Resistance Analysis of Long-Acting Lenacapavir in Highly Treatment-Experienced People with HIV after 26 Weeks of Treatment

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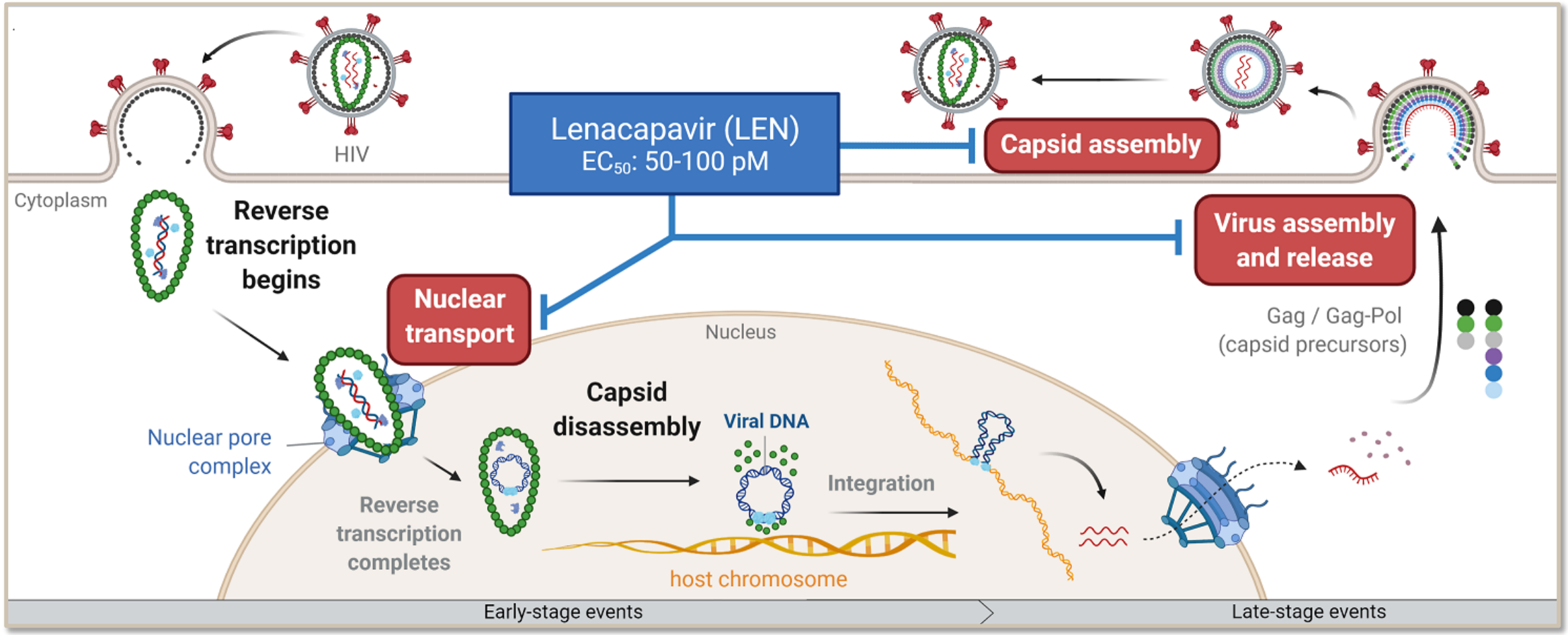
Disclosures

- Nicolas Margot is an employee of Gilead Sciences, Inc.

Lenacapavir targets multiple stages of HIV replication cycle

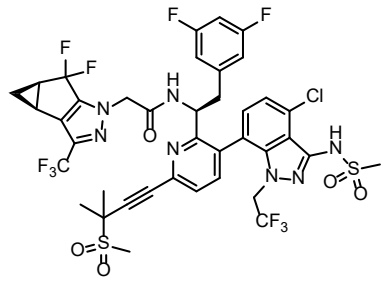


EC_{50}, half-maximal effective concentration.

Link JO, et al. Nature 2020;584:614-8; Zila V, et al. Cell 2021;184:1032-46.

LEN: Long-Acting Inhibitor of HIV-1 Capsid

- Fully active against HIV with resistance to existing drug classes[1-3]
  - NRTI, NNRTI, INSTI, PI
- PK of SC LEN supports its use once every 6 months[4]
- Potent antiviral activity in PWH
  - In **Phase 1** proof-of-concept study:
    - Up to 2.3 $\log_{10}$ HIV-1 RNA decline after 9 days of a single-dose monotherapy[5]
  - In **Phase 2** study in treatment-naïve PWH (CALIBRATE)
    - High rates of viral suppression (94%) at Week 28 when given SC or PO in combination with F/TAF [6]
  - In **Phase 2/3** study in viremic, heavily treatment-experienced PWH with MDR (CAPELLA)
    - High rates of viral suppression (81%) at Week 26 in combination with an optimized background regimen [7,8]



Lenacapavir

INSTI, integrase strand-transfer inhibitor; MDR: multidrug resistance; NRTI, nucleos(t)ide reverse transcriptase inhibitor; PI, protease inhibitor; PK: pharmacokinetics; PWH, people with HIV; SC, subcutaneous.

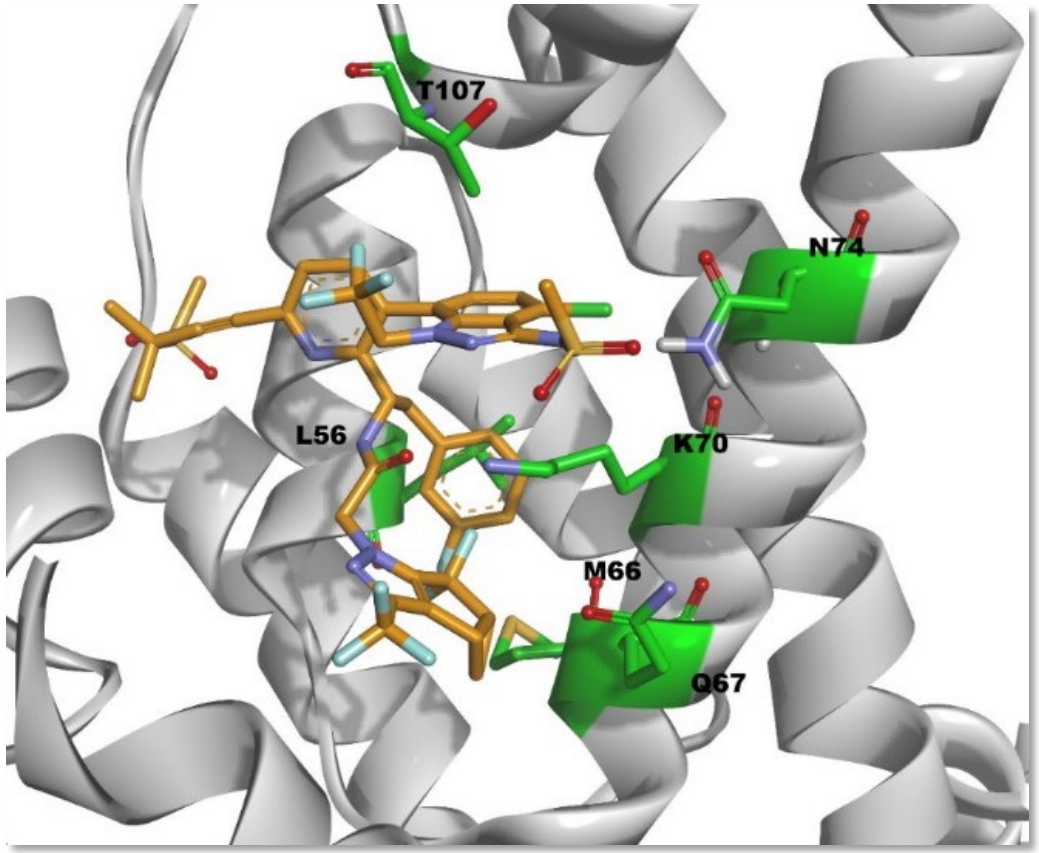
1. Yant SR, et al. CROI 2019; 2. Margot N, et al. CROI 2020; 3. VanderVeen L, et al. CROI 2021; 4. Begley R, et al. AIDS 2020; 5. Daar, et al. CROI 2020;
6. Gupta S, et al. IAS 2021; 7. Segal-Maurer S, et al. CROI 2021; 8. Molina J-M, et al. IAS 2021

LEN In Vitro Resistance Characterization

- In vitro resistance selections in MT-2 cells and human PBMCs identified 7 mutations arising at 6 amino acids in capsid[1]
  - **L56I, M66I, Q67H, K70N, N74S/D, T107N**
  - All mutations map to LEN binding site

- Resistance mutations correlated with low replication capacity for all mutants in vitro, except Q67H

- LEN mutations not found in analysis of 1500 HIV clinical isolates[2]
  - Treatment-naïve or -experienced, with or without PI-treatment failure
  - Lack of pre-existing genotypic resistance to LEN



1. Link JO, *et al. Nature* 2020; 584:614-618; 2. Marcelin A, *et al. J Antimicrob Chemother* 2020 Jun 1;75:1588-1590.

CAPELLA Study Design

Key eligibility criteria:

- HIV-1 RNA ≥400 copies/mL
- Resistance to ≥2 agents from 3 of 4 main ARV classes

NO

1- Randomised cohort (Double blind)

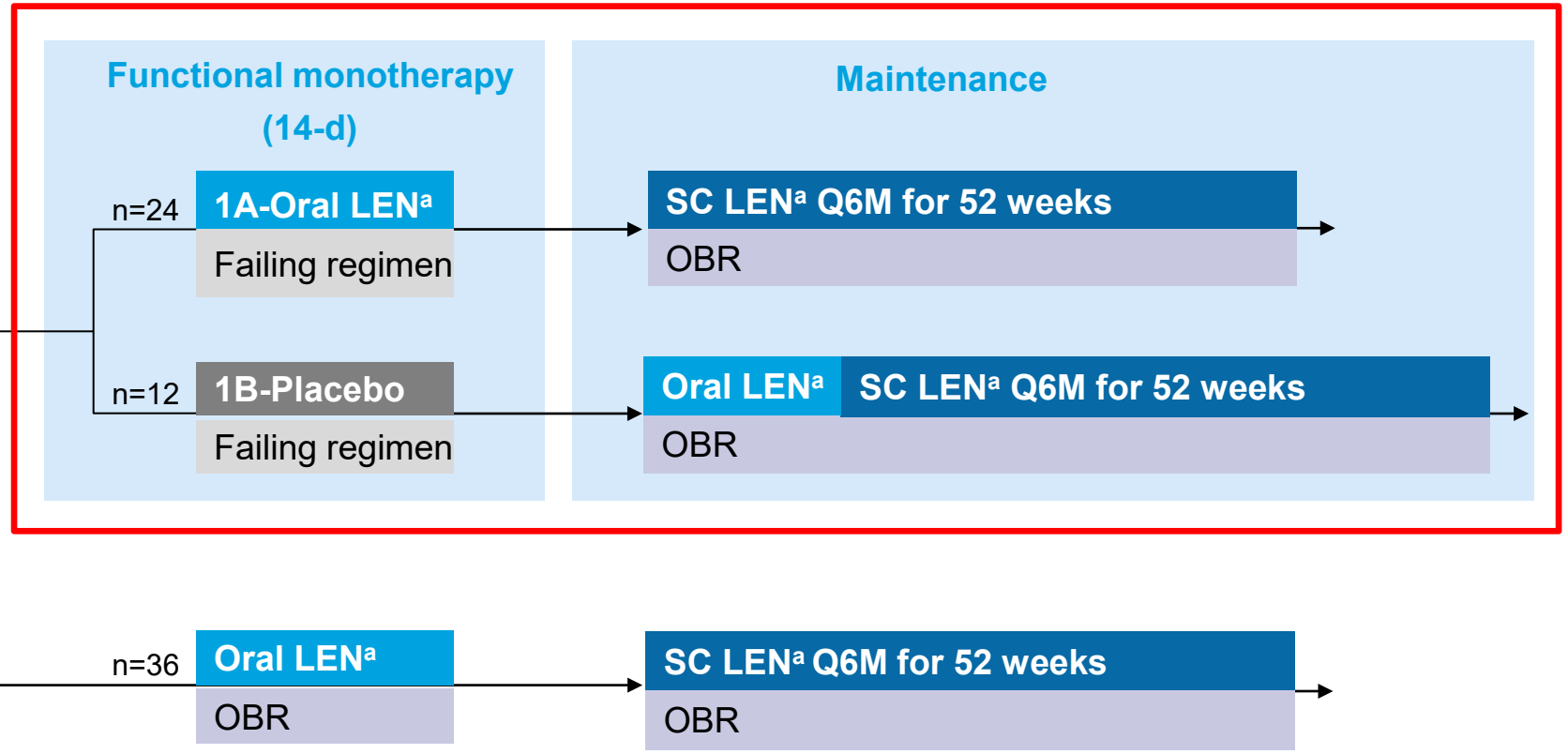
Screening period

Pre-randomisation repeat HIV-1 RNA

- Decline of ≥0.5 log_{10} copies/mL (vs screening) or <400 copies/mL
- Or if Cohort 1 is fully enrolled

YES

2- Non-randomised cohort (Open label)

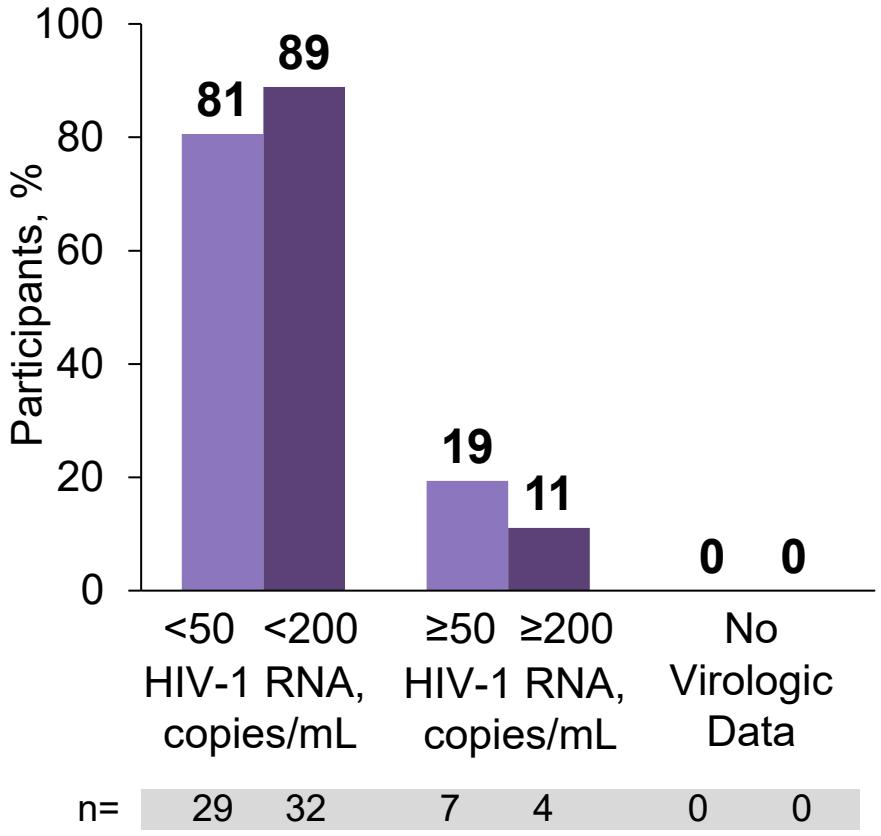


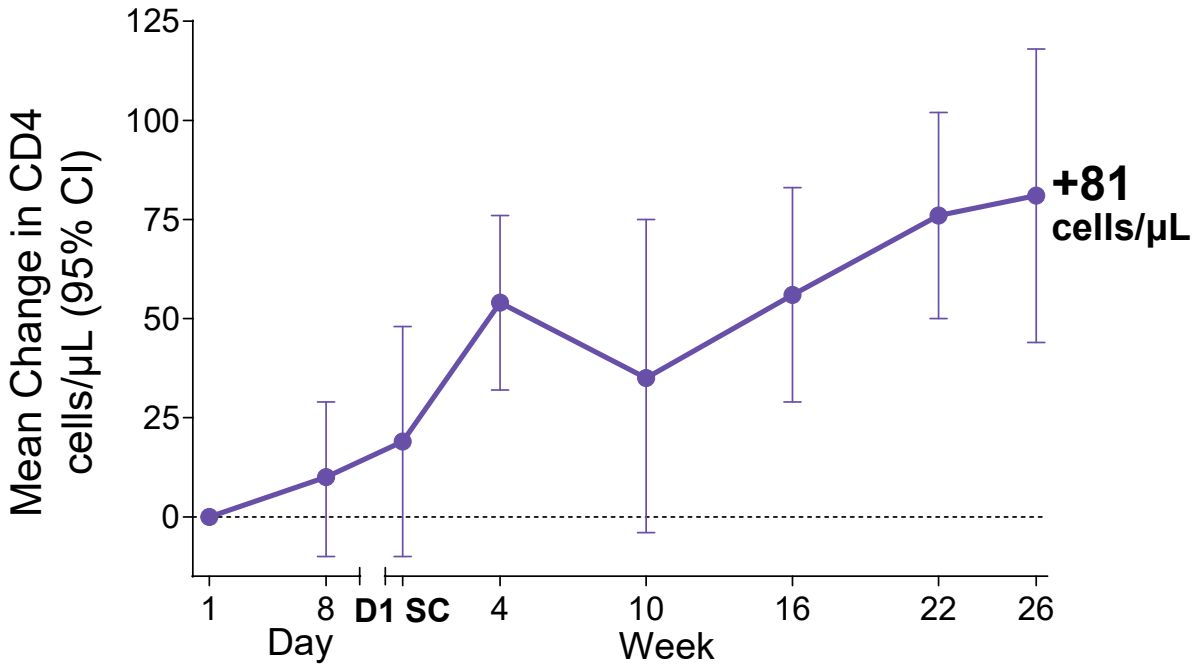
Segal-Maurer S, et al. CROI 2021; Molina J-M, et al. IAS 2021

[a] Oral LEN administered as 600 mg on Days 1 and 2, 300 mg on Day 8 (600 mg on Days 15 and 16, 300 mg on Day 22, for placebo participants); SC LEN administered as 927 mg (2 x 1.5 mL) in the abdomen on Day 15. OBR, (investigational agents, such as fostemsavir, were allowed; atazanavir (ATV), ATV/cobicistat, ATV/ritonavir, efavirenz, entecavir, nevirapine, tipranavir were not allowed). OBR, optimised background regimen; Q6M: once every 6 months.

Efficacy at Week 26: Randomised Cohort (n=36)

HIV-1 RNA (FDA-Snapshot) and CD4 Responses





	Oral lead-in		SC Maintenance					
n =	36	35	35	36	35	36	34	34
Median CD4 =	127	-	-	-	-	-	-	197

Molina J-M, et al. IAS 2021

Resistance Analyses

Baseline Resistance Analyses

- Confirm Baseline resistance criteria are met
  - Resistance to ≥2 ARVs in ≥ 3 of 4 main ARV classes
    - Monogram Biosciences Assays (45 of 72)
    - Historical resistance reports (27 of 72)
- Test susceptibility to entry inhibitors[2] (61 of 72)

Resistance assessment based on Overall Susceptibility Scores (OSS)[1] for each ARV

Post-Baseline Resistance Analyses

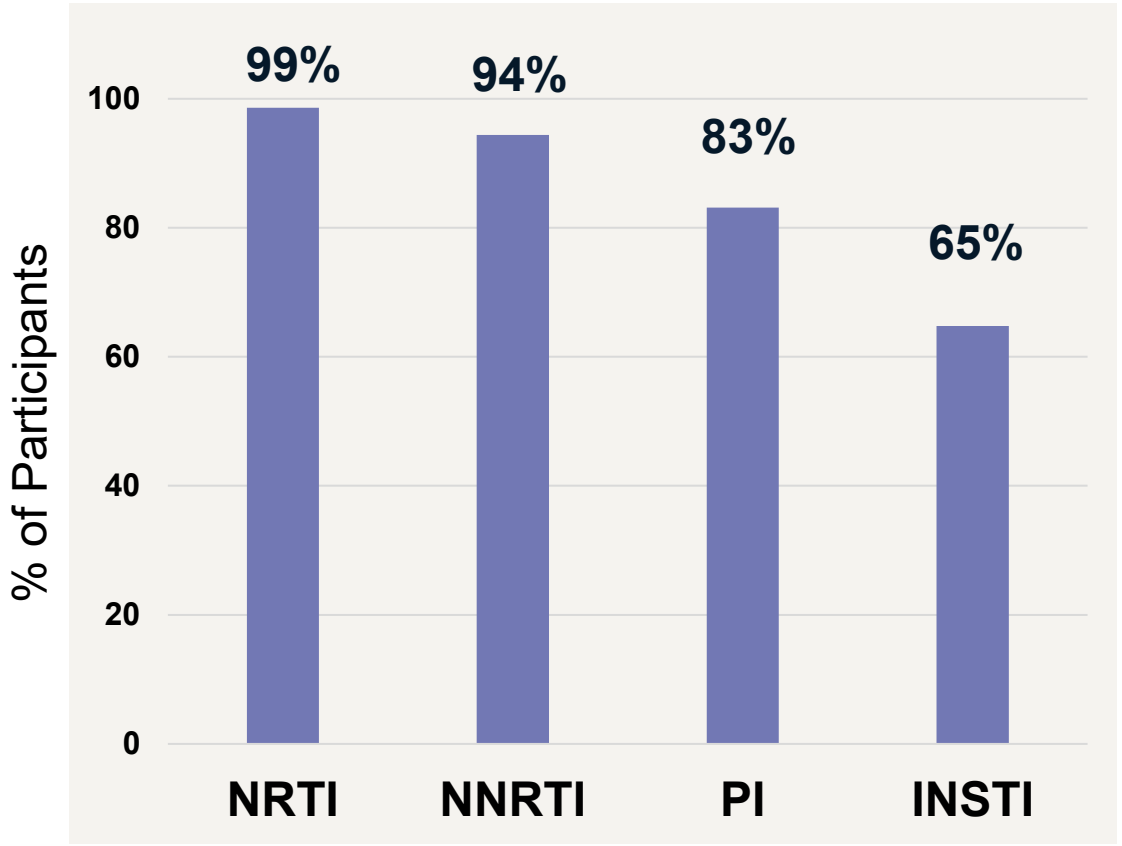
- Suboptimal Virologic Response (SVR)
  - Confirmed HIV-1 RNA ≥ 50 c/mL and < 1 $\log_{10}$ ↓ from LEN start (assessed at Week 4)
- Virologic Rebound (VR)
  - After suppression, confirmed HIV-1 RNA ≥ 50 c/mL or >1 $\log_{10}$ ↑ from nadir
- Viremia at Last Visit

1 OSS is based on both genotypic and phenotypic data
2 Entry inhibitors are enfuvirtide, fostemsavir, ibalizumab and maraviroc.

Baseline Resistance-Associated Mutations

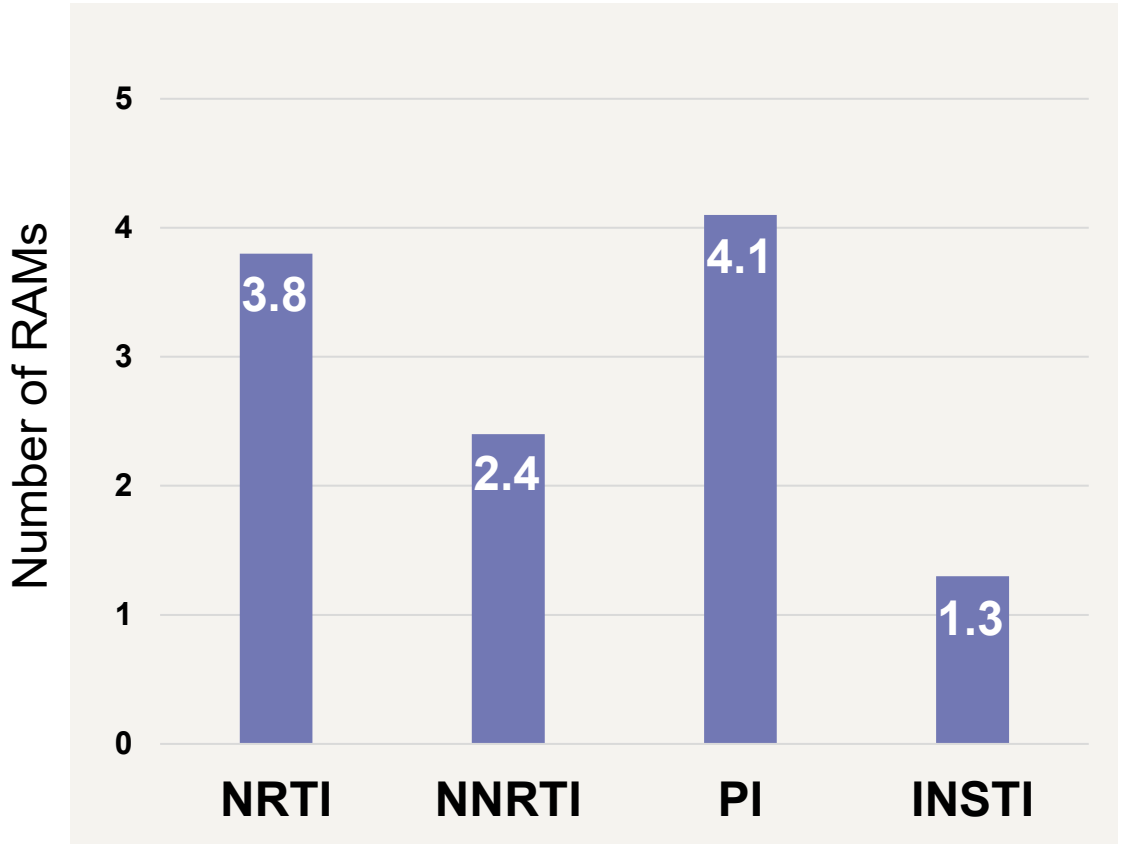
Main ARV Classes

% Participants with RAMs per ARV class



Mean # RAMs per ARV class

N=72



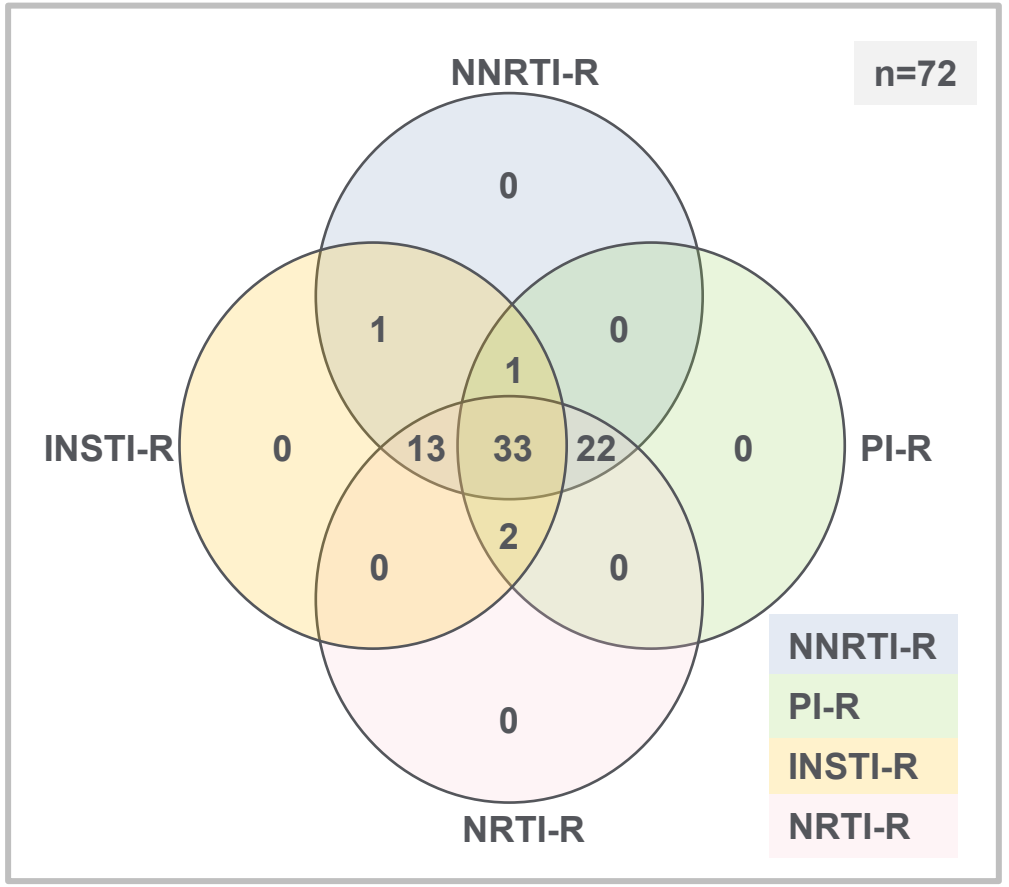
ARV = antiretroviral; INSTI = integrase strand-transfer inhibitor; NRTI = nucleoside RT inhibitor; NNRTI = non-nucleoside RT inhibitor; PI = protease inhibitor; R = resistance; RAM: resistance-associated mutation (primary); . Number of RAMs tallied: NRTI = 16; NNRTI = 14; PI = 15; INSTI = 10

Baseline Class Resistance

4 Main ARV Classes

Entry Criteria: Resistance to ≥2 ARVs in ≥ 3 of 4 main ARV classes

Resistance Class				Number (%) of Participants		
NRTI[a]	NNRTI	PI	INSTI	Cohort 1 (n = 36)	Cohort 2 (n = 36)	All (N = 72)
✓	✓	✓	✓	17 (47%)	16 (44%)	33 (46%)
✓	✓	✓		9 (25%)	13 (36%)	22 (31%)
✓	✓		✓	8 (22%)	5 (14%)	13 (18%)
✓		✓	✓	2 6%)	0	2 (3%)
	✓	✓	✓	0	1 (3%)	1 (1%)
	✓		✓	0	1 (3%)	1 (1%)



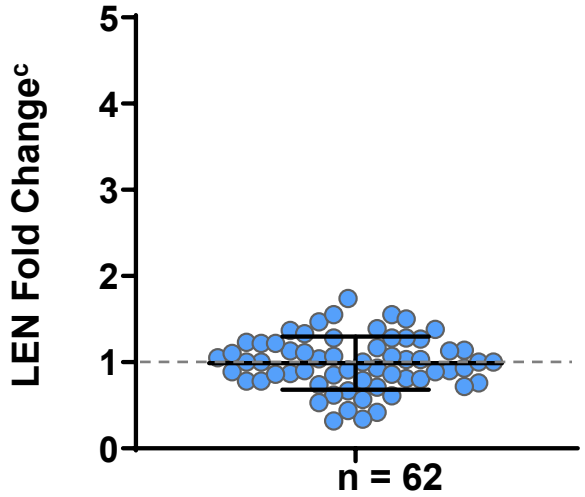
[a] M184V/I alone was not sufficient to fulfill the NRTI resistance criteria in the study.
ARV = antiretroviral; INSTI = integrase strand-transfer inhibitor; NRTI = nucleoside RT inhibitor; NNRTI = non-nucleoside RT inhibitor; PI = protease inhibitor.

Baseline Resistance to Lenacapavir

Genotypic Analysis

LEN RAM[a]	L56I	M66I	Q67H	K70N	N74D/S	T107N
# Participant with RAM[b]	0	0	0	0	0	0

Phenotypic Analysis



- Evaluated with Gag-Pro assay (Monogram)
  - No LEN resistance mutations detected
  - Wild-type LEN phenotypic susceptibility: mean fold-change = 1.0 (0.3–1.7)

a. RAM, resistance associated mutation; mutations identified during in vitro resistance selections (Link JO, et al. Nature 2020;584:614-8).
b. Data available for 62 participants
c. Fold change from wild-type control

Post-Baseline Resistance Analysis

Through Week 26

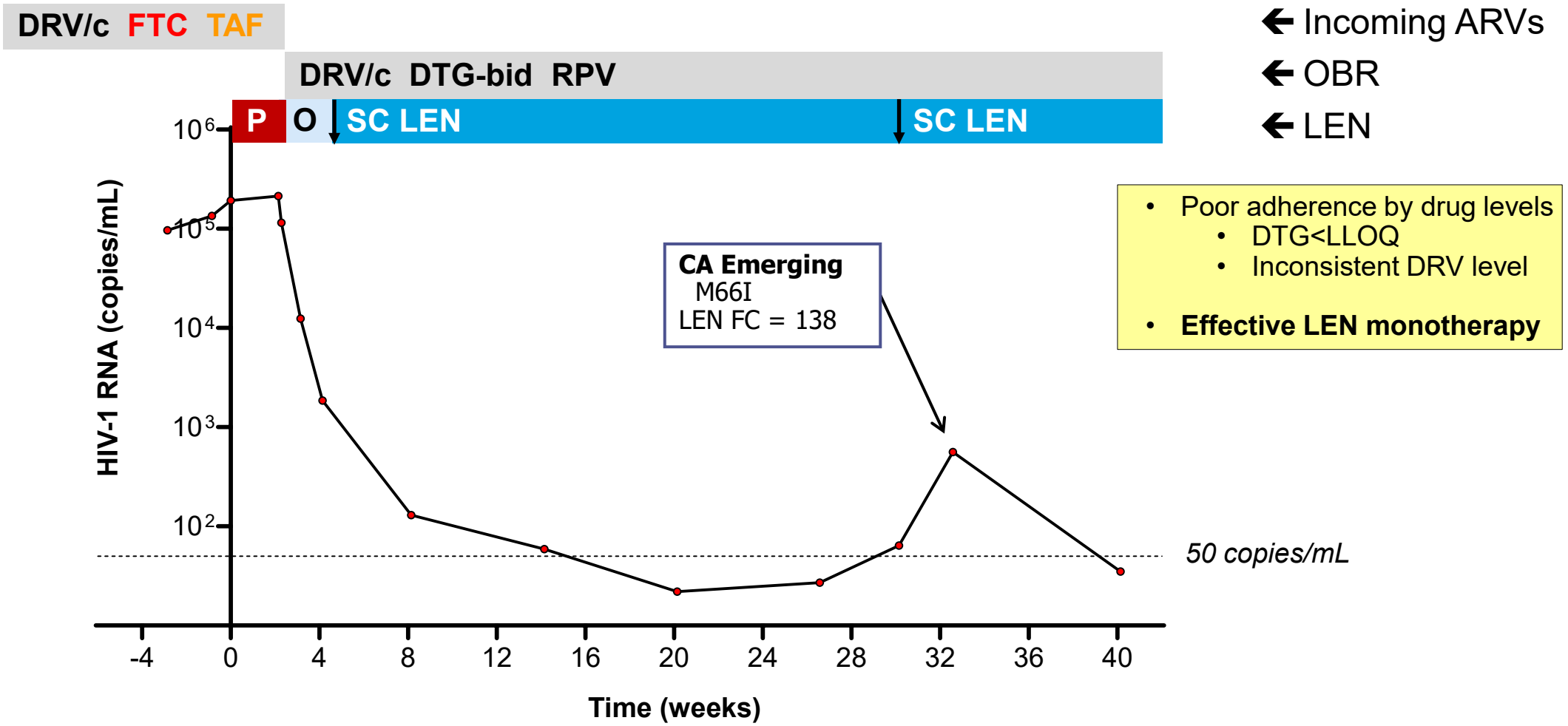
Study Phase/Treatment	Cohort 1A (n = 24)	Cohort 1B (n = 12)	All (N = 36)
Functional Monotherapy	Oral LEN + Failing Regimen	Placebo + Failing Regimen	N/A
➔ Maintenance Therapy	LEN[1] + OBR	LEN[2] + OBR	LEN + OBR

Resistance Categories	Cohort 1A (n = 24)	Cohort 1B (n = 12)	All (N = 36)
Resistance Analysis Population (RAP)	6 (25%)	5 (42%)	11 (31%)
With CA-R Emerging	1 (4%)	3 (25%)	4 (11%)
M66I	*1 (4%)*	*3 (25%)*	*4 (11%)*
Others[3]	*1 (4%)*	*2 (17%)*	*3 (8%)*
No CA-R Emergence	5 (21%)	2 (17%)	7 (19%)

- 11 of 36 participants were analyzed for resistance
- 4 of 36 participants had CA resistance emerging by week 26

1- Subcutaneous LEN; 2- Oral LEN followed by SC LEN; 3- Other mutations include Q67Q/H, K70R/S/H, N74D, A105S/T, and T107N
CA: capsid protein; OBR: optimized background regimen; -R: resistance; RAP: resistance analysis population; SC: subcutaneous

Participant 1
Viral Response and Resistance



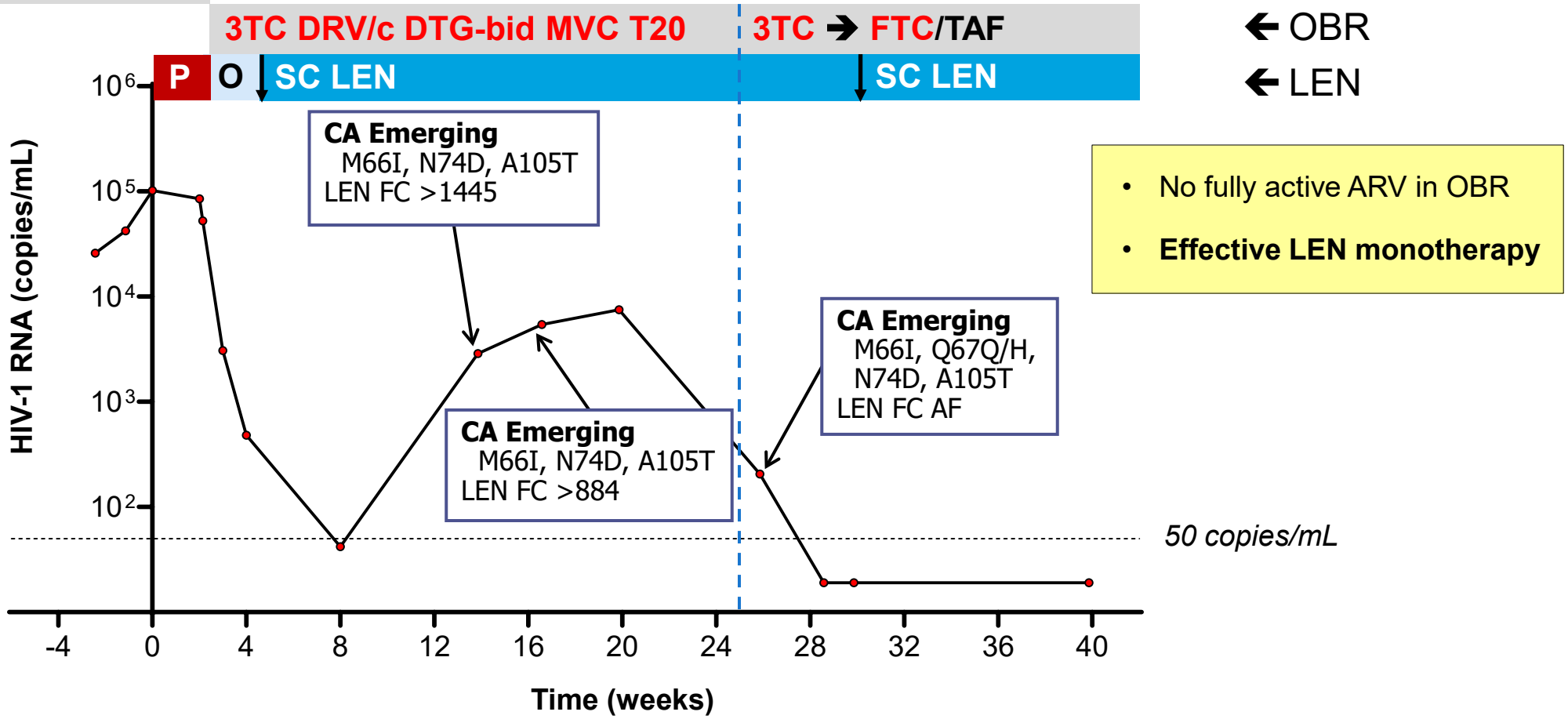
- Poor adherence by drug levels
  - DTG<LLOQ
  - Inconsistent DRV level
- **Effective LEN monotherapy**

Drugs in **red** are not active (OSS = 0); drugs in **orange** are partially active (OSS = 0.5); drugs in **black** are fully active (OSS = 1); 3TC = lamivudine; c = cobicistat boosting; CA = Capsid protein; DRV = darunavir; DTG = dolutegravir; FC = fold-change compared to wild-type control; FTC = emtricitabine; IBA = ibalizumab; LEN = lenacapavir; LLOQ = lower limit of quantification; MVC = maraviroc; O = oral LEN; OBR = optimized background regimen; OSS = overall susceptibility score; P = placebo; PK = pharmacokinetics; r = ritonavir boosting; T20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate;
↓: SC LEN injection

Participant 2
Viral Response and Resistance

3TC DRV/c DTG-bid MVC T20

← Incoming ARVs
← OBR
← LEN



- No fully active ARV in OBR
- **Effective LEN monotherapy**

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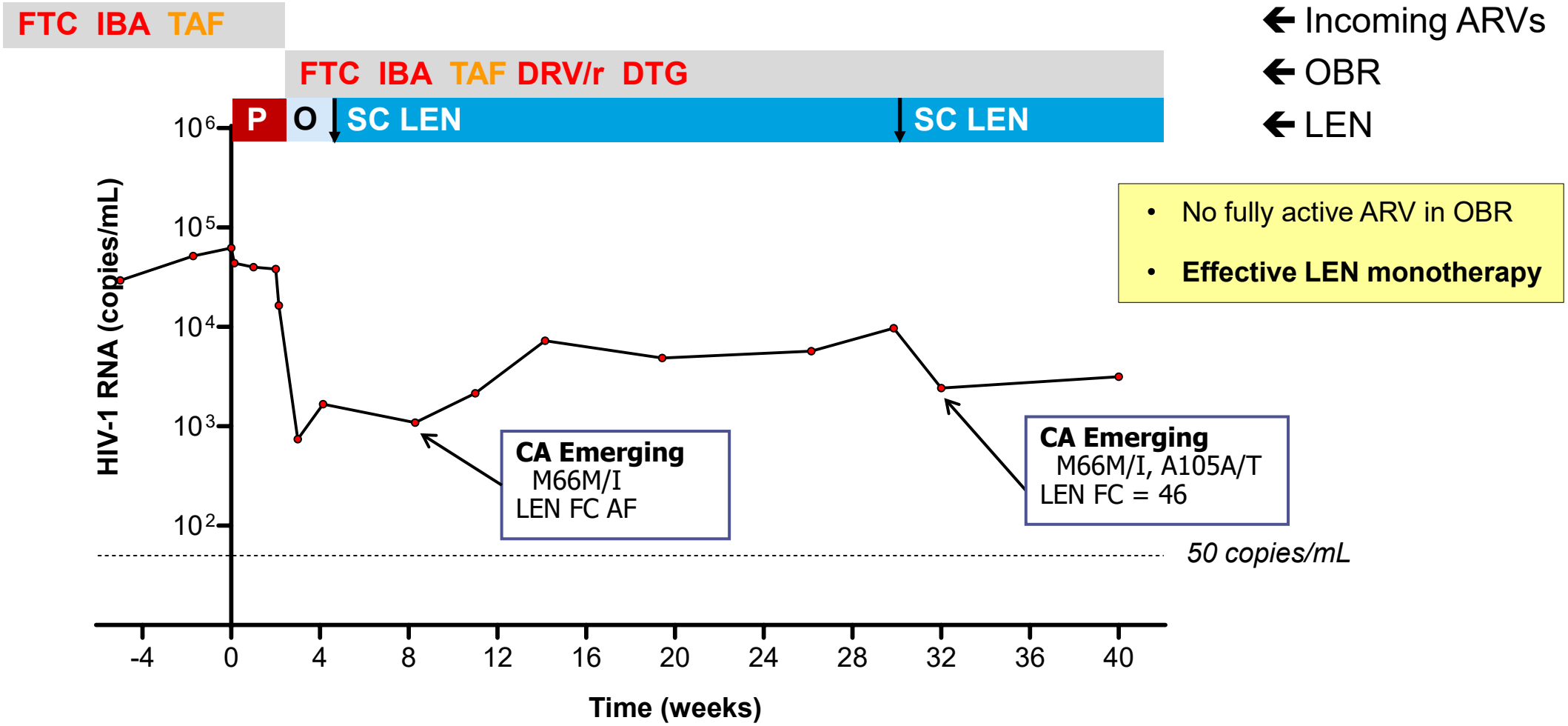
↓: SC LEN injection

Participant 3
Viral Response and Resistance



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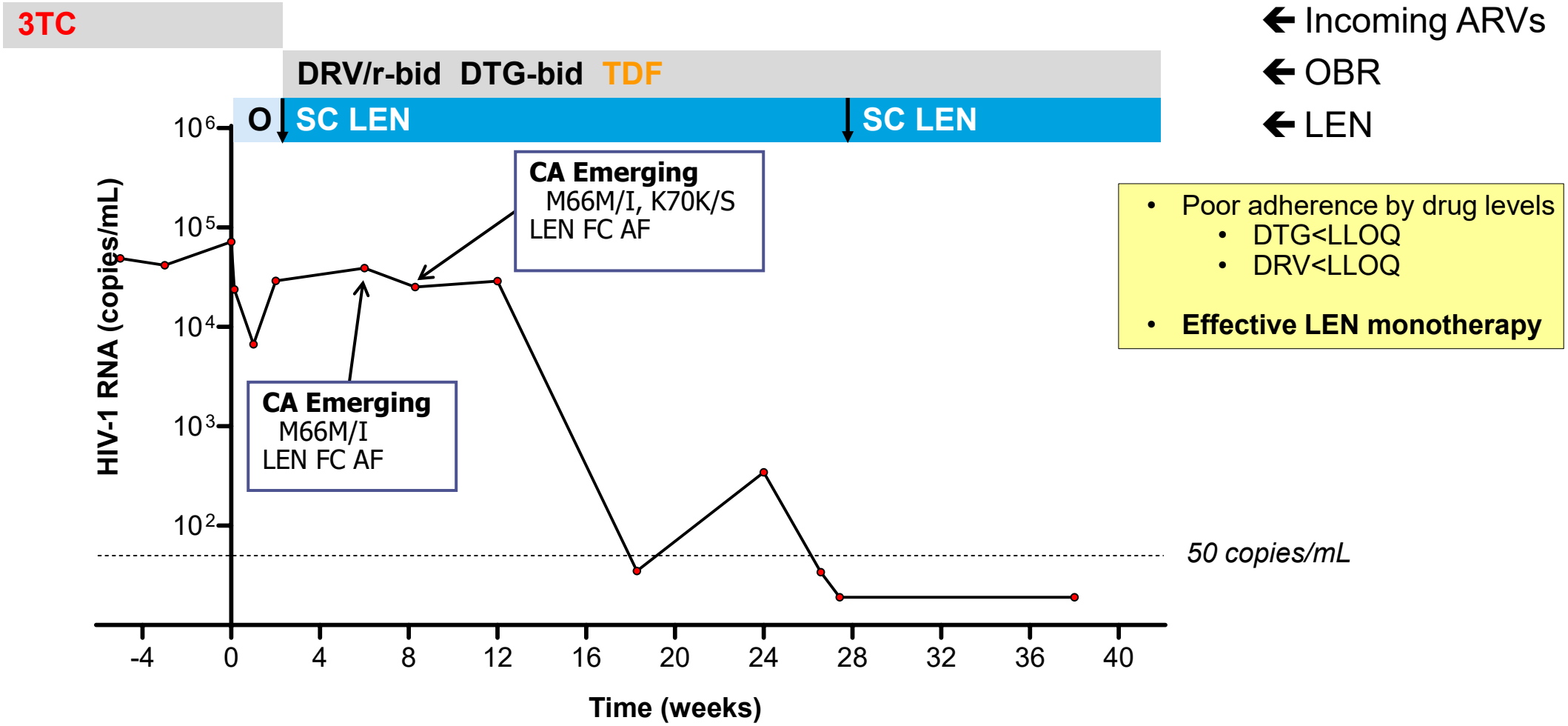
↓: SC LEN injection

Participant 4
Viral Response and Resistance



- Poor adherence by drug levels
  - DTG<LLOQ
  - DRV<LLOQ
- **Effective LEN monotherapy**

Drugs in **red** are not active (OSS = 0); drugs in **orange** are partially active (OSS = 0.5); drugs in **black** are fully active (OSS = 1); 3TC = lamivudine; c = cobicistat boosting; CA = Capsid protein; DRV = darunavir; DTG = dolutegravir; FC = fold-change compared to wild-type control; FTC = emtricitabine; IBA = ibalizumab; LEN = lenacapavir; LLOQ = lower limit of quantification; MVC = maraviroc; O = oral LEN; OBR = optimized background regimen; OSS = overall susceptibility score; P = placebo; PK = pharmacokinetics; r = ritonavir boosting; T20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate;
↓: SC LEN injection

Summary of Participants with CA Resistance

Part. ID	1st Visit with CA-R	CA RAMs	LEN FC[a]	# of Fully Active Drugs	Comments
1	Week 26	M66I	138	3	Effective LEN monotherapy (OBR adherence issue)
2	Week 10	M66I, N74D, A105T	>1445	0	Effective LEN monotherapy (no active ARVs in OBR)
3	Week 4	M66M/I	46	0	Effective LEN monotherapy (no active ARVs in OBR)
4	Week 4	M66M/I, K70K/S	ND	2	Effective LEN monotherapy (OBR adherence issue)

- Emergence of M66I (± others) in all 4 participants with CA resistance
  - LEN susceptibility ranging from 46 to >1445-fold above wild-type control
- Effective LEN monotherapy at the time of CA-R emergence
  - Inadequate OBR drug levels
  - Lack of active agents in OBR

[a] Fold change from Wild-type control
ARV: antiretroviral drug; BL: baseline; CA: capsid; CA-R: capsid resistance; OBR: optimized background regimen; RB: viral load rebound; RAM: resistance associated mutation

Conclusions

- In heavily treatment-experienced PWH with multidrug resistance
  - LEN + OBR led to high rates of virologic suppression (81%) and increases in CD4 cells by Week 26
  - LEN was well tolerated with no AEs leading to discontinuation

- Overall, the level of baseline resistance to the main ARV classes was high and consistent with the enrollment criteria defined in concert with FDA

- Post-baseline Cohort 1: 4 of 36 participants with emergence of LEN-associated mutations
  - no emerging resistance to OBR

- Viral rebound cases associated with effective LEN monotherapy at the time of resistance emergence

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Monogram Biosciences for resistance analyses

Seq-IT for sequence analyses

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