Resistance Analysis of Weekly Islatravir Plus Lenacapavir in People with HIV-1 at 96 Weeks

Poster #586

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Conclusions

- In virologically suppressed people with HIV-1 (PWH) receiving once-weekly (QW) oral islatravir (ISL) + lenacapavir (LEN) for up to 96 weeks:
  - High rates of virologic suppression were maintained
  - Virologic suppression was also maintained in the two participants with pre-existing M184I/V
  - No treatment-emergent resistance was detected
- These findings support the ongoing Phase 3 studies evaluating the QW fixed-dose combination of oral ISL/LEN in virologically suppressed PWH (NCT06630286, NCT06630299)[1,2]

Plain Language Summary

- Lenacapavir is a medicine approved to treat HIV in people who have already tried many other HIV medicines, and is usually given by injection under the skin; islatravir is a new medicine taken orally (by mouth) that is being tested to treat HIV. Both medicines can be given orally once a week and are being tested together in a study with people who already have very low levels of HIV in their blood
- HIV can sometimes become resistant to medicines, which means that the medicines no longer work properly. We looked to see if islatravir plus lenacapavir worked effectively in people who already had HIV resistance before the study, and if any new cases of resistance occurred after people began taking islatravir plus lenacapavir
  - We found that islatravir plus lenacapavir was effective in treating HIV, including in the few people with HIV resistance before starting the study. During the study, no participants had HIV where new resistance to islatravir or lenacapavir occurred

References: **1.** ClinicalTrials.gov. Study to Compare an Oral Weekly Islatravir/Lenacapavir Regimen With Bictegravir/Emtricitabine/Tenofovir Alafenamide in Virologically Suppressed People With HIV-1 (ISLEND-1). Available at: https://clinicaltrials.gov/study/NCT06630286. [Accessed Jan 2026]. **2.** ClinicalTrials.gov. Study to Compare an Oral Weekly Islatravir/Lenacapavir Regimen With Standard of Care in Virologically Suppressed People With HIV-1 (ISLEND-2). Available at: https://clinicaltrials.gov/study/NCT06630299. [Accessed Jan 2026]. **3.** Claborn KR, et al. *Psychol Health Med.* 2015; 20(3): 255–65. **4.** Schürmann D et al. *Lancet HIV.* 2020;7:e164–72. **5.** Squires K, et al. CROI 2023; Abstract 192. **6.** Sunlenca® (lenacapavir) US Prescribing Information. Gilead Sciences, Inc; 2022. **7.** Zhang H, et al. CROI 2022; Abstract 433. **8.** Shaik N, et al. AIDS 2022; Poster PESUB23. **9.** Matthews R, et al. *Clin Trans Sci*. 2021;14:1935–44. **10.** Diamond T, et al. *Antimicrob Agents Chemother*. 2024;68:e0033424. **11.** Marcelin A-G, et al. *J Antimicrob Chemother*. 2020;75:1588–90. **12.** Link, et al. *Nature*. 2020;584:614–18. **13.** Colson A, et al. CROI 2024; Oral 14. **14.** Colson A, et al. IDWeek 2024; Abstract 577. **15.** VanderVeen L, et al. CROI 2025; Poster 736. **16.** Colson A, et al. CROI 2026; Poster #516. **17.** Colson A, et al. EACS 2025; Oral PS15.5.LB. **18.** Wensing AM, et al. *Top Antivir Med.* 2022;30:559–74.

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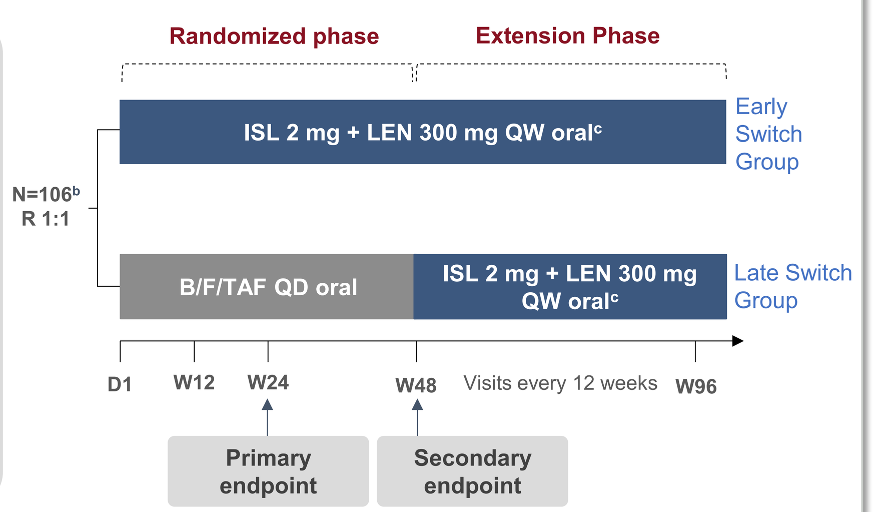
Background

- QW oral antiretrovirals (ARV) may help to improve adherence and reduce pill burden related to daily oral HIV-1 treatment[3]
- ISL, a nucleoside reverse transcriptase translocation inhibitor (NRTTI)[4], and LEN, a capsid inhibitor[5,6], have multiple and distinct mechanisms of action, potent ARV activity at low doses, and long half-lives that allow for QW oral dosing[7–9]
  - ISL and LEN also have non-overlapping resistance profiles and a higher barrier to the emergence of resistance when used combined versus separately[10]
  - Unlike reverse transcriptase inhibitors, capsid inhibitors are a novel class of ARV, and genotypic analyses have demonstrated that pre-existing resistance to LEN is unlikely[11,12]
- The ongoing Phase 2, randomized, open-label, active-controlled study (NCT05052996) is evaluating the efficacy and safety of switching from daily oral bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) to QW oral ISL+LEN in virologically suppressed PWH[13,14] (**Figure 1**)
  - At Week 48, participants were given the option to enter an extension phase to either remain on ISL+LEN (Early Switch Group) or switch from B/F/TAF to ISL+LEN (Late Switch Group)
- At Week 48, high rates of virologic suppression were maintained (**Figure 2A, 2B**), including in one participant with pre-existing M184V, and no participants developed treatment-emergent HIV-1 drug resistance[15]
- QW oral ISL+LEN maintained high levels of virologic suppression in the Early Switch Group through study Week 96 (**Figure 2A**)
- In the Late Switch Group, Week 96 virologic suppression data were similar to Week 48; please see CROI 2026 poster 516[16]

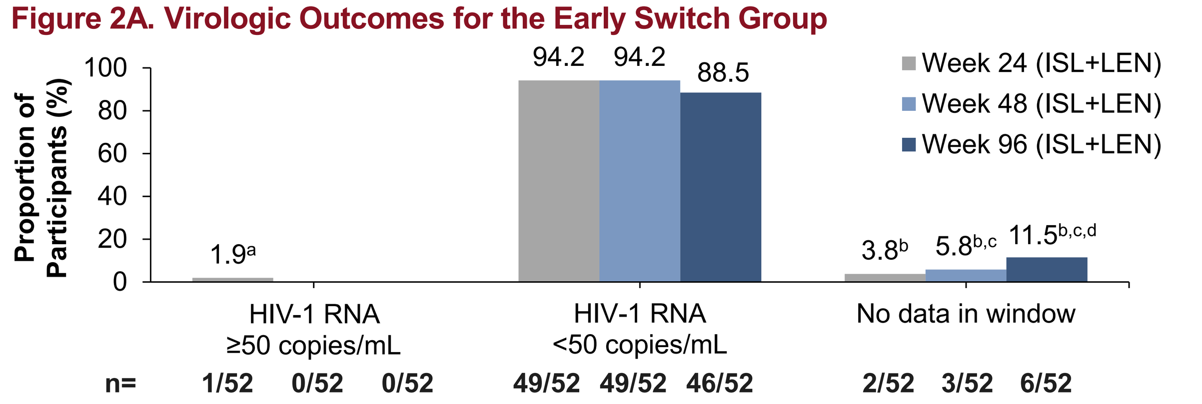
Figure 1. Study Design

Eligibility criteria
- Aged ≥18 years
- On B/F/TAF for >6 months
- HIV-1 RNA <50 copies/mL for >6 months
- No history of virologic failure
- CD4+ T-cell count ≥350 cells/μL
- Lymphocyte count ≥0.9x10³ cells/μL
- No HBV infection
- No NRTI or NNRTI resistance[a]



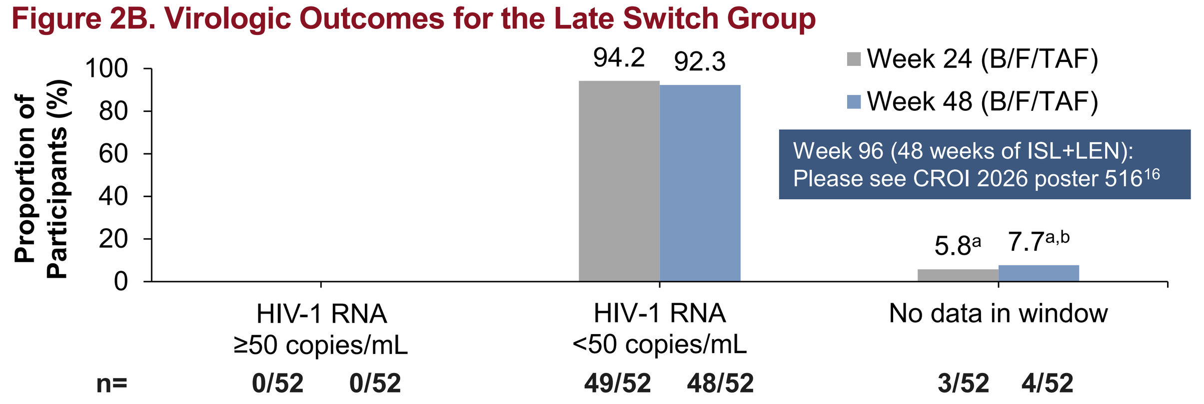
[a]The ongoing Phase 3 clinical trials do not have this resistance exclusion criteria.[1,2]
[b]Randomized, N=106, dosed, n=104; n=52 per group.
[c]600 mg of LEN was given on Day 1 and Day 2 for pharmacologic loading.
B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; D, Day; HBV, hepatitis B virus; ISL, islatravir; LEN, lenacapavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; QD, daily; QW, once-weekly; R, randomized; W, Week.

Figure 2A. Virologic Outcomes for the Early Switch Group



Week 24, Week 48, and Week 96 efficacy data for the Early Switch Group have been reported previously.[13,14,17]
[a]Participant was viremic at Day 1 and resuppressed at Week 30 without change in regimen.
[b]Two participants discontinued study due to unrelated adverse events (large intestine perforation and renal colic in same participant [n=1]; acute hepatitis B [n=1]).
[c]One participant discontinued due to personal reasons.
[d]An additional one participant discontinued due to personal reasons. Two participants completed 48 weeks of the randomized phase and chose not to enter the extension phase due to personal decision. All participants had HIV-1 RNA <50 copies/mL at study discontinuation.
ISL, islatravir; LEN, lenacapavir.

Figure 2B. Virologic Outcomes for the Late Switch Group



Week 24 and Week 48 data for the Late Switch Group have been reported previously.[13,14]
[a]Three participants discontinued study due to other reasons.
[b]One participant was missing data during Week 48 window but remained on study drug. All participants had HIV-1 RNA <50 copies/mL at study discontinuation.
B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; ISL, islatravir; LEN, lenacapavir.

Objective

- To quantify and present data from an exploratory analysis of pre-existing HIV-1 resistance and post-baseline (on-treatment) resistance through Week 96 in the Phase 2 study

Methods

Pre-Treatment (Baseline) Analyses

- Proviral DNA sequencing of HIV-1 protease, reverse transcriptase, and integrase was performed at screening (GenoSure Archive®, Monogram Biosciences); historical HIV-1 genotypes were collected if available
  - Participants with primary nucleoside reverse transcriptase inhibitor (NRTI) or non-NRTI (NNRTI) resistance were not eligible for study enrollment
  - Participants who were eligible at screening but found to have pre-existing NRTI or NNRTI resistance after enrollment remained on study drug and were included in all analyses

On-Treatment (Post-Baseline) Resistance Analyses

- Resistance analyses were completed for participants who had HIV-1 RNA ≥200 copies/mL either at the time of confirmed virologic failure (two consecutive visits with HIV-1 RNA ≥50 copies/mL) or at study discontinuation/last visit
- Plasma HIV-1 RNA genotyping and phenotyping were conducted using the GeneSeq® Gag-Pro, PhenoSense® Gag-Pro, PhenoSense® GT, GeneSeq® Integrase, and/or PhenoSense® Integrase assays (Monogram Biosciences)
- In cases of assay failure, an alternative next-generation sequencing (Seq-IT GmbH & Co. KG, Kaiserslautern, Germany) was used

Resistance-Associated Mutations

- NRTI, NNRTI, protease inhibitor, integrase strand transfer inhibitor, and capsid inhibitor resistance-associated mutations (RAM) are presented in **Table 1**

Table 1. Primary Resistance-Associated Mutations for Relevant ARV Classes[18]

Class	Resistance-Associated Mutations[a]
NRTI[b]	M41L, K65E/N/R, D67N, T69 insertions, K70E/R, L74I/V, V75I, F77L, Y115F, F116Y, Q151M, M184I/V, L210W, T215F/Y, K219E/N/Q/R
NNRTI[b]	L100I, K101E/P, K103N/S, V106A/M, V108I, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188C/H/L, G190A/Q/S, H221Y, P225H, F227C/L, M230I/L
PI	D30N, V32I, M46I/L, I47A/V, G48V, I50L/V, I54L/M/V, Q58E, T74P, L76V, V82A/F/L/S/T, N83D, I84V, N88S, L90M
INSTI	T66A/I/K, E92G/Q/V, G118R, F121C/Y, G140R, Y143C/H/R, S147G, Q148H/K/R, N155H/S, R263K
CAI	L56I, M66I, Q67H/K/N, K70H/N/S/R, N74D/S, A105S/T, T107A/C/N/S

[a]Resistance-associated mutations were based on the International Antiviral Society-USA list.[18]
[b]These mutations were considered exclusionary for enrollment.
CAI, capsid inhibitor; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Results

Pre-Existing (Baseline) Resistance

- Of the participants randomized and dosed (n=52 per arm), most had subtype B HIV-1 (91/104, 87.5%) (**Table 2**)
- Pre-existing primary RAMs detected in the study population were uncommon, and similar between treatment arms (**Table 2**)
- Five participants who enrolled based on historical genotype data were subsequently found to have primary RAMs affecting NRTIs or NNRTIs on screening genotype (**Table 2**):
  - Early Switch Group: L74L/V+K103K/N (n=1), M41M/L+M184M/V (n=1), V108V/I (n=1)
  - Late Switch Group: K219K/R (n=1), M184M/I (n=1)
- All five participants in the Early Switch and Late Switch Groups with pre-existing NRTI or NNRTI resistance remained virologically suppressed at study Week 96, including two participants with pre-existing M184I/V in reverse transcriptase (n=1 per group)

Table 2. Summary of HIV-1 Subtypes and Pre-Existing (Baseline) Primary Resistance to Four Main ARV Classes

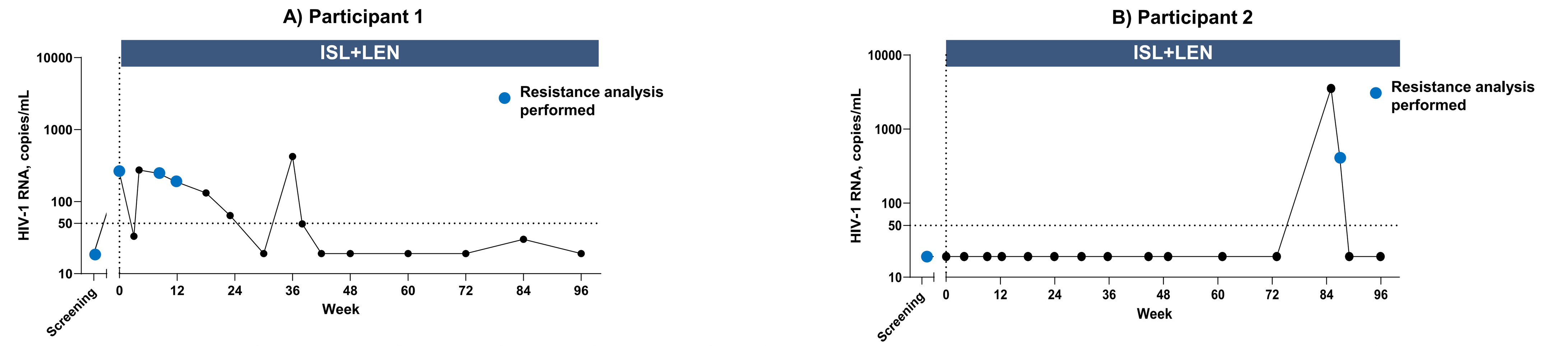
	ISL+LEN (Early Switch) Baseline n=52	B/F/TAF Baseline n=52	B/F/TAF → ISL+LEN (Late Switch) Baseline n=45
Summary of HIV-1 subtypes, n/N (%)			
HIV-1 subtype B	45/52 (86.5)	46/52 (88.5)	40/45 (88.9)
HIV-1 subtype non-B	5/52 (9.6)[a]	3/52 (5.8)[b]	2/45 (4.4)
HIV-1 subtype unknown	2/52 (3.8)	3/52 (5.8)	3/45 (6.7)
Pre-existing primary resistance substitutions, n/N (%)			
NRTI resistance[c]	2/52 (3.8)	2/52 (3.8)	2/45 (4.4)
Any thymidine analog mutation[d]	1/52 (1.9)	1/52 (1.9)	1/45 (2.2)
M41L	1/52 (1.9)	0/52	0/45
L74I/V	1/52 (1.9)	0/52	0/45
M184I/V	1/52 (1.9)	1/52 (1.9)	1/45 (2.2)
K219R	0/52	1/52 (1.9)	1/45 (2.2)
NNRTI resistance[c]	2/52 (3.8)	0/52	0/45
K103N	1/52 (1.9)	0/52	0/45
V108I	1/52 (1.9)	0/52	0/45
PI resistance	4/52 (7.7)	2/52 (3.8)	2/45 (4.4)
M46I/L	3/52 (5.8)	2/52 (3.8)	2/45 (4.4)
I84V	1/52 (1.9)	0/52	0/45
INSTI resistance	0/51	2/49 (4.1)	2/42 (4.8)
T66A/I/K	0/51	2/49 (4.1)	2/42 (4.8)

[a]Subtypes A, A1, and BG (n=1 each), subtype C (n=2).
[b]Subtypes AG, BF, and BG (n=1 each).
[c]Exclusionary RAMs identified post enrollment.
[d]Thymidine analog mutations are M41L, D67N, K70R, L210W, T215F/Y, K219E/N/Q/R in reverse transcriptase.
ARV, antiretroviral; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; INSTI, integrase strand transfer inhibitor; ISL, islatravir; LEN, lenacapavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

On-Treatment (Post-Baseline) Resistance Analysis

- Two participants receiving ISL+LEN in the Early Switch Group met criteria for post-baseline resistance analysis, neither of whom had baseline NRTI or NNRTI RAMs (**Figure 3**)
  - Participant 1 had low-level viremia (50–450 copies/mL) at both Day 1 (baseline) before dosing (HIV-1 RNA 251 copies/mL) and multiple post-baseline timepoints; the participant did not have documented non-adherence and demonstrated adequate plasma ISL and LEN levels (**Figure 3A**)
  - The other participant (Participant 2) had documented non-adherence accompanied by undetectable study drug levels at the time of confirmed virologic failure (Week 84, HIV-1 RNA 422 copies/mL) (**Figure 3B**)
  - Both participants resuppressed while maintaining ISL+LEN, with no treatment-emergent resistance detected
- No participants in the Late Switch Group met the criteria for resistance testing

Figure 3. Virologic Analysis of Participants Meeting Criteria for Post-Baseline Resistance Analysis



A) Participant 1

	Screening	Day 1	Week 8	Week 12
HIV-1 RNA (copies/mL)	Not detected	251	248	187
CD4+ T-cell count (cells/μL)	356	433	450	452
RAMs				
Reverse transcriptase	None	AF	None	AF
Capsid	-	AF	None	None
Susceptibility (FC from wild-type)				
ISL	-	-	AF	AF
LEN	-	-	AF	AF

B) Participant 2

	Screening	Week 84
HIV-1 RNA (copies/mL)	Not detected	422
CD4+ T-cell count (cells/μL)	803	858
RAMs		
Reverse transcriptase	None	AF
Capsid	-	None
Susceptibility (FC from wild-type)		
ISL	-	AF
LEN	-	AF

The horizontal dotted lines denote the HIV-1 RNA 50 copies/mL limit which defined virologic rebound in this study. The Monogram Biosciences Plasma HIV-1 RNA genotyping and phenotyping assays are validated above 500 copies/mL.
AF, assay failure; FC, fold-change; ISL, islatravir; LEN, lenacapavir; RAM, resistance-associated mutation.