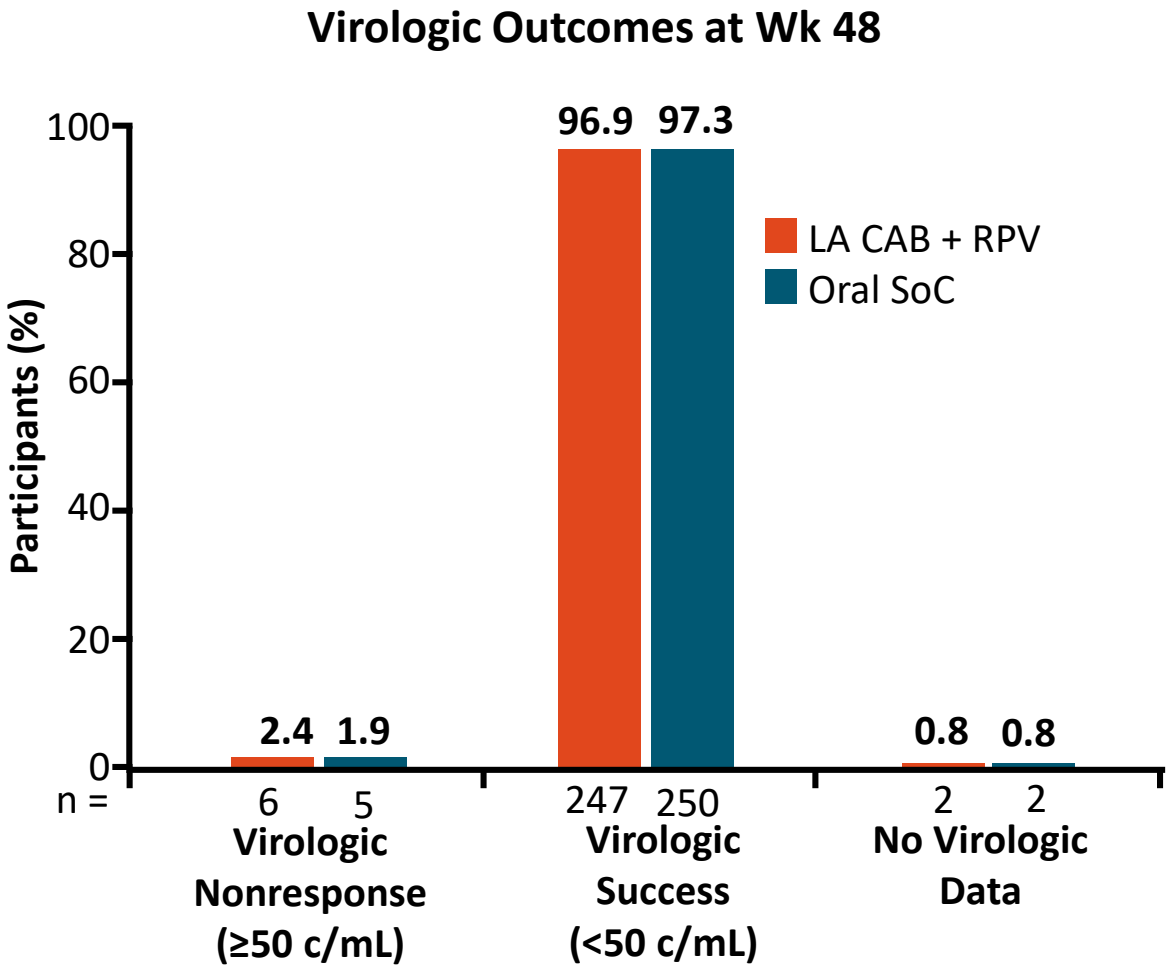
CARES: Baseline Characteristics

Characteristic	All Patients (N = 512)
Median age, yr (IQR)	42 (35-51)
Female, n (%)	295 (57.6)
BMI ≥30 kg/m^2, n (%)	108 (21.1)
Black race, n (%)	510 (99.6)
Median time on first-line ART, yr (IQR)	8 (4-13)
Prior exposure to NNRTI, n (%)	380 (74.2)
INSTI regimen at screening, n (%)	471 (92.0)
NNRTI regimen at screening, n (%)	41 (8.0)
Archived proviral DNA analysis, n/n (%)	
▪ Subtype A1	234/414 (56.5)
▪ RPV resistance mutations	51/377 (13.5)
▪ RPV intermediate/high-level resistance	38/377 (10.1)
▪ CAB resistance mutations	29/180 (16.1)
▪ CAB intermediate/high-level resistance	15/180 (8.3)

- Baseline characteristics evenly distributed among groups
- Participants were enrolled without prior resistance testing
- Archived proviral DNA analysis performed at study conclusion

Kityo. CROI 2024. Abstr 122.

CARES: Efficacy Results

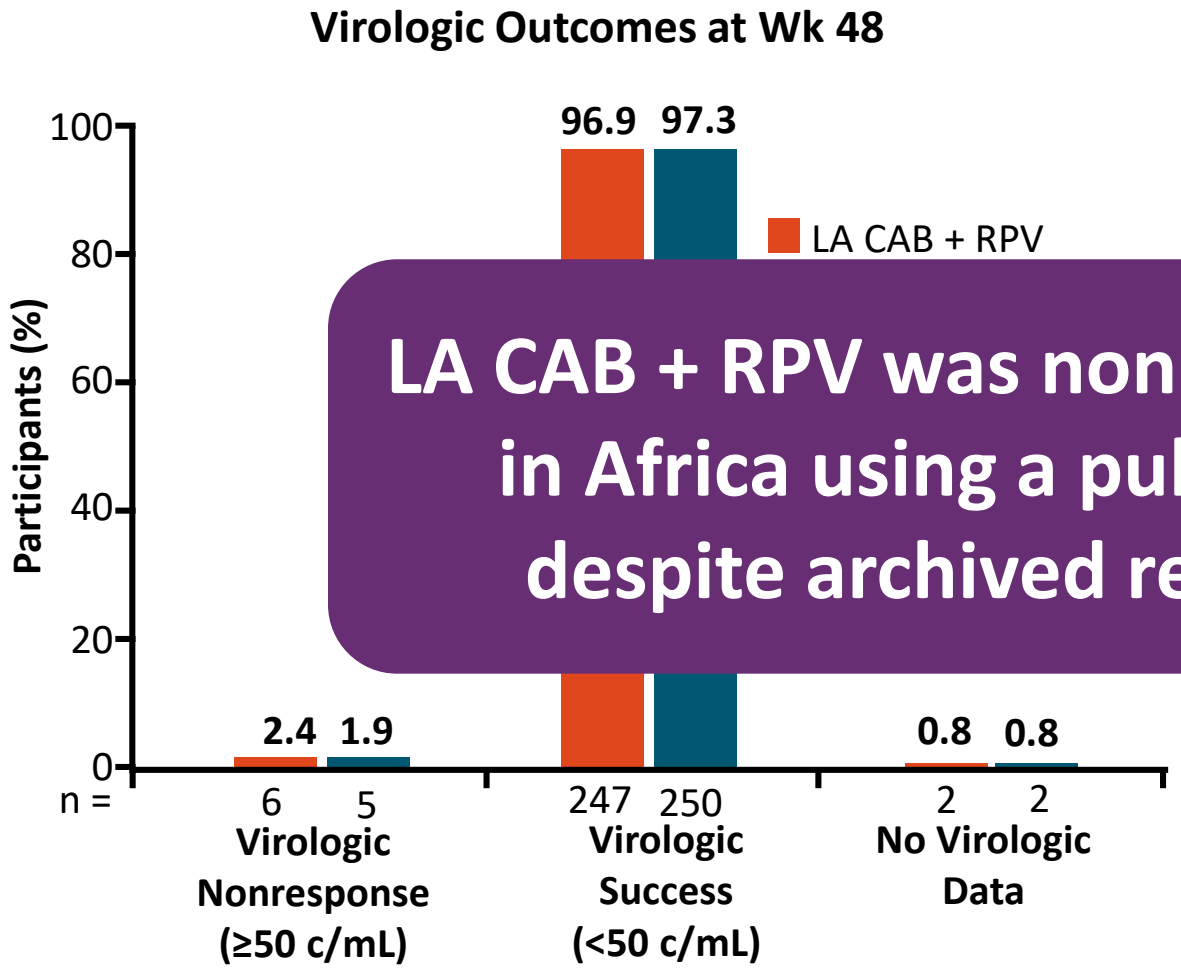


- 82.7% of participants received all injections on time
- 1 confirmed virologic failure on LA CAB + RPV
  - Subtype A1
  - No resistance at baseline; high RPV and intermediate CAB resistance at failure
- 1 additional virologic failure on LA CAB + RPV was unconfirmed due to death (HIV unrelated)

Kityo. CROI 2024. Abstr 122.

Slide credit: clinicaloptions.com

CARES: Efficacy Results



LA CAB + RPV was noninferior to SoC oral ART in Africa using a public health approach despite archived resistance mutations

- 82.7% of participants received all injections on time
- 1 confirmed virologic failure on
- CAB resistance at failure
- 1 additional virologic failure on LA CAB + RPV was unconfirmed due to death (HIV unrelated)

Kityo. CROI 2024. Abstr 122.

Slide credit: clinicaloptions.com

CARES: Safety, Tolerability, and Treatment Satisfaction

≥1 AE, n (%)	LA CAB + RPV (n = 255)	Oral ART (n = 257)
Grade ≥3	24 (9.4)	10 (3.9)
▪ Treatment related	3 (1.2)	2 (0.8)
Serious	3 (1.2)	5 (1.9)
Any (grade 1-4)	220 (86.3)	161 (62.6)
▪ Excluding ISRs	181 (71.0)	161 (62.6)
▪ Leading to d/c	1 (0.4)	3 (1.2)

- ISRs with LA CAB + RPV
  - Grade 1: 161 (63.1%)
  - Grade 2: 26 (10.2%)
  - Grade 3: 1 (0.4%)
- 1 ISR led to treatment discontinuation

HIVTSQ Score ± SD	LA CAB + RPV (n = 253)	Oral ART (SoC) (n = 255)	Adjusted Mean Difference (95% CI)	*P* Value
Baseline (HIVTSQs)	53.6 ± 10.5	52.0 ± 12.5	--	--
Change at Wk 48 (HIVTSQc)	28.0 ± 0.65	17.6 ± 0.64	10.4 (8.7-12.2)	<.001

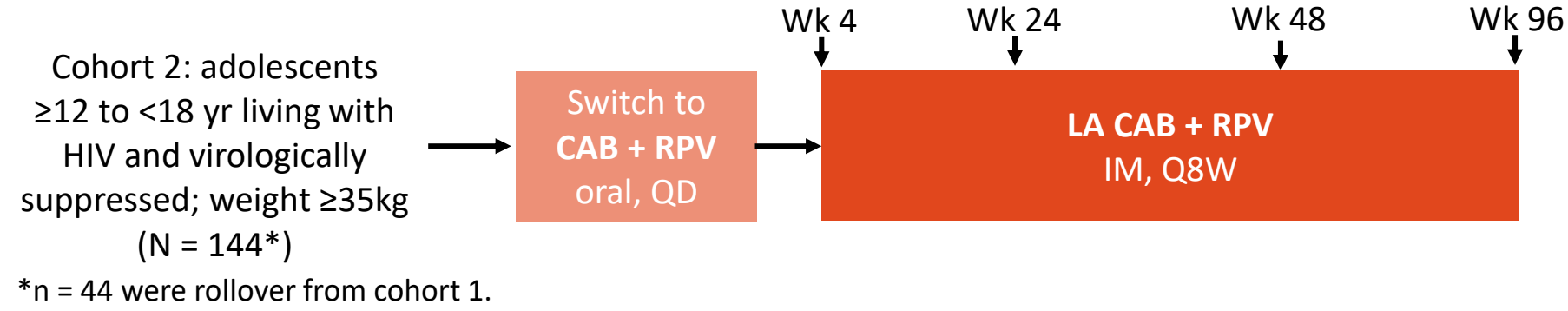
- At Wk 48, HIVTSQc scores **increased** for patients who switched to **LA CAB + RPV** vs patients who continued oral ART (SoC)

Kityo. CROI 2024. Abstr 122.

Slide credit: clinicaloptions.com

IMPAACT 2017/MOCHA: Switching to LA CAB + RPV in Adolescents Living With HIV

- Multicenter, open-label, noncomparative phase I/II study
  - Evidence from cohort 1—where adolescents retained their background combination ART—informed the approval of LA CAB + RPV in adolescents living with HIV
  - Cohort 2 enrolled at 18 global sites including US, Uganda, Botswana, South Africa, Thailand



*n = 44 were rollover from cohort 1.

- **Primary outcome**: safety (adverse events, deaths) through Wk 24
- **Secondary outcomes**: plasma HIV-1 RNA levels, number of participants with virologic failure, and adverse events through Wk 48

NCT03497676. impaactnetwork.org/studies/impaact2017. Moore. CROI 2022. Abstr 738. Guar. CROI 2024. Abstr 188.

Slide credit: clinicaloptions.com

IMPAACT 2017/MOCHA: Baseline Characteristics, Efficacy, and Safety Results

Baseline Characteristic	Cohort 2 (N = 144)
Median age, yr (range)	15 (12-17)
Female sex, %	51
Black, %	74
Vertical HIV acquisition, %	92
Median BMI, kg/m^2 (range)	19.5 (16-34)
Median weight, kg (range)	48 (35-101)

- HIV-1 RNA <50 c/mL maintained in 96.5% of participants at Wk 24
- In PK analysis, CAB and RPV troughs comparable to those previously reported in adults

Safety Parameter	Cohort 2 (N = 144)
Received ≥1 injection, n	142
Completed Wk 24 visit, n	141
Injection-site reaction, n/N (%)	49/142 (35)
▪ Resolved ≤7 days, %	86
▪ Grade 3 injection site abscess,* n	1
▪ Grade 3 injection site abscess and pain,* n	1
Grade ≥3 noninjection-site reaction, n/N (%)	16/144 (11)
▪ Increased creatine phosphokinase, n	6
▪ Systolic blood pressure, n	3
▪ Other AEs, n	7

*Participant continued study.

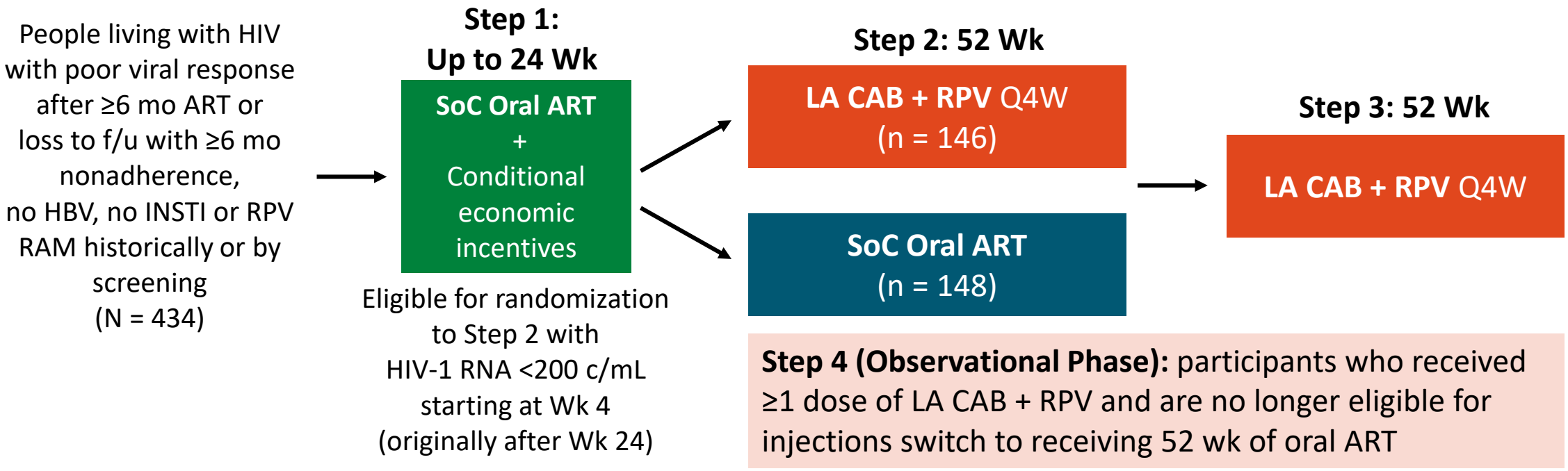
- No permanent discontinuations due to AEs
- 1 pregnancy resulting in a live, term birth

Guar. CROI 2024. Abstr 188.

Slide credit: clinicaloptions.com

ACTG A5359 LATITUDE: LA CAB + RPV in People With Adherence Challenges to Oral ART

- Prospective, randomized, open-label phase III trial



- **Primary endpoint:** treatment 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 Characteristic, Safety, and Injection Timing

Characteristic	Step 1 Total (N = 434)
Median age, yr (Q1, Q3) ▪ ≤30, n (%) ▪ 31-50, n (%) ▪ ≥51, n (%)	40 (32, 51) 88 (20) 232 (53) 114 (26)
Female at birth, n (%)	129 (30)
Transgender spectrum, n (%)	21 (5)
Race, n (%) ▪ Black ▪ White ▪ Other/multiple/unknown	 277 (64) 117 (27) 40 (9)
Hispanic or Latino/a, n (%)	75 (17)
Current or previous injection drug use, n (%)	61 (14)
Nonadherence criteria, n (%) ▪ 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 2

Characteristic	LA CAB + RPV (n = 146)	SoC (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.

- Safety on LA CAB + RPV
  - ≥ 1 ISR: 77 (57%)
  - Grade 3/4 ISR: 3 (2.2%)
- Timing of LA CAB + RPV Injections
  - On time: 1092 (93%)
  - Missed: 36 (3%)

Rana. CROI 2024. Abstr 212.

Slide credit: clinicaloptions.com

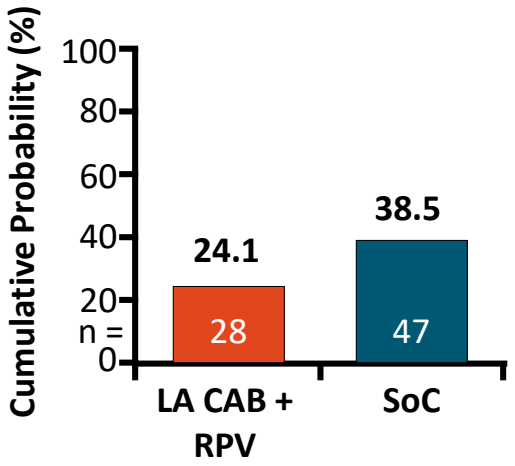
ACTG A5359 LATITUDE: Efficacy Outcomes

Primary Outcome

Regimen Failure

Difference -14.5%

Nominal 98.75% CI (-29.8% to 0.8%)

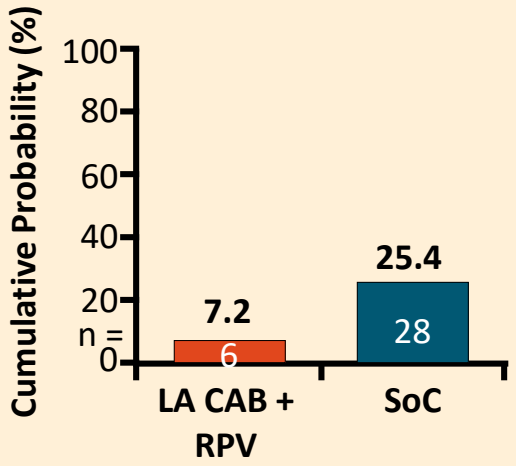


Secondary Outcomes

Virologic Failure

Difference -18.2%

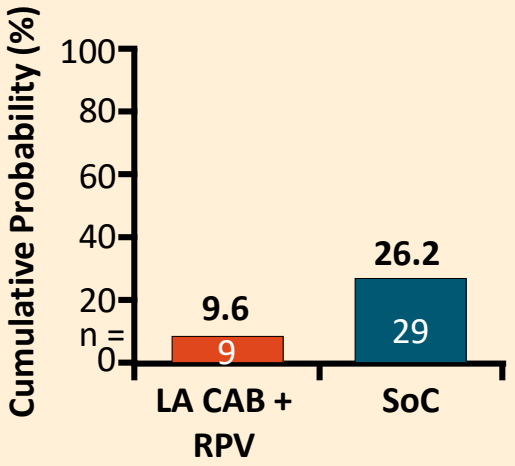
Nominal 98.75% CI (-31.1% to -5.4%)



Treatment-Related Failure

Difference -16.6%

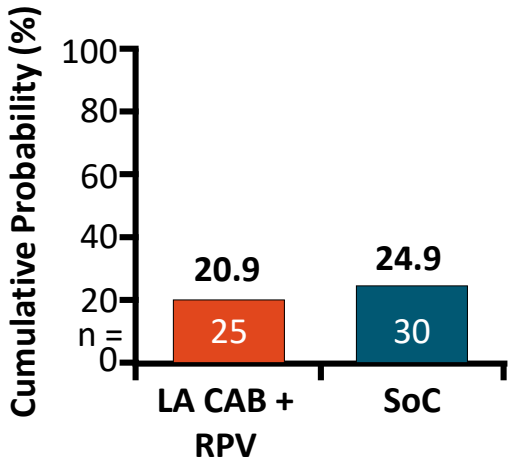
Nominal 98.75% CI (-29.9% to -3.3%)



Permanent Treatment Discontinuation

Difference -4.1%

Nominal 98.75% CI (-18.0% to 9.8%)



1 additional virologic failure after Wk 24 included in secondary endpoints, but not primary

Rana. CROI 2024. Abstr 212.

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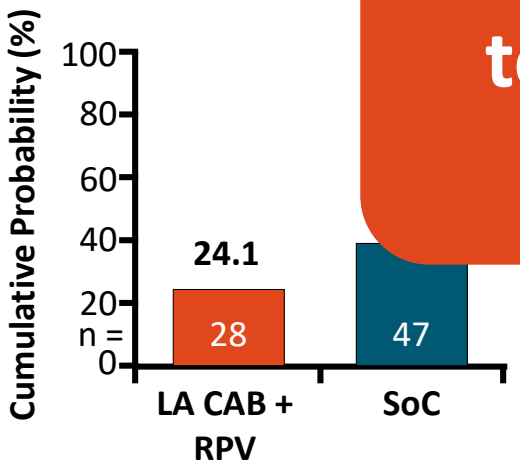
ACTG A5359 LATITUDE: Efficacy Outcomes

Primary Outcome

Regimen Failure

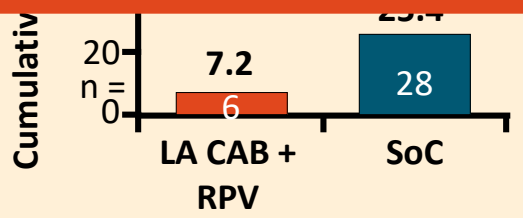
Difference -14.5%

Nominal (-29.8%

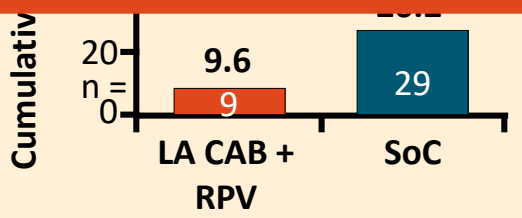


Secondary Outcomes

Virologic Failure

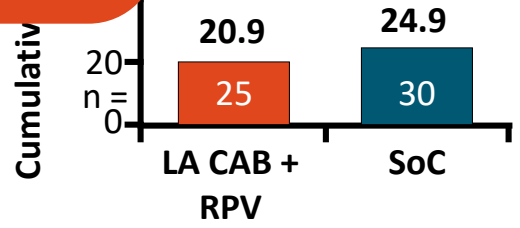


Treatment-Related Failure



Permanent Treatment Discontinuation

Nominal 98.75% CI (-18.0% to 9.8%)



DSMB stopped study randomization due to superior efficacy of LA CAB + RPV in secondary endpoints

1 additional virologic failure after Wk 24 included in secondary endpoints, but not primary

Rana. CROI 2024. Abstr 212.

Slide credit: clinicaloptions.com

LA CAB + RPV in San Francisco's Ward 86 Safety Net Clinic in People Without Viral Suppression at Baseline

- Retrospective cohort study of people living with HIV without CAB or RPV resistance who received LA CAB/RPV at Ward 86, a publicly funded HIV clinic (N = 286)
  - Baseline HIV-1 RNA ≥50 c/mL(n = 101)
  - Baseline HIV-1 RNA ≥50 c/mL with ≥56 wk of therapy before Dec 5, 2022 (n = 59)
- All unsuppressed participants received LA CAB + RPV Q4W per clinic protocol
  - Option for Q8W dosing after 3-6 mo of viral suppression
- **Primary outcome:** HIV viral suppression (<50 c/mL) and LA CAB + RPV persistence using closest VL to 48 ± 8 wk

Hickey. CROI 2024. Abstr 628.

LA CAB + RPV at Ward 86: Baseline Characteristics

Characteristic, n (%)	People Without Baseline Viral Suppression (n = 59)
Gender	
▪ Female	5 (8.5)
▪ Male	53 (89.8)
▪ Gender minority	1 (1.7)
Age, yr	
▪ 18-29	2 (3.4)
▪ 30-49	29 (49.2)
▪ ≥50	28 (47.5)
Race/ethnicity	
▪ White	24 (40.7)
▪ Black	14 (23.7)
▪ Latino/a	17 (28.8)
▪ Other	4 (6.8)
Housing status	
▪ Stable	28 (47.5)
▪ Unstable	26 (44.1)
▪ Unhoused	5 (8.5)

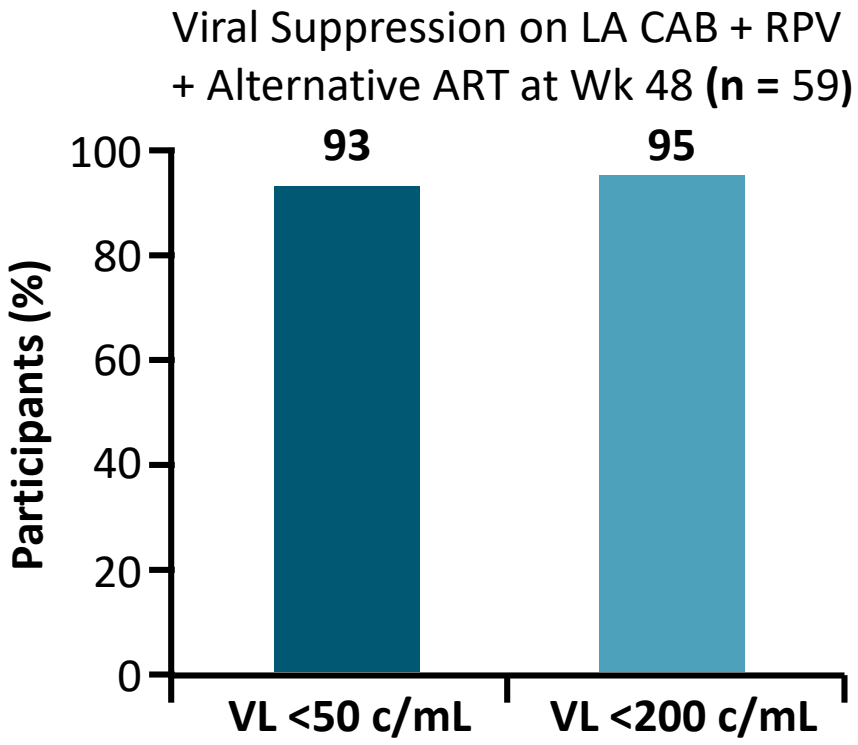
Characteristic, n (%)	People Without Baseline Viral Suppression (n = 59)
Substance use	
▪ Methamphetamine/cocaine	36 (61.0)
▪ Opioids	6 (10.2)
CD4+ count, cells/mm^3	
▪ <50	9 (15.3)
▪ 50-199	20 (33.9)
▪ 200-349	13 (22.0)
▪ 350-499	7 (11.9)
▪ ≥500	10 (16.9)
HIV-1 RNA, c/mL	
▪ 50 to <200	3 (5.1)
▪ 200 to <1000	5 (8.5)
▪ 1000 to <10,000	10 (16.9)
▪ 10,000 to <100,000	22 (37.3)
▪ ≥100,000	19 (32.2)

Hickey. CROI 2024. Abstr 628.

Slide credit: clinicaloptions.com

LA CAB + RPV in People Without Viral Suppression at Baseline: 48 Wk Results

- **81%** (48/59) remained on LA CAB + RPV with **VL <50 c/mL** at Wk 48



Status at Wk 48, n (%)	VL <50 c/mL (n = 55)	VL ≥50 c/mL (n = 4)	Overall (n = 59)
Remained on LA CAB + RPV	48	1*	49 (83)
Discontinued LA CAB + RPV and resumed oral ART	5	–	5 (8)
Failure with resistance			3 (5)
▪ On-time injections	2	–	
▪ Lost to f/u and not receiving oral ART, resistance found	–	1	
Lost to f/u and off oral ART	–	2	2 (3)

*Intensified to LA CAB + RPV with LEN for low-level viremia.

Take home messages L-A

- L-A CAB+RPV in SSA: approccio di salute pubblica;
- MOCHA: adolescenti;
- LATITUDE: efficacia se problemi di aderenza;
- SF’s Ward 86: PWH viremici (VS 48/59).

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

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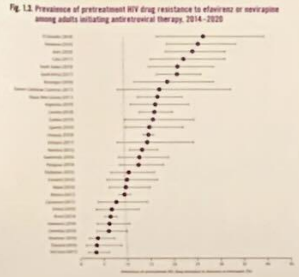
Background

- 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

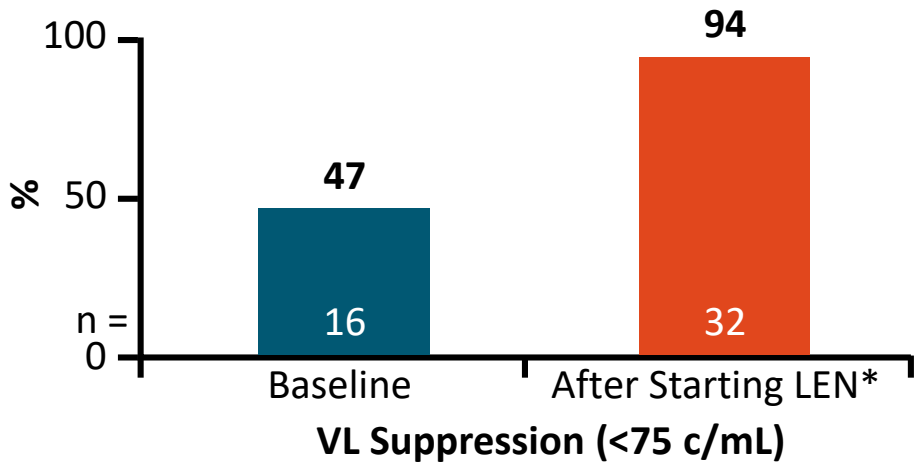
UCSF Penn Case Western Reserve University

UC San Diego MetroHealth

Off-Label Use of LA CAB (± RPV) + LEN: Case Series

- LA CAB + RPV is the only recommended complete LA ART regimen but is not approved by WHO in low- and middle-income countries
  - Many LMICs have >10% resistance to NNRTIs
  - Disparities in availability of LA ART
- Case series of 4 US clinics where use of LA CAB (± RPV) + LEN off-label is occurring for selected patients due to adherence challenges with oral ART (N = 34)
  - Most common reason for off-label combination use was NNRTI mutations
- Call for trial to study LA CAB + LEN in those with NNRTI resistance worldwide

Patient Characteristics/Results	All Patients (N = 34)
Male or cis/trans female, %	76/24
Black/Latino/a, %	41/38
CAB Q4W/CAB Q8W, %	29/71
Reason(s) for using LA CAB (± RPV) + LEN, n (%)	
▪ Documented/suspected NNRTI mutations	21 (59)
▪ Integrase mutations	5 (15)
▪ High VL	6 (18)
▪ Cont. viremia on LA CAB + RPV alone	4 (12)



*Suppression occurred a median of 8 (4-16) wk after starting LEN.

Gandhi. CROI 2024. Abstr 629. who.int/publications/i/item/9789240086319.

Slide credit: clinicaloptions.com

LEN without Fully Active Agents in OBR

Table 1. Participants' Baseline OBRs and ARV Activity Profiles

Participant	OBR		OBR OSS	Activity of antiretrovirals at baseline																						
				INSTIs				NNRTIs				NRTIs						PIs					EIs			
	No activity	Partial activity		BIC	DTG	EVG	RAL	DOR	EFV	ETR	RPV	3TC	FTC	ABC	ddI	TFV*	ZDV	FPV	ATV	DRV	LPV	TPV	FTR	MVC	ENF	IBA
1	3TC, DRVr, DTG, ENF, MVC	-	0																							
2	FTC, DOR, BIC, IBA	TAF	0.5																							
3	3TC, RPV, MVC, IBA	-	0																							
4	FTC, DRVr, DTG, IBA	TAF	0.5																							
5	FTC, TDF, DRVr, DTG	-	0																							
6	FTC, DRVr, DTG, IBA, FTR	TAF	0.5																							
7	FTC, DOR, DRVc	TAF	0.5																							
8	DOR, DTG	-	0																							
9	FTC	TAF, DRVc	1																							
10	DOR, IBA, FTR	-	0																							
11	DRVr, DTG	TDF	0.5																							
12	DOR	DTG	0.5																							

No activity Partial activity Full activity No data

Resistance testing obtained for the agents stavudine, delavirdine, indinavir, nelfinavir, nevirapine, ritonavir, and saquinavir are not shown in the table. *Tenofovir (TFV) is the active drug moiety for both tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF) prodrugs.
3TC, lamivudine; ABC, abacavir; ARV, antiretroviral; ATV, atazanavir; BIC, bictegravir; c, cobicistat; ddI, didanosine; DOR, doravirine; DRV, darunavir; DTG, dolutegravir; EI, entry inhibitor; EFV, efavirenz; ENF, enfuvirtide; ETR, etravirine; EVG, elvitegravir; FPV, fosamprenavir; FTC, emtricitabine; FTR, fostemsavir; IBA, ibalizumab; INSTI, integrase strand transfer inhibitor; LPV, lopinavir; MVC, maraviroc; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; OBR, optimized background regimen; OSS, overall susceptibility score; PI, protease inhibitor; RAL, raltegravir; RPV, rilpivirine; r, ritonavir boosting; TPV, tipranavir; ZDV, zidovudine.

Table 2. Resistance Mutations at Baseline

Participant	Baseline Resistance Mutations			
	INSTIs	NNRTIs	NRTIs	PIs
1	M50I, T97A, S119R, E138K, G140S, Q148H	Y181I, Y188L	M41M/L, M184V, T215F	V32I, I54M, Q58E, I84V, L90M
2	L74IM, S119P, E138E/K, S147S/G, S153S/A/C/G, N155H, E157E/Q	V106M, V108I, Y181V	D67N, K70R, M184V, T215F, K219E	V32I, M46I, I54L, L76V, I84V, L90M
3	M50I, T97A, S119P, E138K, G140S, Q148H	L100I/V, G190Q	M41L, D67N, L74I/V, M184V, L210W, T215Y, K219R	V32I, M46I, I47V, I54L, I84V
4	T97A, E138K, G140S, Q148H	L100I, K103N, V106M	M41L, D67N, L74I, M184V, L210W, T215Y, K219N	M46I, I47V, I50V, L76V, V82T
5	E138K, G140A, S147G, Q148R, E157Q	K101H, Y181C, G190A	M41L, D67N, K70K/R, M184V, T215F, K219Q	V32I, M46L, I54L, N83D, I84V
6	M50I/T, L74M, T97A, S119T, Y143C, S147G, N155H, E157Q	L100I/M, K103S, H221Y	T69(del), V75I, F77L, Y115F, F116Y, Q151M, M184V, K219Q	V32I, M46L, I54L, T74P, V82T, I84V, L90M
7	N155N/H	K101E, Y181I	M41L, M184V, T215F	V32I/I, I47I/V, I54I/M, Q58Q/E, I84I/V, L90M
8	M50M/I, T97A, S119R, S147G, N155H, E157Q	L100I, K103N	M41L, D67N, L74V, L210W, K219Q/N	V32I, M46I, Q58E, I84V, L90M
9	M50I, G140S, Q148H, N155H	E138Q, Y181V, H221Y, M230L	M41L, M184V, T215F	V32I, M46I, I47V, I54L, Q58E, I84V, L90M
10	E138A, G140A, S147G, Q148R, N155H, E157Q	V108I/M, Y181C	M41L, V75I, F77L, F116Y, Q151M	V32I, I54L, Q58E, T74P, V82L, I84V, L90M
11	E138E/A, G140A, Q148R	K103N, E138Q	K70R, T215F, K219E	V32I, M46I, I54L, L76V, I84V
12	G140S, Q148H	K103N	M41L, D67N, L210W, T215Y, K219R	V32I, M46L, I54V, T74P, V82A, I84V, L90M

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

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LEN without Fully Active Agents in OBR

Table 3: Participants' Baseline Characteristics, HIV-1 RNA and CD4 cell count

Participant	Age (years)	Sex	Race	HIV-1 RNA, copies/mL				CD4 cell count, cells/μL	
				Baseline	Week 26	Week 52	Week 104	Baseline	Week 104
1*	27	F	Black or African American	85,100	<50	<50	<50	3	594
2	54	M	White	75,200	342	574	–	33	71
3	64	M	White	14,500	<50	<50	<50	176	181
4	58	M	Black or African American	38,300	2420	2970	1880	50	128
5	24	M	Asian	14,000	<50	<50	<50	189	273
6	61	M	Black or African American	1900	<50	<50	<50	84	98
7†	36	F	White	<50	<50	<50	<50	518	704
8	61	M	White	39,400	<50	<50	<50	159	278
9‡	60	M	Black or African American	91	<50	<50	<50	192	198
10	51	M	White	43,900	200	<50	<50	249	279
11§	41	F	Asian	69,500	<50	<50	–	137¶	–#
12	68	M	White	78,800	<50	<50	<50	313	319

*Developed resistance at Week 10 and resuppressed at Week 26; †HIV-1 RNA at screening was 687 copies/mL; ‡HIV-1 RNA at screening was 4800 copies/mL; §Participant 11 was suppressed at Weeks 26 and 52, but missing virologic data in the Week 104 window and was suppressed at a later visit (Week 114); ¶Value from the screening visit as Participant 11 had missing data for Day 1. #Missing at Week 104, 321 cells/μL at Week 114.
F, Female; M, Male.

Through Week 104, Participant 1 and 10 developed resistances to LEN and were re-suppressed with OBR change; Participant 2 was not suppressed with low-level viremia; Participant 4 was not suppressed and developed resistance to LEN (Table 3)

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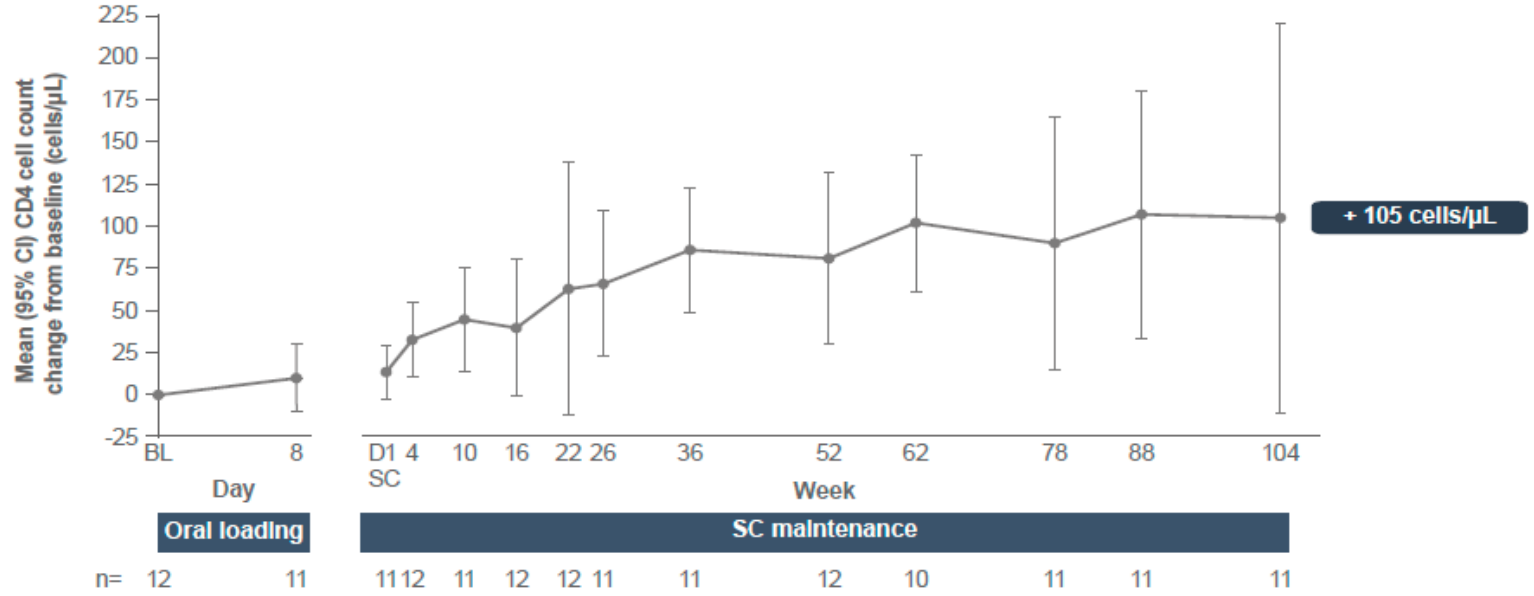
LEN without Fully Active Agents in OBR

Figure 3. Mean CD4 Cell Count Change from Baseline (n=12)



BL, baseline; CI, confidence interval; D, day; SC, subcutaneous.

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ARTISTRY-1 (GS-US-621-6289): Phase 2/3, randomized, open-label study[1,2]

BIC + LEN in PWH Switching From a Complex ART Regimen: Study Design

ARTISTRY 1 ‡

N=671[2]

VSTE PWH on complex ART regimen[1,2,a]

Outcomes (by FDA Snapshot): Proportion of participants With HIV-1 RNA ≥50 copies/mL at Week 24 (Phase 2) and Week 48 (Phase 3)[1,2]

August 2022 – ongoing[2]

Study sites: Argentina, Australia, Canada, Dominican Republic, France, Germany, Italy, Japan, Puerto Rico, South Africa, South Korea, Spain, Taiwan, United Kingdom, United States[2]

Operationally seamless, randomized, open-label, multicenter study[1]

Adults VS for 6 months[1]

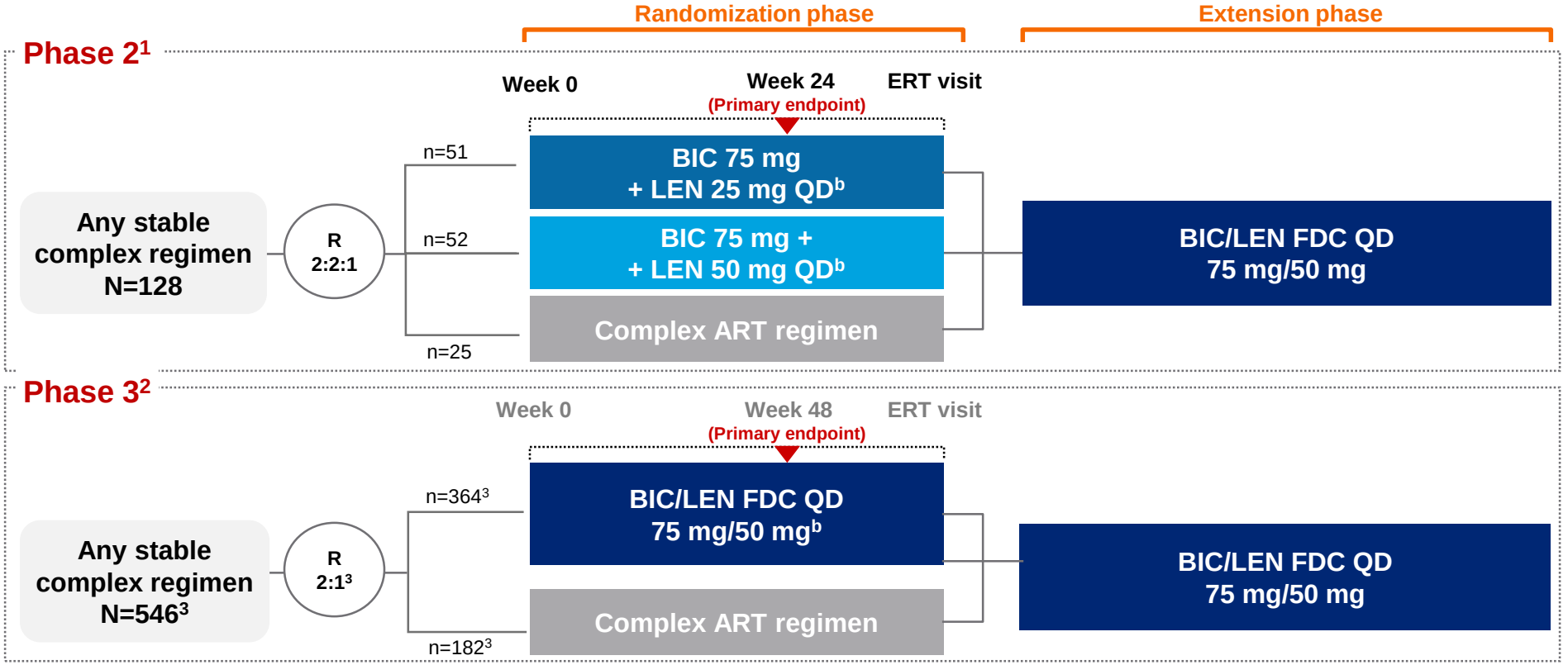
VL <50 copies/mL[1]

On a complex ART regimen[1]

No history of exposure to LEN or resistance to BIC[1]

No history of HBV infection[1]

eGFR ≥15 mL/min, not on renal replacement therapy[1]



[a]Containing bPI or NNRTI plus ≥1 other third agent from a class other than NRTIs; or consisting of ≥2 pills/day, or requiring dosing more than once daily; or containing parenteral ART (excluding a complete long-acting injectable regimen) plus oral ART; [b]Participants will receive a 2-day loading dose of LEN 600 mg in addition to BIC + LEN daily doses. ERT, end of randomized treatment; FDC, fixed dose combination; STR, single tablet regimen; VL, viral load; VS, virologically suppressed; VSTE, virologically suppressed treatment-experienced

1. Mounzer K, et al. CROI 2024, Poster 642; 2. NCT05502341. https://clinicaltrials.gov/study/NCT05502341 (accessed June 6, 2024); 3. Data on file. Gilead Sciences, Inc.

ARTISTRY-1: Phase 2/3, randomized, open-label study

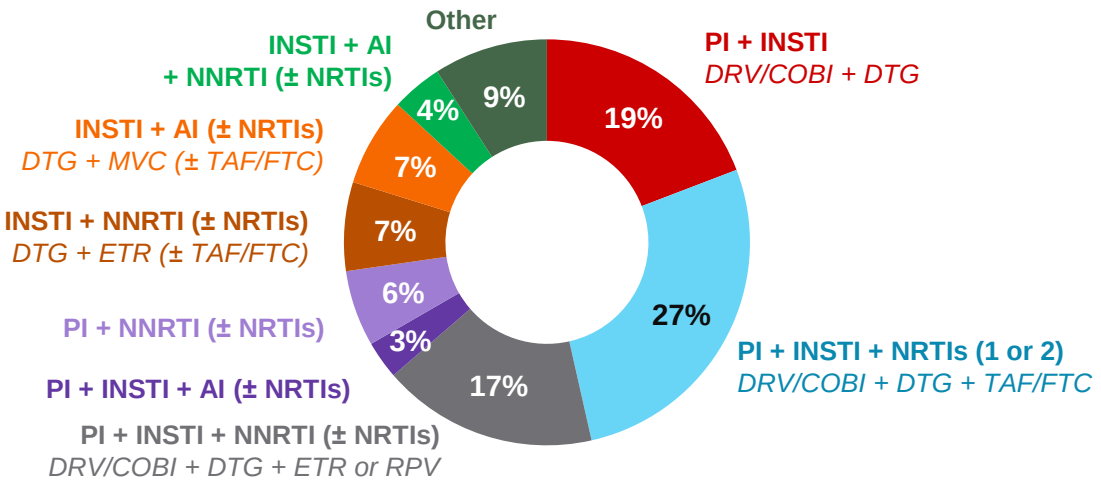
BIC + LEN in PWH Switching From a Complex ART Regimen: Phase 2 Baseline Characteristics

‡

Baseline Characteristics

	BIC 75 mg + LEN 25 mg n=51	BIC 75 mg + LEN 50 mg n=52	SBR n=25
Duration of HIV treatment, years, median (Q1, Q3)[a]	27.8 (22.7, 32.4)	27.0 (18.9, 31.5)	26.9 (19.8, 31.9)
Number of pills/day, median (range)	2.0 (2.0, 8.0)	3.0 (2.0, 9.0)	3.0 (2.0, 8.0)
Dosing frequency of ARTs, n (%)			
Daily	47 (93)	46 (89)	22 (88)
Twice per day	18 (35)	22 (42)	13 (52)
Other	1 (2)	0	0
Reasons for complex ART, n (%)			
History of resistance	44 (86)	40 (77)	20 (80)
Intolerance to components of STRs	20 (39)	11 (21)	7 (28)
Contraindication to STRs	7 (14)	4 (8)	1 (4)
Resistance mutations, n (%)			
INSTI	0	0	0
NNRTI	25 (49)	28 (54)	14 (56)
NRTI	31 (61)	35 (67)	16 (64)
PI	18 (35)	17 (33)	11 (44)

Diversity of Complex ART Regimens[b]



Participants enrolled in ARTISTRY-1 were VSTE PWH receiving complex ART regimen, primarily due to a history of resistance

[a]N=50 for BIC 75 mg + LEN 25 mg group; [b]Most common regimen(s) in each category shown in italics; percentages do not sum to 100% due to rounding
AI, attachment inhibitor; SBR, stable baseline regimen; STR, single tablet regimen; VSTE, virologically suppressed treatment-experienced
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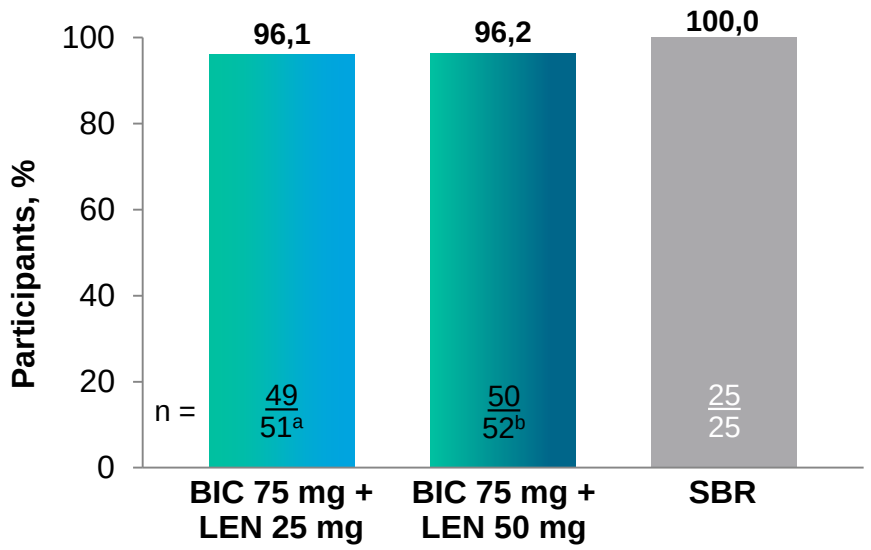
ARTISTRY-1: Phase 2/3, randomized, open-label study

Efficacy and Safety Results of Switch to BIC + LEN from a Complex ART Regimen: Phase 2 Results

‡

VS (HIV-1 RNA <50 c/mL) at Week 24 (FDA Snapshot Algorithm)



1 participant in the BIC 75 mg + LEN 50 mg arm had **HIV-1 RNA ≥50 c/mL** in Week 24 window (later suppressed to <50 c/mL without regimen change)

TEAEs up to Week 24

	BIC 75 mg + LEN 25 mg n=51	BIC 75 mg + LEN 50 mg n=52	SBR n=25
Any TEAE, n (%)	39 (76)	33 (63)	17 (68)
Related to study drug or SBR	9 (18)	3 (6)	0
Grade 3 or higher	4 (8)	2 (4)	1 (4)
SAEs	2 (4)	1 (2)	2 (8)
Leading to discontinuation[c]	1 (2)	1 (2)	0
TEAEs with frequency ≥5%, n (%)			
COVID-19	4 (8)	2 (4)	2 (8)
Diarrhea	5 (10)	2 (4)	1 (4)
Hypertension	0	4 (8)	1 (4)
Constipation	3 (6)	2 (4)	0
Cough	3 (6)	1 (2)	0
Nasopharyngitis	4 (8)	0	0

All TEAEs with frequency ≥5% were **Grade 1 or 2** apart from 1 occurrence of Grade 3 diarrhea (unrelated to study drug)

BIC + LEN maintained high rates of VS in TE participants on a complex ART regimen and was generally well tolerated. Based on these data, a BIC 75 mg/LEN 50 mg STR will be assessed in the Phase 3 part of the study

[a]Data missing for 2 participants; [b]Data missing for 1 participant, and 1 participant had HIV-1 RNA ≥50 c/mL; [c]Grade 1 nausea (BIC 75 mg + LEN 25 mg group, n=1) and Grade 3 worsening of vomiting (BIC 75 mg + LEN 50 mg group, n=1)

SBR, stable baseline regimen; STR, single tablet regimen; TE, treatment-experienced; TEAE, treatment-emergent adverse event; VS, virologic suppression

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Development of Individualized Antibody Treatment Regimens for Patients With Multidrug-Resistant HIV

00690

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Background and Rationale

- People living with HIV (PLWH) with multidrug-resistant (MDR) viruses have limited therapeutic options and present challenges regarding clinical management.
- Recent studies have shown that passive transfer of combination broadly neutralizing antibodies (bNAbs) against HIV and anti-domain 1 CD4 antibody UB-421 can sustain virologic suppression in PLWH in the absence of antiretroviral therapy (ART).
- Yet studies addressing the therapeutic potential of these antibodies and/or detailed characterization of immunologic and virologic parameters in PLWH with MDR HIV are lacking. We conducted the present ex vivo study to address this issue.

Materials and Methods

Study population: We conducted an extensive analysis of eleven treatment-experienced PLWH with MDR HIV. Blood from study participants was collected in accordance with a protocol approved by the National Institutes of Health. All study participants provided written informed consent.

HIV reservoir quantification: The frequency of cells carrying intact HIV proviruses was determined by Intact Proviral DNA Assay (IPDA).

Immunologic parameters: Immunologic phenotyping was done using flow cytometry.

HIV neutralization/suppression: Near-clonal replication-competent HIV isolates were derived from CD8⁺ T cells-depleted peripheral blood mononuclear cells (PBMCs) of the MDR participants. Each viral isolate was incubated with 10μg/ml of bNAbs and anti-CD4 antibodies for 90 minutes followed by incubation with TZM-bl cells for 48 h. Cells were subsequently lysed and substrate (Promega) was added to measure the luciferase activity (Tecan).

Table 1

Clinical Characteristics of Study Participants

Study participant	Age	Sex	Race or ethnic group	Plasma Viremia (copies of HIV RNA/ml)	CD4⁺ T cell count (cells/μl)	% CD4⁺ T cells	CD8⁺ T cell count (cells/μl)	% CD8⁺ T cells
1	24	F	AA	84,626	16	2	599	73
2	54	M	Caucasian	39,950	23	1	1,896	84
3	50	M	AA	143,379	222	20	610	55
4	42	M	AA	11,464	4	1	197	46
5	44	M	AA	80,156	42	4	593	57
6	26	F	AA	49,585	69	7	550	56
7	52	M	Hispanic	43,873	48	2	1,071	45
8	50	F	AA	99,051	13	1	403	32
9	61	F	AA	33,669	42	5	535	63
10	29	M	AA	73,265	16	2	512	64
11	52	M	Caucasian	5,053	149	13	655	57

Table 2

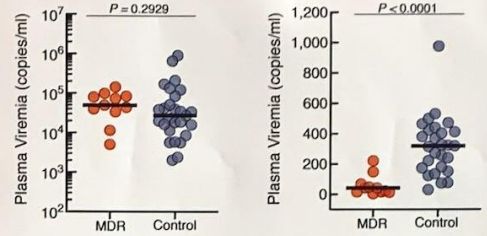
HIV Genotypic Resistance Testing in Study Participants

Drug Class	Participant 1		Participant 2		Participant 3		Participant 4		Participant 5		Participant 6		Participant 7		Participant 8		Participant 9		Participant 10		Participant 11	
Nucleoside Reverse Transcriptase Inhibitors	Score	Profile	Score	Profile	Score	Profile	Score	Profile	Score	Profile	Score	Profile	Score	Profile	Score	Profile	Score	Profile	Score	Profile	Score	Profile
Lamivudine (3TC)	25	L	95	R	95	R	55	I	65	R	75	R	80	R	75	R	80	R	70	R	80	R
Abacavir (ABC)	75	R	145	R	100	R	155	R	85	R	125	R	100	R	95	R	100	R	90	R	105	R
Zidovudine (AZT)	100	R	115	R	105	R	140	R	60	R	95	R	140	R	130	R	130	R	45	I	135	R
Stavudine (D4T)	110	R	115	R	105	R	175	R	70	R	95	R	170	R	115	R	130	R	70	R	120	R
Didanosine (DDI)	105	R	155	R	105	R	170	R	125	R	135	R	145	R	85	R	100	R	105	R	90	R
Emtricitabine (FTC)	25	L	95	R	95	R	55	I	65	R	75	R	90	R	75	R	80	R	70	R	80	R
Tenofovir DF (TDF)	40	I	75	R	75	R	135	R	15	L	55	I	70	R	50	I	70	R	35	I	55	I
Non-Nucleoside Reverse transcriptase Inhibitors																						
Efavirenz (EFV)	75	R	130	R	115	R	90	R	10	P	115	R	135	R	0	S	75	R	130	R	70	R
Etravirine (ETR)	55	I	115	R	90	R	75	R	10	P	40	I	50	I	0	S	60	R	40	I	70	R
Nevirapine (NVP)	120	R	205	R	190	R	120	R	10	P	135	R	150	R	0	S	120	R	130	R	70	R
Rilpivirine (RPV)	55	I	120	R	135	R	120	R	10	P	75	R	90	R	0	S	90	R	75	R	105	R
Protease Inhibitors																						
Atazanavir (ATV/r)	25	L	150	R	160	R	125	R	105	R	90	R	155	R	185	R	160	R	45	I	130	R
Darunavir (DRV/r)	0	S	90	R	85	R	95	R	15	L	30	I	70	R	105	R	100	R	70	R	80	R
Fosamprenavir (FPV/r)	20	L	225	R	255	R	235	R	90	R	100	R	230	R	305	R	265	R	175	R	225	R
Indinavir (IDV/r)	30	I	200	R	190	R	170	R	110	R	90	R	170	R	240	R	205	R	85	R	150	R
Lopinavir (LPV/r)	15	L	140	R	130	R	145	R	60	R	55	I	120	R	155	R	135	R	85	R	115	R
Nelfinavir (NFV)	75	R	200	R	270	R	190	R	150	R	115	R	245	R	315	R	275	R	125	R	245	R
Saquinavir (SQV/r)	40	I	125	R	160	R	130	R	105	R	75	R	155	R	190	R	170	R	30	I	105	R
Tipranavir (TPV/r)	0	S	115	R	60	R	65	R	35	I	95	R	60	R	75	R	70	R	70	R	110	R
Integrase Inhibitors																						
Dolutegravir (DTG)	0	S	10	P	45	I	100	R	90	R	0	S	80	R	0	S	0	S	0	S	45	I
Elvitegravir (EVG)	0	S	75	R	90	R	115	R	105	R	0	S	130	R	30	I	0	S	0	S	90	R
Raltegravir (RAL)	0	S	75	R	90	R	120	R	105	R	0	S	130	R	15	L	0	S	0	S	90	R

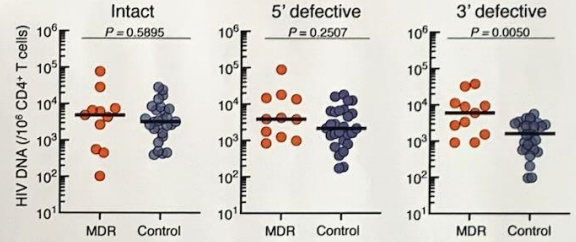
S, susceptible; P, potentially low-level resistance; L, low-level resistance; I, intermediate resistance; R, high-level resistance

Results

Comparison of Plasma Viremia and CD4⁺ T-cell Counts

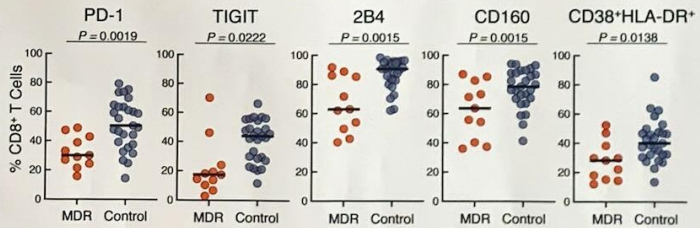


Levels of Intact and Defective HIV Proviral DNA



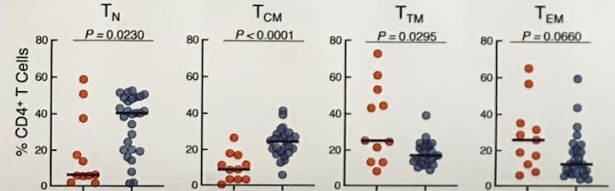
- The level of CD4⁺ T cell-associated intact and 5'-defective HIV proviral DNA was comparable between the groups. However, the size of the reservoir carrying 3'-defective HIV DNA was higher in MDR group.

Immune Exhaustion and Activation Markers on CD8⁺ T cells



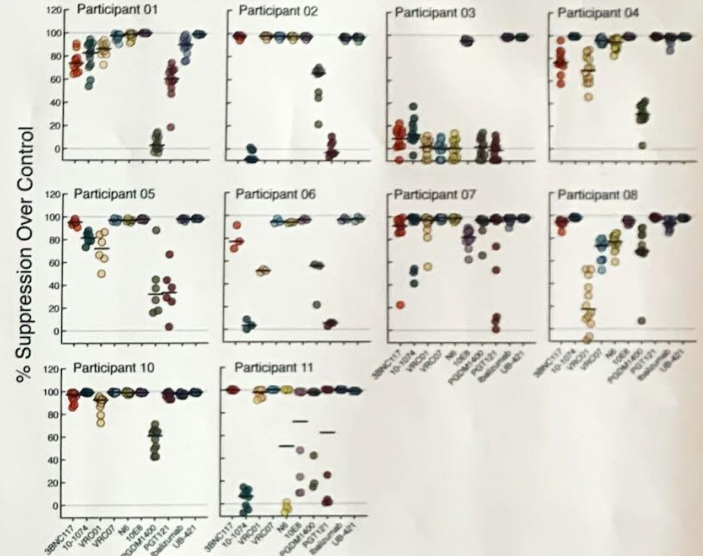
- Expression levels of activation and exhaustion markers PD-1, TIGIT, 2B4, CD160 and CD38⁺/HLA-DR⁺ were significantly lower in the CD8⁺ T cells of the MDR HIV group compared to the control group.

Comparison of the Levels of CD4⁺ T cell Subsets



- The levels of naïve and central memory CD4⁺ T cells were significantly lower in the MDR group. In contrast, the level of transitional memory CD4⁺ T cells was significantly higher in the MDR group.

Neutralization/Suppression Capacity of bNAbs and Anti-CD4 Antibodies against Replication-competent Viral Isolates derived from Study Participants with MDR HIV



- The infectious viral isolates from each study participant with MDR HIV were resistant to at least 2 bNAbs (average 4 bNAbs per participant). However, with the exception of Participant 03, the infectious viral isolates from all study participants were sensitive to at least one of the CD4-binding site (3BNC117, VRC01, VRC07, and N6) and one of the non-CD4 binding site Abs (10-1074, 10E8, and PGT121)
- Notably, none of the 93 infectious viral isolates obtained from the study participants were resistant to UB-421

Study Limitations

- Major limitation of this study is the small sample size; necessary to confirm our findings in a larger cohort of PLWH with MDR HIV and to conduct clinical trials of HIV-specific bNAbs and/or UB-421 in the presence of optimized background regimens.
- It remains a challenge to perform extensive pre-screening of autologous HIV to determine sensitivity profiles against the antibodies being considered for treatment.

Conclusions

- We demonstrate that the infectious viral isolates derived from the majority of study participants could potentially be neutralized by a combination(s) of two bNAbs that bind to two non-competing regions on the HIV envelope protein.
- To our knowledge, this is the first study to examine the immunologic and virologic parameters associated with MDR virus.
- Our data suggest that the therapeutic options for heavily treatment-experienced PLWH with MDR viruses could be potentially expanded to include HIV-specific bNAbs and UB-421, an avenue that has until now not been explored.

References

- WHO. Latest HIV drug resistance report. https://apps.who.int/iris/rest/bitstreams/1394483/retrieve.
- Emu, B., et al. Phase 3 Study of Ibalizumab for Multidrug-Resistant HIV-1. N Engl J Med 379, 645-654 (2018).
- Wang, C.Y., et al. Effect of Anti-CD4 Antibody UB-421 on HIV-1 Rebound after Treatment Interruption. N Engl J Med 380, 1535-1545 (2019).
- Kozal, M., et al. Fostemsavir in Adults with Multidrug-Resistant HIV-1 Infection. N Engl J Med 382, 1232-1243 (2020).

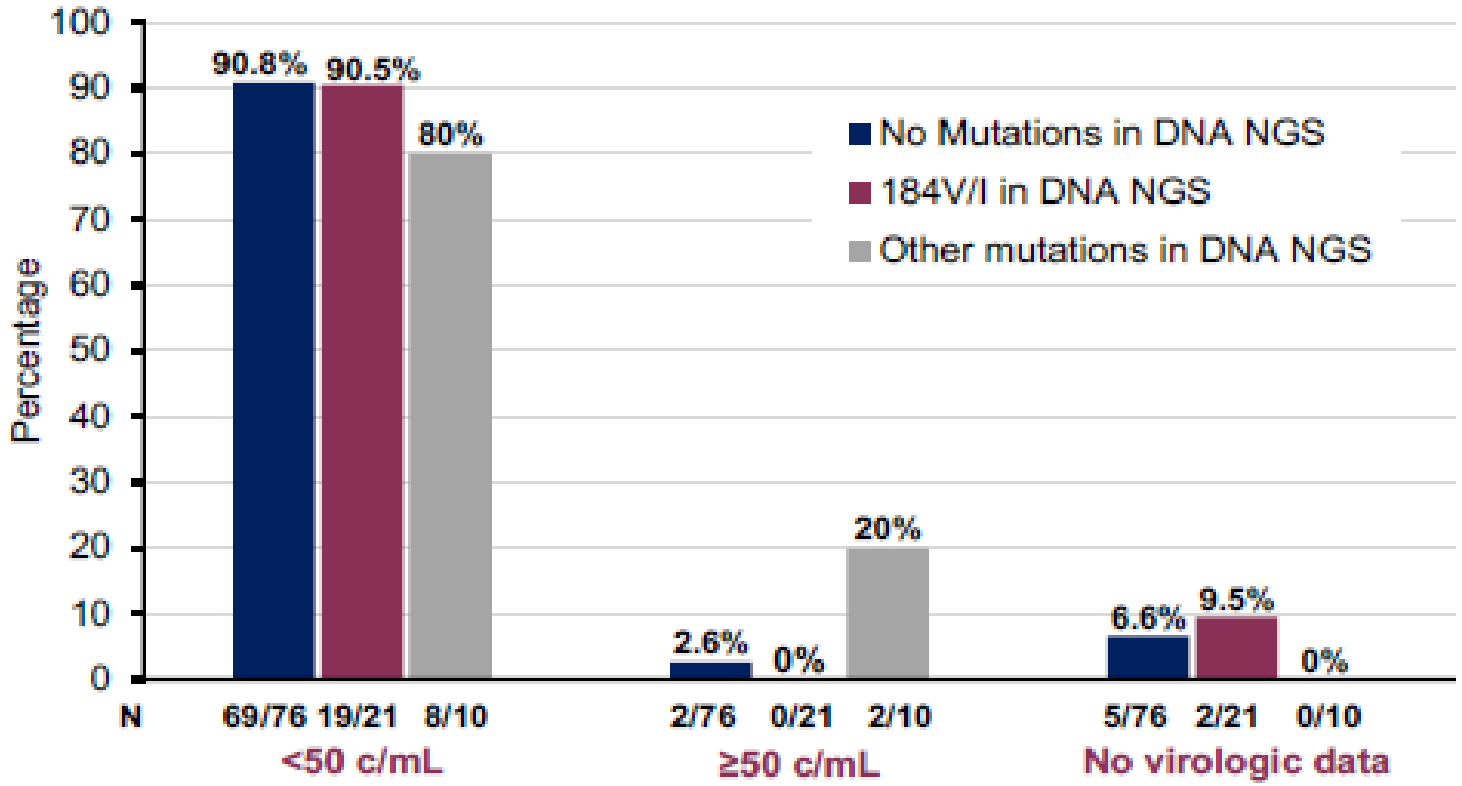
Impact of Archived Minority Populations With M184V/I on DTG/3TC for Maintenance of Viral Suppression

693

Rosa De Miguel Buckley[1], Mayra Sigcha[2], Maria de Lagarde[2], Jose Luis Blanco[3], Rocio Montejano[1], Angela Gutiérrez Liarte[4], Esperanza Cañas-Ruano[5], Arkaitz Imaz[6], Cristina Hernández[7], Antonio Ocampo Hermida[8],Pedro Gil[9], Rafael Delgado[2], Federico Pulido[2], Jose R. Arribas[1], for VOLVER-GESIDA 11820 study group

[1]Hospital Universitario La Paz, Madrid, Spain; [2]Hospital Universitario 12 de Octubre, Madrid, Spain; [3]Hospital Clinic, Barcelona, Spain;[4] Hospital Universitario La Princesa, Madrid, Spain; [5]Hospital del Mar, Barcelona, Spain; [6] Hospital Universitario Bellvitge, Barcelona, Spain; [7]Hospital Universitario Príncipe de Asturias,Madrid, Spain;[8] Hospital Universitario Alvaro Cunqueiro, Vigo, Spain; [9]Fundación SEIMC-GeSIDA, Madrid, Spain.

Week 48 Efficacy (FDA- Snapshot ITT-e) by baseline PBMC proviral DNA NGS



Impact of Archived Minority Populations With M184V/I on DTG/3TC for Maintenance of Viral Suppression

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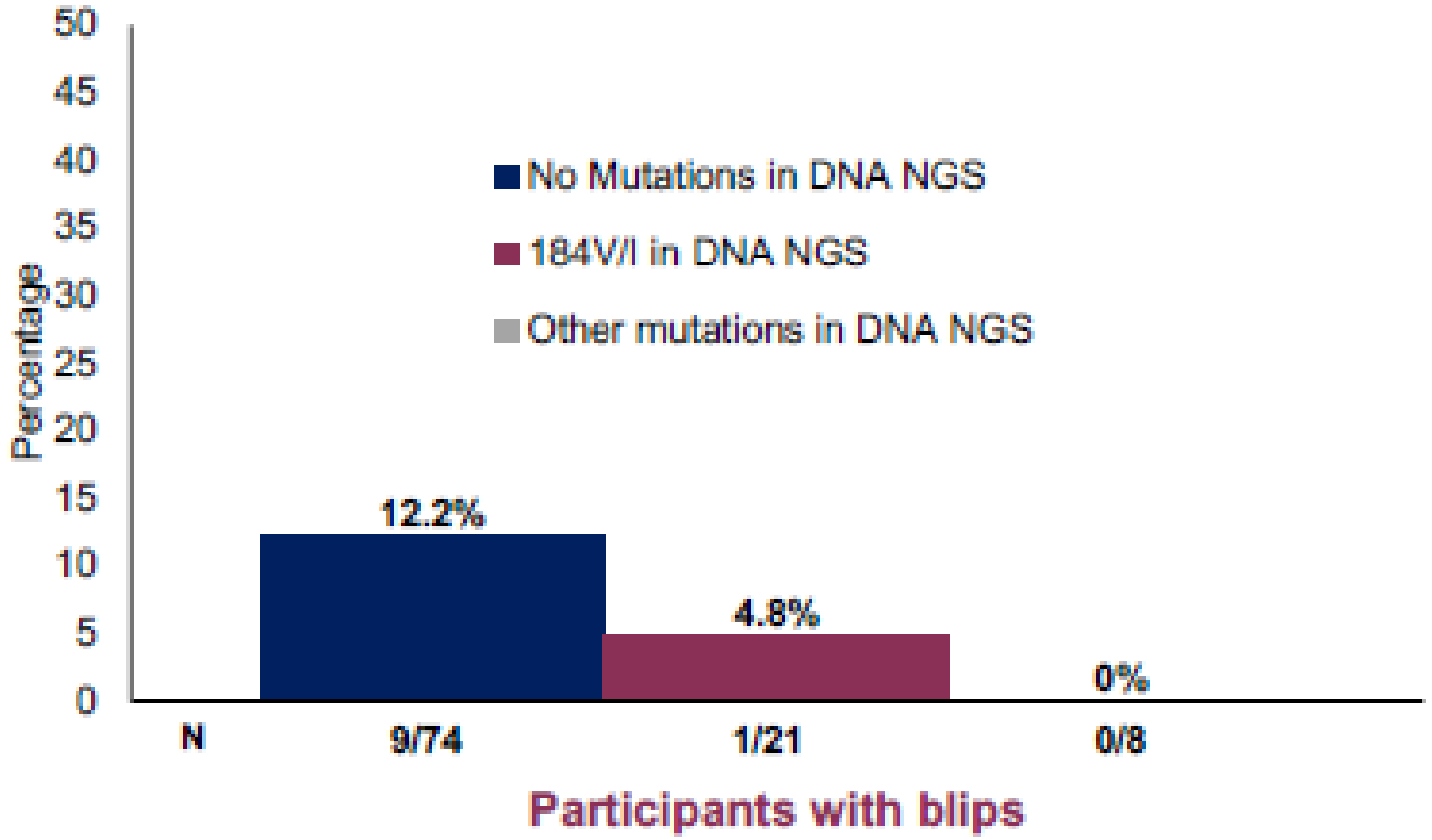
Transient Viral Rebounds (Blips) after switching to DTG/3TC in participants* with HIV-RNA <50 copies/mL at week 48 ** and available baseline DNA NGS (n=103)



State-Level PrEP Coverage and Diagnosis

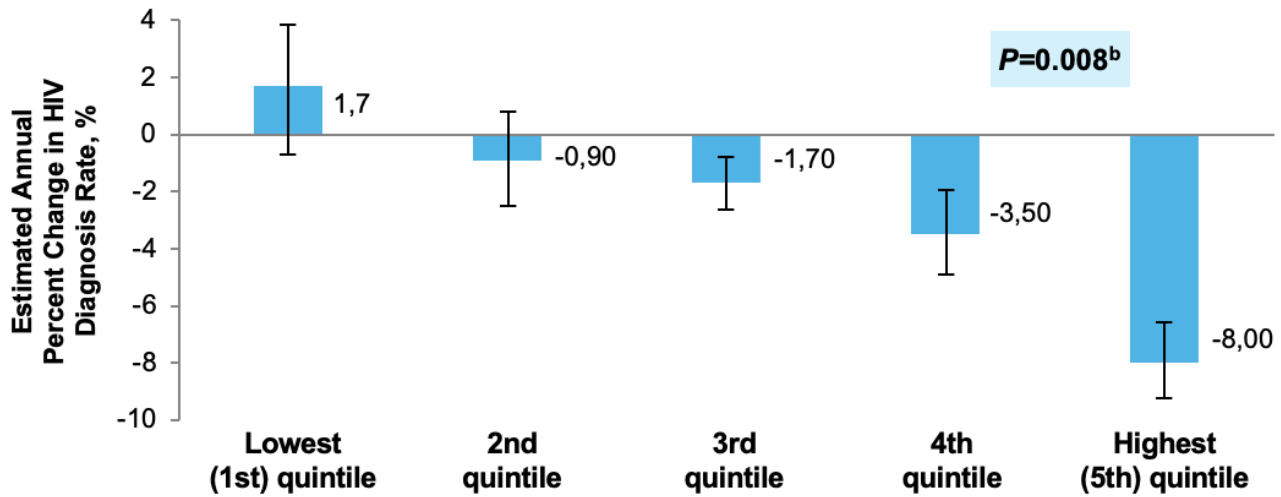
State-specific PrEP prescriptions

Outcomes

PrEP coverage, estimated annual percent change in HIV diagnoses overall and by quintile of PrEP coverage

2012–2021

Estimated Annual Change in HIV Diagnoses by Quintile of PrEP Use[a]



Mean PrEP Coverage[c] by Quintile of Use,[d] %	6	8	9	11	16

- **Relationship** exists between PrEP coverage and magnitude of decline in HIV diagnoses
  - Areas with **higher levels** of PrEP coverage had **larger declines** in HIV diagnoses[a]
- Combined approaches to HIV prevention, including timely diagnosis and availability of effective PrEP, are key to **reducing HIV transmission**

PrEP coverage is a meaningful measure to assess the population-level impact of PrEP programs

[a]Adjusted for yearly jurisdiction-specific VS; [b]*P* value for trend; [c]PrEP coverage calculation: number of PrEP users/100 persons with indications; [d]50 US states
VS, virologic suppression

Sullivan PA, et al. CROI 2024, Oral 165

Oral PrEP Non-Persistence and New HIV Diagnoses

N=123,901

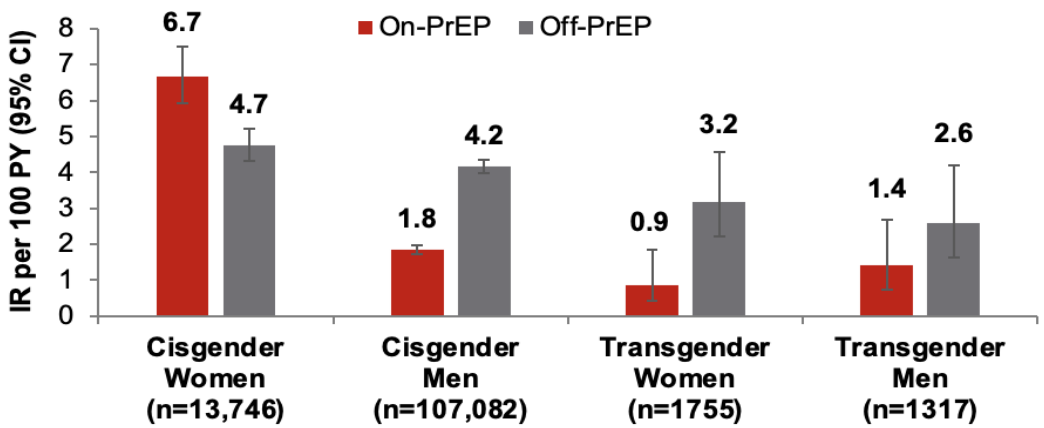
PrEP-naïve adults aged ≥18 years followed for up to 12 months after ≥1 oral F/TAF or F/TDF PrEP prescription

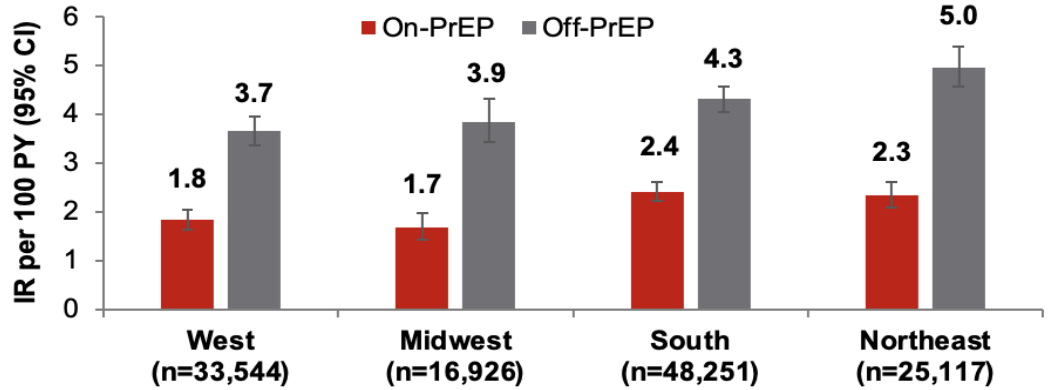
Outcomes

- HIV incidence rates during periods of PrEP persistence and non-persistence
- Number needed to remain on PrEP to prevent one new HIV acquisition

April 2021–March 2022

HIV Incidence Rates for On-PrEP Versus Off-PrEP Periods, by Gender and Region[a]





HIV incidence rates:

- **Highest** among **cisgender women** overall
- **Lowest** among **transgender women** during **on-PrEP** periods

The **Northeast region** of the US had the **highest off-PrEP** HIV incidence rate

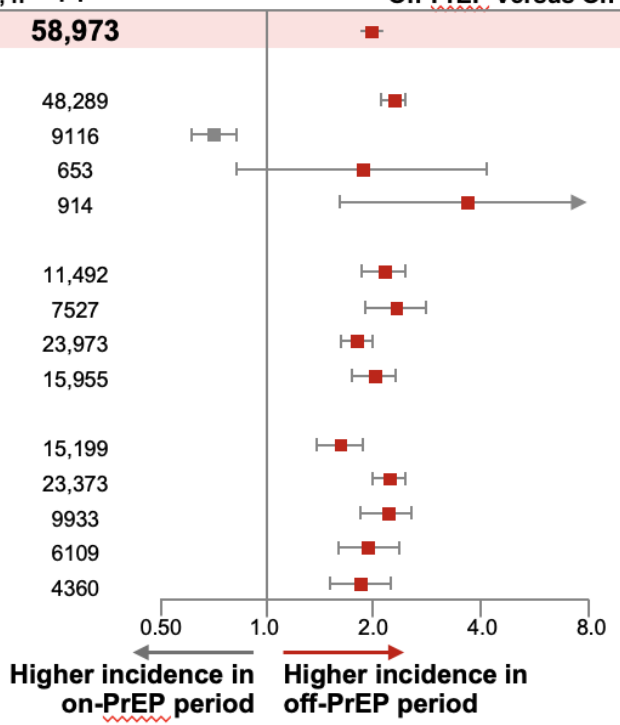
[a]Off-PrEP periods (PrEP non-persistence) were defined as gaps in prescription claims (>30 days following the end of the calculated PrEP supply until the start of the next PrEP claim) or discontinuation of PrEP (from the end of the calculated supply for the last PrEP claim to the end of follow-up, without re-initiation or additional claims); on-PrEP periods were when individuals had PrEP on hand. IR, incidence rate; PY, person-years

Tao L, et al. CROI 2024, Poster 1124

Relative HIV Incidence Rates Among Subgroups

HIV IRRs in Off-PrEP Versus On-PrEP Periods, by Subgroup[a]

	Total, N	On-PrEP HIV Infections, n	On-PrEP PY	Off-PrEP HIV Infections, n	Off-PrEP PY	IRR (95% CI), Off-PrEP Versus On-PrEP
All	**123,901**	**1343**	**62,526**	**2488**	**58,973**	**1.96 (1.84, 2.10)**
Gender						
Cisgender men	107,082	1046	56,864	2010	48,289	2.26 (2.10, 2.44)
Cisgender women	13,746	281	4215	432	9116	0.71 (0.61, 0.83)
Transgender men	1317	9	644	17	653	1.86 (0.83, 4.17)
Transgender women	1755	7	803	29	914	3.64 (1.59, 8.31)
Region						
Northeast	25,117	304	13,058	569	11,492	2.13 (1.85, 2.45)
Midwest	16,926	153	9120	290	7527	2.30 (1.89, 2.79)
South	48,251	562	23,289	1033	23,973	1.79 (1.61, 1.98)
West	33,544	312	17,034	582	15,955	1.99 (1.74, 2.29)
Age at first PrEP claim						
18–24 years	27,655	277	11,966	562	15,199	1.60 (1.38, 1.84)
25–34 years	49,846	511	25,485	1027	23,373	2.19 (1.97, 2.44)
35–44 years	22,394	226	12,023	405	9933	2.17 (1.84, 2.55)
45–54 years	13,952	160	7586	248	6109	1.92 (1.58, 2.35)
55+ years	10,054	169	5466	246	4360	1.82 (1.50, 2.22)



The number of individuals needed to remain on oral PrEP to avoid one new HIV acquisition varied by US state

- **Lowest:** Alabama (n=31), Louisiana (n=32), Massachusetts (n=32), Illinois (n=32) and Georgia (n=35)
- **Highest:** Mississippi (n=160), Kansas (n=197) and Nevada (n=377)

High HIV incidence during off-PrEP periods highlights the need to address barriers to sustained PrEP use

[a]Off-PrEP periods (PrEP non-persistence) were defined as gaps in prescription claims (>30 days following the end of the calculated PrEP supply until the start of the next PrEP claim) or discontinuation of PrEP (from the end of the calculated supply for the last PrEP claim to the end of follow-up, without re-initiation or additional claims); on-PrEP periods were when individuals had PrEP on hand. IRR, incidence rate ratio; PY, person-years

Tao L, et al. CROI 2024, Poster 1124

B/F/TAF as HIV PEP

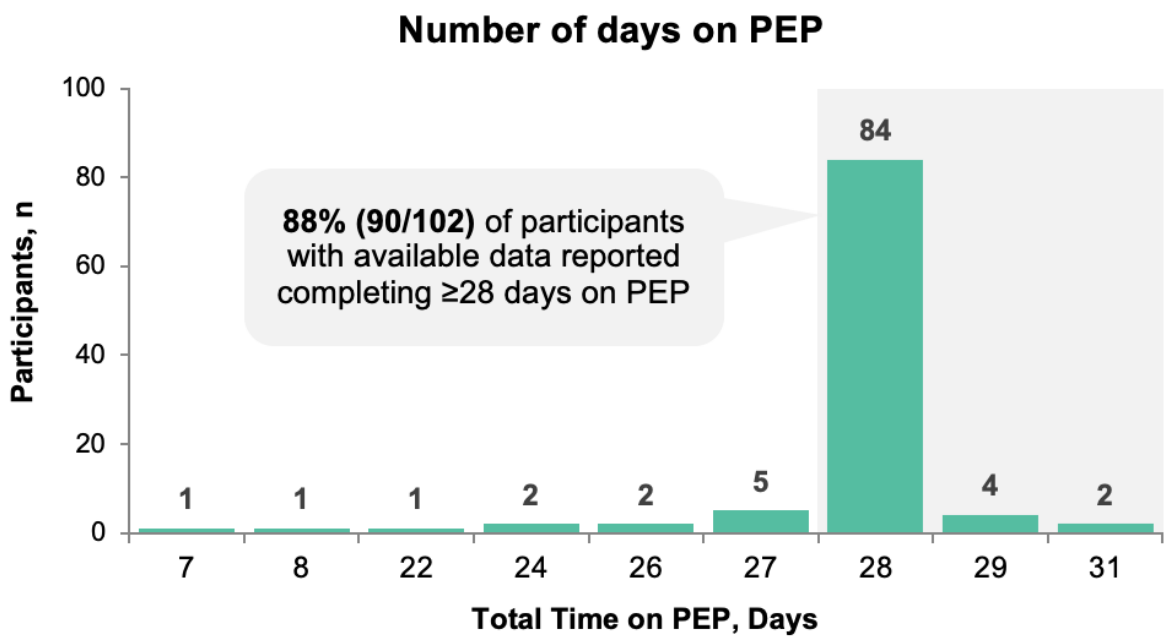
N=119

Adults without HIV who had initiated PEP within prior 6 days and had switched to B/F/TAF for 28 days

Outcomes

Tolerability (AEs), adherence, HIV seroconversions

Not reported



Tolerability

10% of participants experienced Grade ≥2 AEs

HIV seroconversions

0 seroconversions among 66 participants tested at Week 12

PrEP initiation

Only 23% (n=28) initiated PrEP by final visit

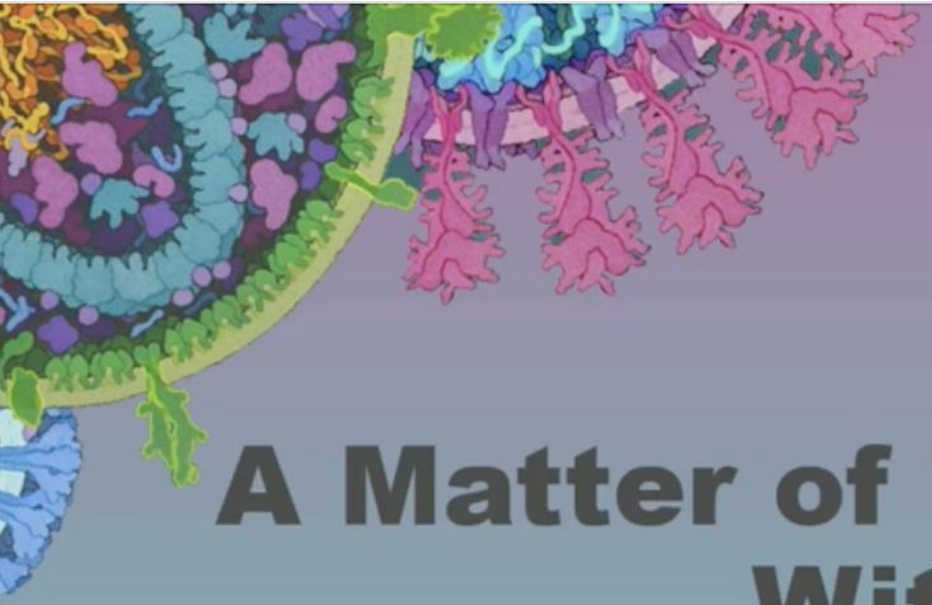
Prior knowledge of PrEP

- 12% of participants were unaware of PrEP
- 73% were aware but had never used PrEP
- 15% had previously used PrEP

B/F/TAF was associated with high tolerability, high adherence and no seroconversions, supporting its potential use as HIV PEP post-sexual exposure.
Strategies are needed to improve linkage to PrEP among those with continued HIV exposure

PEP, postexposure prophylaxis

Tan DHS, et al. CROI 2024, Poster 1134



Themed Discussion-03

Monday, March 4, 2024

A Matter of Time: Factors Associated With Delayed nPEP Initiation

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Disclosure: Dr Bana reported no relevant financial relationships with ineligible companies.

CROI 2024

«PEP should start ideally within 4 hours from risk exposure, and not later than 48/72 hours»[1]
Efficacy granted within the first 24 hours.[2]
BUT WHAT HAPPENS IN REAL LIFE?

AIM

Evaluate factors associated to nPEP start time since risk exposure assessing:

- Time from sex to ED access.
- Time while in the ED waiting for nPEP prescription.

Retrospective Monocentric Observational study

WHERE?

WHO AND WHEN?

560 individuals presenting to our ED between Jan 2011 and Feb 2024 asking for nPEP.

WHAT?

Demographic data and sexual orientation, type of risk exposure, additional risky behaviors, previous HIV serology and nPEP courses, HIV serostatus of source individual, time (hour, day, month).

HOW?

Binary regression analysis to test factors associated to ED early presentation (<24 hours). Poisson regression analysis to test factors associated with longer waiting time in ED.

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[1](EACS Guidelines 12.0, 2023). [2]García-Lerma JG et Al., Intermittent prophylaxis with oral truvada protects macaques from rectal SHIV infection. Sci Transl Med, 2010.

			Overall (N=560)	Arrived within 24 hours (N=415)	Arrived after 24 hours (N=145)
Sex, n (%)	Male		522 (93.2)	389 (93.7)	133 (91.7)
	Female		36 (6.4)	25 (6.0)	11 (7.6)
	TGW		2 (0.4)	1 (0.3)	1 (0.7)
Age, years, median (IQR)			32.1 (26.9-39.4)	31.9 (27.0-39.7)	32.4 (26.6-38.2)
Born in Italy, n (%)			457 (81.6)	349 (84.1)	108 (74.5)
Sexual orientation, n (%)		MSM	382 (68.2)	286 (68.9)	96 (66.2)
		MSW/WSM	163 (29.1)	117 (28.2)	46 (31.7)
		Not applicable	15 (2.7)	12 (2.9)	3 (2.1)
Type of exposure, n (%)	Anal, receptive		239 (42.7)	176 (42.4)	63 (43.4)
	Anal, insertive		151 (26.9)	112 (27.0)	39 (26.9)
	Vaginal, insertive		81 (14.5)	59 (14.2)	22 (15.2)
	Vaginal, receptive		24 (4.3)	15 (3.6)	9 (6.2)
	Oral		44 (7.9)	37 (8.9)	7 (4.8)
	Ocular		6 (1.1)	4 (1.0)	2 (1.4)
	Nonsexual		15 (2.7)	12 (2.9)	3 (2.1)
Condomless intercourse, n (%)			247 (45.3)	172 (42.7)	75 (52.8)
Semen/ano-genital mucosa contact, n (%)			283 (60.2)	212 (61.3)	71 (57.2)
Additional risk factors, n (%)	None		353 (63.0)	268 (64.6)	85 (58.6)
	Sex work		104 (18.6)	82 (19.8)	22 (15.2)
	Sex under alcohol or recreational drugs		60 (10.7)	33 (7.9)	27 (18.6)
	Violence		19 (3.4)	14 (3.4)	5 (3.5)
	Group sex/Cruising sex venue		18 (3.2)	14 (3.4)	4 (2.7)
	PHI		6 (1.1)	4 (0.9)	2 (1.4)
HIV status of source individual, n (%)		Unknown	411 (73.4)	303 (73.0)	108 (74.5)
		Positive	122 (21.8)	94 (22.7)	28 (19.3)
		On PrEP	27 (4.8)	18 (4.3)	9 (6.2)
Previous nPEP course, n (%)			98 (17.5)	81 (19.6)	17 (11.7)
Previous HIV testing, n (%)			434 (77.6)	333 (80.4)	101 (69.7)
Accessing Emergency Department during weekend, n (%)			266 (47.6)	216 (52.1)	50 (34.7)
Accessing Emergency Department during summer months, n (%)			137 (24.5)	107 (25.8)	30 (20.7)

Table 1. Population main demographic and behavioural features, stratified by Emergency Department presentation time since risk exposure.

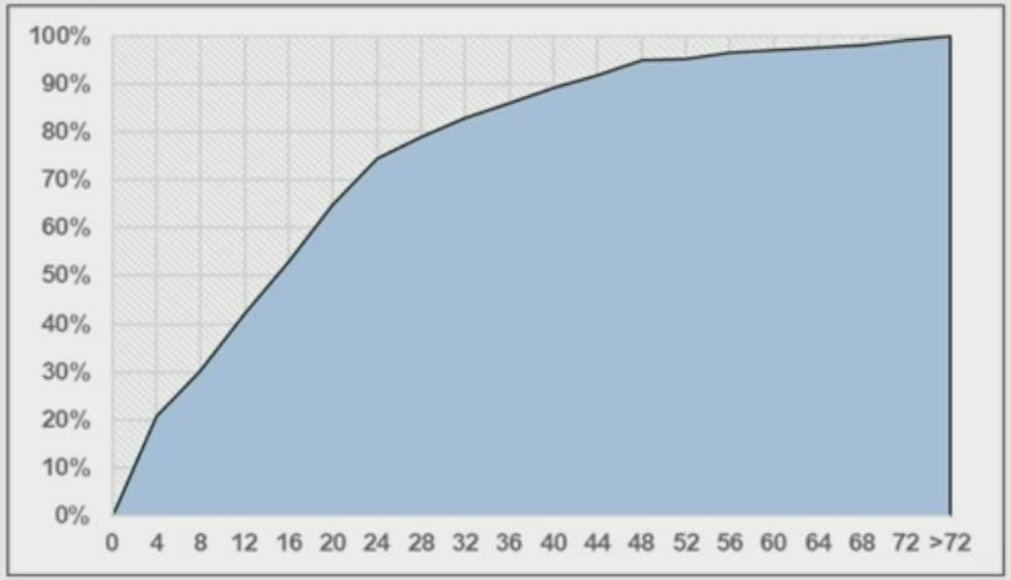

Figure 1. ED Presentation Time distribution (hours since risk exposure) and cumulative perchentage.

ED access <24 hours	415 (74.1%)
ED access <4 hours	112 (20%)
Overall median ED arrival time	14.88 hours (IQR 5.52-24.48)
Overall median time for nPEP initiation	16.56 hours (IQR 6.96-25.92)

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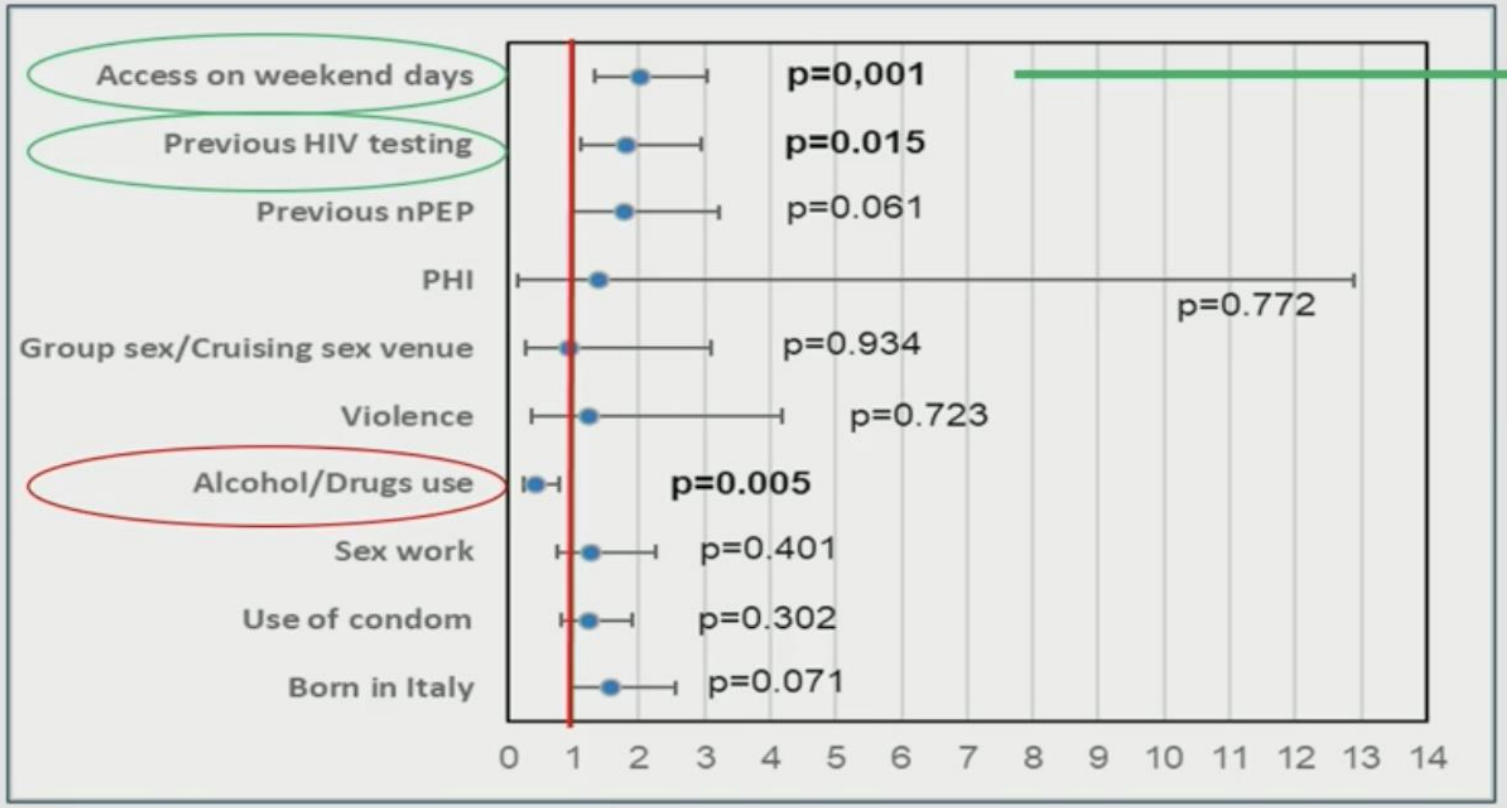

Figure 2. Binary regression analysis showing factors associated to early (<24 hours) ED presentation (adjusted odds-ratios, aOR). Results are adjusted for all the items listed.

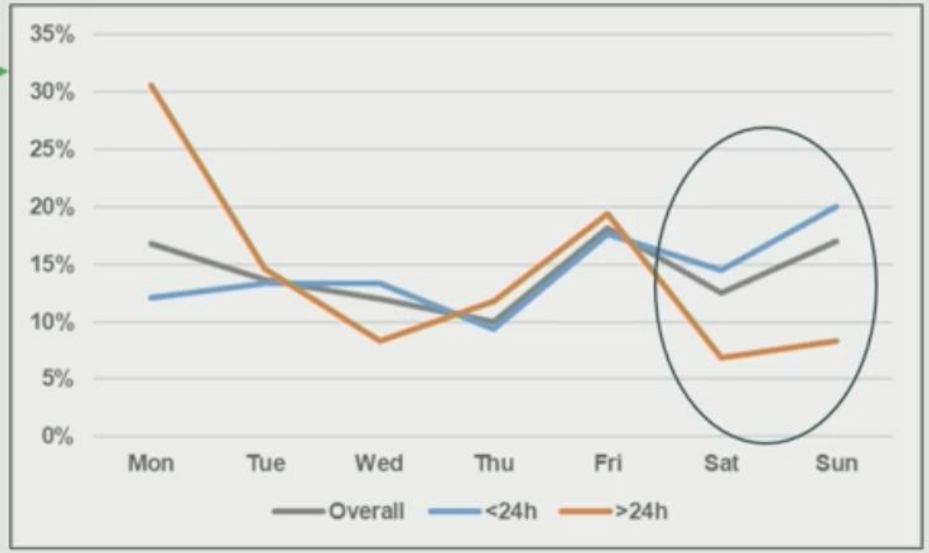

Figure 3. ED accesses: distribution over the days of a week.

- **ED ACCESS ON WEEKEND DAYS:** aOR 2.02, 95% CI 1.34-3.05
- **PREVIOUS HIV SEROLOGY:** aOR 1,82, 95% CI 1.12-2.94
- **ALCOHOL/DRUGS USE:** aOR 0.43, 95% CI 0.24-0.48

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WHAT ABOUT WAITING TIME IN ED?

			IRR	95%CI	p
Age			0.99	0.96-1.03	0.687
Sex	Female		1	Ref	
	Male		1.11	0.30-4.19	0.876
	TGW		0.68	0.00-0.24	0.980
Born in Italy			0.82	0.38-1.77	0.617
Sexual orientation	MSW/WSM		1	Ref	
	MSM		0.89	0.45-1.75	0.733
	Nonsexual		0.74	0.09-6.38	0.783
Use of condom			1.08	0.57-2.05	0.804
Additional risk factor	None		1	Ref	
	Sex work		1.12	0.50-2.51	0.791
	Sex under alcohol or recreational drugs		1.15	0.44-3.00	0.772
	Violence		0.89	0.13-5.89	0.904
	Group sex/Cruising sex venue		1.25	0.25-6.24	0.786
	PHI		0.75	0.02-24.9	0.874
HIV status of source individual		Unknown	1	Ref	
		Positive	0.95	0.44-2.03	0.886
		PrEP	0.76	0.14-4.22	0.756
Previous nPEP			0.84	0.35-2.01	0.692
Access during weekend			0.94	0.50-1.75	0.837
Access during night shift			0.83	0.43-1.61	0.581
Access during summer months			0.85	0.40-1.82	0.684

Table 2. Poisson regression analysis investigating features associated to longer waiting time in Emergency Department.

- Overall median waiting time in ED before nPEP prescription: 1.44 hours (IQR 0.72-2.40)
- No factor was associated with longer waiting time.

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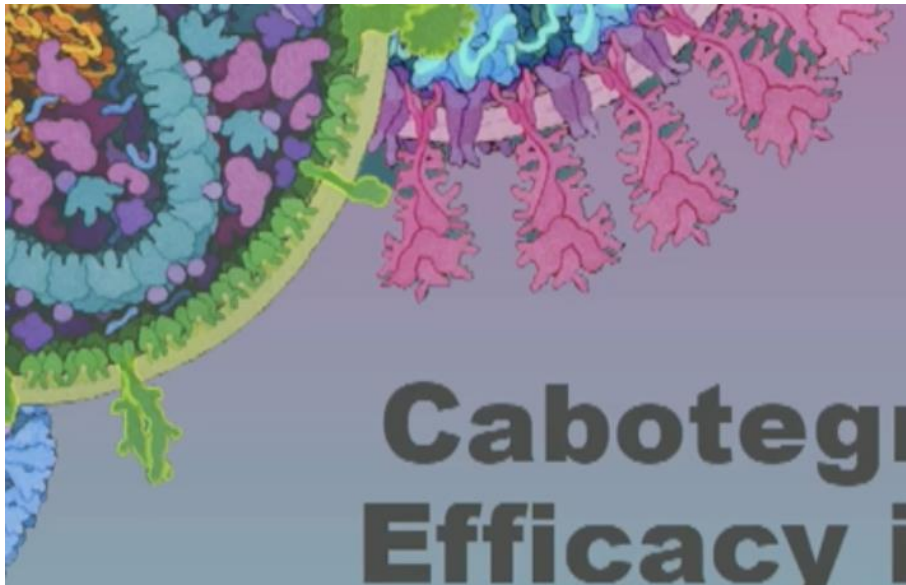
CONCLUSIONS AND DISCUSSION POINTS

- Most of individuals included in our study experienced an early access to nPEP, even if there is still someone who presented too late.
- Previous HIV testing is associated to an early ED presentation, especially for subjects undergoing regular STIs screening, who might be more «educated».
- Sexual intercourses during weekend seem to be associated with a prompt nPEP start. Daily working routine might be a barrier to prompt ED access, and might represent also a risk underestimation.
- Use of alcohol and recreational drugs during sexual intercourses represents an important risk factor for HIV acquisition not only in terms of dangerous exposure, but also for delayed nPEP start.
- According to our study, no factor has influence on ED waiting time before nPEP prescription.



Oral Abstract Session-04

Monday, March 4, 2024

Cabotegravir Maintains Protective Efficacy in the Setting of Bacterial STIs: HPTN 083

Meredith Clement
Louisiana State University, New Orleans, LA, USA

Disclosures: Dr Clement reported Self: Consulting or advisor fees (ViiV Healthcare); Institution: Grants/grants pending (Gilead Sciences, Inc).

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Background

- Bacterial sexually transmitted infections (STIs) facilitate HIV transmission and acquisition
- Mucosal inflammation and genital ulcers can lower the barrier to HIV infection
- It is important to determine whether STIs diminish efficacy of each pre-exposure prophylaxis (PrEP) agent

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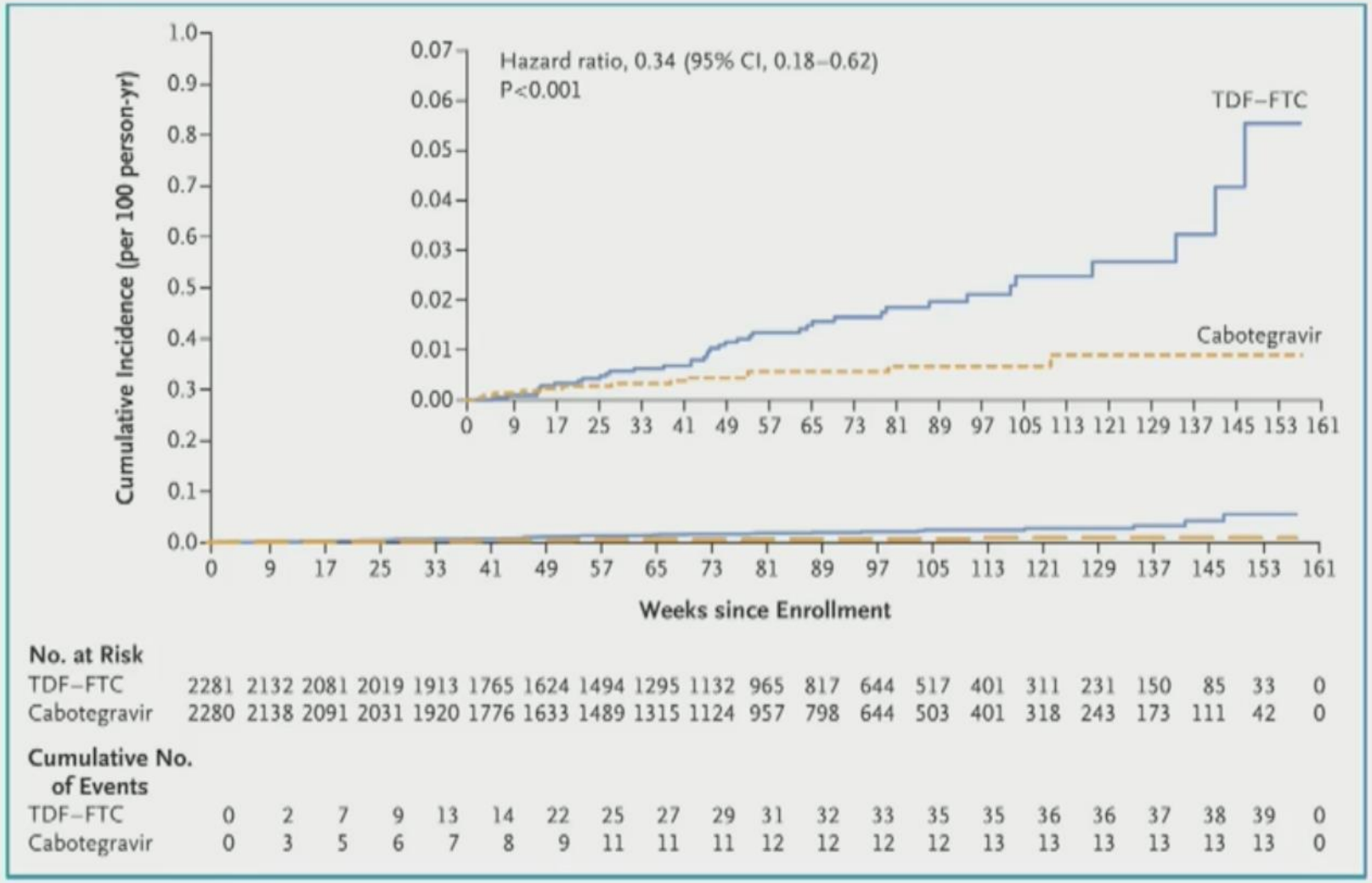
/asserheit JN. Sex Transm Dis. 1992; 19:61–77; Cohen, et al. Int AIDS Soc. 2019 Aug;22 Suppl 6:e25355.

Background



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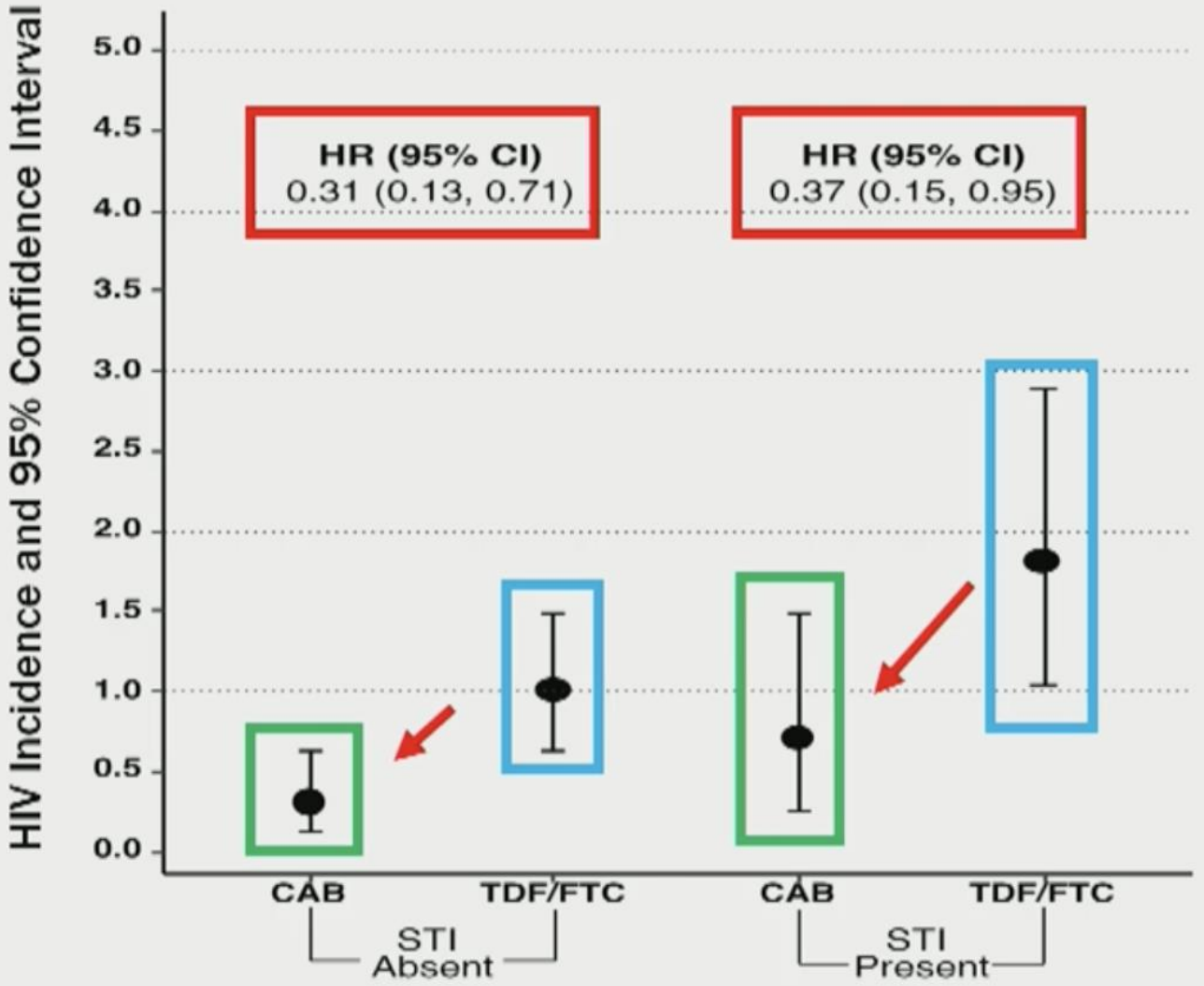
Results: Maintenance of Efficacy



CROI 2024

Phase I Safety, Tolerability and Pharmacokinetics of Tenofovir Alafenamide Implants in African Women

Tanuja N. Gengiah

Centre for the AIDS Programme of Research in South Africa, Durban, South Africa

Disclosure: Dr Gengiah reported no relevant financial relationships with ineligible companies.

Introduction

- > 50% of all new HIV infections in the world are in Africa
- South Africa: > 3,100 cases per week in young women
- Urgent need for a long-acting, preferably annual or longer, HIV prevention technology (to overcome oral PREP adherence issues)

OAK CREST INSTITUTE OF SCIENCE

Annual tenofovir alafenamide (TAF) implant

- Silicone implant: ±40mm (length), ±2.5mm (OD), 2 delivery channels
- With ±110mg TAF free-base micro-tablets; target release ±0.25mg/day
- TAF: potent NtRTI, good safety profile, oral widely used in HIV treatment and prevention

CAPRISA

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Methods and Participant characteristics

Study Population → Inclusion / Exclusion Criteria and Study Outcomes → Phase I Group 1 (1 implant) → Phase I Group 2 (1 or 2 implants)

Healthy
HIV- women
Cisgender

Trial site:
Durban,
South Africa

- 18-40 years
- Low HIV risk profile
- Normal clinical & laboratory results
- Willing to provide informed consent
- Not relocating
- No tattoo or skin condition on bicep

Study outcomes

- Systemic safety
- Implant site reactions
- Tolerability & Acceptability
- Pharmacokinetics
- Behavioural assessments

N=6
First in human
110mg TAF implant
Bicep insertion
28 days *in situ*

N=30, randomised
Dose escalation
1 implant (n=15)
2 implants (n=15)
4:1 active to placebo
Up to 48 weeks *in situ*

Screened = **245**
Enrolled = **36** Retention: **97%**
Median (IQR) Age: **26 (22 - 30) years**
Median (IQR) weight: **72 (61 - 80) kg**
Past/current contraceptive implant use: **5**

CAPRISA

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Systemic and local insertion site adverse events

5 most frequent systemic adverse events	N (36)	%
↓**Creatinine clearance –** all changes within the normal range	27	75%
Vitamin D deficiency	23	64%
↑**Parathyroid hormone**	20	56%
Haematuria	19	53%
Bacterial vaginosis	16	44%

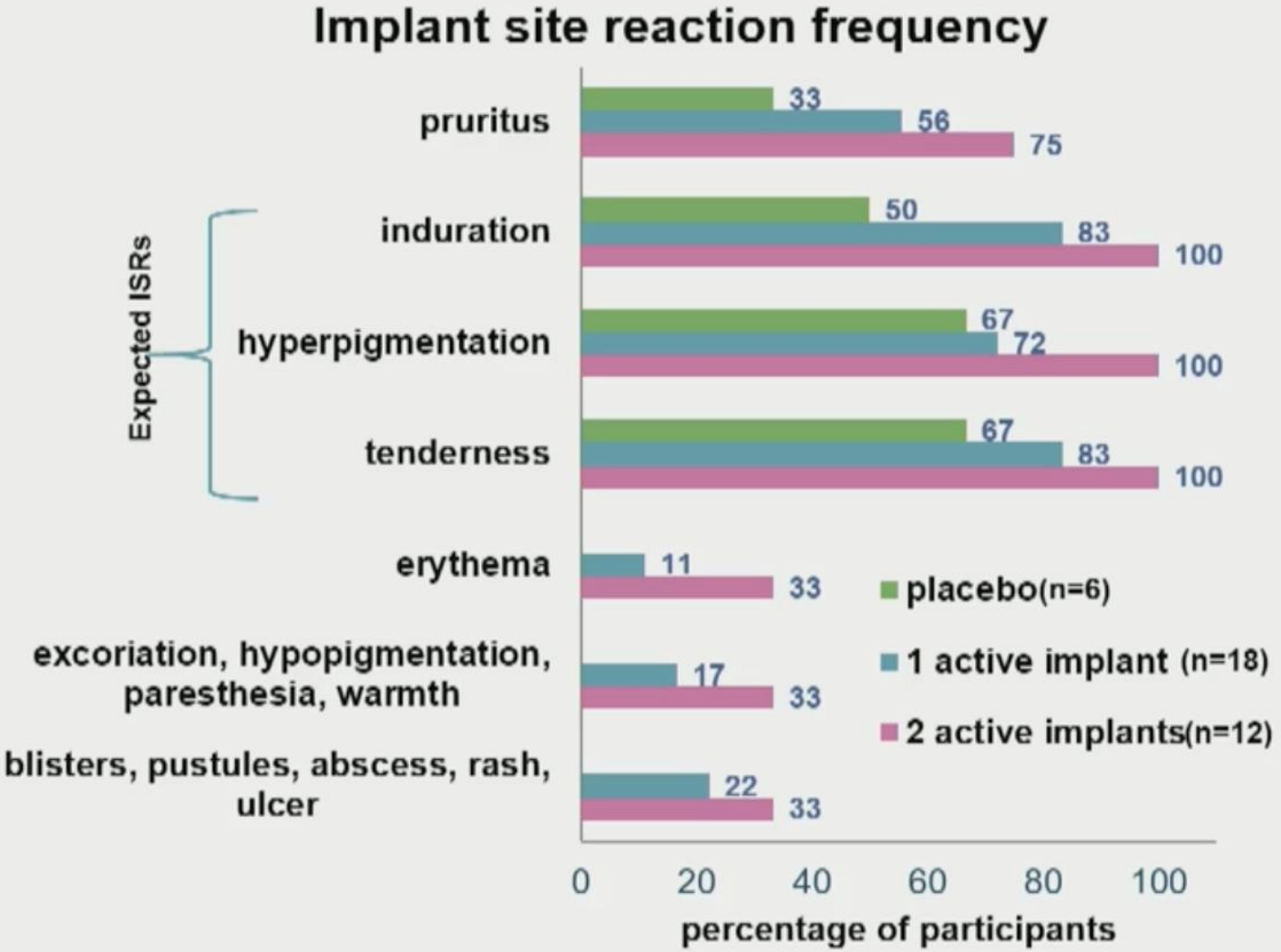
Systemic AE severity:

Grade 1: 55.3 %
Grade 2: 42.5%
Grade 3: 2.2%

Implant local site reaction severity:

Grade 1: 90.9%
Grade 2: 8.3%
Grade 3: 0.8%*

*2 of the 36 women had grade 3 local reactions: both had implant site abscesses → early removal



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Tolerability

Implants removed prior to scheduled study end: 31% (11/36)

- Median time (weeks) to early removal: 19 (range: 2 - 27)
- 55% (6/11) were participant-initiated, other 5 were clinician-initiated
- 33% (10/30) of TAF implants & 17% (1/6) of placebo implants removed early
- 22% (4/18) of single & 50% (6/12) of double TAF implants removed early
- Implant site reaction incidence (95%CI) per person-month:
  2.1 (1.8 -2.6) in early removals vs **0.8** (0.6-0.9) in scheduled removals
- Removal procedure (mean) time :
  - *1 implant*: 40 mins early vs 19 mins scheduled
  - *2 implants*: 81 mins early vs 33 mins scheduled

CAPRISA

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Conclusions

- First in human study to assess safety, tolerability and PK of a silicone TAF implant
- No systemic safety concerns; mild implant site reactions (tenderness, hyperpigmentation, induration, etc) common - in both TAF and placebo implants
- Most ISRs were Grade 1 for all implants but more grade 2/3 events with TAF implants
- Poor tolerability: 31% of implants removed early → these more difficult to remove
- No dose dumping, drug released over 1 year, but residual TAF levels high at removal
- Lower than planned drug release – the implant needs to release more TAF: 2 implants had median TFV-DP of 14.8, well below the target of 36 fmol/10^6 cells
- Challenge: ↑ drug release and ↓ ISRs - if tolerability can be improved, increasing the release of TAF from each of 2 implants could achieve target TFV-DP levels for a year

Take home messages

- Molte evidenze sull'efficacia terapeutica dei composti L-A;
- Approcci pseudo-vaccinali con bnAbs ogni 6 mesi;
- PWH HTE rappresentano ancora una domanda aperta;
- PEP e PrEP sono una certezza, ma rimangono quesiti sulla sostenibilità e sull'efficacia su grande scala (CAB PrEP);
- Nuove tecnologie.


MEDICI
CON L'AFRICA
CUAMM
QUELLO CHE
NON SI VEDE
HEADS Collective/ Photo Ruggero Zigliotto
Si dice che il battito d'ali di una farfalla
possa provocare un uragano dall'altra
parte del mondo.
Allo stesso modo la guerra in Ucraina
sta provocando danni devastanti
in Africa, dove l'aumento dei prezzi
rende ancora più grave una situazione
già drammatica.
Sono gli effetti di una guerra quotidiana
che non si vede e di cui nessuno parla.
Aiutaci a non lasciare da soli
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