

Resistance Analysis of Weekly Islatravir Plus Lenacapavir in People With HIV at 48 Weeks

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Conclusions

- In virologically suppressed adults with HIV-1 treated with oral once-weekly (QW) islatravir (ISL) plus lenacapavir (LEN) for 48 weeks:
 - High rates of virologic suppression were maintained
 - One participant with pre-existing M184V/I also maintained virologic suppression
 - No participant developed treatment-emergent HIV-1 drug resistance
- These findings support the ongoing evaluation of ISL+LEN as an oral, QW treatment for HIV-1
 - Phase 3 studies evaluating the fixed-dose combination of QW oral ISL/LEN in virologically suppressed people with HIV-1 (PWH) are ongoing (ISLEND-1, NCT06630286; ISLEND-2, NCT06630299)^{1,2}

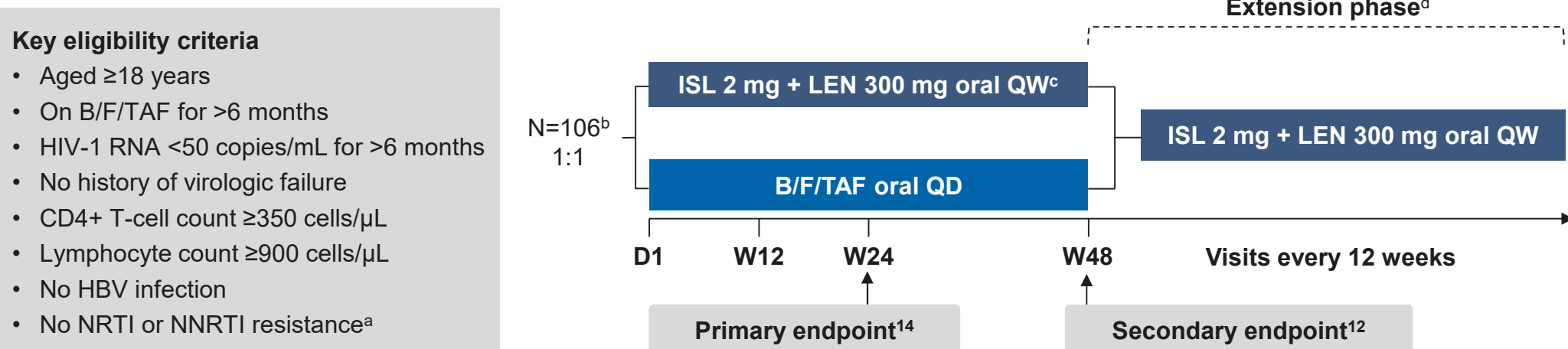
Plain Language Summary

- Islatravir (a new medicine being studied for HIV-1 treatment) and lenacapavir (a medicine already approved as a twice-yearly injection for HIV-1 treatment) is a new combination of medicines that can be taken by mouth as a tablet once a week to treat HIV-1, unlike many other HIV-1 medicines that need to be taken every day
- An ongoing study is looking at how well islatravir plus lenacapavir work for HIV-1 treatment, and how safe it is. In this study, people with HIV-1 who were already taking the medication bictegravir/emtricitabine/tenofovir alafenamide for HIV-1 treatment either stayed on this treatment, or switched to islatravir plus lenacapavir
- Sometimes, the HIV-1 virus can develop resistance to medicines, which means that the medicines no longer work against the HIV-1 virus. We looked to see if participants with HIV-1 resistance that was present before the study affected how well islatravir plus lenacapavir worked, and if any new cases of resistance developed after people started islatravir plus lenacapavir
- We found that treatment with islatravir plus lenacapavir was effective in treating HIV-1, including in the few participants with HIV-1 resistance before starting the new treatments. In addition, no one developed resistance to islatravir plus lenacapavir during the study

Background

- Oral QW antiretrovirals have the potential to address pill fatigue and adherence challenges related to daily oral treatment for HIV-1 and reduce the injection burden associated with long-acting injectables³
- ISL is a nucleoside reverse transcriptase translocation inhibitor being investigated as an HIV-1 therapy⁴
- LEN is a first-in-class capsid inhibitor currently licensed as a twice-yearly subcutaneous injection for use in combination with other antiretrovirals in heavily treatment-experienced PWH⁵
- ISL and LEN both have novel mechanisms of action and additive inhibition of HIV-1, with non-overlapping resistance profiles and a higher barrier to the emergence of resistance when combined versus alone⁶
 - As capsid inhibitors are a new class of antiretrovirals, pre-existing resistance to LEN is unlikely^{7,8}
- Both ISL and LEN have pharmacokinetic profiles suitable for oral QW dosing^{9–11}
- NCT05052996 is an ongoing Phase 2 study evaluating the efficacy and safety of switching from oral once-daily bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) to oral QW ISL+LEN in virologically suppressed PWH (**Figure 1**)
 - Efficacy and safety data have been previously reported; oral QW ISL+LEN maintained a high rate (94.2%) of viral suppression at Week 48 (**Figure 2**)^{12,13}

Figure 1. Study Design



^aThe ongoing Phase 3 clinical trials do not have this resistance exclusion criteria.^{1,2} ^bRandomized, N=106; dosed, n=104 (n=52 per group). ^c600 mg of LEN was given on D1 and D2 for pharmacologic loading. ^dParticipants could elect to continue the study in post-W48 extension phase. 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, once daily; QW, once weekly; W, Week.

Figure 2. Virologic Outcomes at Week 48 by FDA Snapshot Algorithm^{12,13}

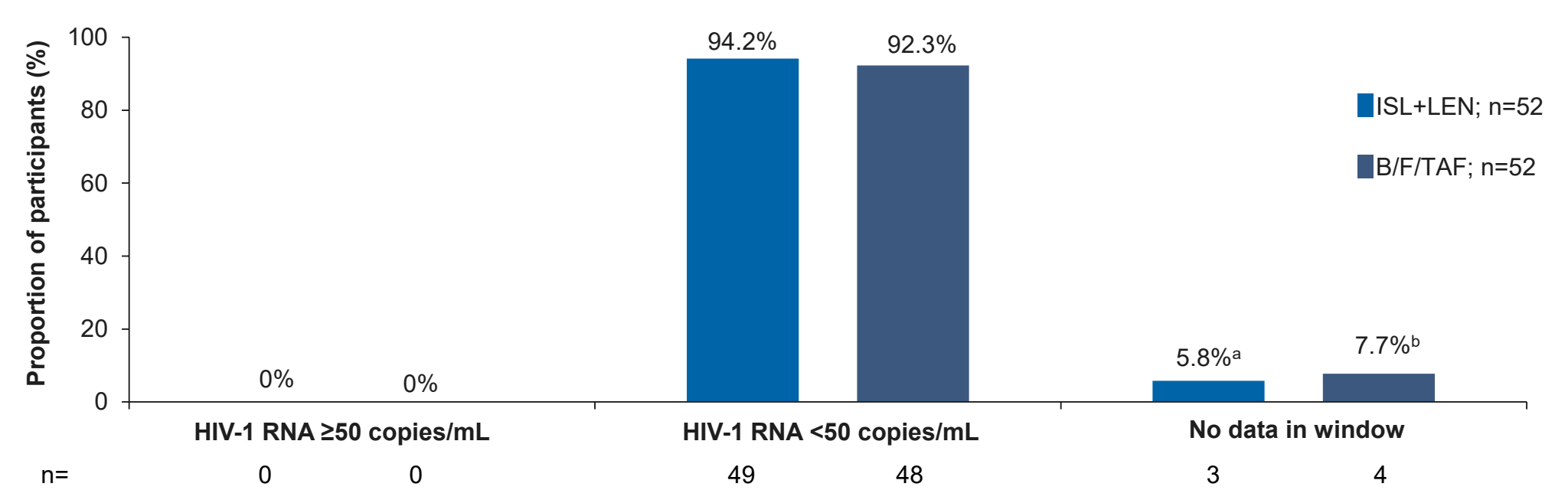


Figure adapted from Colson A, et al. IDWeek 2024. ^aTwo participants discontinued due to adverse events not related to study drug and one participant discontinued due to other reasons not related to study drug; all participants had HIV-1 RNA <50 copies/mL at study discontinuation. ^bThree participants discontinued due to other reasons not related to study drug and had HIV-1 RNA <50 copies/mL at study discontinuation; one participant had missing data during window but remained on study drug. B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; FDA, Food and Drug Administration; ISL, islatravir; LEN, lenacapavir.

Objective

- To quantify and report interim data from an exploratory analysis of pre-existing HIV-1 resistance and post-baseline (on-treatment) resistance through Week 48 in the Phase 2 study

Methods

Pre-Treatment (Baseline) Analyses

- Protease (PR), reverse transcriptase (RT), and integrase (IN) genotyping was performed at screening (GenoSure Archive®, Monogram Biosciences), and historical HIV-1 genotype reports were collected if available
 - Nucleoside reverse transcriptase inhibitor (NRTI), non-NRTI (NNRTI), protease inhibitor (PI), and integrase strand transfer inhibitor (INSTI) resistance associated mutations (RAM) are presented in **Table 1**
- Absence of primary NRTI or NNRTI RAMs by historical or screening resistance genotype was required for study eligibility
- Participants who were eligible based on information available at the time of screening but found later to have pre-existing resistance after enrollment remained on study drug and were included in all analyses

Table 1. Primary RAMs for NRTI, NNRTI, PI, and INSTI Classes

Class	RAMs ^a
NRTI ^b	M41L, K65E/N/R, D67N, T69 insertions, K70E/R, L74I/V, V75I, F77L, Y115F, F116Y, Q151M, M184V/I, L210W, T215F/Y, K219E/N/Q/R
NNRTI ^b	L100I, K101E/H/P, K103N/S, V106A/M, V108I, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188C/H/L, G190A/Q/S, H221Y, P225H, F227C, 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

^aRAMs were based on the International Antiviral Society-USA list.¹⁵ ^bThese mutations were considered exclusionary for enrollment. INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RAM, resistance associated mutation.

On-Treatment (Post-Baseline) Resistance Analyses

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

Single-Genome Sequencing

- Clonality of plasma HIV-1 RNA samples was evaluated by single-genome sequencing of the p6-RT (HXB2 nucleotides 1849–3410) region
 - RNA was extracted, reverse transcribed and cDNA subjected to nested polymerase chain reaction following endpoint dilution. Amplicons were sequenced using next-generation deep sequencing
 - Phylogenetic analysis of the sequences was performed by constructing a maximum likelihood tree (FastTree)

Results

Pre-Existing (Baseline) Resistance

- Pre-existing primary RAMs detected in the study population were uncommon, and similar between treatment arms (**Table 2**)
- Few participants who enrolled based on historical genotype data were subsequently found to have primary RAMs affecting NRTIs or NNRTIs on screening genotype:
 - ISL+LEN: M41M/L+M184M/V (n=1), V108V/I (n=1), L74L/V+K103K/N (n=1)
 - B/F/TAF: M184M/I (n=1), K219K/R (n=1)
- All participants in both the ISL+LEN and B/F/TAF groups with pre-existing NRTI or NNRTI resistance remained virologically suppressed at Week 48, including two participants with pre-existing M184V/I in RT (n=1 per group)

Table 2. Pre-Existing (Baseline) Primary Resistance to Four Main ARV Classes

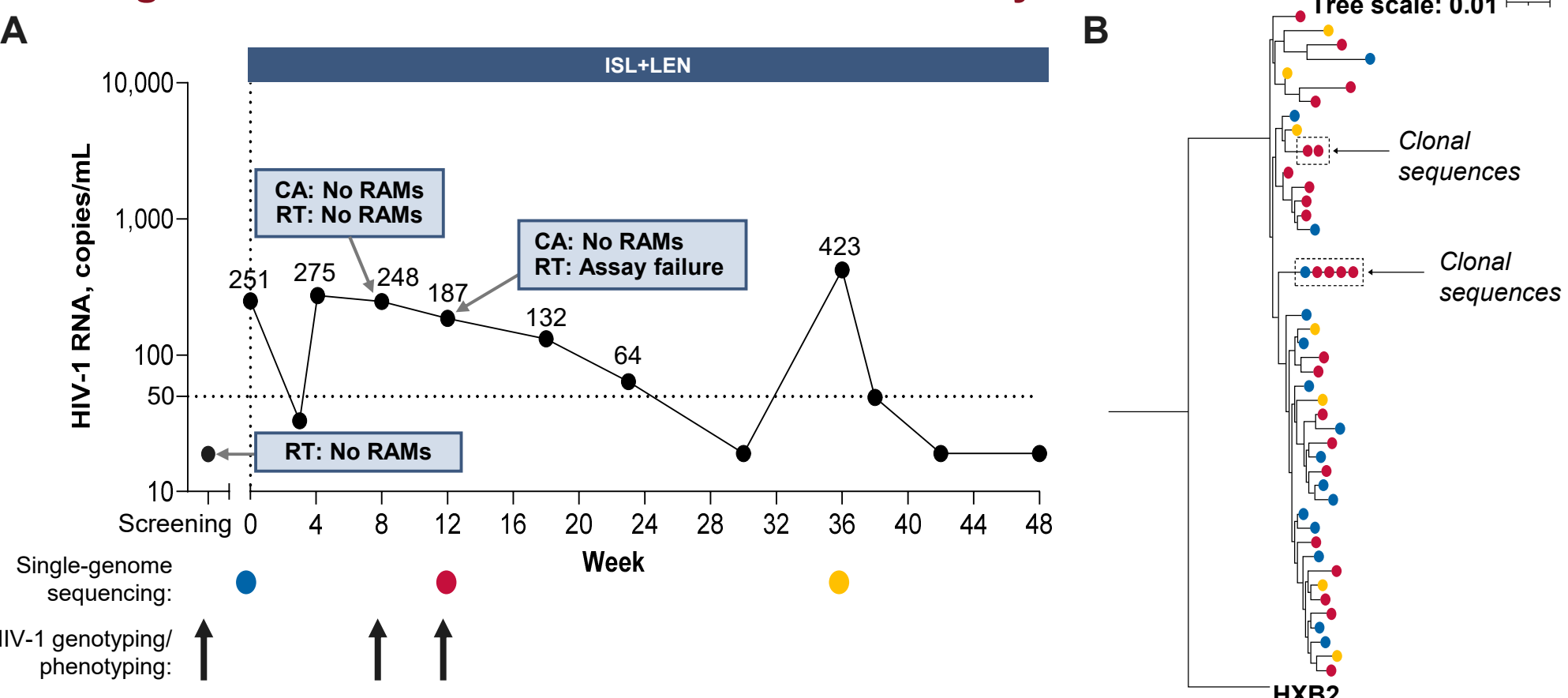
Pre-existing primary resistance substitutions, n/N (%)	ISL+LEN (n=52)	B/F/TAF (n=52)	All (N=104)
NRTI resistance	2/52 (3.8)	2/52 (3.8)	4/104 (3.8)
Any TAM ^a	1/52 (1.9)	1/52 (1.9)	2/104 (1.9)
M41L	1/52 (1.9)	0/52	1/104 (1.0)
L74V	1/52 (1.9)	0/52	1/104 (1.0)
M184V/I	1/52 (1.9)	1/52 (1.9)	2/104 (1.9)
K219R	0/52	1/52 (1.9)	1/104 (1.0)
NNRTI resistance	2/52 (3.8)	0/52	2/104 (1.9)
K103N	1/52 (1.9)	0/52	1/104 (1.0)
V108I	1/52 (1.9)	0/52	1/104 (1.0)
PI resistance	4/52 (7.7)	2/52 (3.8)	6/104 (5.8)
M46I/L	3/52 (5.8)	2/52 (3.8)	5/104 (4.8)
I84V	1/52 (1.9)	0/52	1/104 (1.0)
INSTI resistance	0/51	2/49 (4.1)	2/100 (2.0)
T66A	0/51	2/49 (4.1)	2/100 (2.0)

^aTAMs are M41L, D67N, K70R, L210W, T215F/Y, K219E/N/Q/R in RT. 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; RT, reverse transcriptase; TAM, thymidine analog mutation.

On-Treatment (Post-Baseline) Analysis

- One participant in the ISL+LEN group met criteria for post-baseline resistance analysis (**Figure 3**)
 - The participant had no pre-existing primary NRTI or NNRTI RAMs and was viremic at Day 1 (HIV-1 RNA 251 copies/mL)
 - The participant did not have treatment-emergent drug resistance and achieved sustained viral suppression after Week 36 while maintaining ISL+LEN (**Figure 3A**)
 - The participant demonstrated adequate plasma ISL and LEN levels
 - Single-genome analysis of longitudinal plasma sequences identified 15% (7/47) identical HIV-1 RNA sequences, suggesting clonal T-cell expansion may have contributed to low-level viremia (**Figure 3B**)

Figure 3. Virologic Analysis (A) and Phylogenetic Tree (B) of Participant Meeting Criteria for Post-Baseline Resistance Analysis



LEN RAMs are L56I, M66I, Q67H/K/N, K70H/N/S/R, N74D/S, A105S/T, T107A/C/N/S. In Figure 3A, the horizontal dotted line denotes the HIV-1 RNA 50 copies/mL limit which defined virologic rebound in this study. Figure 3B shows the phylogenetic tree of plasma HIV-1 RNA single genome sequences, rooted to HXB2 consensus sequence. In Figure 3B, clonal sequences are indicated with dashed line boxes. CA, capsid; ISL, islatravir; LEN, lenacapavir; RAM, resistance-associated mutation; RT, reverse transcriptase.

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