2nd Long-Acting Treatment and Prevention Conference

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What are the treatment options for patients with multidrug-resistant HIV1 infection

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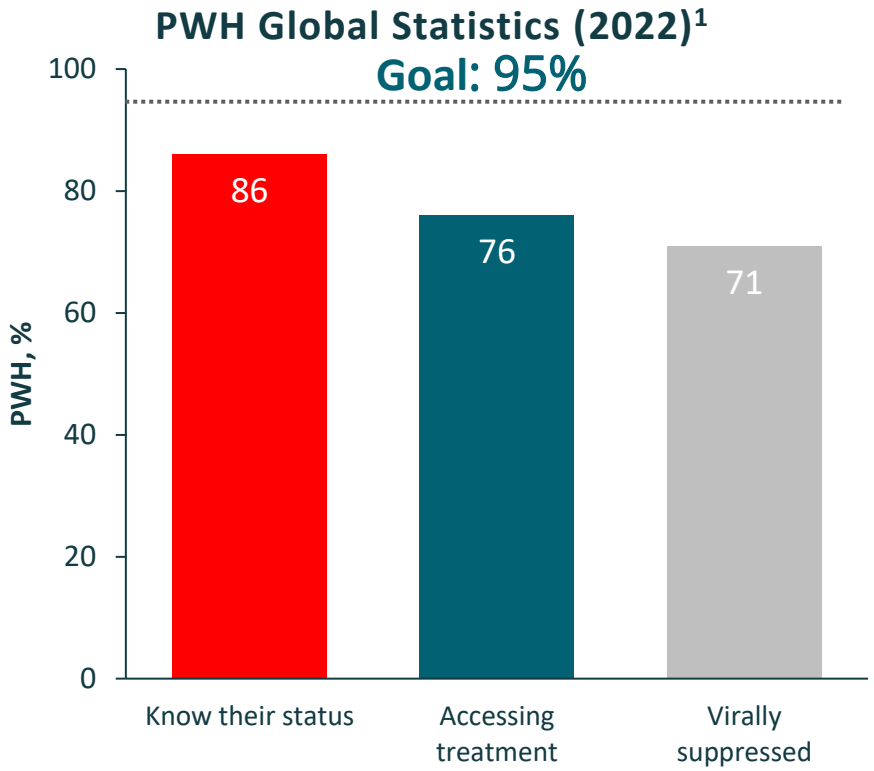
Disclaimers

- Part of the National 3rd line ART committee
- PI on Gilead Capella Study

Introduction



~39 million PWH globally in 2022[1]

Due to the availability of well-tolerated, efficacious and simplified regimens:[2,3]

- The number of persons with long-term VS has **increased**
- The number of persons experiencing treatment failure, progression to AIDS and death has **decreased**

There remains a subset of HTE individuals with unmet needs who may benefit from:

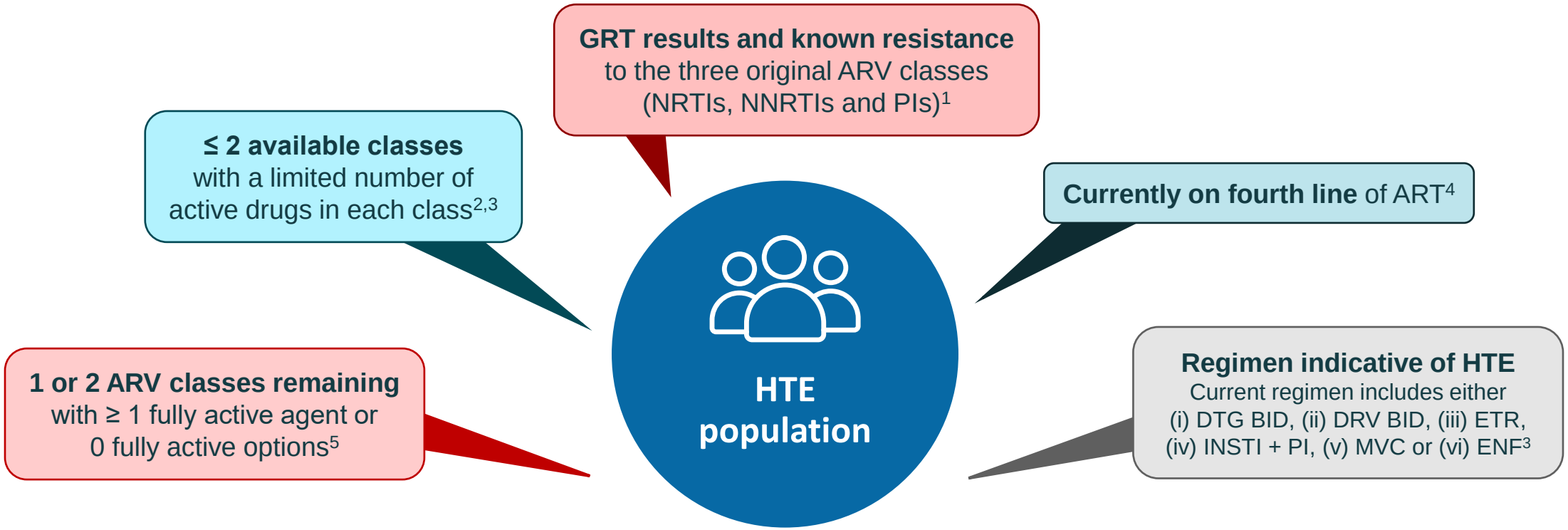
- **Effective ART** with favorable safety profile[4]
- **Novel mechanism of action**, with lack of cross-resistance to other ARV classes[4]
- **Innovative approaches** that are convenient and support patient adherence[4]

HTE, heavily treatment-experienced; VS, viral suppression

1. UNAIDS Global AIDS Update, 2023 https://www.unaids.org/sites/default/files/media_asset/2023-unaids-global-aids-update_en.pdf (accessed Aug. 2023); 2. WHO. Guidelines for the Managing Advanced HIV Disease and Rapid Initiation of Antiretroviral Therapy. 2017. https://apps.who.int/iris/bitstream/handle/10665/255884/9789241550062-eng.pdf (accessed Feb. 2021); 3. ART Cohort Collaboration. Lancet 2008;372(9635):293-299; 4. DHHS

Challenges With Defining the HTE Population

Heavily treatment-experienced (HTE) patients are individuals living with HIV who have limited treatment options due to factors like drug resistance, intolerance, or previous treatment failures.



Various criteria have been used to define the HTE population across a range of studies

GRT, genotypic resistance testing; HTE, heavily treatment-experienced

1. Pelchen-Matthews A, et al. JADIS 2021;87:806-817; 2. Bajema KJ, et al. IAS 2019, Poster MOPEB246; 3. Bajema K, et al. AIDS 2020;34:2051-2059; 4. Hsu R, et al. AIDS 2020, Poster PEB0234; 5. Kozal M, et al. N Engl J Med 2020;382:1232-1243

Epidemiology

- The prevalence of HTE patients varies by region and over time.
- For instance, a study in Europe found that approximately 10.4% of participants were classified as HTE, with the prevalence increasing from 5.8% in 2010 to 8.9% in 2016
- In another cohort study, the prevalence of HTE patients was reported to be between 1.9% and 10.4% depending on the definitions used
- In Africa it ranges from 0,1% to 10% depending on the definitions used

Epidemiology of HTE PWH

CNICS cohort (2000–2017)[1]

Definition: ≤ 2 available classes with a limited number of active drugs in each class

Estimated prevalence by 2017:

< 1% (N = 27,133)

EuroSIDA cohort (2010–2016)[2]

Definition: Positive GRT results and known resistance to the three original ARV classes (NRTIs, NNRTIs and PIs)

Estimated prevalence by 2016:

10.4% (N = 15,570)

Despite the use of different definitions between cohorts, the number of HTE PWH among the global population of PWH is generally low

CNICS, Centers for AIDS Research Network of Integrated Clinical Systems; GRT, genotypic resistance testing; HAART, highly active antiretroviral therapy; HTE, heavily treatment-experienced

1. Bajema K, et al. AIDS 2020;34:2051-2059; 2. Pelchen-Matthews A, et al. JADIS 2021;87:806-817

Guideline-Based Definitions and Management of Treatment Experienced PWH

EACS[1]

When a 2–3-drug active regimen cannot be constructed, a drug with a new mechanism of action, such as LEN, FTR or IBA, can be added to obtain a 2-3 drug active regimen

IAS-USA[2]

In the setting of multiclass resistance (3-class resistance), the next regimen should be constructed using drugs from new classes, if available (evidence rating: BIII); e.g., FTR (AIb) or IBA (BII), with at least one additional active drug in an optimized ART regimen

DHHS[3]

Failing regimen	Resistance considerations	New regimen options	Goal
Drug resistance **with fully active treatment** options	• Use past and current genotypic +/- phenotypic resistance testing and ART history when designing new regimen	• Two fully active agents, at least one of which has a high barrier to resistance; otherwise, three fully active agents are preferred • Partially active drugs may be used when no other options are available • Consider using an ARV drug with a different mechanism of action	• Resuppression
Multiple or extensive drug resistance **with few treatment** options	• Use past and current genotypic and phenotypic resistance testing to guide ART • Confirm with viral tropism assay when use of MVC is considered • Consult an expert in drug resistance, if needed	• Identify as many active or partially active drugs as possible based on resistance test results • Consider using an ARV drug with a different mechanism of action (i.e., LEN, IBA, FTR) • Clinical trials or expanded access programs for investigational agents may be available • Discontinuation of ARV drugs **is not recommended**	• Resuppression, if possible • Otherwise, keeping viral load as low as possible and CD4 count as high as possible

LEN is now recommended in the DHHS guidelines for managing PWH with virologic failure

DHHS; the US Department of Health and Human Services; EACS, European AIDS Clinical Society; FTR, fostemsavir; IAS-USA, International Antiviral Society–USA; IBA, ibalizumab

Resistance testing is generally only possible if the VL is > 500 copies/mL. However, in the era of DTG- and PI-based therapy, we generally recommend it only be performed with a 2-3 consecutive VL > 1000 copies/mL, which would satisfy the definition of virological failure.

	DTG-based therapy	PI-based therapy	NNRTI-based therapy
Resistance testing criteria	• Patient on regimen for > 2 years, OR • Patient recently exposed to drug-drug interaction that would have lowered DTG drug levels significantly, OR • Patient known to have prior InSTI resistance. • DTG monotherapy inadvertently taken.	• Patient is on regimen for > 2 years, OR • Patient recently exposed to drug-drug interaction that would have lowered PI drug levels significantly, OR • Patient known to have prior PI resistance.	• Not routinely required (see text for more information).
Resistance test required	*Integrase* gene (may be possible to do without testing *protease* and *reverse transcriptase* gene, depending on laboratory)	*Protease* gene (almost always done in conjunction with *reverse transcriptase* gene)	*Reverse transcriptase* gene (almost always done in conjunction with *protease* gene)

Management of Confirmed Virological Failure on TLD

(also [illegible]LD and other DTG-containing regimens)

Two or more consecutive **VLs ≥ 1000** c/mL

On **TLD** for **at least 2 years**
and 2 elevated VLs were taken two or more years after starting TLD regimen

Adherence > 80%
Proven by an objective measurement [1]

TLD 2
Clients who have failed a previous ART regimen

TLD 1
Clients who have never failed a previous ART regimen

Adherence < 80% [1]

As a rule, resistance testing is **not indicated** for clients on **TLD1** [2]

Special circumstances[4]
e.g., incorrect classification as TLD1 (including perinatally infected adolescents), or drug interactions

On TLD for **less than** 2 years, irrespective of VL

Repeat VL at next scheduled routine VL (i.e., in 6 months' time)

Intensify efforts to **resolve adherence issues**[3] as outlined on ***"Enhanced Adherence Support" on page 22***

Discuss with an HIV expert [5]
to authorise and interpret a resistance test*

Individualised regimen
as recommended by HIV expert [5]

Repeat VL 3 months after starting the new regimen
to confirm viral re-suppression

Additional considerations if VL > 1000 c/mL:

- Monitor CD4 count every 6 months see ***"Monitoring on ART" on page 19***
- If CD4 < 200 cells/mm3, discuss with an HIV expert
- Consider eligibility for cotrimoxazole prophylaxis see ***"Indications for Starting and Stopping Cotrimoxazole Preventive Therapy" on page 8***

! ***Resistance testing** is expensive and should be done only for exceptional cases failing TLD1. Provinces should ensure that a gatekeeping function is in place by using either a designated provincial mechanism, the National TL committee, or one of the HIV ***"Helplines" on page 23*** to authorise resistance testing.

Current Guidelines

	NNRTI-based Regimen		PI-based Regimen for > 2 years			InSTI-based Regimen for > 2 years	
Regimen	**ABC/AZT/TDF** + 3TC/FTC + **EFV/NVP**		**ABC/AZT/TDF** + 3TC/FTC + **LPV/r or ATV/r**			**ABC/AZT/TDF** + 3TC/FTC + **DTG**	
Resistance Testing	**Resistance test not required**		**Resistance test required**			**Resistance test required**	
Resistance Test Results	Not applicable		**No PI resistance**		**PI resistance** (or genotype unsuccessful)	**No InSTI resistance**	**InSTI resistance**
Weight	**< 20 kg**	**≥ 20 kg**	**< 20 kg**	**≥ 20 kg**	**All**	**All children/adolescents on DTG will be ≥ 20 kg**	
New Regimen or Other Action Required	**ABC/AZT + 3TC + LPV/r** [3]	**2 NRTIs + DTG**[2] In consultation with an expert, ensure that at least 1 NRTI is active[5, 6] If NRTI activity cannot be confirmed, expert will recommend **2 NRTIs + PI/r**	Continue current regimen and address adherence	**2 NRTIs + DTG**[2] In consultation with an expert, ensure that at least 1 NRTI is active[5] If NRTI activity cannot be confirmed, expert will recommend **2 NRTIs + PI/r.** Adherence must be addressed	Refer to Third- line committee	**2 NRTIs + DTG**[2] In consultation with an expert, ensure that at least 1 NRTI is active[5] If NRTI activity cannot be confirmed, refer to Third-line committee	Refer to Third-line committee

Drug Regimens - Rationale

1. If DRV fully susceptible (i.e. Stanford <10): Tenofovir/lamivudine/Dolutegravir (TLD)
2. If DRV score 10-59: Tenofovir/lamivudine/Dolutegravir + Darunavir/r 600mg/100mg bd (TLD+DRV/R)
3. If DRV score 60 or above: Individualised regimen

Drug Options

- Boosted Darunavir (DRV): A preferred option for HTE patients due to its high genetic barrier to resistance.
- Integrase Strand Inhibitors (INSTIs): Such as Dolutegravir (DTG), which has shown efficacy in heavily treatment-experienced populations.
- Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) Etravirine
- Other ARVs: Options may include Maraviroc, and Enfuvirtide, depending on individual resistance profiles and treatment history.

Bictegravir and Elvitegrivir

Doravirine

Lenacapavir and Ibalizumab

LEN Overview (*In Vitro*)

Low-dose long-acting ARV

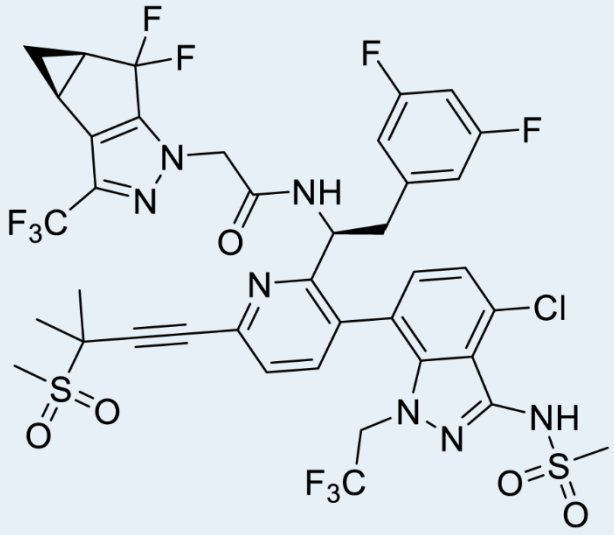
- Picomolar antiviral potency (≥ 10 × more potent than current ARVs)[1]
- Low predicted clearance (< 1% of hepatic blood flow)[2]
- Low aqueous solubility (< 1 µM at pH 2–7)[2]

Sustained exposure in preclinical[2] and clinical[3] studies

- No dose adjustment in mild, moderate, or severe renal impairment or mild to mode hepatic impairment[8,9,10,11]

Desirable *in vitro* resistance profile

- Active against a broad range of HIV-1 isolates[4,5]
- A unique *in vitro* resistance profile relative to existing ARVs[5]
- High potency demonstrated with picomolar activity against clinical isolates with Gag polymorphisms and protease mutations[6]
- No mutations associated with *in vitro* resistance to LEN in treatment-naïve and treatment-experienced PWH (N = 1,500)[7]

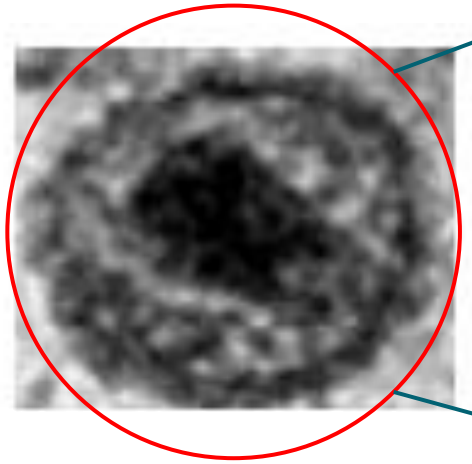


LEN Structure

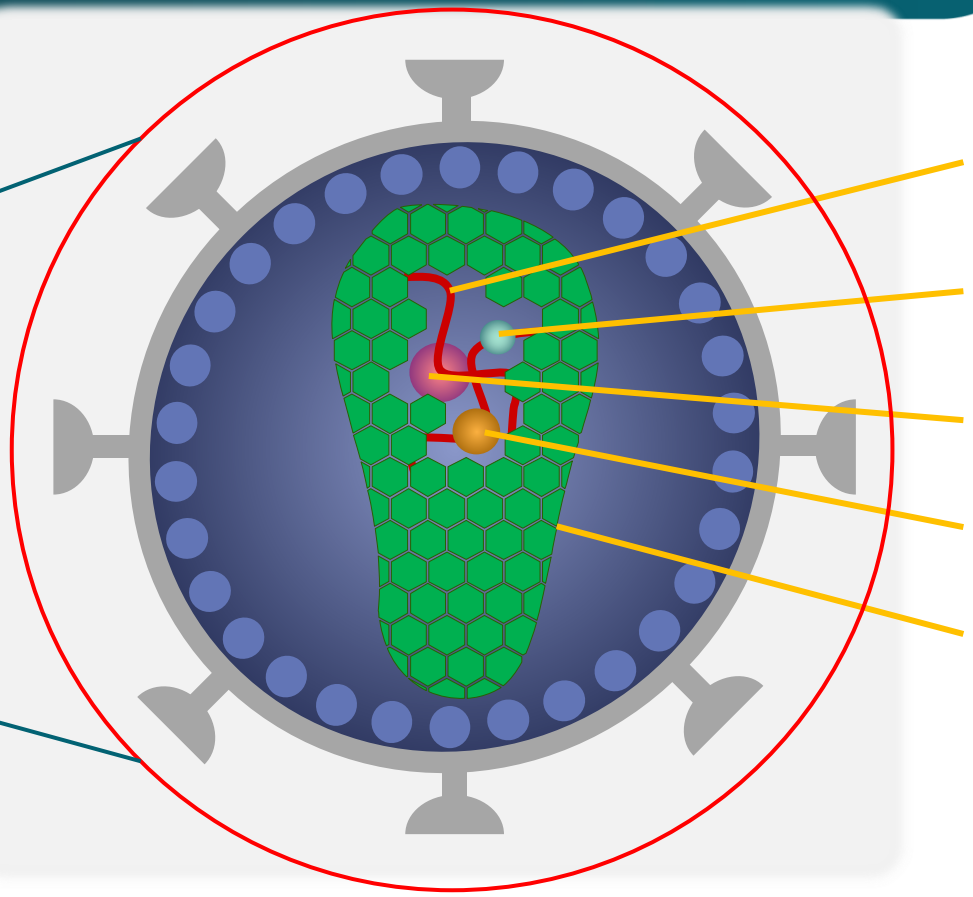
*Panel of 23 HIV clinical isolates in human peripheral blood mononuclear cells

1. Dvory-Sobol H, et al. Curr Opin HIV AIDS 2022,17:15-21; 2. Zheng J, et al. LEAP 2019, Oral; 3. Begley R, et al. AIDS 2020, Poster PEB0265; 4. Yant SR, et al. CROI 2019, Poster 480; 5. Link J, et al. Nature 2020;584:614-618; 6. Margot N, et al. EACS 2019, Poster PE13/22; 7. Marcelin AG, et al. EACS 2019, Poster PE13/15 8. Weber EJ, et al. CROI 2022, Poster 434 9. Jogiraju V, et al. vCROI 2021, Poster 375 10. SUNLENCA. Prescribing Information. Gilead Sciences, Inc.; 2022. Available at https://www.sunlenca.com/. 11. SUNLENCA Summary of Product Characteristics. Gilead Sciences Ireland UC. 25/08/2022. Available at

HIV Capsid Structure



Electron micrograph of HIV[1]



The capsid protects essential components of the virus and is thus important for viral survival[1,2]

1. Link J, et al. Nature 2020;584:614-618; 2. Yant SR, et al. CROI 2019, Oral/Poster 1504

Capsid Is Critical at Multiple Stages of HIV Replication Cycle

The HIV capsid is transported intact along microtubules to the site of nuclear import

▼

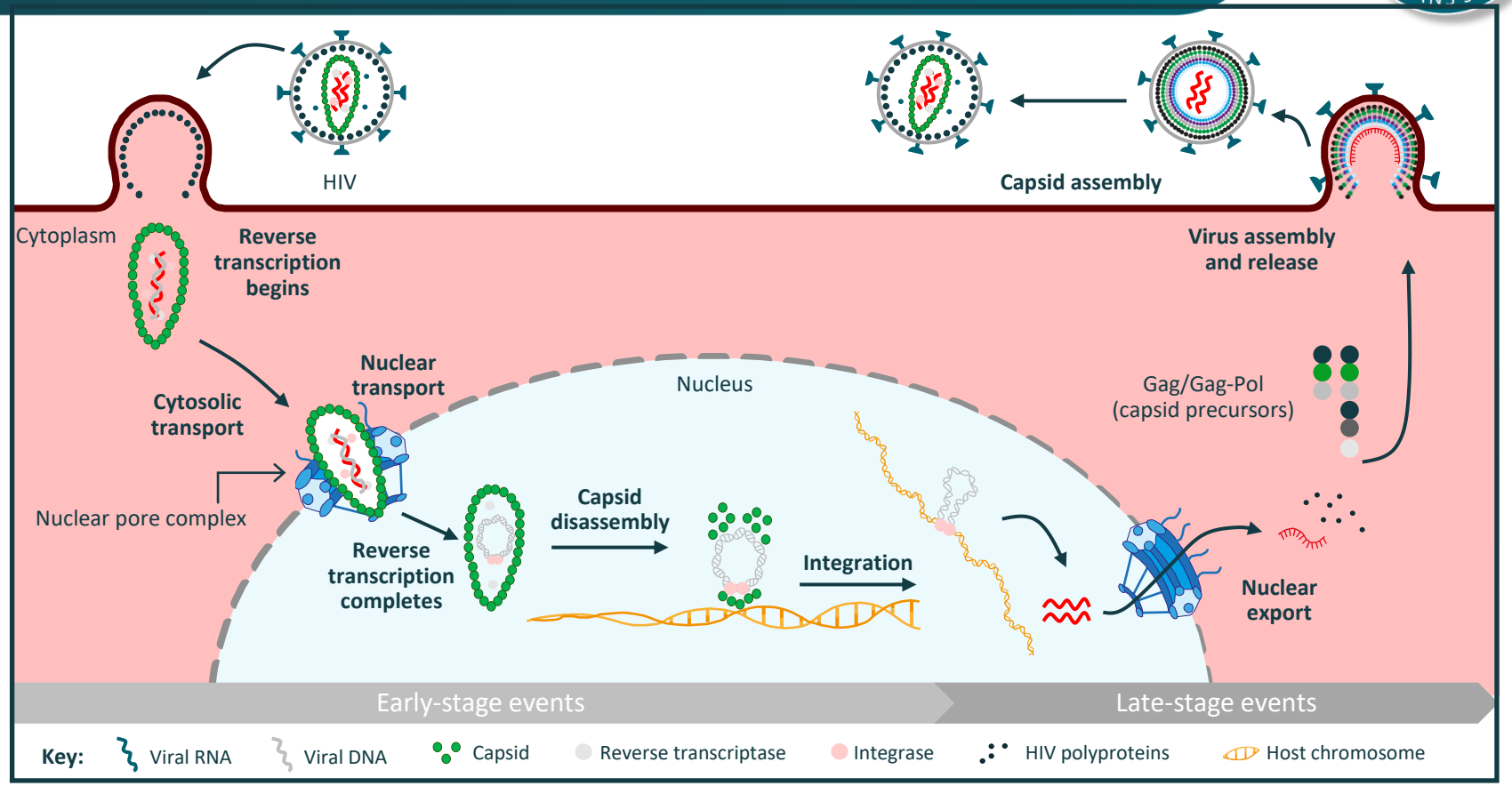
The capsid passes through the nuclear pore intact

▼

Reverse transcription is completed within an intact capsid in the nucleus

▼

The capsid disassembles prior to, and near the site of, integration



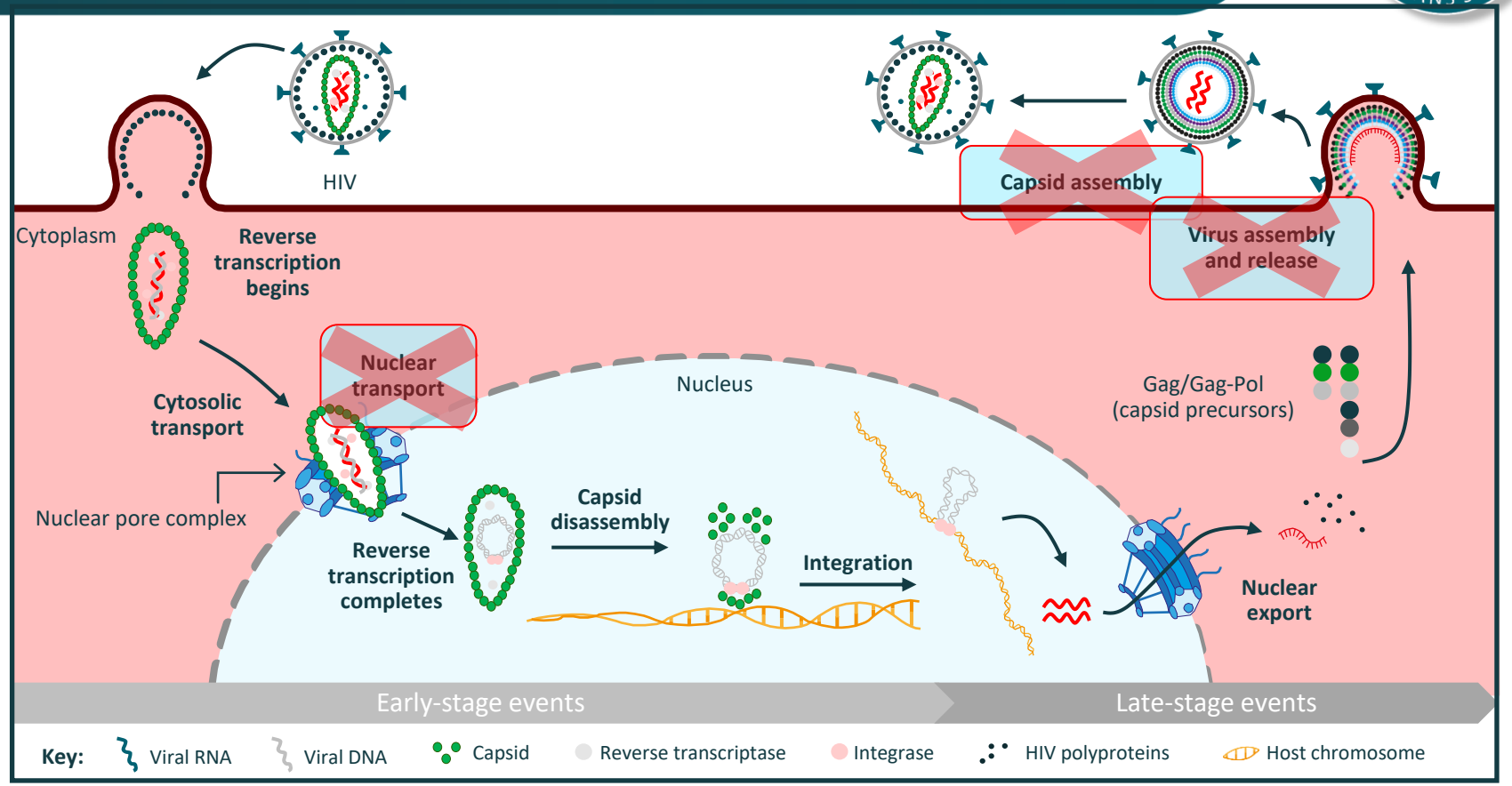
Capsid plays an important role in the HIV lifecycle

Figure developed based on the following references: Link J, et al. Nature 2020;584:614-618; Bester SM, et al. Science 2020;370:360-364; Cihlar T, et al. vCROI 2021, Oral 22; Muller B, et al. vCROI 2021, Oral 19; Pathak VK, et al. vCROI 2021, Oral 20; Ganser-Pornillos B, et al. vCROI 2021, Oral 21

LEN Targets Multiple Stages of the HIV Replication Cycle

LEN
EC_{50}: 50 – 100 pM

Interrupts
multiple distinct stages
of the viral lifecycle



LEN binds directly between capsid protein subunits, modulating the stability and/or transport of capsid complexes, leading to inhibition of essential steps of the viral lifecycle

Figure developed based on the following references: Link J, et al. Nature 2020;584:614-618; Bester SM, et al. Science 2020;370:360-364; Cihlar T, et al. vCROI 2021, Oral 22; Muller B, et al. vCROI 2021, Oral 19; Pathak VK, et al. vCROI 2021, Oral 20; Ganser-Pornillos B, et al. vCROI 2021, Oral 21. EC_{50}, 50% effective concentration of half maximal response

Study Design

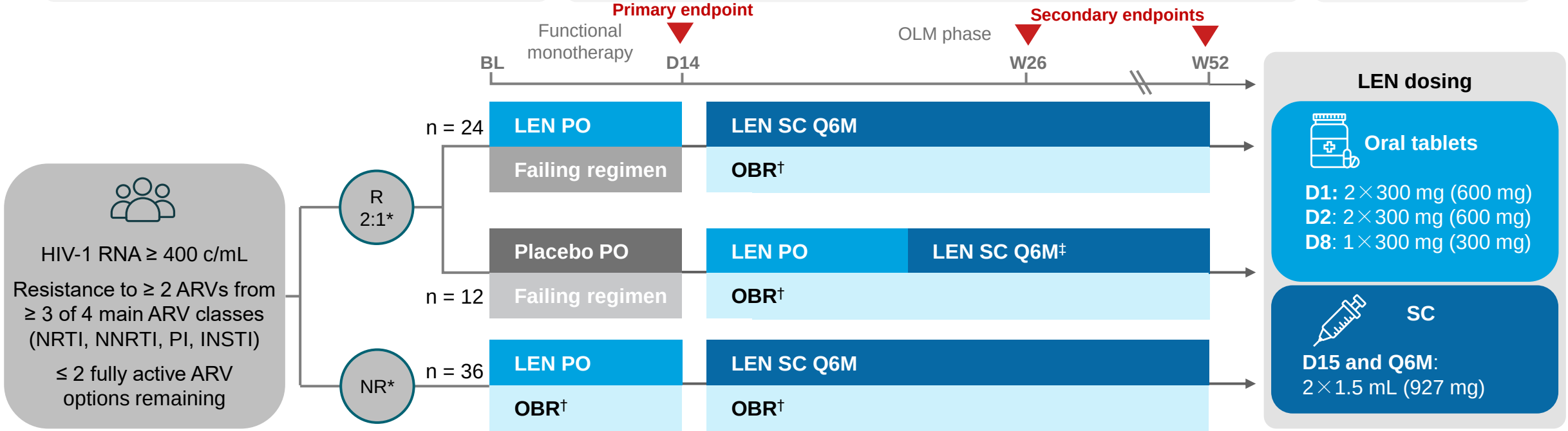
N = 72

HTE PWH with MDR, aged ≥ 12 years and weighing ≥ 35 kg

Outcomes (randomized cohort)

Primary: ≥ 0.5 $\log_{10}$ c/mL reduction in HIV-1 RNA from BL at D15
Secondary: HIV-1 RNA < 50 c/mL and < 200 c/mL at W26 and W52 (FDA Snapshot)

2019–present (ongoing)



*Participants with < 0.5 $\log_{10}$ c/mL decline in HIV-1 RNA during screening entered the randomized cohort; participants with ≥ 0.5 $\log_{10}$ c/mL decline in HIV-1 RNA during screening entered the nonrandomized cohort; †Investigational agents (e.g., FTR) permitted; ATV, ATV/c, ATV/r, EFV, ETR, NVP, TPV not permitted
BL, baseline; D, day; FDA, U.S. Food and Drug Administration; HTE, heavily treatment-experienced; MDR, multidrug resistance; NR, nonrandomized; OBR, optimized background regimen; OLM, open-label

Baseline Characteristics

Characteristic	Randomized		Nonrandomized	Total
	LEN n = 24	Placebo n = 12	LEN n = 36	N = 72
Age, years, median (range)	55 (24–71)	54 (27–59)	49 (23–78)	52 (23–78)
Female at birth, %	29	25	22	25
Black race, %	42	55	31	38
Hispanic/Latinx %	25	36	14	21
HIV-1 RNA, log_{10} c/mL, median (range)	4.2 (2.3–5.4)	4.9 (4.3–5.3)	4.5 (1.3–5.7)	4.5 (1.3–5.7)
HIV-1 RNA > 75,000 c/mL, %	17	50	28	28
CD4 count, cells/µL, median (range)	172 (16–827)	85 (6–237)	195 (3–1,296)	150 (3–1,296)
CD4 count ≤ 200 cells/µL, %	67	92	53	64
Years since HIV diagnosis, median (range)	27 (13–39)	26 (14–35)	23 (9–44)	24 (9–44)
Number of prior ARV agents, median (range)	9 (2–24)	9 (3–22)	13 (3–25)	11 (2–25)
Number of ARV agents in failing regimen, median (range)	3 (1–7)	3 (2–6)	4 (2–7)	3 (1–7)
Known resistance to ≥ 2 drugs in class, %				
NRTI	96	100	100	99
NNRTI	92	100	100	97
PI	83	67	83	81
INSTI	83	58	64	69

HTE, heavily treatment-experienced

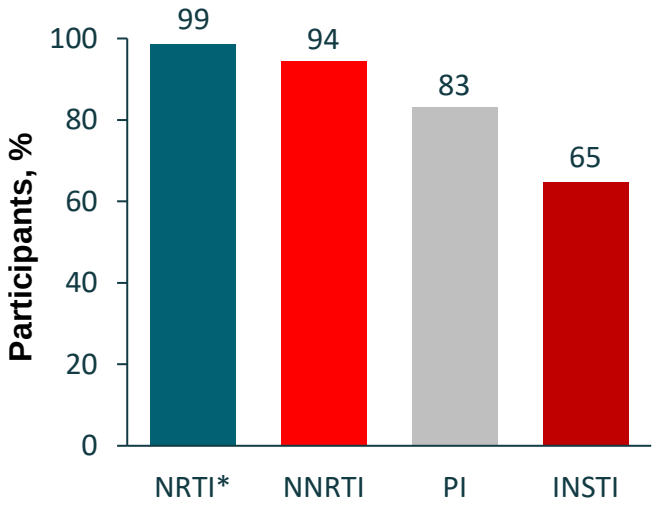
1. Segal-Maurer S, et al. vCROI 2021, Oral 127; 2. Molina JM, et al. vIAS 2021, Oral OALX01LB02; 3. Segal-Maurer S, et al. N Engl J Med 2022;386:1793-803

Baseline Resistance-Associated Mutations

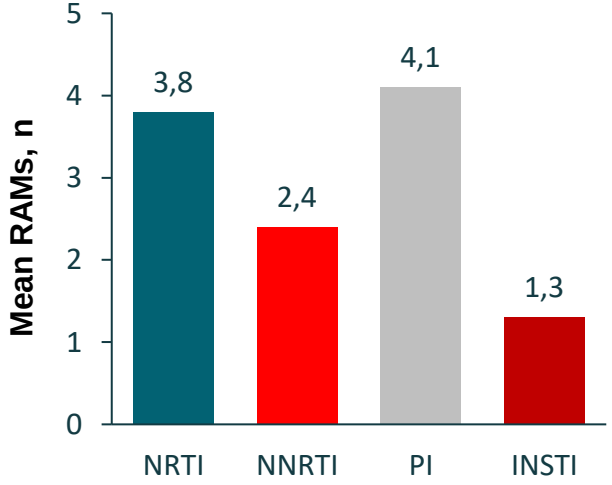
Entry criteria: Resistance to ≥ 2 ARVs in ≥ 3 of 4 main ARV classes; N = 72

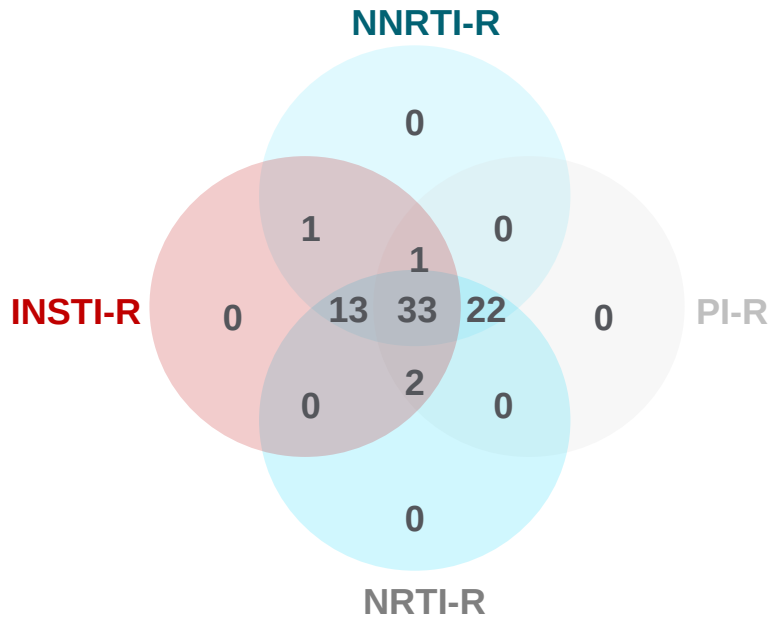
No LEN resistance mutations were detected at baseline

% RAMs per ARV Class



Number of RAMs per ARV Class





- **46%** of participants with 4-class resistance
- **53%** of participants with 3-class resistance
- **1%** of participants with 2-class resistance

**M184V/I* alone was not sufficient to fulfill the NRTI resistance criteria in the study. Number of RAMs tallied: NRTI = 16; NNRTI = 14; PI = 15; INSTI = 10
HTE, heavily treatment-experienced; R, resistance
Margot N, et al. EACS 2021, Oral OS1/1

Composition of the Failing Regimen and OBR

	Randomized cohort n = 36		Total N = 72	
	Failing regimen	OBR	Failing regimen	OBR
Class/Agent, %				
NRTI	83	89	82	85
INSTI	69	69	68	65
PI	56	58	63	63
NNRTI	25	28	31	33
IBA (CD4-directed, post-attachment inhibitor)	11	33	18	24
MVC (CCR5 entry inhibitor)	11	17	14	14
FTR (attachment inhibitor)	6	8	6	11
Enfuvirtide (fusion inhibitor)	6	8	6	7
No. of fully active ARV agents, %				
0	53	17	42	17
1	31	39	36	38
≥ 2	17	44	22	46
Overall susceptibility score, median*	0.8	1.8	1.0	2.0

No changes in OBR in

22% (16/72)
of participants in the total cohort

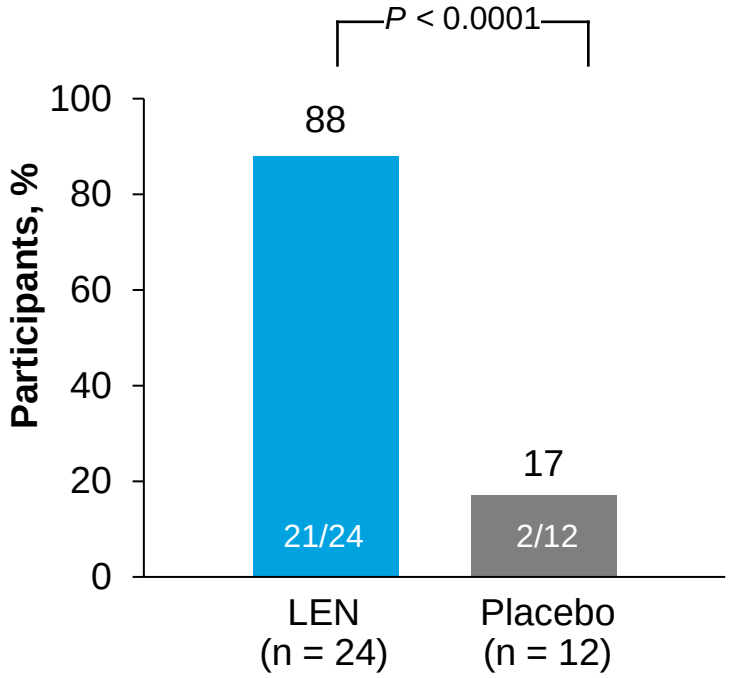
and

33% (12/36)
of participants in the randomized cohort

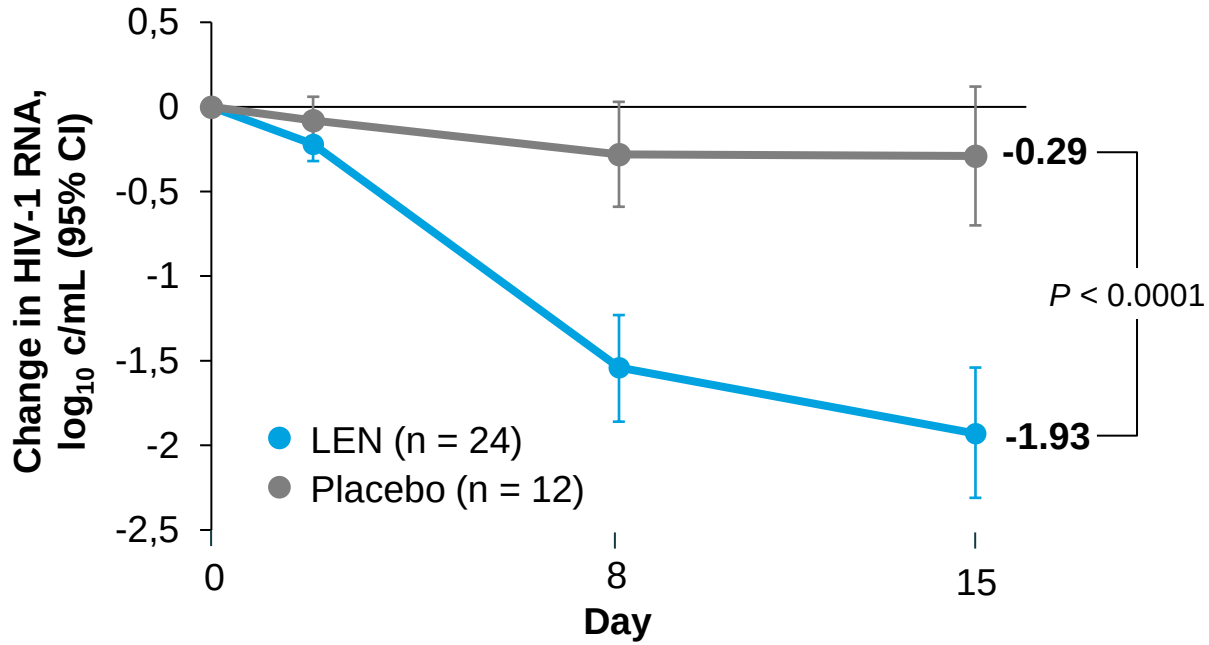
*Overall susceptibility scores (1, 0.5 or 0 for full, partial or no susceptibility, respectively) were determined based on a proprietary algorithm. For historical resistance reports, they were derived from data provided by investigators. The overall susceptibility score of the OBR was the sum of the individual scores. CCR5, C-C chemokine receptor 5; HTE, heavily treatment-experienced; OBR, optimized background regimen

Antiviral Activity During Functional Monotherapy: Randomized Cohort

Primary Endpoint:
% Achieving HIV-1 RNA Decline ≥ 0.5 log_{10} c/mL



Mean Change in HIV-1 RNA by Visit (95% CI)

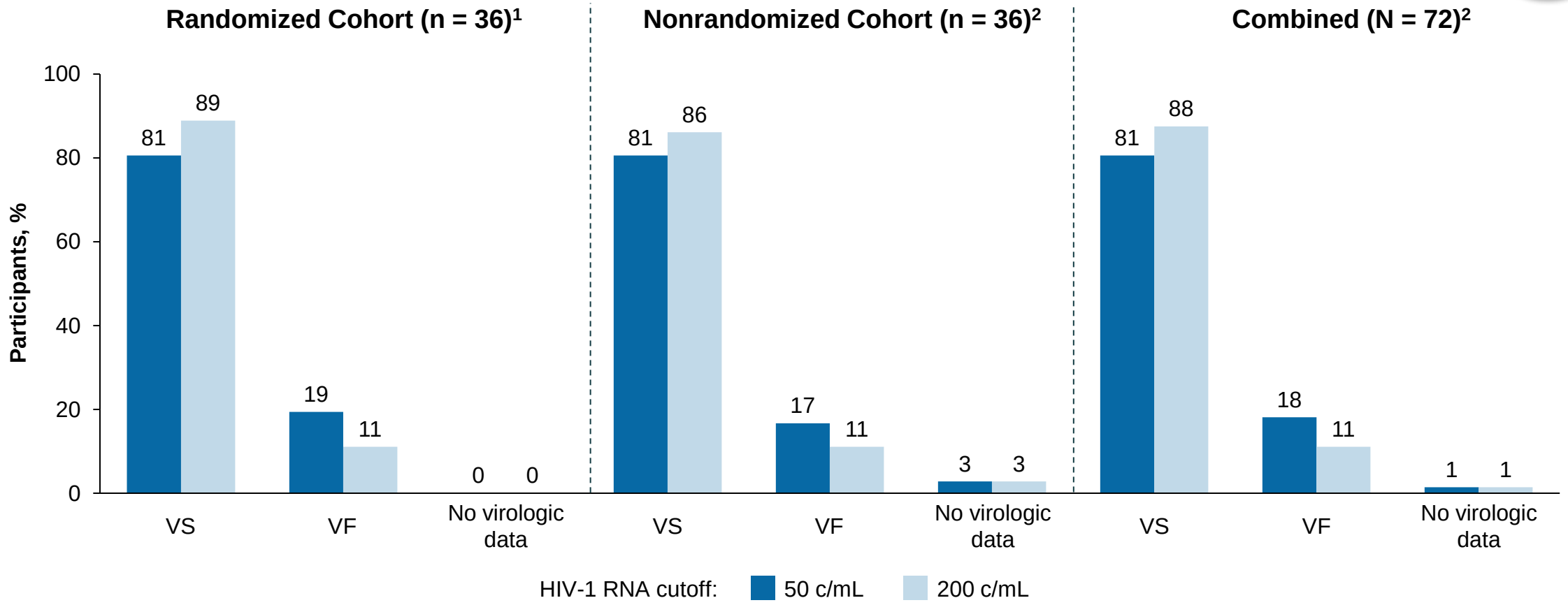


LEN showed potent antiviral activity when added to a failing regimen

HTE, heavily treatment-experienced

1. Segal-Maurer S, et al. vCROI 2021, Oral 127; 2. Segal-Maurer S, et al. N Engl J Med 2022;386:1793-803

Efficacy at Week 26: Randomized and Nonrandomized Cohorts

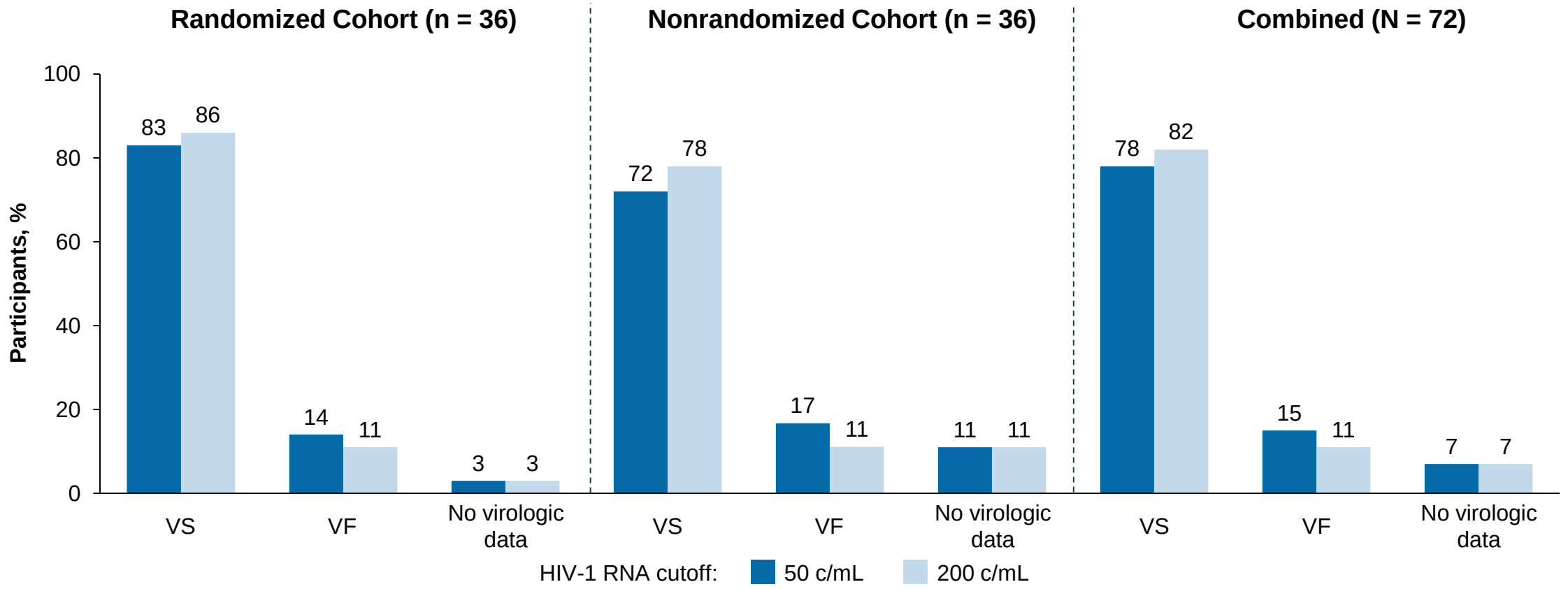


LEN in combination with OBR achieved high rates of viral suppression at Week 26 in HTE PWH

HTE, heavily treatment-experienced; OBR, optimized background regimen; VF, virologic failure; VS, viral suppression

1. Molina JM, et al. vIAS 2021, Oral OALX01LB02; 2. Ogbuagu O, et al. CROI 2022, Poster 491; 3. Segal-Maurer S, et al. N Engl J Med 2022;386:1793-803

Efficacy at Week 52: Randomized and Nonrandomized Cohorts*



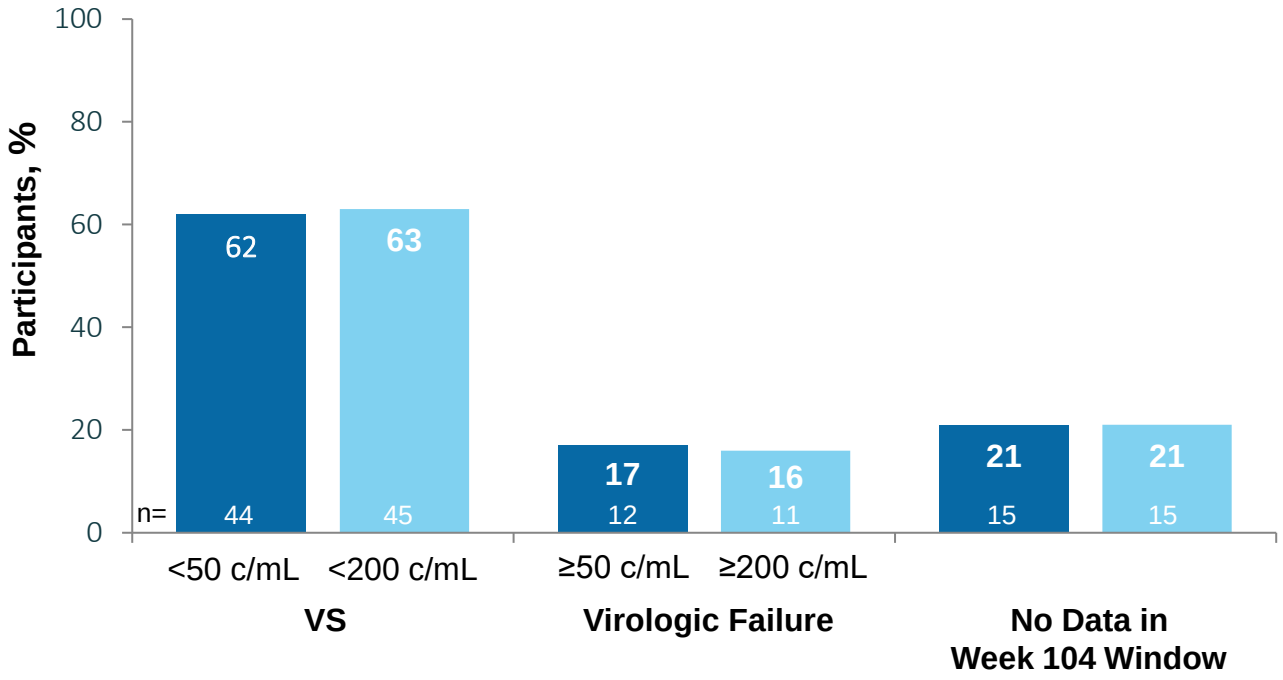
LEN in combination with an OBR maintained high rates of virologic suppression at Week 52 in both cohorts

*Due to the clinical hold on SC LEN by the FDA during the study, by Week 52, 17 participants took ≥ 1 dose of oral LEN bridging (300 mg QW)
HTE, heavily treatment-experienced; OBR, optimized background regimen; VF, virologic failure; VS, viral suppression
Ogbuagu O et al. Lancet 2023; 10(8): E497-E505

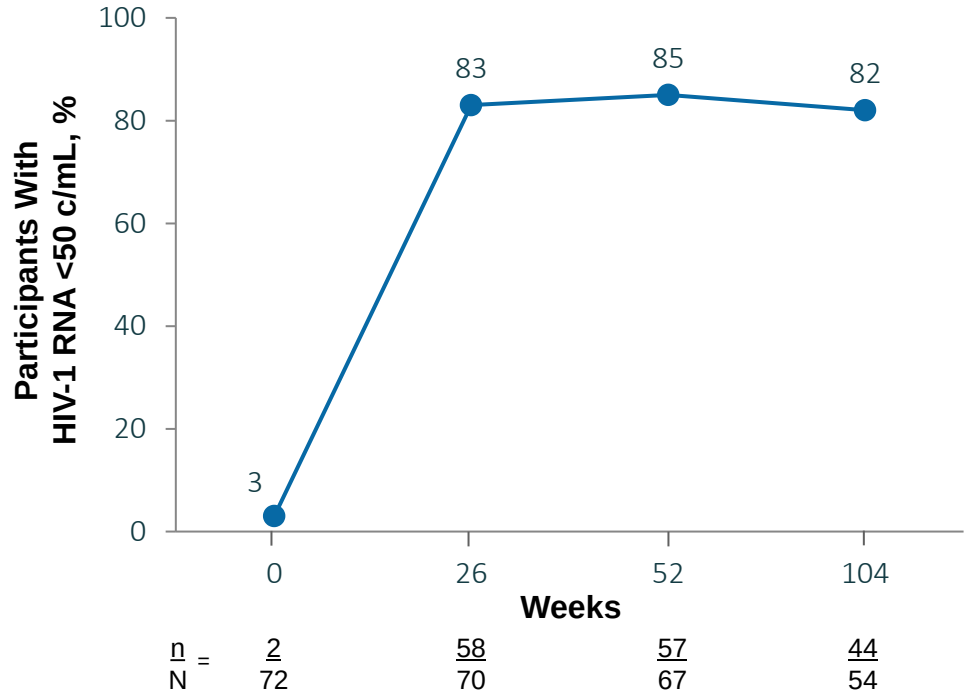
- Phase 2/3: LEN in HTE PWH

Efficacy at Week 104 (Randomized and Non-Randomized Cohorts)

Viral Load: FDA Snapshot Analysis at Week 104*



HIV-1 RNA <50 c/mL by M=E From Baseline to Week 104†



CAPELLA participants continued to maintain high rates of VS (82% by M=E analysis at Week 104)

*The Week 104 window is Day 688 to Day 778 (inclusive); participants who had missing HIV-1 RNA at Week 104 and had completed the study before reaching the upper limit of the analysis window for Week 104 were excluded (n=1); †The denominator for percentages is the number of participants with non-missing HIV-1 RNA values at each timepoint.
HTE, heavily treatment-experienced; M=E, missing=excluded; VS, virologic suppression
Ogbuagu O, et al. IDWeek 2023. Poster 1596

- CAPELLA: Phase 2/3 trial

Efficacy of LEN in HTE PWH With No Fully Active Agents in OBR[1]

N=12

HTE PWH with MDR virus, treated with SC LEN and an OBR that had no fully active ARVs

Outcomes

VS (HIV-1 RNA <50 c/mL; FDA Snapshot algorithm); change from baseline in HIV-1 RNA and CD4 cell count; emergent resistance-associated mutations up to Week 104

2019–ongoing[2]

VS by FDA Snapshot Algorithm

Participants with emergent LEN resistance

HIV-1 RNA ≥50 c/mL

HIV-1 RNA <50 c/mL

No virologic data in the FDA Snapshot window

Participant	Baseline CD4 cell count, cells/µL	HIV-1 RNA, c/mL			
		Baseline	Week 26	Week 52	Week 104
1[a]	**3**	**85,100**	**<50**	**<50**	**<50**
4	**50**	**38,300**	**2420**	**2970**	**1880**
10	**249**	**43,900**	**200**	**<50**	**<50**
2[b]	33	75,200	342	574	–
3	176	14,500	<50	<50	<50
5	189	14,000	<50	<50	<50
6	84	1900	<50	<50	<50
7[c]	518	<50	<50	<50	<50
8	159	39,400	<50	<50	<50
9[d]	192	91	<50	<50	<50
11[e]	137	69,500	<50	<50	–
12	313	78,800	<50	<50	<50

9/12 (75%) participants with no fully active ARVs in OBR **were suppressed at Week 104**

- **Nearly half** of these had an ARV with partial activity

3 participants developed emergent LEN resistance[f]:

- **2 had VS at Week 104** and both had a change in OBR (one at Week 21 and one at Week 25)

Mean (95% CI) increase in CD4 cell count from baseline to Week 104:
105 (-10, 220) cells/µL

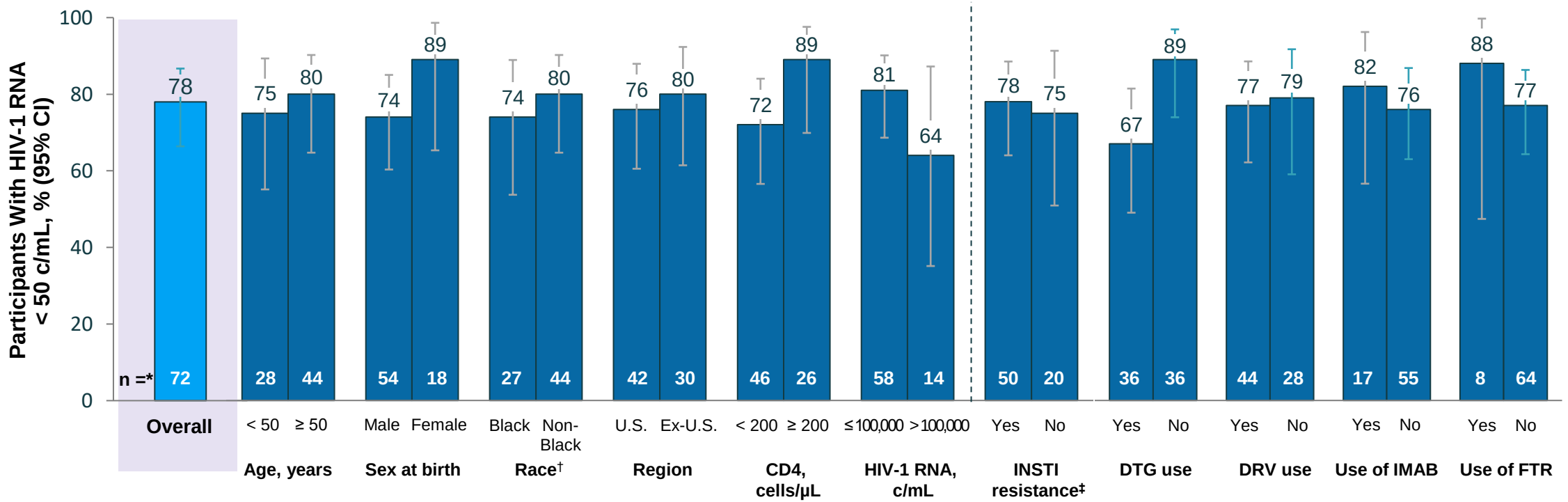
A subset of participants in CAPELLA received LEN with no fully active ARVs in their OBR, and most achieved VS; however, for optimal clinical outcomes, monotherapy with LEN should be avoided

[a]Developed resistance at Week 10 and resuppressed at Week 26; [b]Not suppressed with low-level viremia; [c]HIV-1 RNA at screening was 687 c/mL; [d]HIV-1 RNA at screening was 4800 c/mL; [e]Suppressed at Weeks 26 and 52, but missing virologic data in the Week 104 window and was suppressed at a later visit (Week 114); [f]LEN-resistance emergence was associated with LEN functional monotherapy (no fully active agent in OBR). HTE, heavily treatment-experienced; MDR, multidrug-resistant; OBR, optimized background regimen; VS, virologic suppression

1. Ogbuagu O, et al. CROI 2024, Poster 630; 2. NCT04150068. https://clinicaltrials.gov/study/NCT04150068 (accessed March 23, 2024)

Post Hoc Subgroup Analysis at Week 52 of HIV-1 RNA < 50 c/mL
Randomized and Nonrandomized Cohorts

Efficacy by Baseline Demographics and Characteristics | **Efficacy by ARVs in OBR**



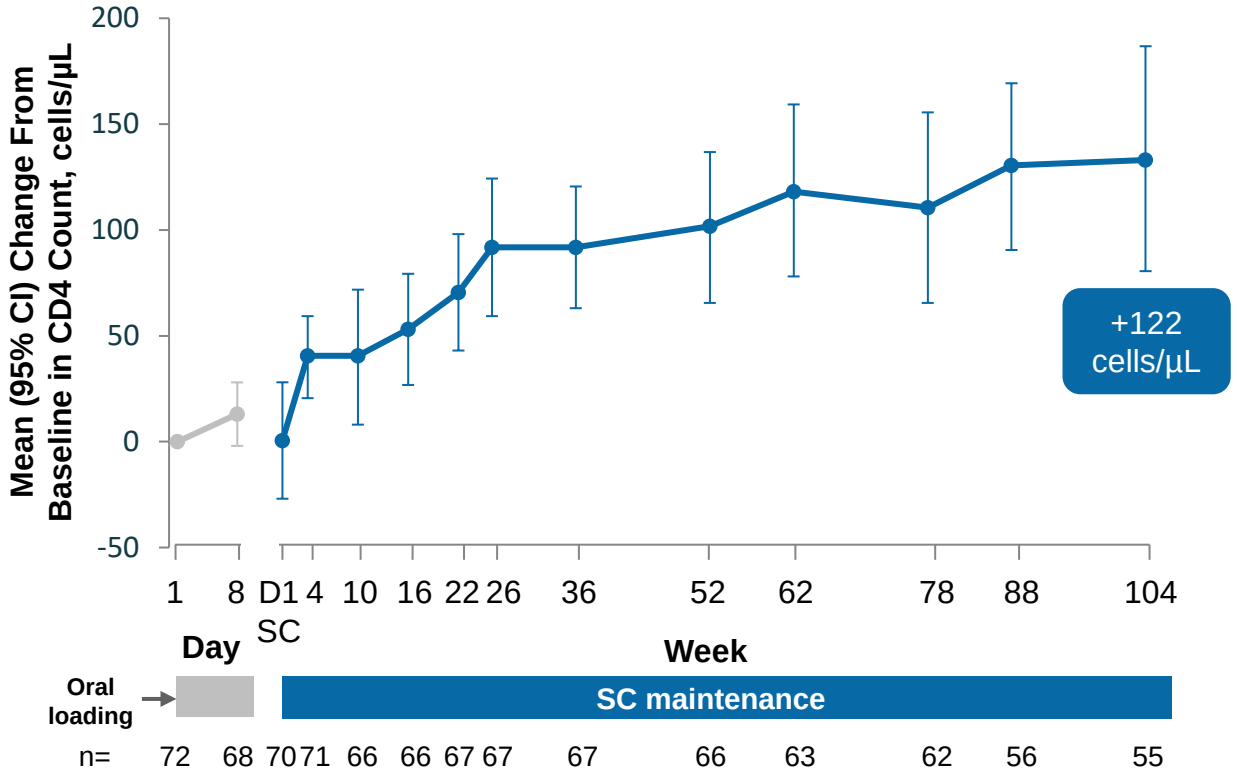
The efficacy of LEN in combination with an OBR was consistent across diverse subgroups

*Total n in each subgroup; †Reported as "not permitted" for one participant; ‡Included phenotypic and genotypic resistance to bictegravir, cabotegravir, dolutegravir, elvitegravir and raltegravir; data missing for two participants. FTR, fostemsavir; HTE, heavily treatment-experienced; IMAB, ibalizumab; OBR, optimized background regimen

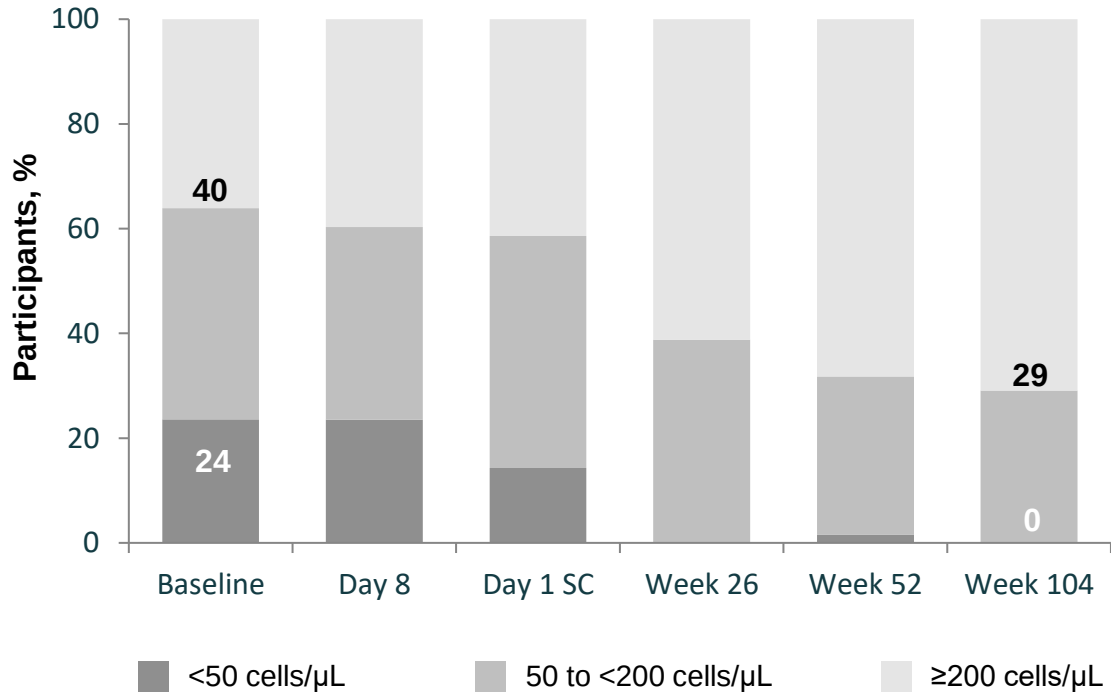
Ogbuagu O, et al. CROI 2023, Poster 523

Changes in CD4 at Week 104: Randomized and Nonrandomized Cohort

Change From Baseline in CD4 Cell Count



CD4 Cell Count Change By Category



Consistent with earlier analyses, clinically meaningful increases in CD4 cell count were achieved after starting LEN and maintained through Week 104, with a majority achieving CD4 counts ≥200 cells/µL

D, Day; HTE, heavily treatment-experienced

Ogbuagu O, et al. IDWeek 2023, Poster 1596

LEN Resistance Mutations in HTE PWH Through Week 104

N=27

HTE PWH with MDR* HIV and HIV-1 RNA ≥400 c/mL who experienced virologic failure† in the CAPELLA study (resistance analysis population)

Outcomes

LEN RAMs; resuppression; virologic failure by OBR non-adherence and inactivity

LEN RAMs at Week 104

Status, n (%)	Participants (N=72)
Resistance analysis population	27 (38)
Developed LEN RAM (Week 104)	**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	3 (4)
No LEN RAM emergence	13 (18)

- In the resistance analysis population, 14/27 (52%) participants developed LEN RAMs through Week 104
- Of these 14 participants, 7 (50%) achieved VS while continuing LEN treatment
- Emergence of LEN RAMs occurred in the setting of inadequate OBR adherence or with OBR lacking fully active ARVs
- Some participants with LEN resistance resuppressed upon resumption of OBR or with OBR change while continuing LEN

All 14 cases of LEN-emergent resistance occurred in the setting of inadequate adherence to OBR or absence of fully active ARVs in the OBR

*Resistance to ≥2 agents from 3/4 main ARV classes, ≤2 fully active agents from 4 main ARV classes; †Defined as rebound ≥50 c/mL or <1 $\log_{10}$ decline from baseline at Week 4
HTE, heavily treatment-experienced; MDR, multidrug-resistant; OBR, optimized background regimen; VS, virologic suppression
Margot N, et al. EACS 2023, Oral PS8 O4

Summary of Participants With Emergent LEN Resistance through Week 104

Participant	Visit with LEN resistance	LEN RAMs	LEN fold change	Outcome after resistance	Reason for LEN resistance
3	Week 4	M66I, K70S	NA	Resuppressed	Non-adherence to OBR (≥1 fully active agent)*
10	Week 4	Q67H, K70R	14.8	Did not resuppress	
5	Week 52	Q67H	6.6	Resuppressed	
6	Week 52	M66I, N74D, A105T	>869	Did not resuppress	
4	Week 72	N74D	NA	Resuppressed	
2	Week 78	K70N, N74K	289	Resuppressed	
9	Week 78	Q67H, K70R, T107N	393	Did not resuppress	
1	Week 88	Q67H	4.5	Resuppressed	
7	Week 88	Q67H, K70R, A105T	105	Did not resuppress	
8	Week 88	Q67K, K70H	342	Did not resuppress	
14	Week 4	M66I, Q67H, K70R, T107C	12.2	Did not resuppress	Suboptimal OBR (no fully active ARVs in OBR)
11	Week 10	M66I, Q67H, N74D, A105T	>869	Resuppressed†	
12	Week 10	M66I, T107A	234	Resuppressed†	
13	Week 52	M66I, A105T	111	Did not resuppress	

All cases of emergent LEN resistance occurred in the setting of inadequate adherence to OBR or absence of fully active ARVs in the OBR

*Adherence based on drug plasma concentrations of OBR; †Change to OBR
HTE, heavily treatment-experienced; NA, not available; OBR, optimized background regimen
Margot N, et al. EACS 2023, Oral PS8 O4

Grade 3 or 4 Laboratory Abnormalities through Week 52

Laboratory abnormality, n (%)	N = 72
Any Grade 3 or 4 laboratory abnormality	23 (32)
Low creatinine clearance (eGFR)*	12 (16.7)
Elevated creatinine†	9 (12.5)
Glycosuria	4 (5.6)
Nonfasting/fasting hyperglycemia	3 (4.1)

- None of the Grade 3 or 4 laboratory abnormalities were clinically relevant[2]
- Low creatinine clearance/eGFR and/or high creatinine were transient or unconfirmed abnormalities
- Hyperglycemia/glycosuria were transient, unconfirmed or related to underlying diabetes

There were no clinically relevant laboratory abnormalities related to LEN in HTE PWH

*Per DAIDS scale, Grade 3 creatinine clearance is < 60–30 mL/min or 30–< 50% decrease from baseline; †Grade 3 creatinine elevation is > 1.8–< 3.5 × upper limit of normal or increase to 1.5–< 2.0 × baseline. DAIDS, The Division of AIDS; HTE, heavily treatment-experienced

1. Ogbuagu O et al. Lancet 2023; 10(8): E497-E505 2. Ogbuagu O, et al. CROI 2022, Poster 491

Safety Profile of LEN Through Week 104

Safety Summary

TEAEs, n (%)	Total (N=72)
Most common TEAEs (occurring in ≥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)
TEAEs	71 (98.6)
Grade ≥3	24 (33.3)
TRAEs	57 (79.2)
Grade 3	6 (8.3)*
Serious TEAEs	15 (20.8)
TRAEs leading to premature study drug discontinuation	1 (1.4)†
All deaths	3 (4.2)§

- Median (IQR) duration of follow-up on LEN was 125 (111–140) weeks
- No serious TRAEs or Grade ≥4 TRAEs were reported
- There were three deaths during the study:
  - Two previously reported (malignant neoplasm, acute respiratory failure)[1,2]
  - One due to unknown cause[1] (occurred after Week 52[3])

The safety profile of LEN was consistent with findings from earlier timepoints; no participants discontinued LEN due to TEAEs after Week 52, and no participants experienced a serious TRAE

*ISR, n=4; immune reconstitution inflammatory syndrome, n=1; abdominal abscess, n=1; rash, n=1; †Due to Grade 1 injection-site nodule (prior to Week 52); §Due to: malignant neoplasm, n=1; acute respiratory failure, n=1; unknown cause, n=1

HTE, heavily treatment-experienced; ISR, injection-site reaction; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event

1. Ogbuagu O, et al. IDWeek 2023. Poster 1596; 2. Ogbuagu O, et al. Lancet 2023;10:E497-E505; 3. Data on file, Gilead Sciences, Inc.

Acknowledgements

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- Thank you