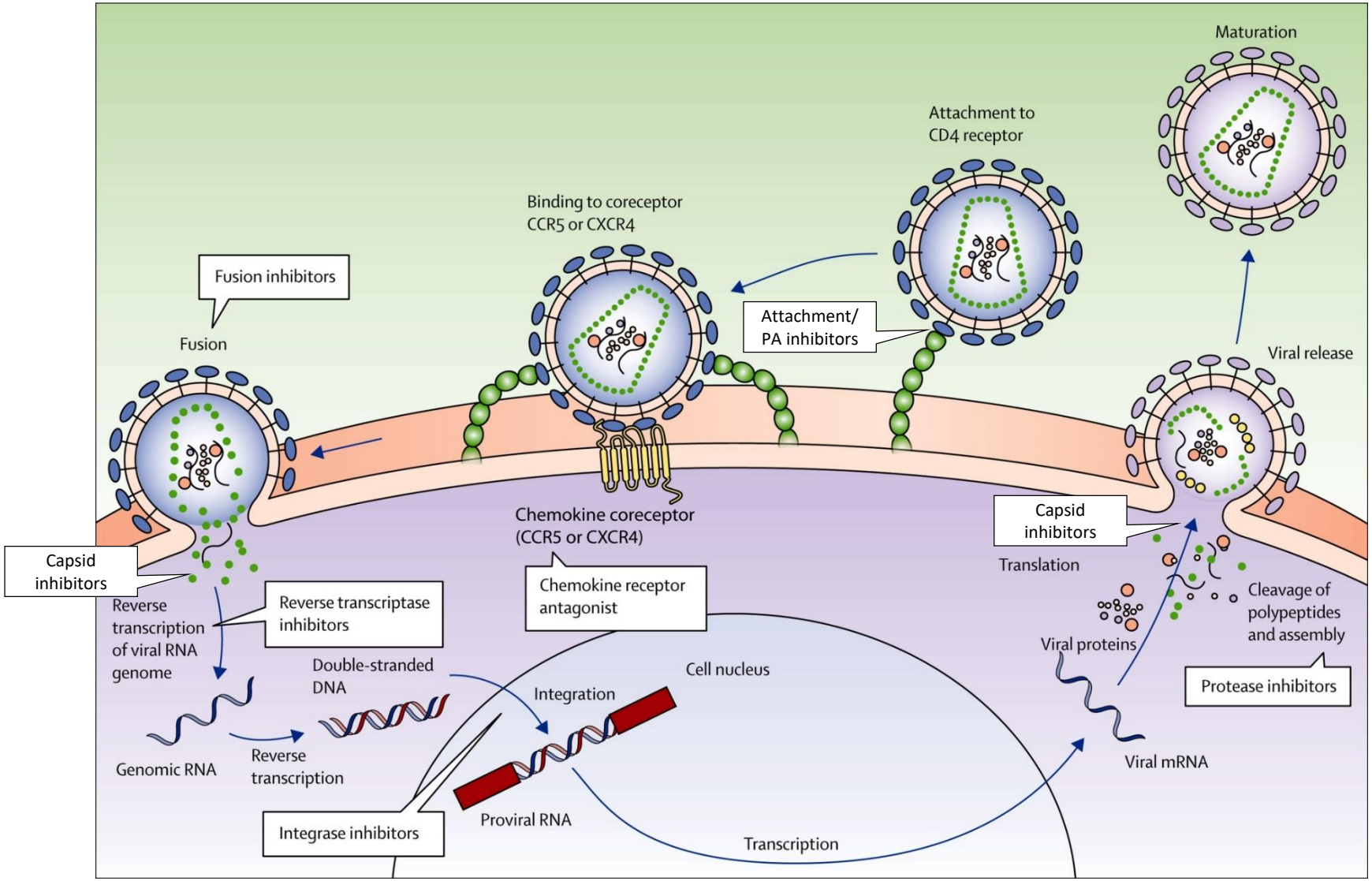


Modified by Marteens et al. Lancet2014

BEYOND HIV. TAKING HIV TO ANOTHER LEVEL.
CLUSTER 2.0 - BEYOND COMORBIDITIES

Vincenzo Spagnuolo; IRCCS Ospedale San Raffaele, Padova 03.07.2024

FINANCIAL DISCLOSURES

- Speakers' honoraria: Gilead Sciences, ViiV Healthcare and Merck Sharp and Dohme
- Advisory board: Gilead Sciences
- Research Grants: Gilead Sciences

OUTLINE

- **HTE Definition**

- **Fostemsavir** (Week 240 BRIGHTE results, impact on immunologic recovery, inflammation)

- **Lenacapavir** (Week 104 CAPELLA results, resistance profile)

- **Islatravir** (comes back with LEN?)

- **TAB** and **ZAB**

HTE: DEFINITION

No standardized definition of the heavily treatment-experienced (HTE) status.

HTE patients can be described as having **two or less** antiretroviral **(ARV) classes available** for use with limited fully active ARV agents within each class.

<u>Other possible definitions:</u>

- individuals who had undergone ≥ 4 combination ART (cART) anchor agent switches

- PLWH who ever used a regimen with ≥4 ARVs.

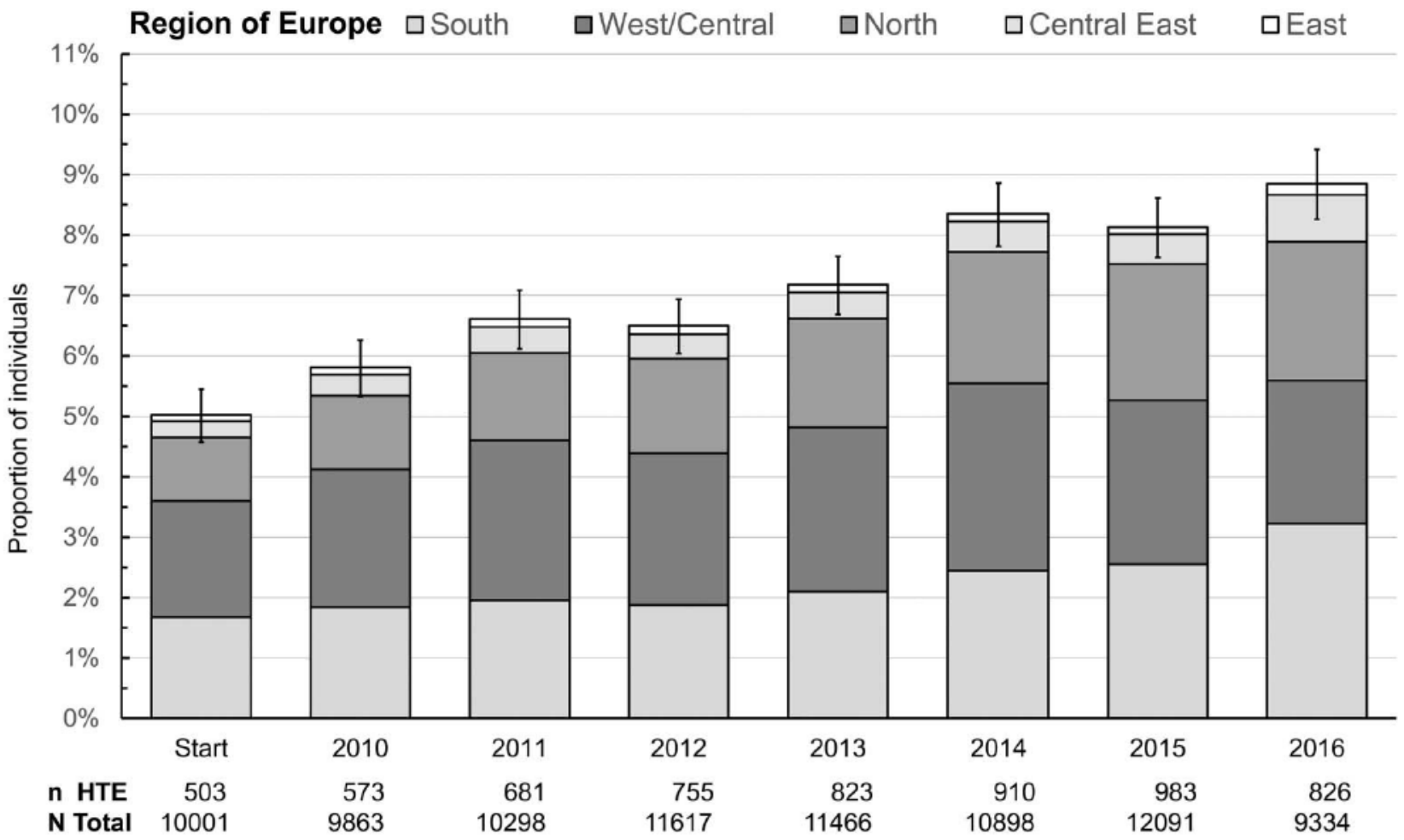
- Everyone with GRT results and known resistance to the 3 original ARV classes (NRTIs, NNRTIs, and PIs)

- Any PLWH treated with the following regimens:

- Dolutegravir BID
- Darunavir BID
- Enfuvirtide
- Etravirine plus maraviroc or 1 of the preceding agents
- ≥2 core ART agents plus any other ART agent

J Acquir Immune Defic Syndr 2021;87:806–817
Open Forum Infectious Diseases, Volume 8, Issue 12, December 2021, ofab562
Drugs Context. 2022;11:2021-9-1

PREVALENCE OF HTE IN EUROPE, 2010–2016

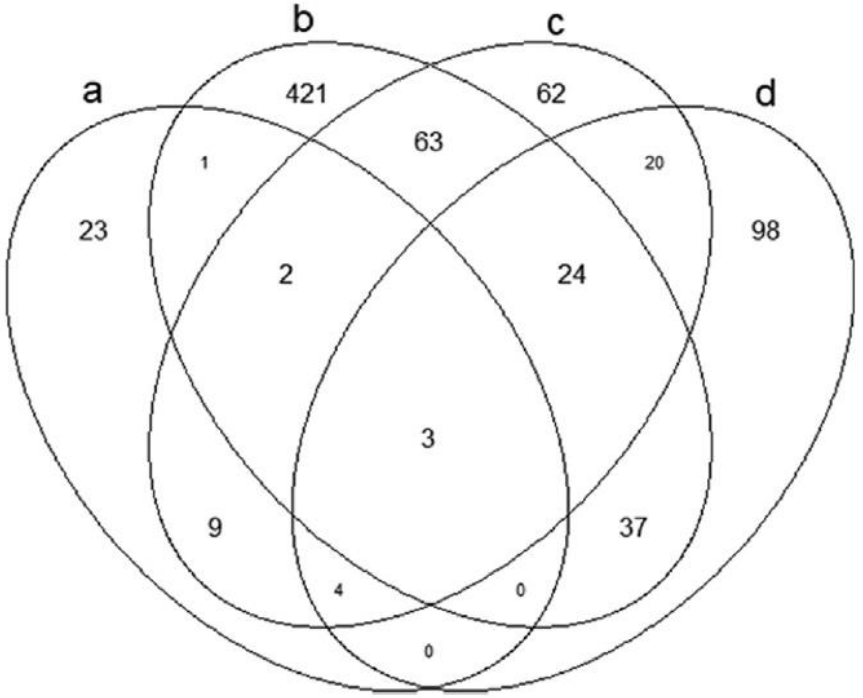


HTE definition 1: 2 ARV drugs classes with at least one active drug (or 2 active NRTIs) remaining,
HTE definition 2 :individuals who had undergone≥4 combination ART (cART) anchor agent switches,
HTE definition 3: those who ever used a regimen with ≥4 ARVs.

J Acquir Immune Defic Syndr 2021;87:806–817

HEAVILY TREATMENT-EXPERIENCED PERSONS LIVING WITH HIV CURRENTLY IN CARE IN ITALY: CHARACTERISTICS, RISK FACTORS, AND THERAPEUTIC OPTIONS—THE ICONA FOUNDATION COHORT STUDY

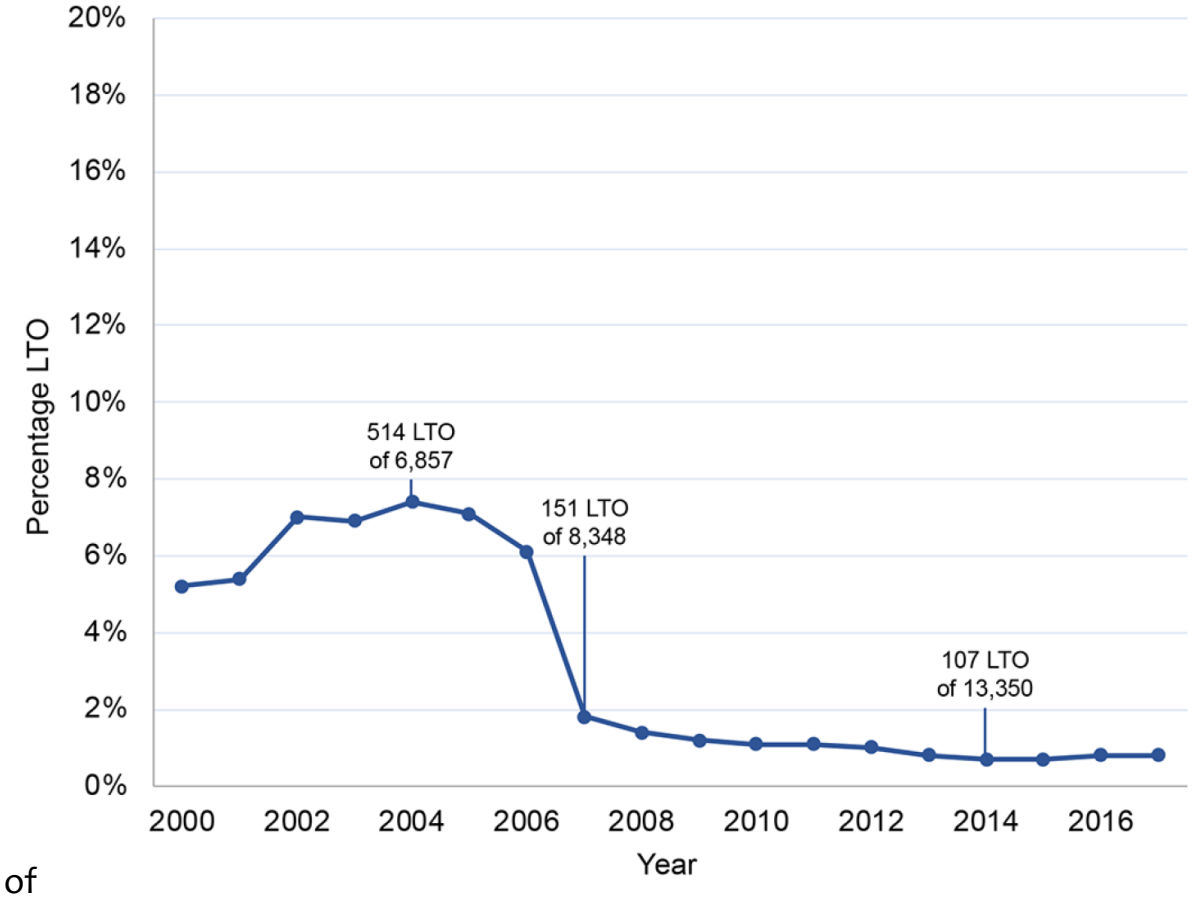
HTE=163/8758 (1.9%)



Four definitions used to identify HTE subjects: (a) current regimen indicative of HTE; (b) at least three core ARV classes prior to current regimen; (c) individuals who had at least four anchor drug switches at any previous time; (d) ≥three virological failures followed by a treatment switch

Lo Caputo S. et al. International Journal of Infectious Diseases 143 (2024) 106956

ANNUAL PREVALENCE OF PWH WITH LIMITED TREATMENT OPTIONS (LTO) AMONG ART-EXPERIENCED PERSONS IN CARE BY YEAR (2000–2017)



LTO definition: having only 2 active ARV classes available in which there were a limited number of active drugs or ≤1 ARV class available

AIDS. 2020 November 15; 34(14): 2051–2059

4-DRUG CLASSES RESISTANCE

PLWH, heavily treatment-experienced with resistance to all the 4 standard antiretroviral drug classes (NRTI, NNRTI, PI, INSTI) represent a rare subset of PLWH with:

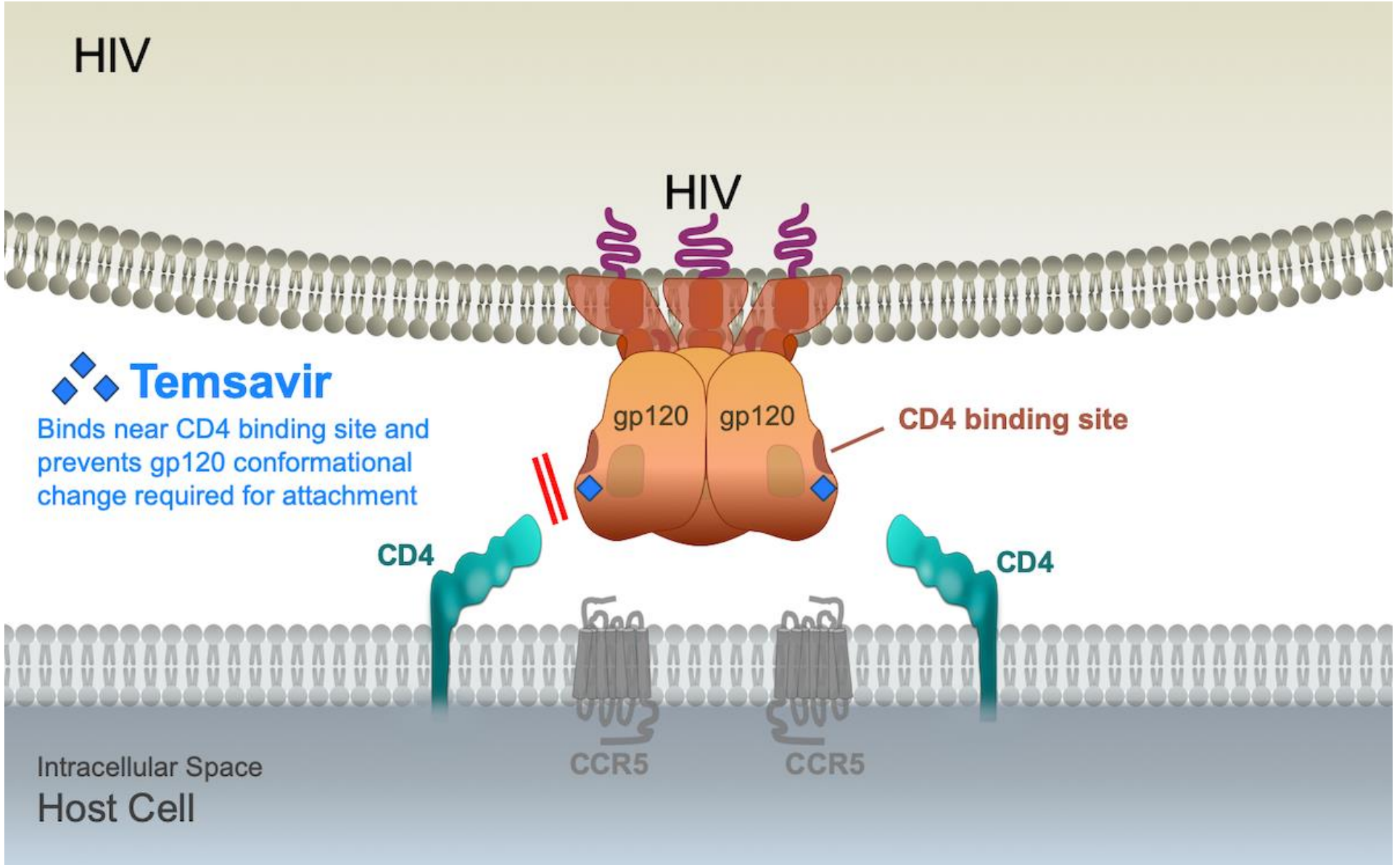
- **very limited treatment options**
- **low chances of treatment success**
- **elevated risk** of **disease progression** and **death** with rates ranging from 27% to 33% at 4 years.

Data on true incidence and prevalence of PLWH-4DR in Europe are limited; Italian prevalence estimated at 1-3%

To better characterize this population of PLWH-4DR and meet their needs, the Italian PRESTIGIO registry (39 participating centers, 257 PLWH enrolled) was established.

Lombardi F. et al. 10th Italian Conference on AIDS and Antiviral Research, OC 60. June 5-7, 2019, Milan, Italy.
Multiple drug class-wide resistance associated with poorer survival after treatment failure in a cohort of HIV-infected patients. Zaccarelli M. et al. AIDS, 2005 Jul 1;19 (10):1081-9
Trends in virological and clinical outcomes in individuals with HIV-1 infection and virological failure of drugs from three antiretroviral drug classes: a cohort study.
Pursuing Later Treatment Option II (PLATO II) project team; Observational HIV Epidemiological Research Europe (COHERE) Group. Lancet Infect Dis. 2012 Feb;12(2):119-27.

FOSTEMSAVIR



https://cdn.hiv.uw.edu/pdf/antiretroviral-therapy/general-information/core-concept/all

BRIGHTE STUDY

Figure 1. Study Design

HTE participants failing current regimen with confirmed HIV-1 RNA ≥400 c/mL and

Randomized Cohort[a]
- 1 or 2 ARV classes remaining with ≥1 approved fully active[b] agent per class
- Unable to construct viable regimen from remaining approved agents

Non-randomized Cohort[a]
- 0 ARV classes remaining and no remaining approved fully active[b] agents[c]

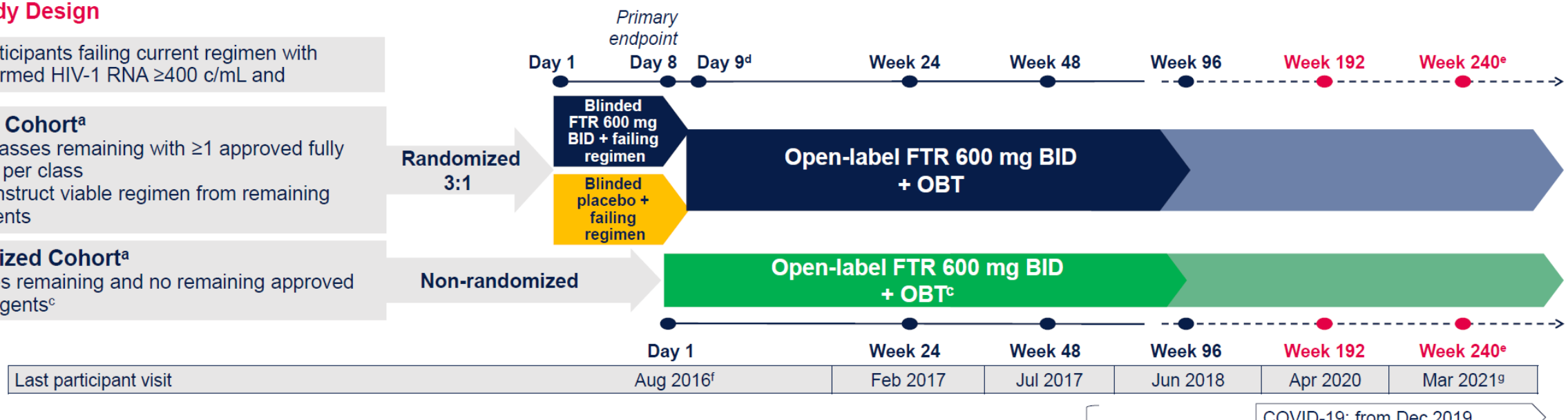
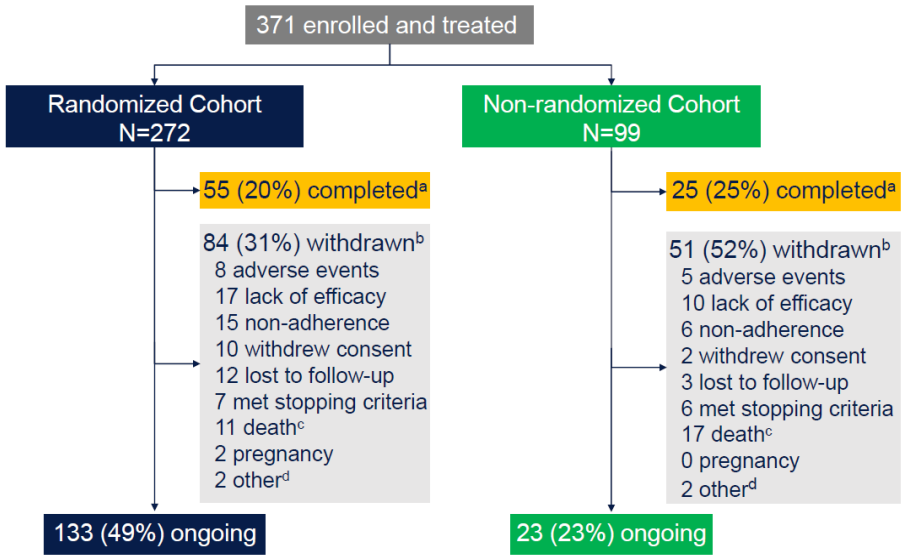


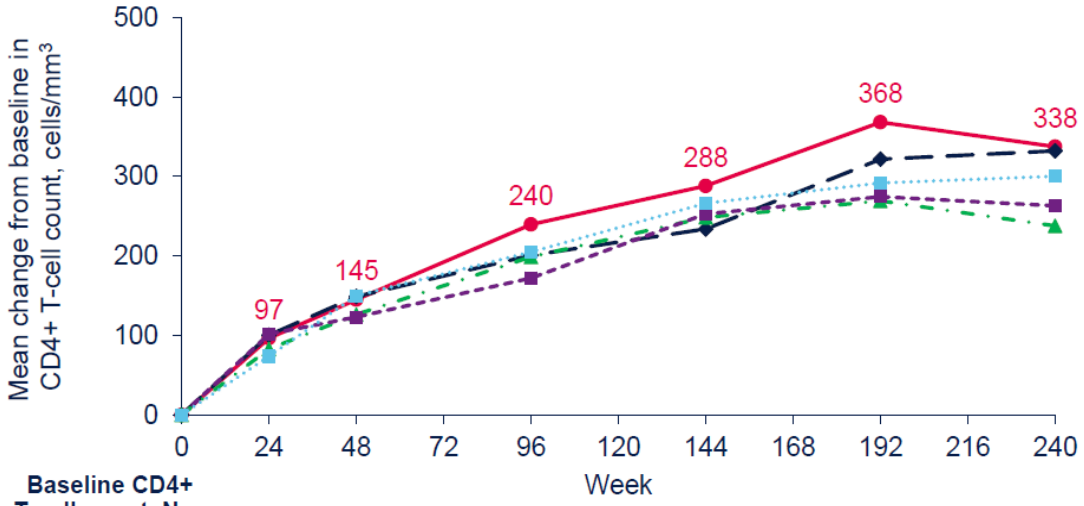
Figure 2. Participant Disposition Through the Week 240 Database Lock



Poster P061; HIV Drug Therapy Glasgow; October 23-26, 2022

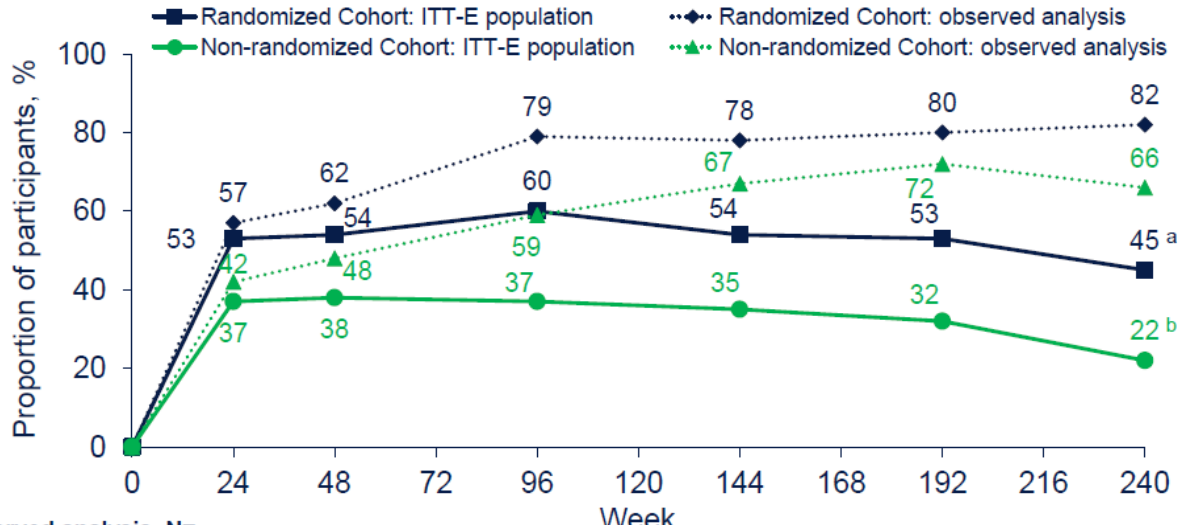
BRIGHTE STUDY: WEEK 240 EFFICACY AND IMMUNOLOGICAL RECOVERY

Figure 5. Change in CD4+ T-Cell Count From Baseline to Week 240 by Baseline CD4+ T-Cell Count (Randomized Cohort, Observed Analysis)



Baseline CD4+ T-cell count, N=						
<20 (n=72)	64	58	54	49	47	33
20 to <50 (n=25)	24	20	17	18	15	13
50 to <100 (n=39)	34	30	26	26	24	16
100 to <200 (n=63)	59	57	52	47	40	32
≥200 (n=73)	67	63	64	57	53	45

Figure 3. HIV-1 RNA <40 c/mL Through Week 240 by Snapshot Analysis (ITT-E) and Observed Analysis



Observed analysis, N=						
Randomized Cohort	247	233	214	206	195	164
Non-randomized Cohort	89	83	66	57	50	35

ITT-E participants without an HIV-1 RNA value at the relevant time point or those who changed OBT due to lack of efficacy up to each time point counted as failures. [a]ITT-E population, N=267. [b]ITT-E population, N=92.

Poster P061; HIV Drug Therapy Glasgow; October 23-26, 2022

BRIGHTE STUDY: WEEK 240 SAFETY

Parameter, n (%)	Randomized Cohort (N=272)		Non-randomized Cohort (N=99)		Total (N=371)	
	Week 96	Week 240	Week 96	Week 240	Week 96	Week 240
Any AE	249 (92)	259 (95)	98 (99)	98 (99)	347 (94)	357 (96)
Any grade 2-4 AE	216 (79)	242 (89)	87 (88)	94 (95)	303 (82)	336 (91)
Drug-related grade 2-4 AEs[a]	57 (21)	65 (24)	22 (22)	23 (23)	79 (21)	88 (24)
Any grade 3-4 AE	78 (29)	110 (40)	49 (49)	60 (61)	127 (34)	170 (46)
Any SAE[b]	92 (34)	122 (45)	48 (48)	55 (56)	140 (38)	177 (48)
Drug-related SAEs[c]	9 (3)	10 (4)	3 (3)	3 (3)	12 (3)	13 (4)
Any AE leading to D/C[d]	14 (5)	17 (6)	12 (12)	13 (13)	26 (7)	30 (8)
Any CDC class C event	23 (8)	25 (9)	15 (15)	19 (19)	38 (10)	44 (12)
Deaths[e]	12 (4)	15 (6)	17 (17)	20 (20)	29 (8)	35 (9)

D/C, discontinuation. [a]Drug-related grade 2-4 AEs occurring in ≥2% of participants were nausea (n=17), diarrhea (n=8), headache (n=7), and immune reconstitution inflammatory syndrome (IRIS, n=7); all except 3 cases of nausea were reported before the Week 96 data cutoff. [b]SAEs occurring in ≥2% of participants were pneumonia (n=25), cellulitis (n=10), acute myocardial infarction (n=8), acute kidney injury (n=8, all with identified reversible causes not related to study drug), COVID-19 (n=7), sepsis (n=6), and coronary artery disease (n=6). [c]Drug-related SAEs (16 events in 13 participants) included IRIS (n=3); nephrolithiasis (n=2); and 1 each of acute kidney injury, hyperglycemia, hyperkalemia, loss of consciousness, myocarditis, hepatocellular cytolysis, rhabdomyolysis, fetal growth restriction, disorientation, and rash through the Week 96 data cutoff and supraventricular tachycardia (n=1) after the Week 96 data cutoff. [d]The most common AEs leading to discontinuation were related to infections (n=12); 4 participants discontinued because of an AE after the Week 96 cutoff (1 each for pneumonia, cytomegaloviral pneumonia, polyneuropathy, and rash). [e]Of the 35 deaths, 6 occurred since Week 96; 12 deaths were AIDS related (5 since Week 96), 12 were acute infections (1 since Week 96), 6 were non–AIDS-related malignancies, and the remaining 5 were related to other conditions. Six deaths occurred after the participant withdrew from the study. One death occurred on the day of study withdrawal for AEs.

Poster P061; HIV Drug Therapy Glasgow; October 23-26, 2022

WEEK 96 GENOTYPIC AND PHENOTYPIC RESULTS OF THE FOSTEMSAVIR PHASE 3 BRIGHTE STUDY IN HEAVILY TREATMENT-EXPERIENCED ADULTS LIVING WITH MULTIDRUG-RESISTANT HIV-1.

TABLE 3 Treatment-emergent genotypic changes among participants meeting PDVF criteria at Week 96[a]

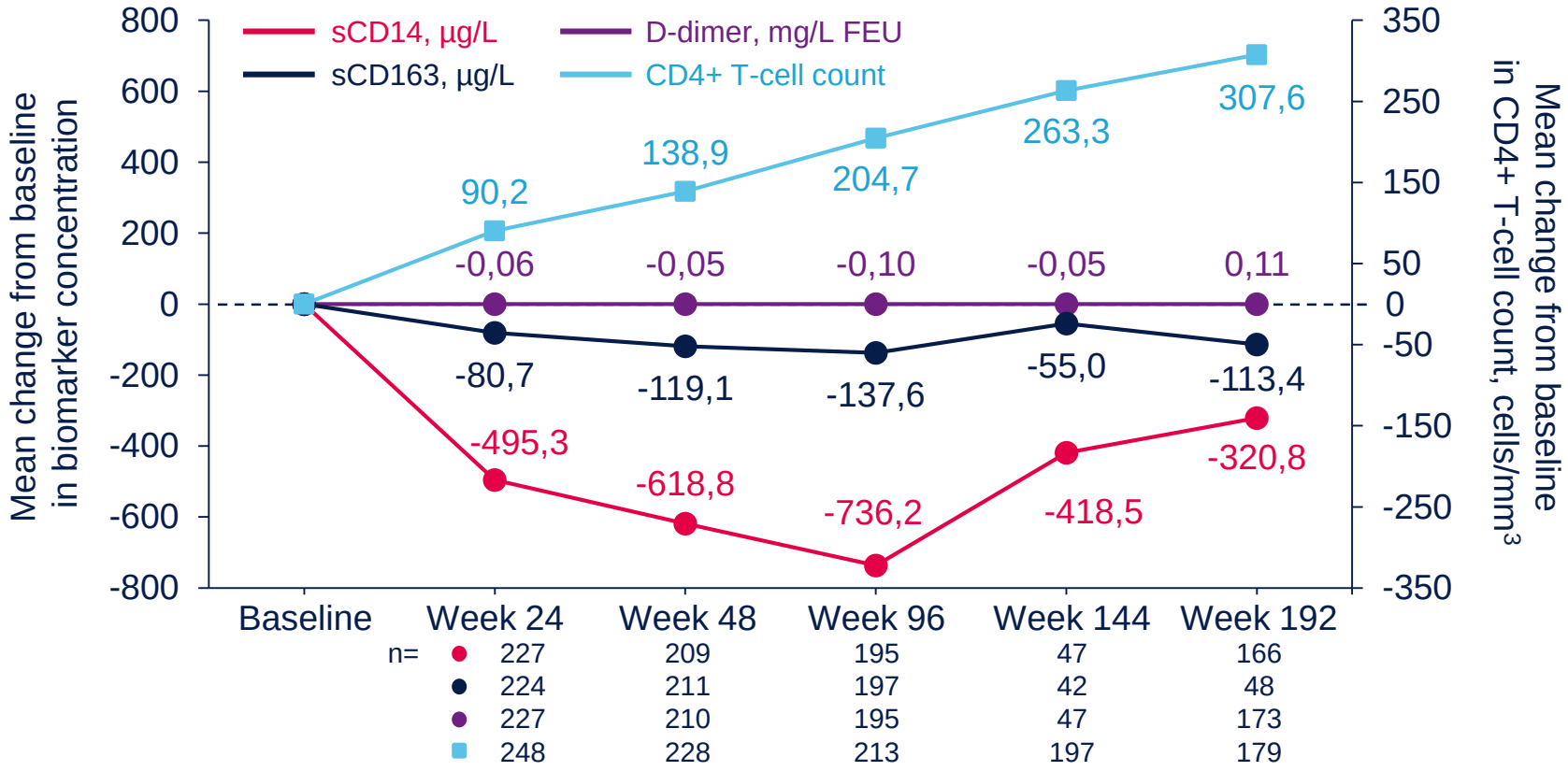
Cohort	Randomized Cohort (N = 272)	Non-randomized Cohort (N = 99)
Participants meeting PDVF, *n* (%)	63 (23)	49 (49)
gp160 sequenced, *n*[b]	50	44
Treatment-emergent predefined amino acid substitutions in gp120, *n* (%)[c]		
None	26 (52)	11 (25)
Any	24 (48)	33 (75)
S375H/I/M/N/T	15 (30)	22 (50)
S375H	0	1 (2)
S375H/N	1 (2)[d]	1 (2)
S375M	0	3 (7)
S375N	7 (14)	8 (18)
S375N/T	1 (2)	2 (5)
S375S/I	0	1 (2)
S375S/M/T	1 (2)	0
S375S/N	4 (8)	6 (14)
S375S/T	1 (2)	0
M426L	16 (32)	21 (48)
M426L	10 (20)	13 (30)
M426M/L	7 (14)	8 (18)
M434I	5 (10)	4 (9)
M434I	1 (2)	1 (2)
M434M/I	4 (8)	3 (7)
M434M/I/T	1 (2)	0
M475I	6 (12)	5 (11)
M475I	4 (8)	1 (2)
M475M/I	2 (4)	4 (9)

[a]PDVF, protocol-defined virologic failure.
[b]Most missing genotypic data were the result of assay failure, usually because of low HIV-1 RNA levels.
[c]Predefined amino acid substitutions in gp120 are S375H/I/M/N/T, M426L/P, M434I/K, and M475I; M426P and M434K were not present in any baseline or on-treatment samples from this study population. Numbers include mixtures. The denominator is the number of participants with gp120 sequenced at baseline and on treatment. For each participant, results at additional on-treatment time points around the time of PDVF are included where available (not limited to only the PDVF time point).
[d]Only S375H was emergent; S375N was present at baseline.

Antimicrob Agents Chemother. 2022 Jun 21;66(6):e0175121

Inflammatory Biomarkers in the Overall Analysis

- In the overall analysis of the Randomized Cohort, mean decreases from baseline in sCD14 and sCD163 were observed through Week 192; D-dimer decreased at Weeks 24 through 144, but an increase was observed at Week 192

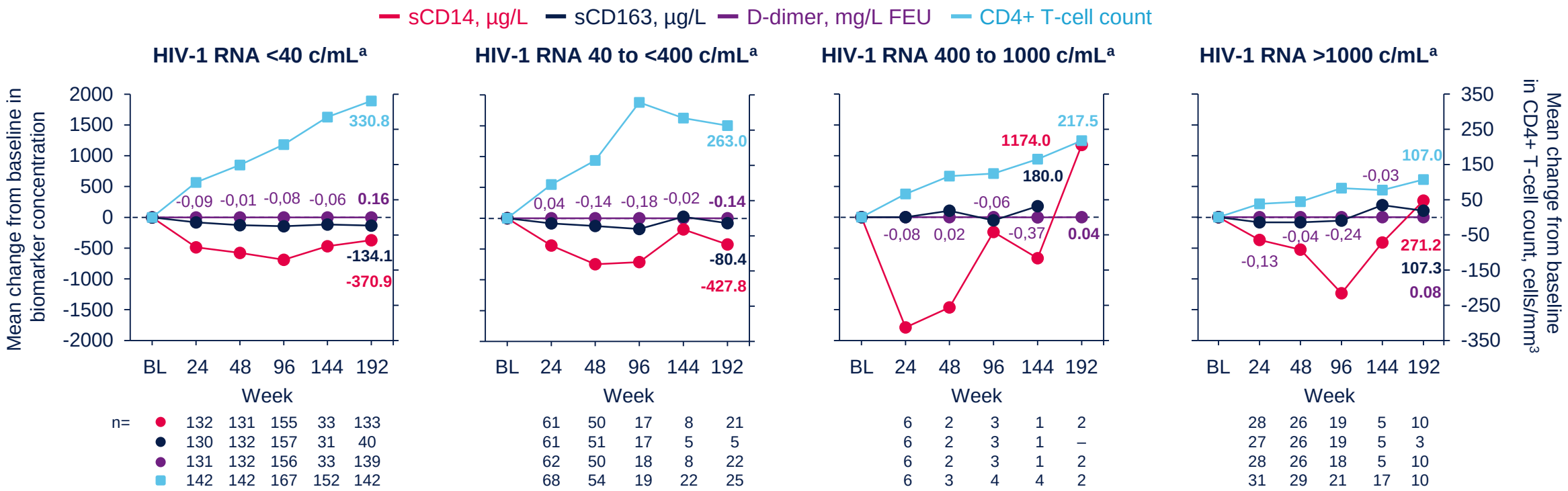


FEU, fibrinogen-equivalent units; s, soluble.

Spagnuolo et al. ICAR 2024; Rome, Italy. Oral presentation 159 OC 36.

Inflammatory Biomarkers Across Viral Load Categories

- In the Randomized Cohort, mean change from baseline in biomarkers fluctuated with time in some viral load subgroups and varied by viral load category; in general, the greatest improvements were observed in participants with undetectable viral load and lower LLV (<400 c/mL)

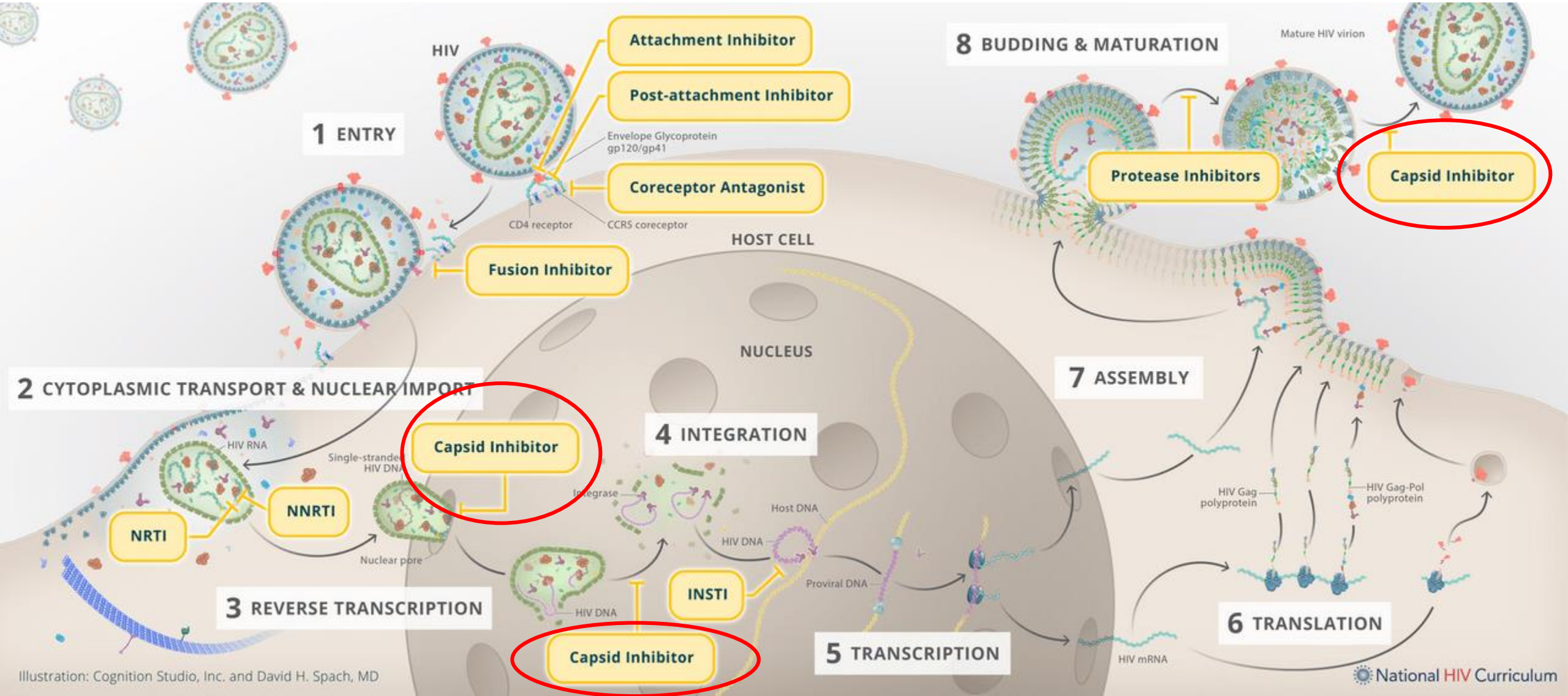


BL, baseline; FEU, fibrinogen-equivalent units; LLV, low-level viremia; s, soluble.

Mean change in D-dimer is displayed for each week because the scale of change in D-dimer was smaller than the other biomarkers; bolded values represent the mean change at the last available time point. [a]Data are presented by viral load category at each visit.

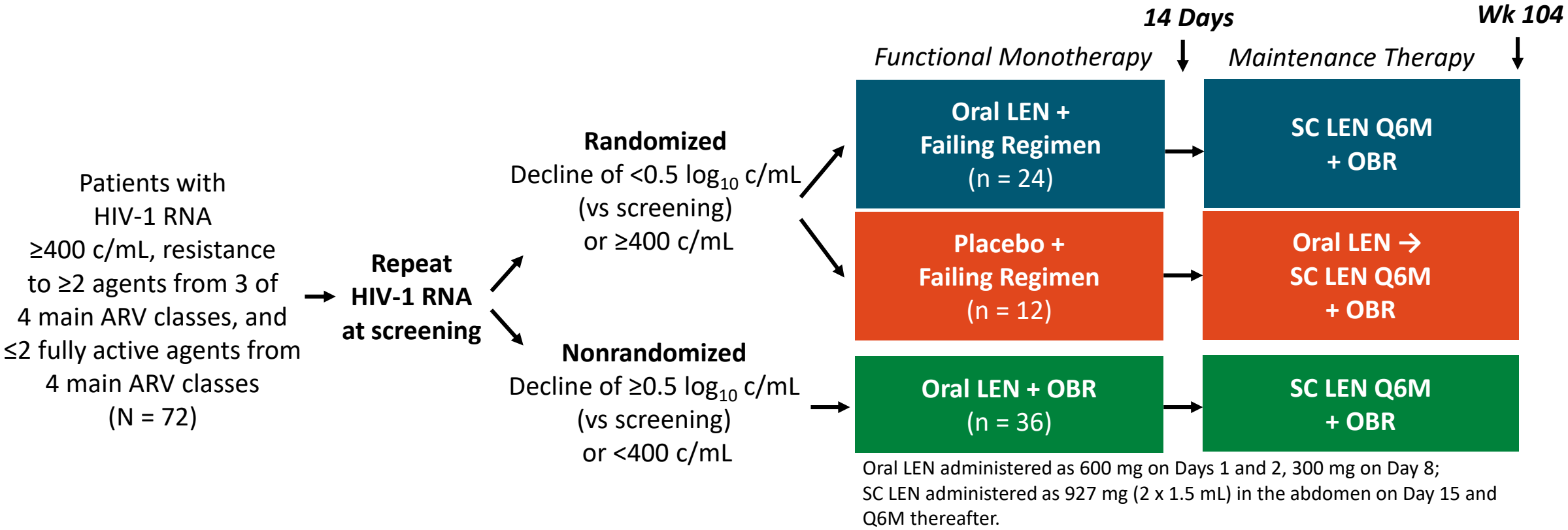
Spagnuolo et al. ICAR 2024; Rome, Italy. Oral presentation 159 OC 36.

LENACAPAVIR



CAPELLA: Study Design

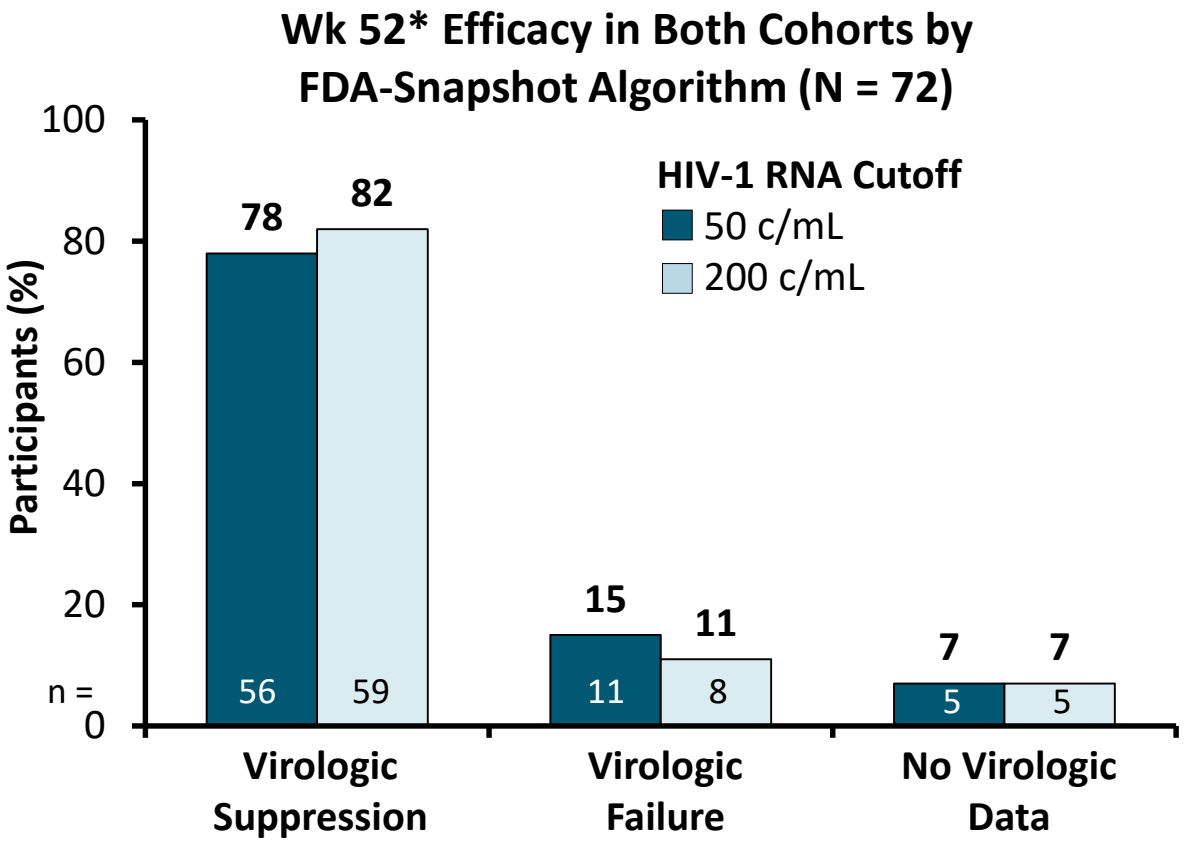
- Ongoing, 2-cohort phase II/III trial

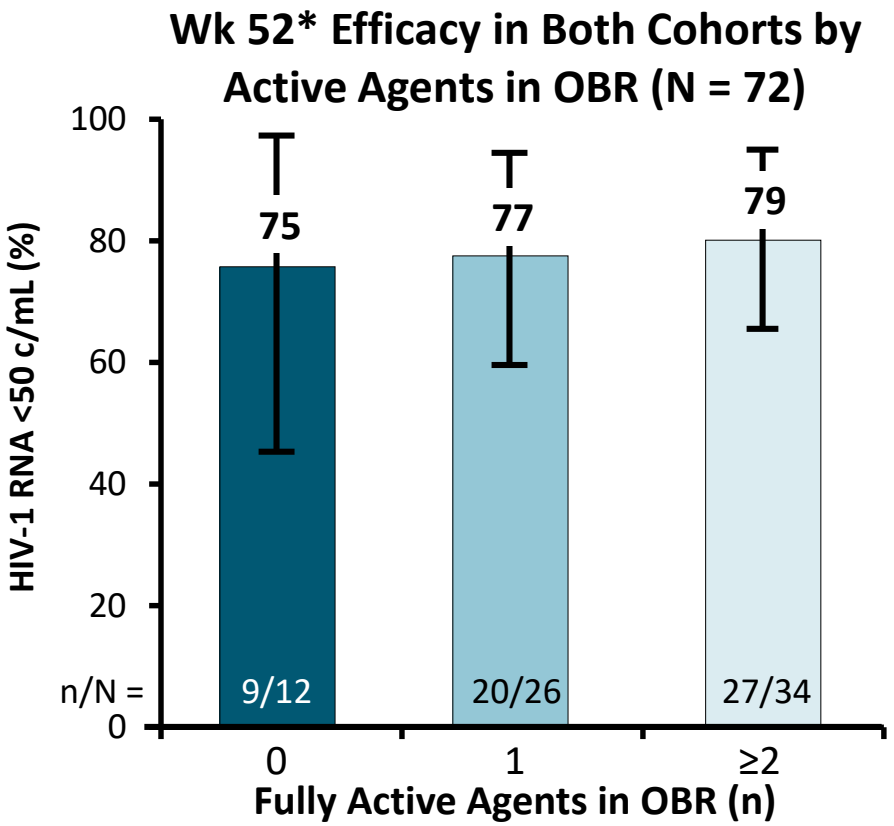


Oral LEN administered as 600 mg on Days 1 and 2, 300 mg on Day 8; SC LEN administered as 927 mg (2 x 1.5 mL) in the abdomen on Day 15 and Q6M thereafter.

- **Endpoints:** efficacy (FDA snapshot), resistance emergence, and safety at Wk 104

CAPELLA: LEN Efficacy at Wk 52 in Randomized and Nonrandomized Cohorts and by Fully Active Agents



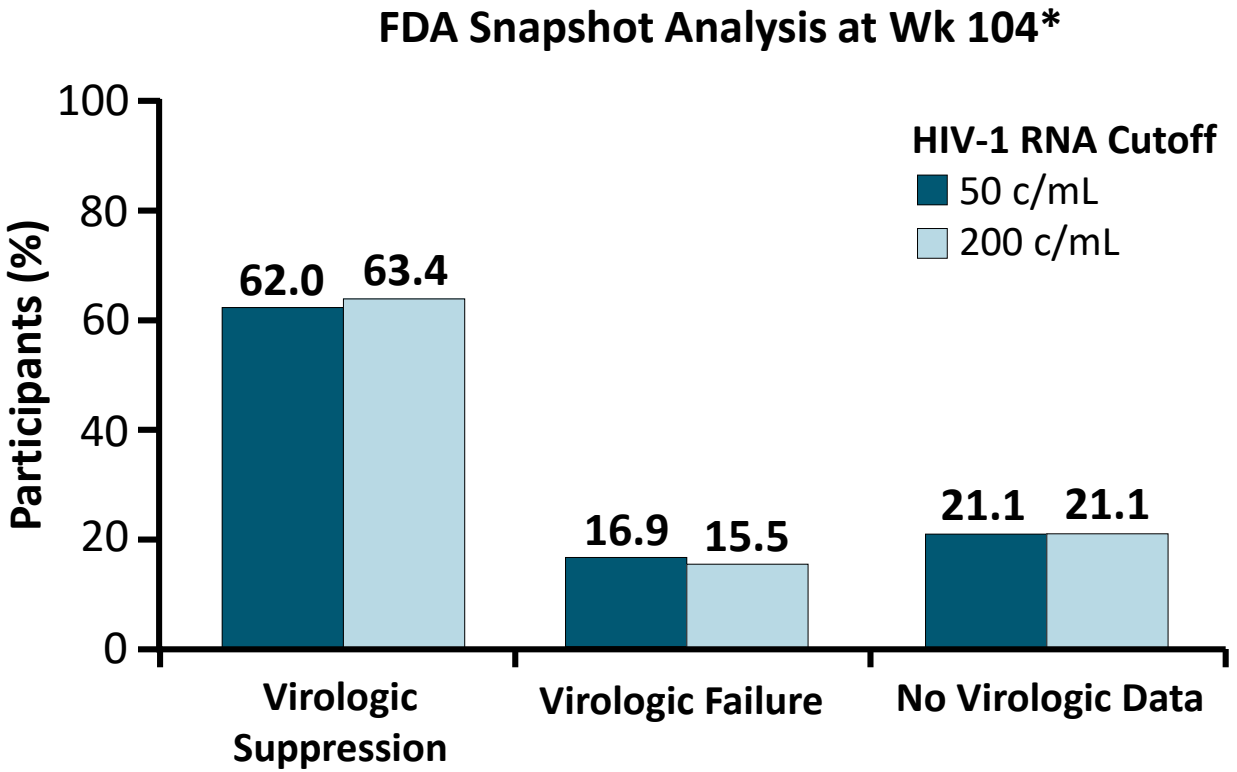


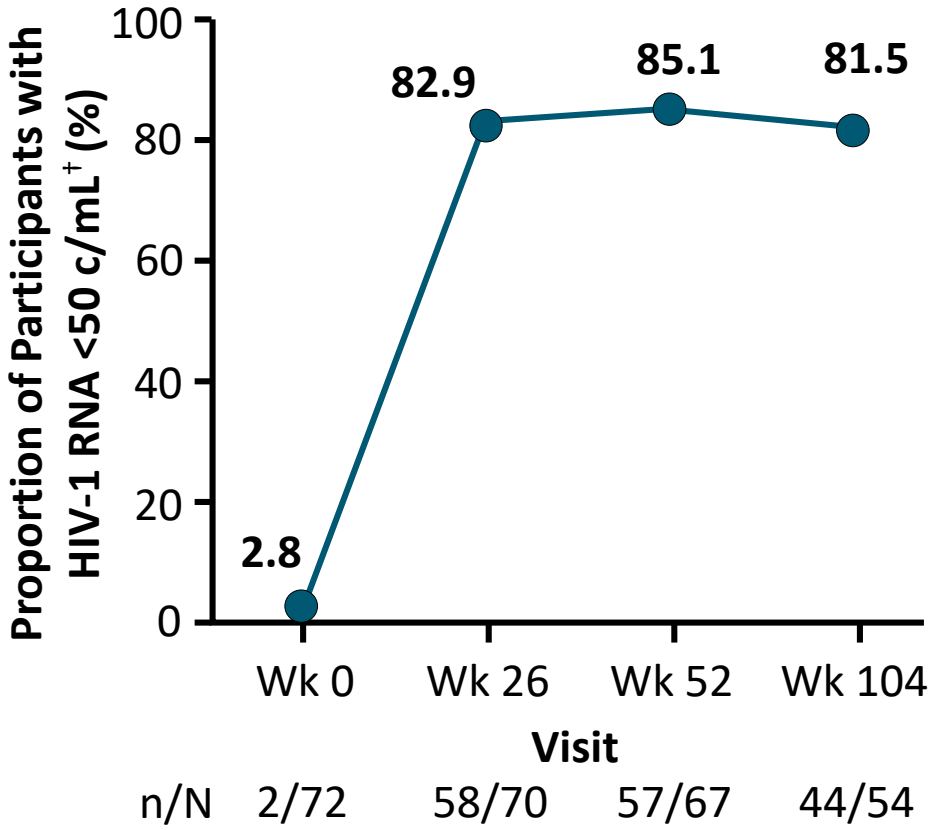
*By Wk 52, 17 participants took ≥1 dose or oral LEN bridging (300 mg QW) because of FDA clinical hold on SC LEN.

Ogbuagu. IDWeek 2022. Abstr 1585.

Slide credit: clinicaloptions.com

CAPELLA: LEN Efficacy at Wk 104



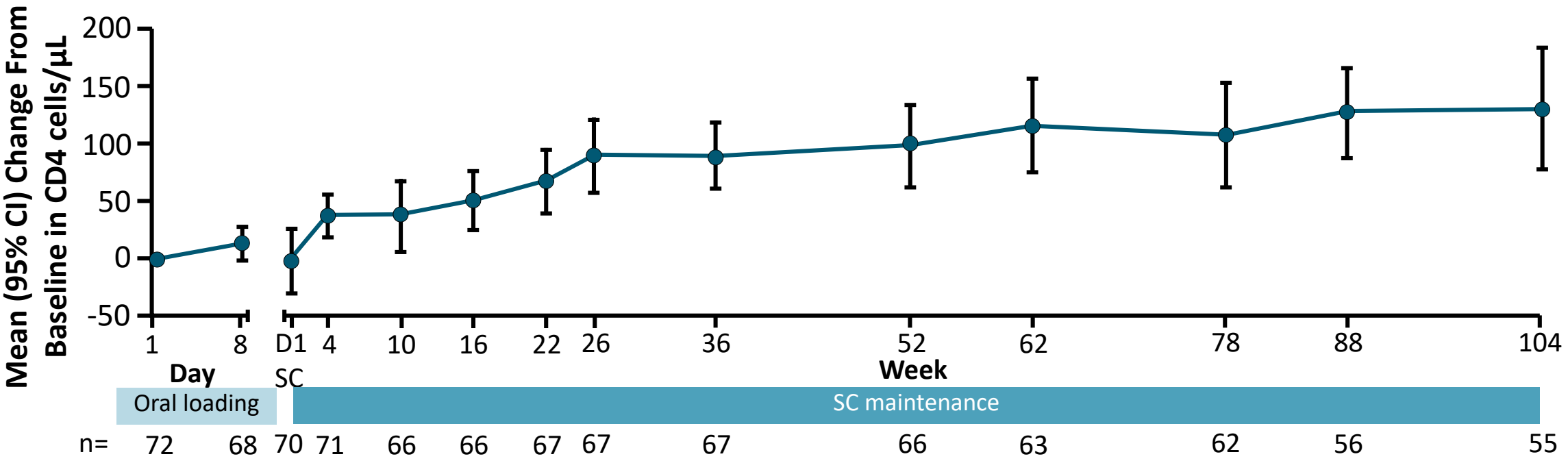


*Wk 104 window: Day 688 to Day 778; n = 71 (1 participant completed study before Wk 104 and missing HIV-1 RNA at Wk 104).

†Denominator for percentages is number of participants missing HIV-1 RNA values at each time point.

Ogbuagu. IDWeek 2023. Abstr 1596. Reproduced with permission.

CAPELLA: Changes in CD4+ Cell Counts to Wk 104



- CD4+ cell counts improved, mean increase of 122 cells/µL (95% CI: 80-165 cells/µL)
  - Proportion with CD4 cell counts <50 cells/µL decreased from 24% to 0%
  - Proportion with CD4 cell counts <200 cells/µL decreased from 64% to 29%

Ogbuagu. IDWeek 2023. Abstr 1596. Reproduced with permission.

Slide credit: clinicaloptions.com

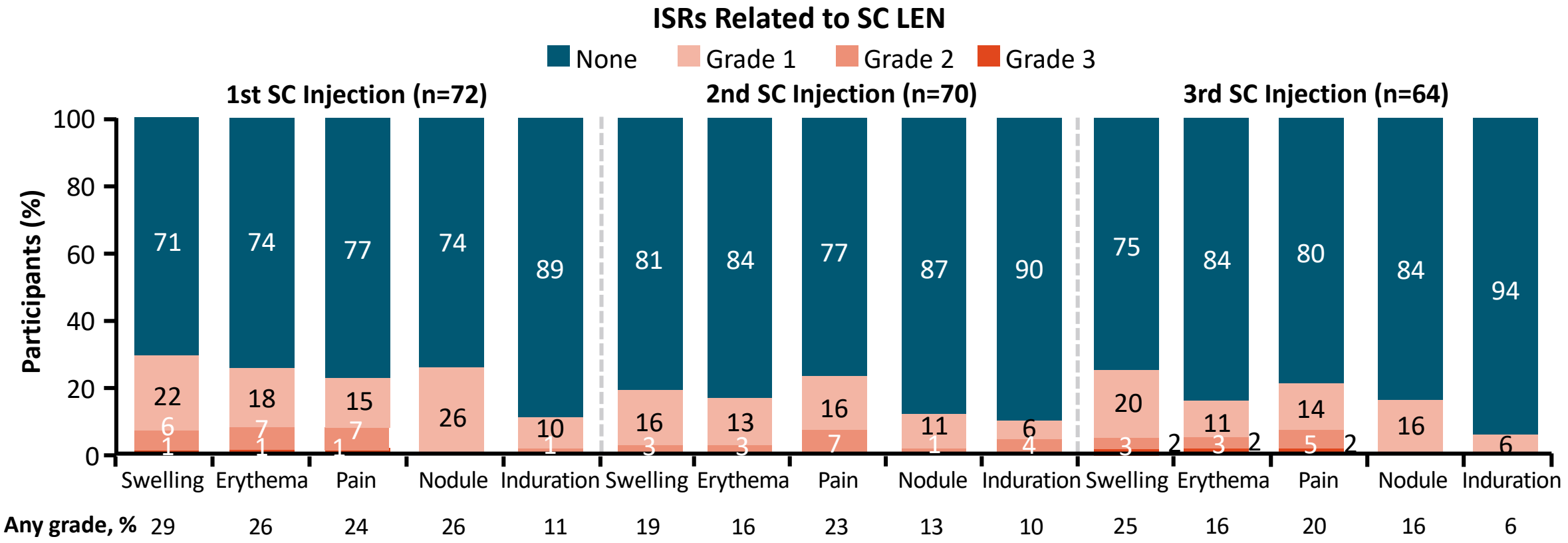
CAPELLA: Safety at Wk 104

Outcome, n (%)	LEN + OBR (N = 72)
Most common treatment-emergent AE (occurring ≥15% of participants, excluding ISRs and COVID-19)	
▪ Diarrhea	14 (19.4)
▪ Nausea	14 (19.4)
▪ Urinary tract infection	12 (16.7)
▪ Cough	11 (15.3)
Treatment emergent AE	71 (98.6)
▪ Grade ≥3	24 (33.3)
Treatment related AE	57 (79.2)
▪ Grade 3	6 (8.3)*
Serious treatment emergent AEs	15 (20.8)
Treatment related serious AE	0 (0)
Treatment emergent AE leading to study drug discontinuation	1 (1.4)†
All deaths	3 (4.2)‡

*ISR (n = 4), IRIS (n = 1), abdominal abscess (n = 1), rash (n = 1). †Due to grade 1 injection site nodule. ‡Malignant neoplasm (n = 1), acute respiratory failure (n = 1), unknown (n = 1).

Ogbuagu. IDWeek 2023. Abstr 1596.

CAPELLA: Injection-Site Reactions at Wk 104



- Most ISRs mild or moderate; swelling most common
  - 4 participants (5.6%) with Grade 3 and no participants with grade 4 ISR

Ogbuagu. IDWeek 2023. Abstr 1596. Reproduced with permission.

Slide credit: clinicaloptions.com

Resistance Analysis Population and Emerging LEN RAMs at Week 104

- Genotypic/phenotypic analyses (capsid, protease, RT, integrase) performed at virologic failure*

Category, n (%)	CAPELLA (N=72)
Resistance analysis population	**27** (38)
LEN RAM emergence	**14** (19)
M66I	6 (8)
Q67H/K/N	8 (11)
K70H/N/R/S	7 (10)
N74D/H/K	3 (4)
A105T/S	4 (6)
T107A/C/N/S	3 (4)
No LEN RAM emergence	**13** (18)

- Plasma OBR drug concentrations quantification (LC-MS/MS methods)
  - DRV, DTG, TAF/TFV, FTC

*Virologic failure defined as confirmed rebound ≥50 copies/mL or <1 $\log_{10}$ decline from baseline at Week 4. Resistance assays conducted at Monogram Biosciences.
DRV, darunavir; DTG, dolutegravir; FTC, emtricitabine; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LEN, lenacapavir; OBR, optimized background regimen; RAM, resistance-associated mutation; RT, reverse transcriptase; TAF, tenofovir alafenamide; TFV, tenofovir.

Margot N et al. Oral PS8 O4; EACS 2023, Warsaw

Summary of Participants with LEN RAMs Through Week 104 (n=14)

Outcome After VF	VF participants with LEN RAMs (n=14)	
	Non-adherence to OBR (had at least 1 fully active agent)	Suboptimal OBR (had no fully active agents)
Resuppressed	1. Q67H 2. K70N, N74K 3. M66I, K70S 4. N74D 5. Q67H	11. M66I, Q67H, N74D, A105T 12. M66I, T107A
Did not resuppress	6. M66I, N74D, A105T 7. Q67H, K70R, A105T 8. Q67K, K70H 9. Q67H, K70R, T107N 10. Q67H, K70R	13. M66I, A105T 14. M66I, Q67H, K70R, T107C

With OBR Change

- *Post* VF, 7 of 14 participants with LEN RAMs achieved HIV-1 RNA <50 c/mL on LEN + OBR

LEN, lenacapavir; OBR, optimized background regimen; RAM, resistance-associated mutation; VF, virologic failure.

Margot N et al. Oral PS8 04; EACS 2023, Warsaw

LEN Phenotypic data

Patient Clones and Site-Directed Mutants

Patient Clones and Site-Directed Mutants					
#	Genotype			RC (%)[a]	LEN FC[a]	LEN FC MT-2[b]
A.	M66I			0.6	>869.0	*Non-infectious*
B.	M66I	A105T		1.2	>869.0	*Non-infectious*
C.	M66I			1.5	>869.0	*Non-infectious*
D.	M66I	Q67H	K70R	3.1	>869.0	*Non-infectious*
E.	M66I			12.0	>869.0	*Non-infectious*
F.	M66I	T107S		24.0	>869.0	*Non-infectious*
G.	M66I	K70S		*AF*	*AF*	*Non-infectious*
H.	A105T			*AF*	*AF*	*Non-infectious*
I.	K70R			9.7	1.2	*Non-infectious*
J.	K70H			9.8	154.2	*Non-infectious*
K.	K70H			37	84.8	345
L.	K70S			*AF*	*AF*	*Non-infectious*
M.	N74D			49.0	17.0	42.4
N.	Q67H			58.0	4.8	7.7
O.	Q67H	K70R	T107S	109.0	46.3	45.3

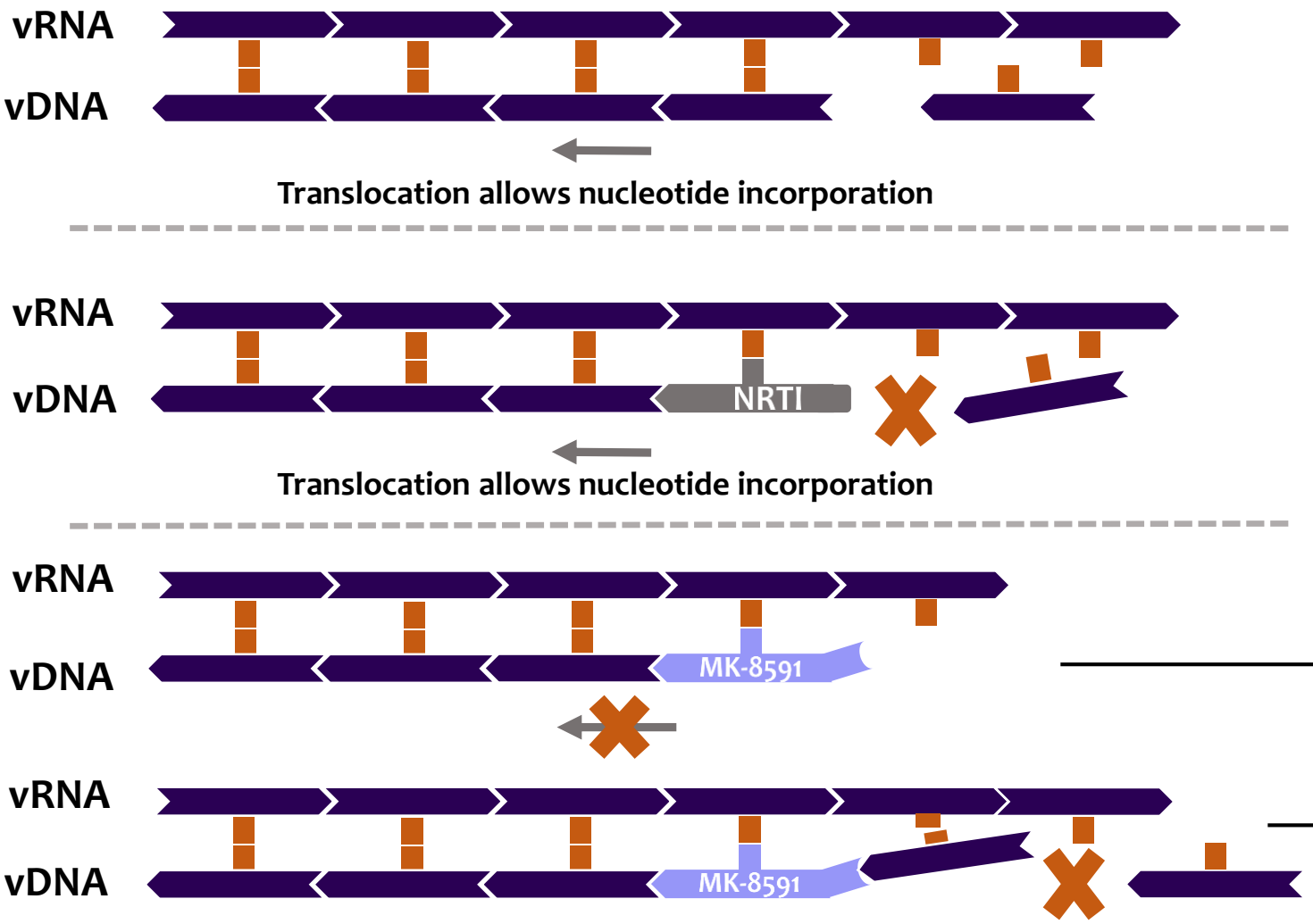
- Additional characterization:
  - Reasonable correlation between assays
  - Lack of replication in multicycle assays
  - High LEN FC associated with low RC

[a]Monogram Gag-Pro PhenoSense single-cycle assay; FC, fold-change compared to wild-type (WT); [b]MT-2, 5-day multicycle in-house assay.
AF, assay failure; FC, fold-change; NA, not available; RC, replication capacity; SDM, site-directed mutants;

Margot N et al. Oral PS8 O4; EACS 2023, Warsaw

ISLATRAVIR: The first NRTTI (Nucleoside Reverse Transcriptase Translocation Inhibitor)

Acosta-Hoyas AJ, et al. *Viruses*. 2010;2(2):372-394.
Arts EJ, et al. *Cold Spring Harb Perspect Med*. 2012;2(4):a00761.
Iyidogan P, et al. *Viruses*. 2014;6(10):4095-4139.
Michailidis E, et al. *J Biol Chem*. 2014;289(35):24533-24548.



Normal HIV Replication
Next nucleotide incorporates into the vDNA and continues to build the vDNA chain

NRTI: Single mechanism of action
Following translocation, the NRTI is incorporated into the vDNA, blocking the next nucleotide from attaching, which RESULTS IN CHAIN TERMINATION

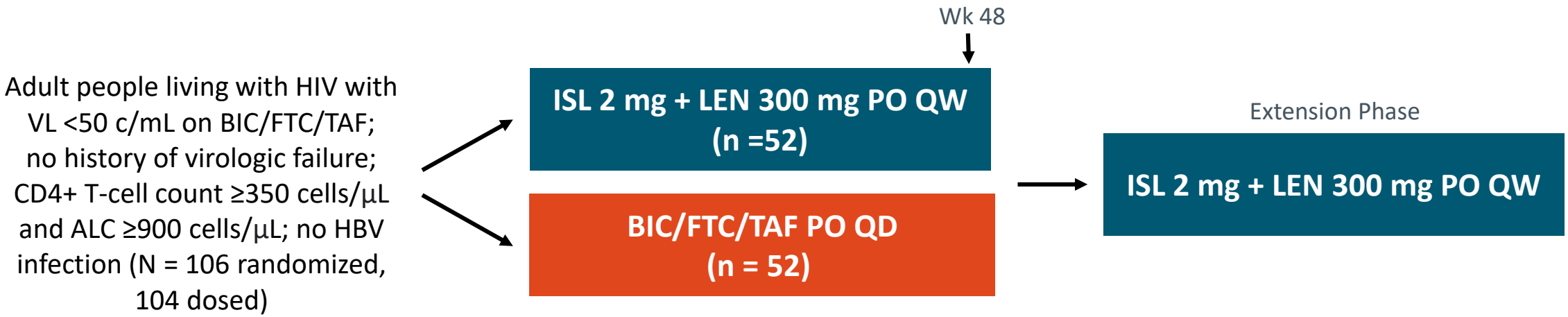
MK-8591 (NRTTI): Multiple mechanisms of action
TRANSLOCATION BLOCKED
MK-8591 is incorporated into the vDNA preventing nucleotide binding and incorporation. This results in IMMEDIATE CHAIN TERMINATION

In the event that tanslocation does occur and additional nucleotides are incorporated, MK-8591 causes structural change to vDNA resulting in DELAYED CHAIN TERMINATION

Grobler J et al. Efficacy of MK-8591 against diverse HIV-1 subtypes and NRTI-resistant clinical isolates; HIV Glasgow 28-31 October 2018

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

- Open-label, active-controlled phase II trial



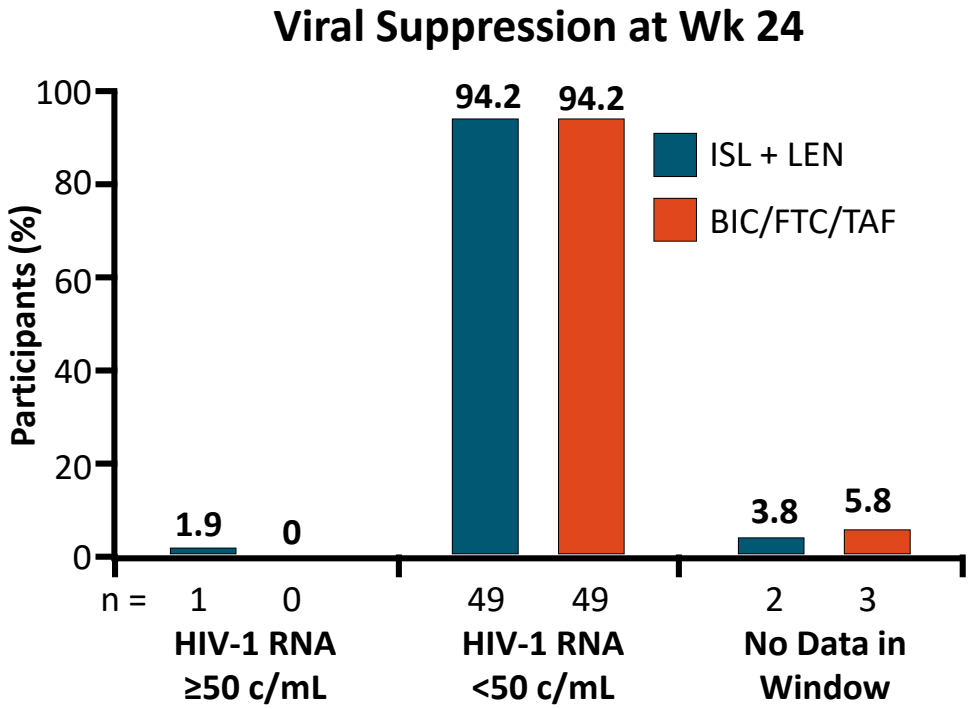
- **Primary endpoint:** proportion of participants with HIV-1 RNA ≥50 c/mL at Wk 24 by FDA Snapshot algorithm
- **Secondary endpoints:** proportion of participants with HIV-1 RNA ≥50 c/mL by Wk 12 and 48; proportion with HIV-1 RNA <50 c/mL at Wk 12, 24, and 48; change from baseline in CD4+ T-cells, AEs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

Colson. CROI 2024. Abstr 208.

Slide credit: clinicaloptions.com

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

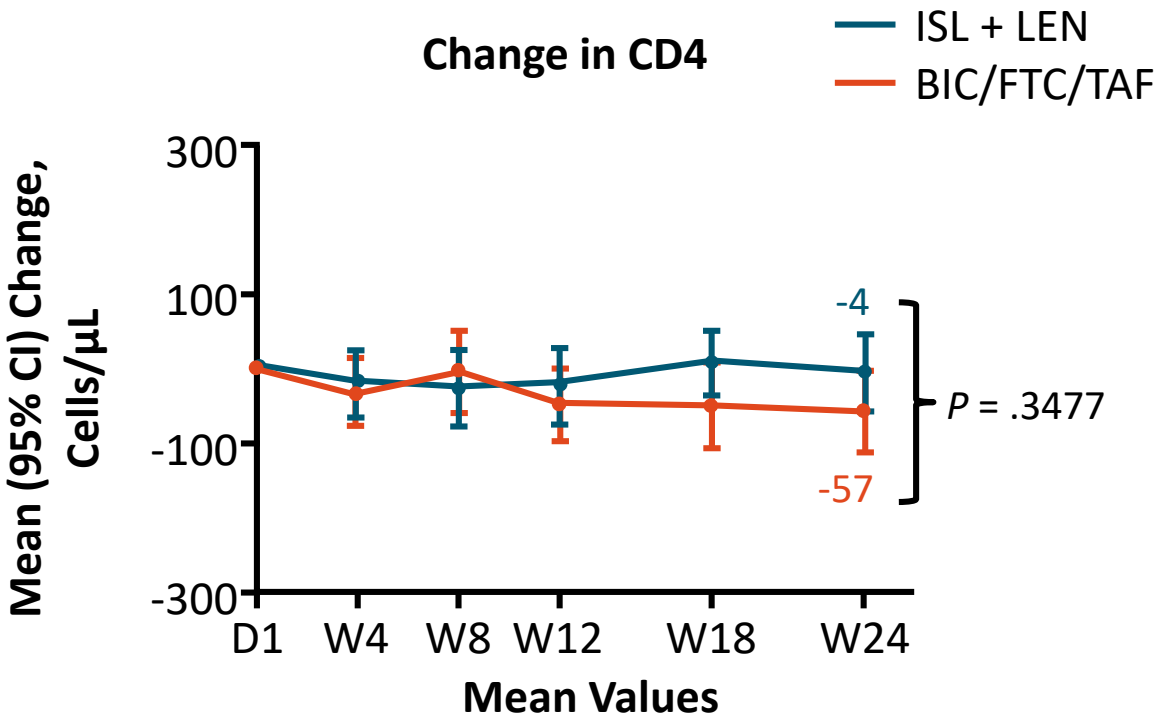
Patients With AE, n (%)	ISL + LEN (n = 52)	BIC/FTC/TAF (n = 52)
Any AE	40 (76.9)	38 (73.1)
Any TRAE	9 (17.3)	3 (5.8)
Grade 1/2 TRAEs in ≥2 on ISL + LEN	9 (17.3)	3 (5.8)
▪ Dry mouth	2 (3.8)	0
▪ Nausea	2 (3.8)	0
Grade 3/4 TRAEs	0 (0)	0 (0)
Serious AE	3 (5.8)	0
AE leading to d/c	2 (3.8)	0

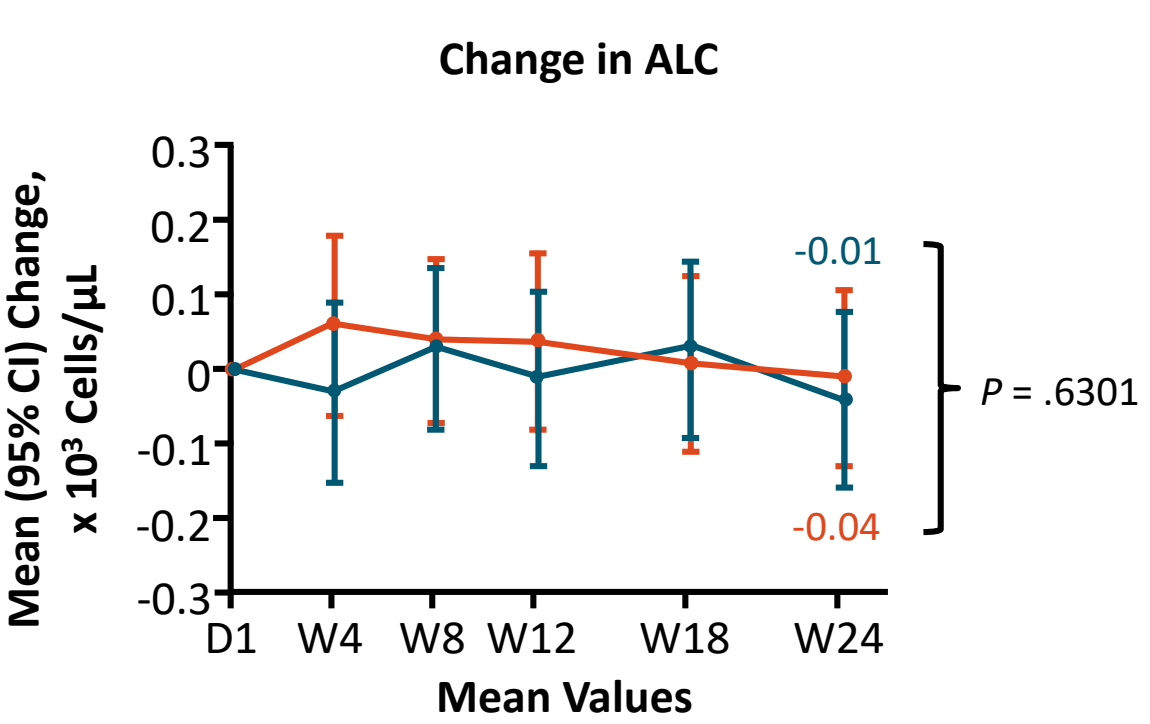
Patients With Grade 3/4 Lab Abnormality, n (%)	ISL + LEN (n = 52)	BIC/FTC/TAF (n = 52)
Grade 3	5 (9.6)	4 (7.8)
▪ Increased ALT	1 (1.9)	0
▪ Increased SCr	1 (1.9)	0
▪ Decreased CrCl	2 (3.8)	2 (3.9)
▪ Fasting hyperglycemia	0	1 (2.6)
▪ Non-fasting hyperglycemia	1 (2.5)	2 (4.9)
▪ Hyperkalemia	1 (1.9)	0
▪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

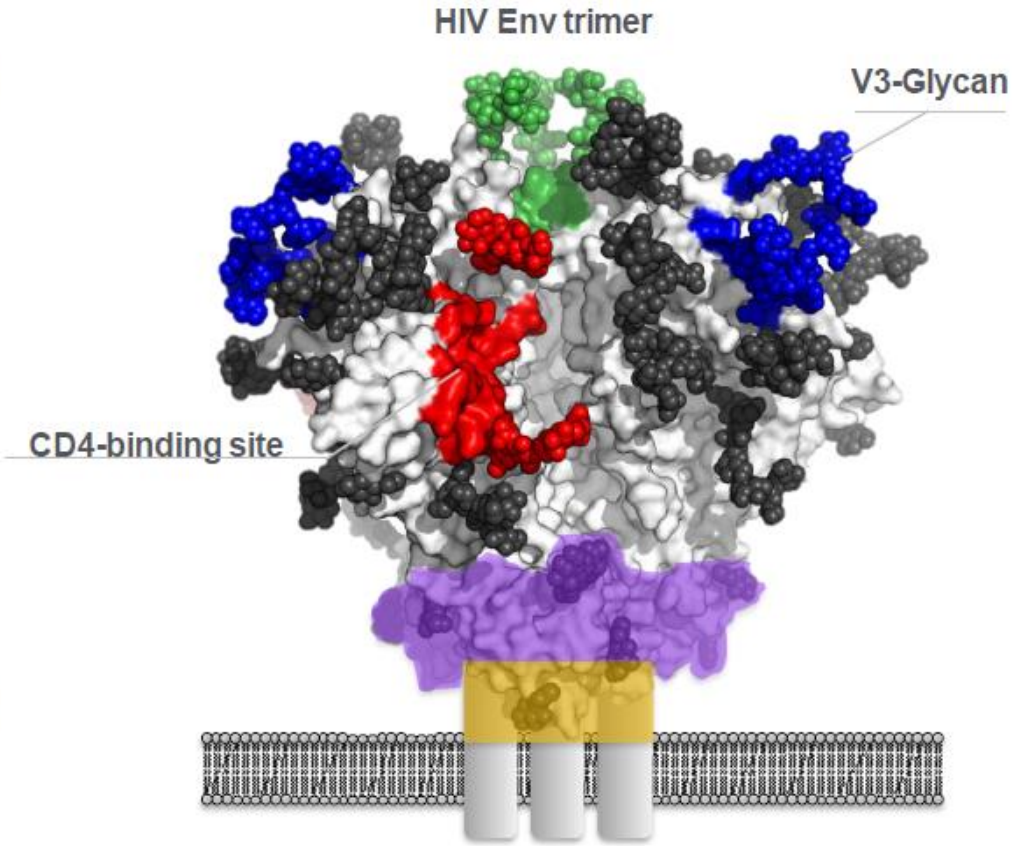
- No person discontinued treatment due to decline in CD4+ T-cells or ALC

Colson. CROI 2024. Abstr 208.

Slide credit: clinicaloptions.com

LENACAPAVIR WITH BNABS TEROPAVIMAB (GS-5423) AND ZINLIRVIMAB (GS-2872) DOSED EVERY 6 MONTHS IN PEOPLE WITH HIV

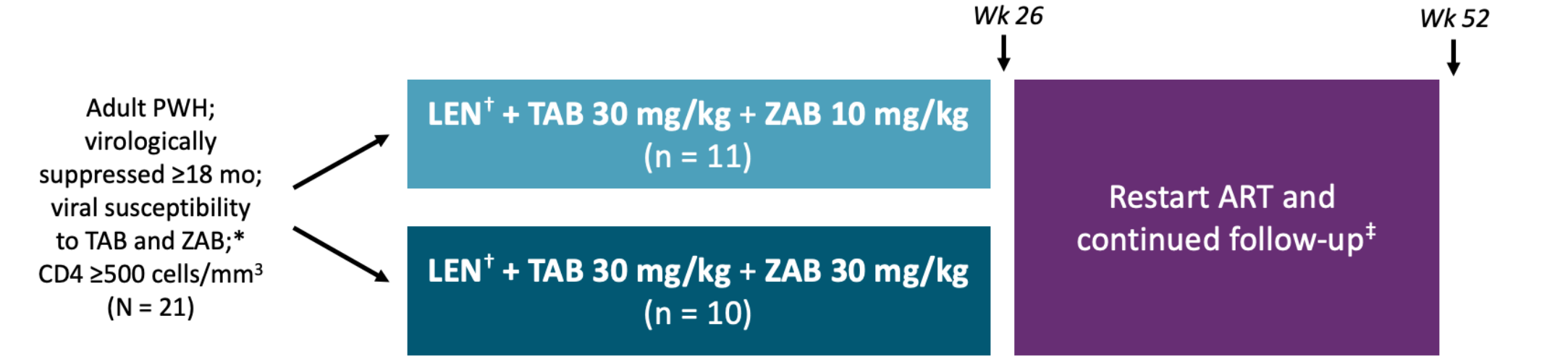
- Teropavimab (TAB; GS-5423; 3BNC117-LS) and zinlirvimab (ZAB; GS-2872; 10-1074-LS) are broadly neutralizing antibodies (bNAbs) against the CD4-binding site of gp120 and a non-overlapping epitope on the V3 glycan of HIV-1 Env, respectively.
- Both antibodies were modified to extend their half-lives for long-acting therapy that may allow for dosing every 6 months.
- An estimated > 50% of clade B viruses are highly susceptible to both bNAbs and > 90% are highly susceptible to either bNAb with a 90% inhibitory concentration (IC_{90}) < 2 µg/mL.[1]



Eron et al. CROI 2023. Abstract OA12

STUDY DESIGN

- Multicenter, randomized, blinded phase Ib study of LEN combined with 2 bNAbs



*44% of those screened met criterion for viral susceptibility.

†Day 1: LEN 600 mg PO x 2 + LEN 927 mg SC.
Day 2: LEN 600 mg PO x 2.

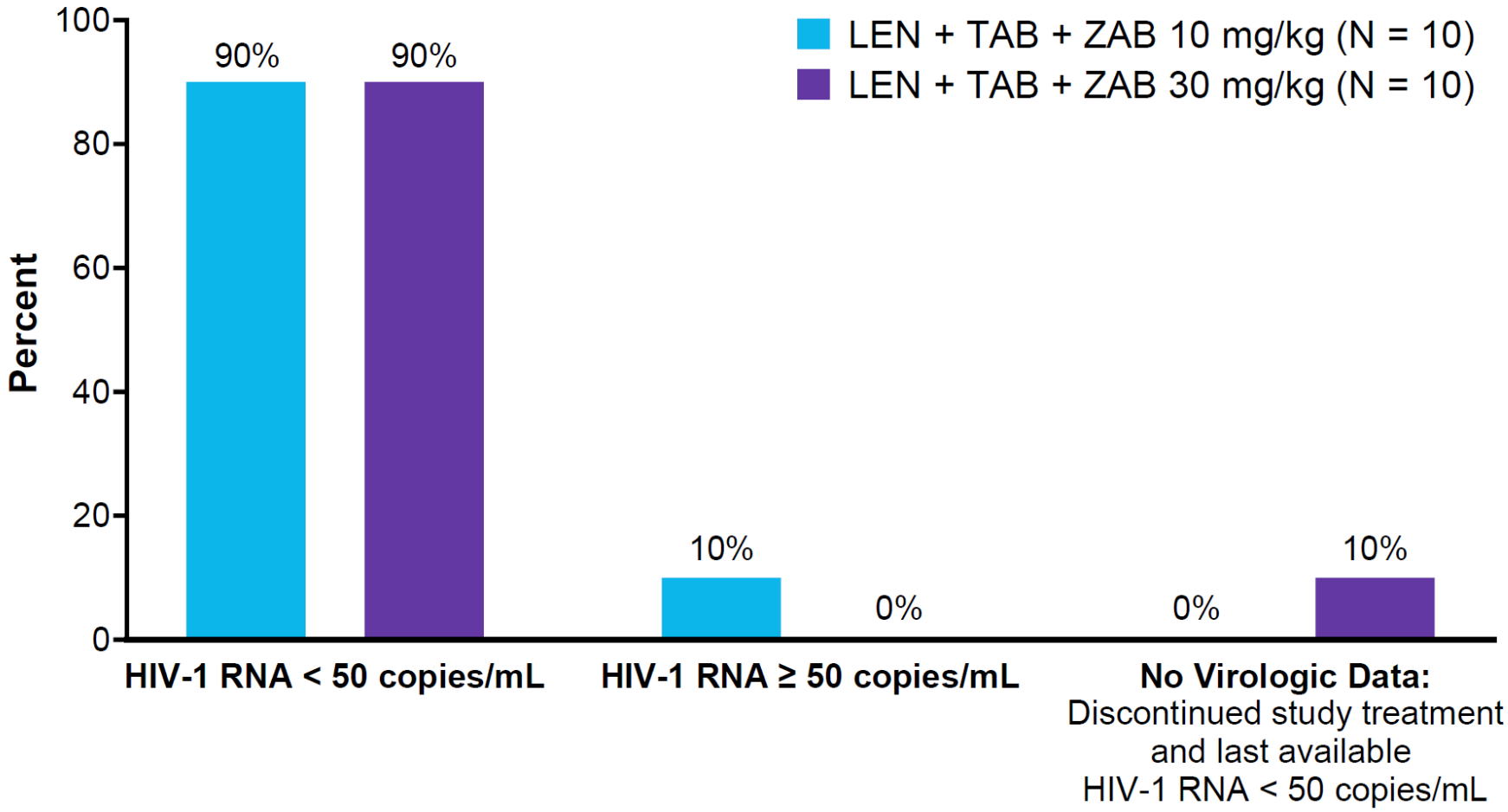
‡Study protocol amended to restart ART at Wk 26 instead of Wk 52 when LEN became unavailable.

- Endpoints assessed at Wk 26:
  - Proportion of patients with plasma HIV-1 RNA <50 c/mL and ≥50 c/mL
  - Change in CD4 count in cells/mm^3 from baseline
  - Serum concentrations of LEN, TAB, and ZAB
  - Safety and tolerability

Eron. CROI 2023. Abstr OA12.

Slide credit: clinicaloptions.com

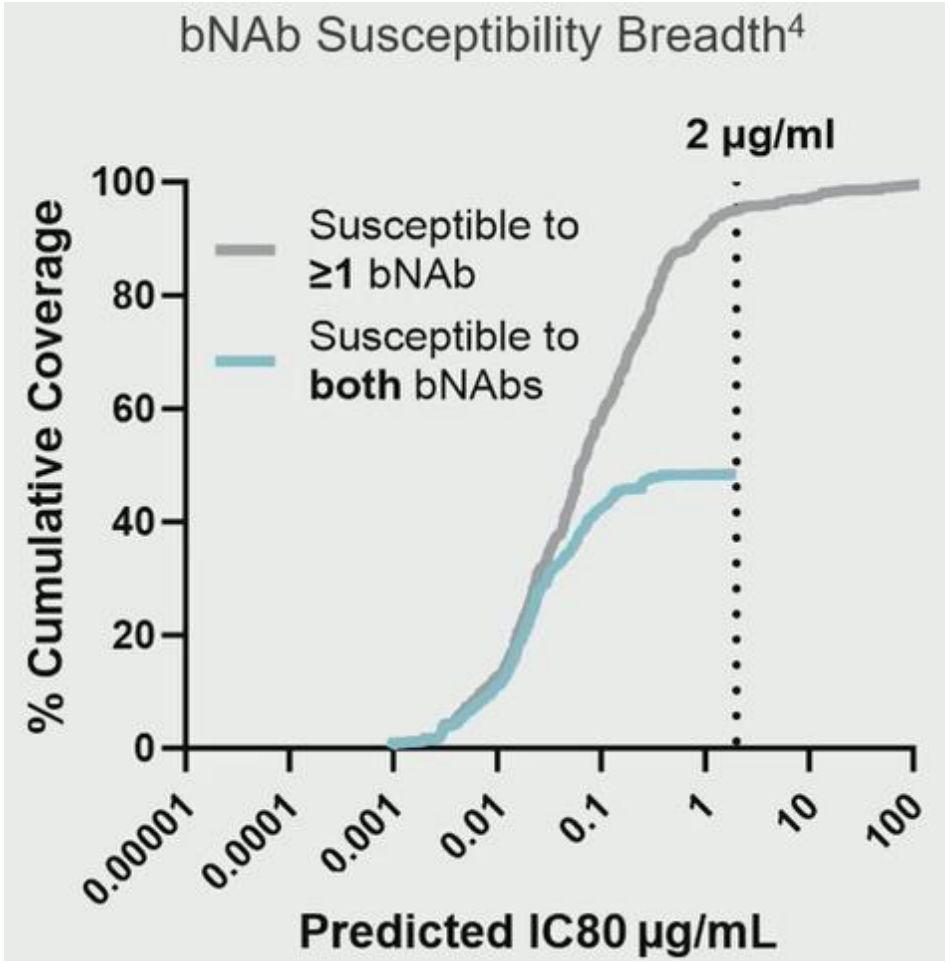
VIROLOGIC EFFICACY OUTCOMES AT WEEK 26 BY FDA SNAPSHOT ALGORITHM

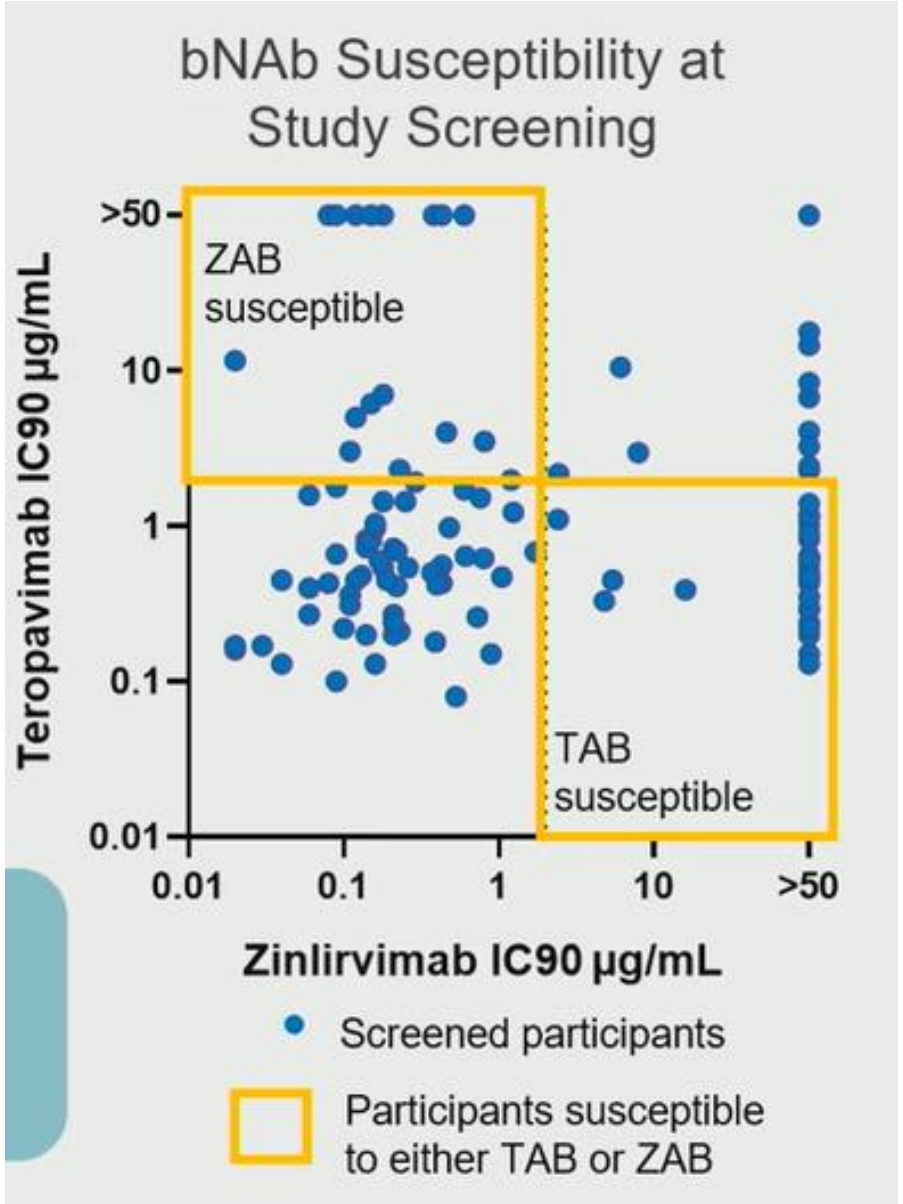


- 18 out of 20 participants maintained viral suppression on study regimen through Week 26.
- One participant withdrew[1] at Week 12 with HIV-1 RNA < 50 copies/mL.
- One participant had a confirmed virologic rebound at Week 16 and was resuppressed on baseline oral ART.

Eron et al. Lancet HIV 2024

LENACAPAVIR PLUS BNABS FOR PEOPLE WITH HIV AND SENSITIVITY TO EITHER TEROPAVIMAB OR ZINLIRVIMAB





Eron JJ et al. Abstract 120; CROI 2024; Denver

Participant Disposition and Susceptibility

Randomized (N=11)

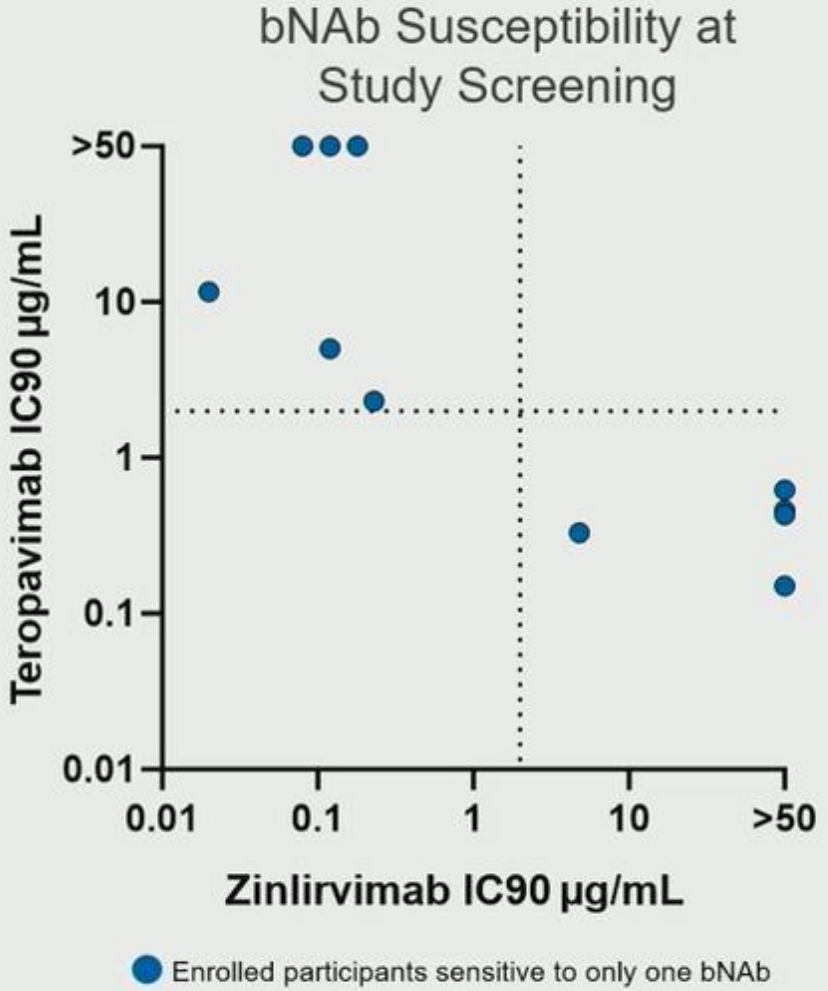
Received LEN + TAB + ZAB 10 mg/kg (n=5)
- Susceptible to TAB (n=2)
- Susceptible to ZAB (n=3)

Received LEN + TAB + ZAB 30 mg/kg (n=6)
- Susceptible to TAB (n=3)
- Susceptible to ZAB (n=3)

Prematurely discontinued study drug (n=1)
- Protocol violation (chronic HBV) restarted ART
- Included in safety analysis
- VS at discontinuation

Completed treatment regimen W26 (n=4)[a]

Completed treatment regimen W26 (n=6)



Eron JJ et al. Abstract 120; CROI 2024; Denver

[a]1 and 3 participants were susceptible to TAB and ZAB, respectively

ART, antiretroviral therapy; **bNAb**, broadly neutralizing antibody; **HBV**, Hepatitis B virus; **LEN**, lenacapavir; **TAB**, teropavimab; **VS**, virologic suppression; **W**, Week; **ZAB**, zinlirvimab.

Baseline Characteristics

	LEN + TAB + ZAB 10 mg/kg (n=5)	LEN + TAB + ZAB 30 mg/kg (n=6)	Total (N=11)
Age (years), median (range)	49 (28–63)	51 (29–57)	49 (28–63)
Female sex at birth, n	2	1	3
Race, n			
Black	2	2	4
White	3	3	6
Other	0	1	1
Hispanic or Latino ethnicity, n	2	1	3
Weight (kg), median (range)	86.4 (67.6–104.5)	86.3 (84.2–117.6)	86.4 (67.6–117.6)
CD4 cell count (per mL), median (range)	861 (449–1916)	942 (673–1196)	916 (449–1916)
Duration of baseline ART (years), median (range)	2.5 (1.0–5.5)	4.9 (3.1–6.4)	3.7 (1.0–6.4)
Time since HIV-1 diagnosis (years), median (range)[a]	16 (5–25)	13.5 (3–24)	16 (3–25)

[a]These data are self-reported by the participant

ART, antiretroviral therapy; **LEN**, lenacapavir; **TAB**, teropavimab; **ZAB**, zinlirvimab.

Eron JJ et al. Abstract 120; CROI 2024; Denver

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

[a]One participant restarted ART prior to Week 26 due to a protocol violation (chronic HBV) and is excluded from the efficacy analysis.
HBV, hepatitis B; **LEN**, lenacapavir; **TAB**, teropavimab; **ZAB**, zinlirvimab.

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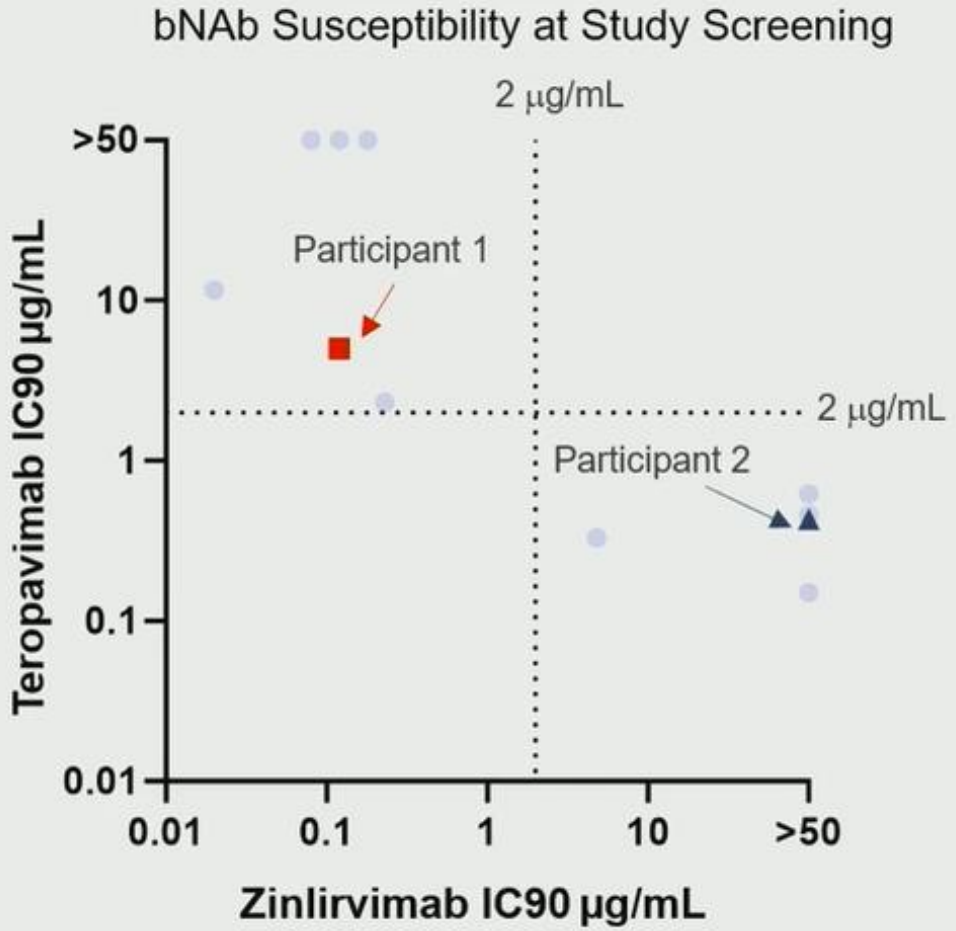
Participants with Virologic Rebound



Participant Characteristics at Baseline

	Participant #1	Participant #2
Age, years	36	60
Sex	Male	Female
Weight, kg	86.4	89.7
CD4 count, cells/µL	449	1916
TAB IC90, µg/mL	5.02	**0.43**
ZAB IC90, µg/mL	**0.12**	>50

- LEN, TAB, and ZAB PK was within the range observed for other participants in Group 1

[a]Resistance was conducted using genotypic and phenotypic analyses of HIV-1 envelope and capsid.
LEN, lenacapavir; **TAB**, teropavimab; **ZAB**, zinlirvimab.

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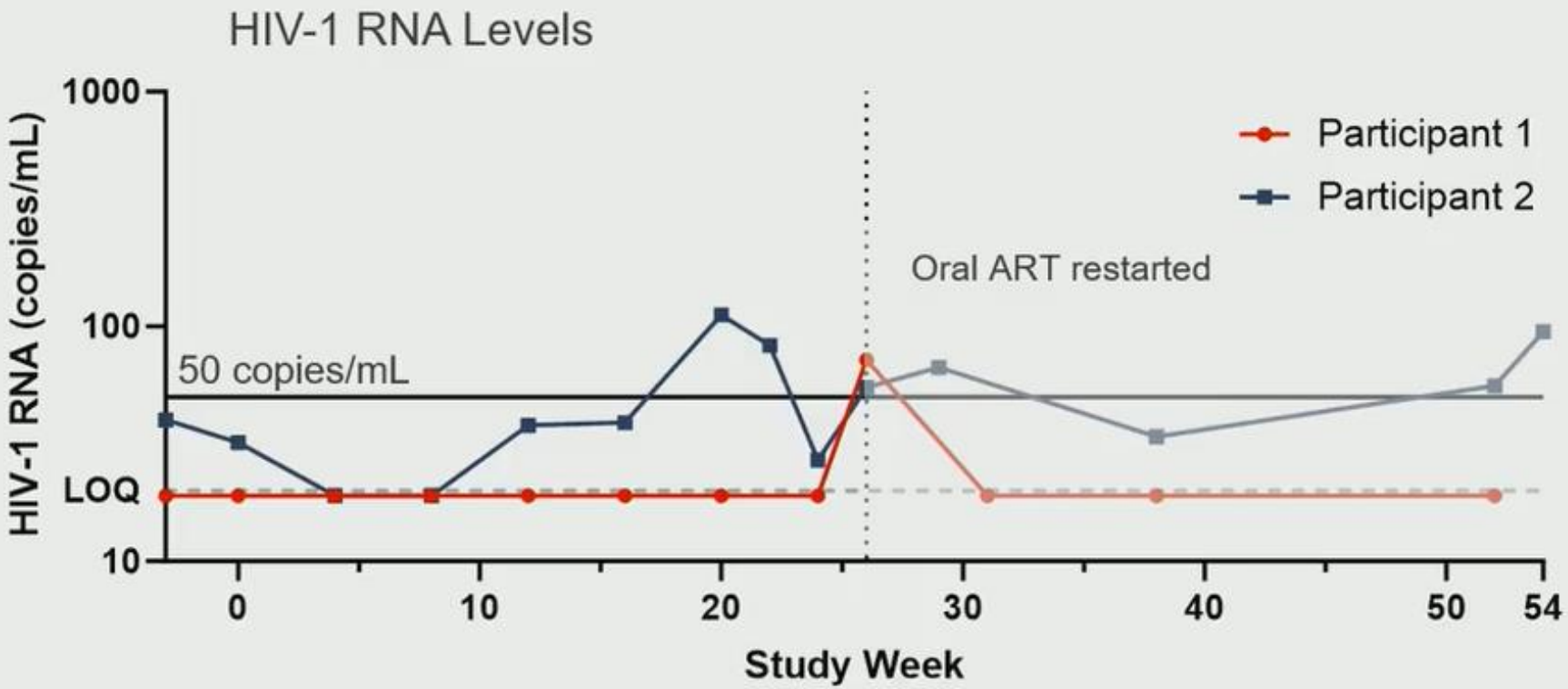
Participants with Virologic Rebound



- Participant 1 resuppressed by the following visit after restarting oral ART
- Participant 2 continued to have low-level, detectable HIV-1 RNA after restarting oral ART
- Neither participant had detectable treatment-emergent resistance to study drugs

ART, antiretroviral therapy; **LOQ**, limit of quantification

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THANK YOU