

Efficacy and Safety of Once-Weekly Oral Islatravir/Lenacapavir (ISL/LEN) Compared With Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/F/TAF) or Standard of Care (SOC) in People With HIV-1 (PWH) and Virologic Suppression: Week 48 Integrated Analysis From the Phase 3 ISLEND-1 and ISLEND-2 Trials

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Devi SenGupta is an employee and shareholder of Gilead Sciences, Inc.; co-chair of the International AIDS Society HIV Cure Industry Collaborative Group; and board member of the San Francisco AIDS Foundation and the California HIV/AIDS Research Program.

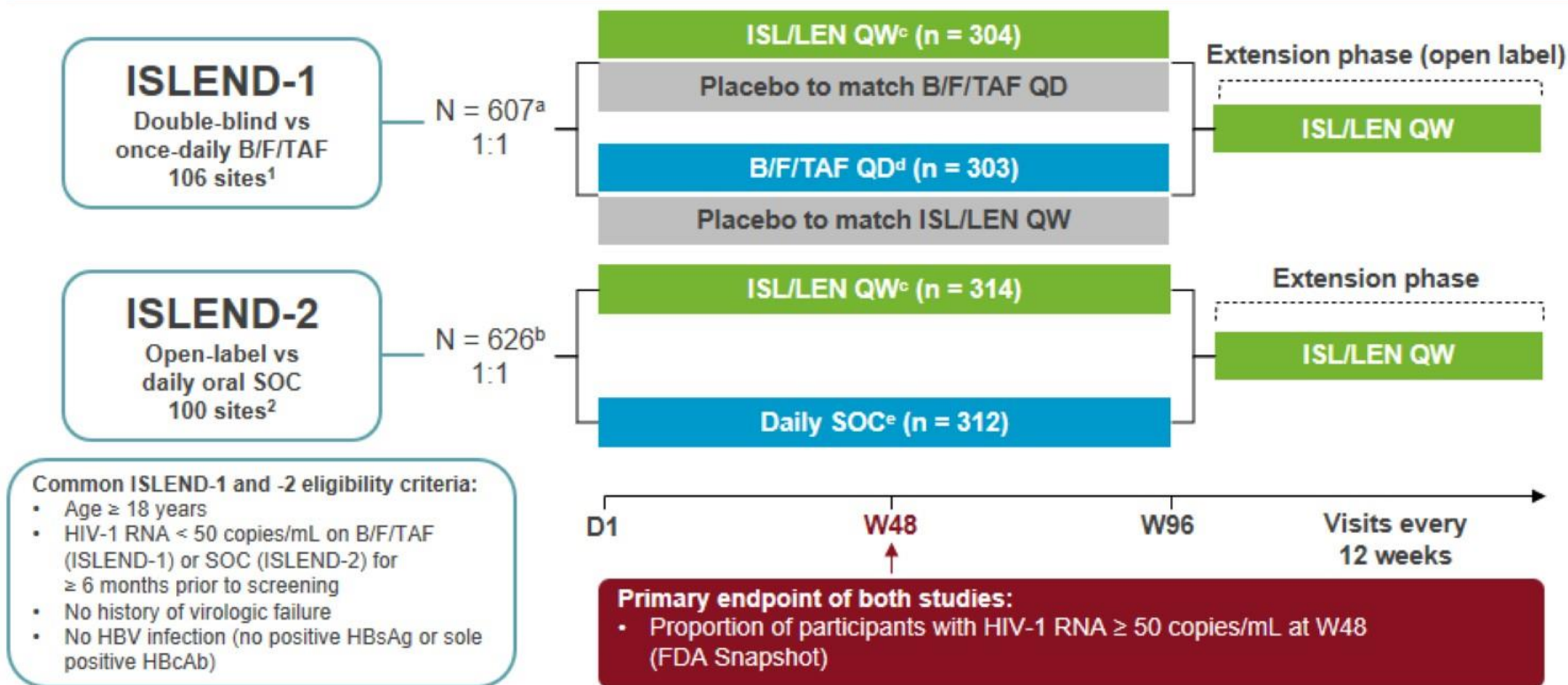
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Background and Objectives

- Once-weekly oral therapy represents a novel treatment option that may reduce treatment burden, improve adherence, and expand therapeutic choice for PWH^{1,2}
- The combination of islatravir (ISL), a nucleoside reverse transcriptase translocation inhibitor,^{3,4} and lenacapavir (LEN), a capsid inhibitor,⁵ is being developed as a once-weekly oral single-tablet regimen for virologically suppressed PWH
- In the ISLEND-1 (double-blind; NCT06630286) and ISLEND-2 (open-label; NCT06630299) Phase 3 studies, switching to once-weekly oral ISL/LEN demonstrated noninferior efficacy to continuing daily B/F/TAF or SOC after 48 weeks of treatment and was well tolerated^{1,2}
 - Both studies enrolled populations that were diverse across key demographic factors at baseline, including age, sex at birth, race, ethnicity, and geographic location, and clinical factors such as the presence of the M184V/I mutation and CD4+ T-cell count^{1,2}

This prespecified pooled analysis of data from both studies aims to determine whether efficacy and safety were maintained across demographic and clinical subgroups

ISLEND-1 and ISLEND-2 Study Designs



^aRandomized: N = 609, dosed: N = 607. ^bRandomized: N = 634, dosed: N = 626. ^cParticipants received two oral tablets, each containing 0.5 mg ISL (initiation dose) and 300 mg LEN (loading dose) on D1 and D2, then one oral tablet of ISL/LEN 2/300 mg QW from D8, without regard to food (+ matching B/F/TAF placebo in ISLEND-1). ^dParticipants continued oral tablet of B/F/TAF 50/200/25 mg administered QD, without regard to food, and received matching ISL/LEN placebo (initiation/loading dose and weekly treatment). ^eParticipants continued guideline-recommended SOC oral therapy consisting of two or three antiretroviral agents (INSTI + one or two NRTIs; boosted PI + two NRTIs; NNRTI + two NRTIs) – all SOC treatments were taken QD, including fixed-dose combinations and single-tablet regimens, except for raltegravir, which could be taken once or twice daily. B/F/TAF, bictegravir/emtricitabine/tenofovir disoproxil fumarate; D, Day; FDA, US Food and Drug Administration; HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; INSTI, integrase strand-transfer inhibitor; ISL, islatravir; LEN, lenacapavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; QD, once daily; QW, once weekly; SOC, standard of care; W, Week 1. Rockstroh JK, et al. *N Engl J Med*. Published online July 29, 2026. doi:10.1056/NEJMoa2607973. 2. Colson AE, et al. *Lancet*. 2026;408(10557):821-32.

Baseline Demographic and Clinical Characteristics

Participants, n (%)		Pooled ISL/LEN (n = 618)	B/F/TAF (n = 303)	SOC (n = 312)	Combined B/F/TAF & SOC (n = 615)
Sex assigned at birth	Male	446 (72)	245 (81)	206 (66)	451 (73)
	Female	172 (28)	58 (19)	106 (34)	164 (27)
Age, years	≥ 50	331 (54)	143 (47)	184 (59)	327 (53)
	≥ 65	99 (16)	40 (13)	42 (13)	82 (13)
Race ^a	Black	183 (30)	100 (33)	99 (32)	199 (32)
	White	278 (45)	128 (42)	134 (43)	262 (43)
	Other ^b	130 (21)	58 (19)	68 (22)	126 (20)
Hispanic or Latine ethnicity ^a		135 (22)	87 (29)	61 (20)	148 (24)
Geographic region	US	344 (56)	183 (60)	162 (52)	345 (56)
	Non-US	274 (44)	120 (40)	150 (48)	270 (44)
Presence of M184V/I mutation		31 (5)	18 (6)	19 (6)	37 (6)
CD4+ T-cell count, mean (SD), cells/μL		767 (320.5)	745 (319.3)	761 (319.0)	753 (319.0)
CD4+ T-cell count, cells/μL	< 200	6 (1)	6 (2)	5 (2)	11 (2)
	≥ 200 to < 350	30 (5)	20 (7)	14 (4)	34 (6)
	≥ 350 to < 500	87 (14)	37 (12)	47 (15)	84 (14)
	≥ 500	495 (80)	240 (79)	246 (79)	486 (79)
Absolute lymphocyte count, mean (SD), × 10 ³ cells/μL		1.92 (0.584)	1.90 (0.617)	1.94 (0.616)	1.92 (0.616)
eGFR, ^c median (IQR), mL/min		99.9 (81.1–122.3)	101.0 (82.8–121.6)	94.9 (76.5–117.9)	97.6 (78.6–119.4)

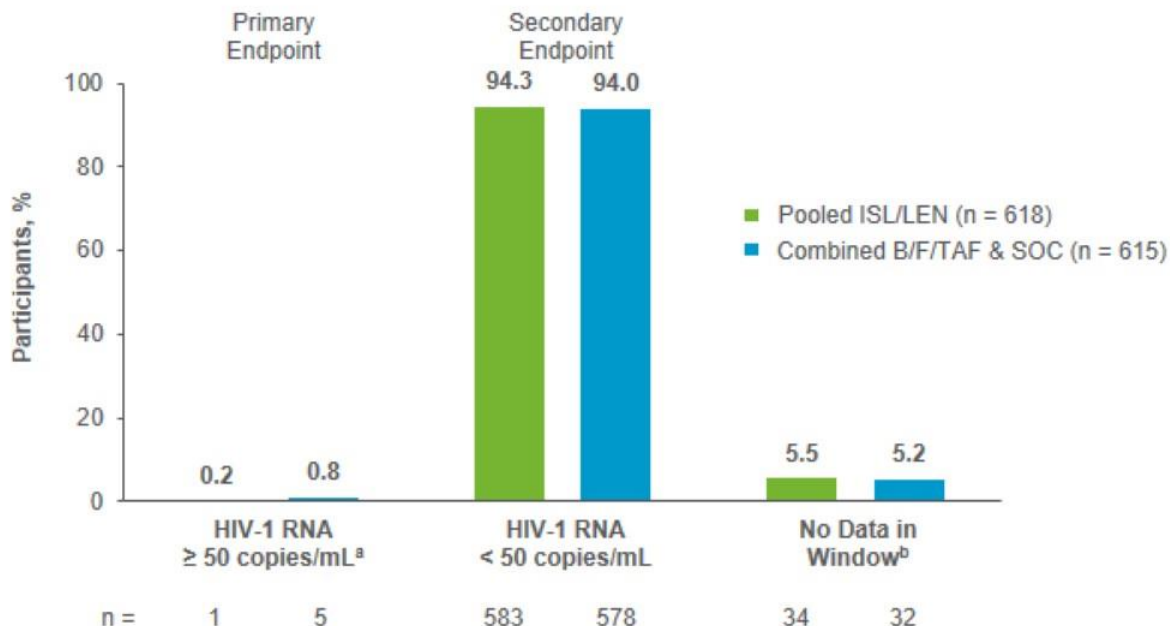
Participants were stratified after randomization by geographic region and CD4 cell count category.

^aIn some countries, local regulators did not allow the collection of race or ethnicity information (race was not collected for 55/1233 [4.4%] participants and ethnicity for 53/1233 [4.3%] participants).

^bIncludes American Indian or Alaska Native, Asian, Native Hawaiian or Pacific Islander, and other. ^cCalculated using the Cockcroft-Gault formula.

B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; CD4, cluster of differentiation 4; eGFR, estimated glomerular filtration rate; ISL/LEN, islatravir/lenacapavir; SOC, standard of care.

Integrated Virologic Outcomes (FDA Snapshot) at Week 48

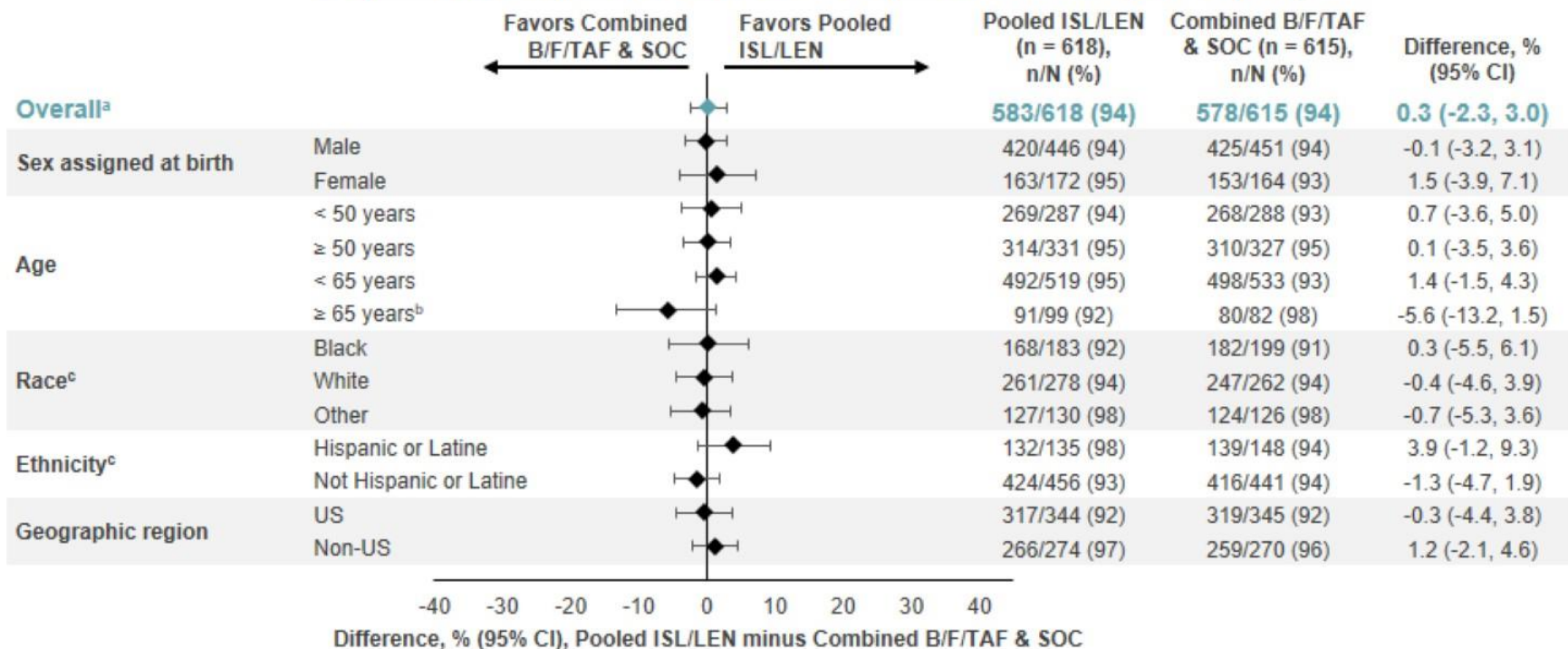


ISL/LEN maintained high rates of virologic suppression in the integrated analysis

^aDiscontinued study drug due to other reasons and last available HIV-1 RNA was ≥ 50 copies/mL: Pooled ISL/LEN, n = 1. ^bDiscontinued study drug due to adverse event: Pooled ISL/LEN, n = 9; Combined control, n = 6. Discontinued study drug due to other reasons and last available HIV-1 RNA was < 50 copies/mL: Pooled ISL/LEN, n = 22; Combined control, n = 19. Missing data during analysis window but still on study drug: Pooled ISL/LEN, n = 3; Combined control, n = 7. B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; FDA, US Food and Drug Administration; ISL/LEN, islatravir/lenacapavir; SOC, standard of care.

Maintenance of Virologic Suppression at Week 48 by Baseline Demographics

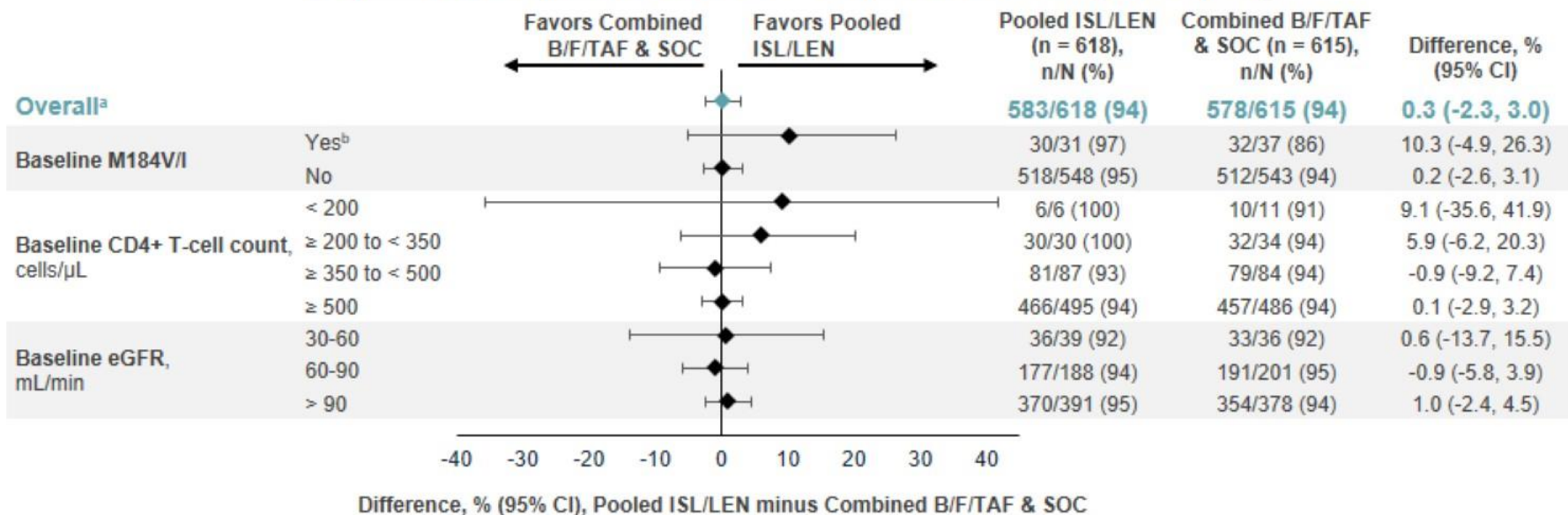
Proportion of Participants With HIV-1 RNA < 50 copies/mL at Week 48 (FDA Snapshot)



^aFor the overall group, difference between treatment groups (Pooled ISL/LEN minus Combined B/F/TAF & SOC) and two-sided 95% CIs were constructed based on stratum-adjusted Mantel-Haenszel proportion and adjusted by geographic region; for subgroups, an unconditional exact method using two inverted one-sided tests was used. ^bLower point estimate is driven by missing data for eight participants in the Pooled ISL/LEN group versus two in the Combined B/F/TAF & SOC group. ^cIn some countries, local regulators did not allow the collection of race or ethnicity information (race was not collected for 55/1233 [4%] participants and ethnicity for 53/1233 [4%] participants). B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; FDA, US Food and Drug Administration; ISL/LEN, islatravir/enacavir; SOC, standard of care.

Maintenance of Virologic Suppression at Week 48 by Baseline Clinical Characteristics

Proportion of Participants With HIV-1 RNA < 50 copies/mL at Week 48 (FDA Snapshot)



^aFor the overall group, difference between treatment groups (Pooled ISL/LEN minus Combined B/F/TAF & SOC group) and two-sided 95% CIs were constructed based on stratum-adjusted Mantel-Haenszel proportion and adjusted by geographic region; for subgroups, an unconditional exact method using two inverted one-sided tests was used. ^bHigher point estimate is driven by missing data for four participants in the Combined B/F/TAF & SOC groups versus one in the Pooled ISL/LEN group. B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; CD4, cluster of differentiation 4; eGFR, estimated glomerular filtration rate; FDA, US Food and Drug Administration; ISL/LEN, islatravir/lenacapavir; SOC, standard of care.

CD4+ T-Cell Count Through Week 48



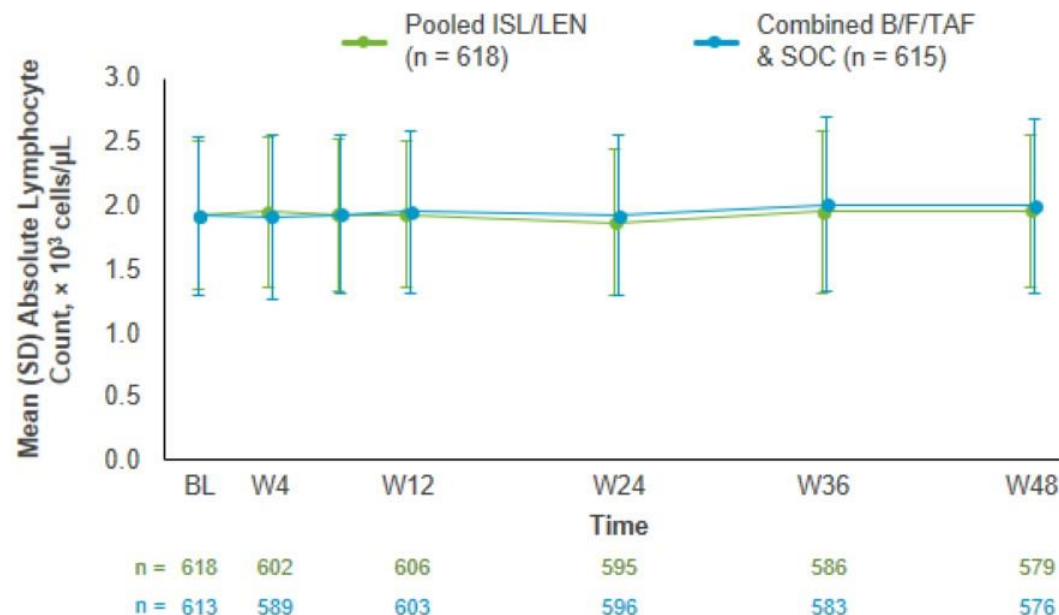
Mean (95% CI) Change From BL at W48, cells/μL

Pooled ISL/LEN	Combined B/F/TAF & SOC
-28 (-43, -14)	-13 (-28, 2)

Difference in LSMs (95% CI):
-11 (-30, 8) cells/μL

CD4+ T-cell counts remained stable, with no clinically meaningful differences between treatment groups and no discontinuations due to decline in CD4+ T-cell count

Absolute Lymphocyte Count Through Week 48



Mean (SD) Change From BL at W48,
 $\times 10^3$ cells/ μ L

Pooled ISL/LEN	Combined B/F/TAF & SOC
0.03 (0.432)	0.09 (0.469)

Absolute lymphocyte counts remained stable in both groups, and there were no discontinuations due to decline in lymphocyte count

Overall Incidence of Adverse Events by Treatment Group

Participants, n (%)	Pooled ISL/LEN (n = 618)	B/F/TAF (n = 303)	SOC (n = 312)
AEs – any grade	490 (79)	238 (79)	241 (77)
Grade ≥ 3	46 (7)	22 (7)	28 (9)
Most common Grade ≥ 3 AEs (≥ 2 participants in any treatment group)			
Acute kidney injury	2 (< 1)	0	3 (1)
Pulmonary embolism	2 (< 1)	0	0
Road traffic accident	2 (< 1)	1 (< 1)	0
Syncope	2 (< 1)	1 (< 1)	1 (< 1)
Treatment-related AEs – any grade^a	99 (16)	40 (13)	1 (< 1)
Most common treatment-related AEs ($\geq 2\%$ of participants in any treatment group)			
Headache	24 (4)	8 (3)	0
Nausea	18 (3)	10 (3)	0
Diarrhea	14 (2)	3 (1)	0
Serious AEs	38 (6)	14 (5)	27 (9)
AEs leading to treatment discontinuation	8 (1)	5 (2)	1 (< 1)
Deaths	1 (< 1)	0	2 (1)

- The incidence of Grade ≥ 3 laboratory abnormalities was similar between treatment groups^{1,2}
- Treatment-related serious AEs:
 - ISLEND-1: maculopapular rash (n = 1^b; treatment group not specified); ISLEND-2: seizure (n = 1^c; ISL/LEN group)

^aThe difference in frequency of treatment-related AEs between the two studies is not unexpected given the open-label nature of ISLEND-2. ^bBecause of the very low frequency and the potential for functional unblinding in the ongoing ISLEND-1 study, this event is reported without treatment-group attribution; the affected participant discontinued the study. ^cThis event occurred in a participant with a prior history of epilepsy, after suboptimal adherence to antiseizure medication; the participant remained on ISL/LEN.

AE, adverse event; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; ISL/LEN, islatravir/lenacapavir; SOC, standard of care.

1. Rockstroh JK, et al. *N Engl J Med*. Published online July 29, 2026. 2. Colson AE, et al. *Lancet*. 2026;408(10557):821-32.

Most Common Adverse Events^a

Most common AEs (≥ 5% of participants in the pooled ISL/LEN treatment group, any grade) by preferred term, n (%)	Pooled ISL/LEN (n = 618)	B/F/TAF (n = 303)	SOC (n = 312)
Upper respiratory tract infection	73 (12)	28 (9)	27 (9)
Headache	50 (8)	23 (8)	5 (2)
Nasopharyngitis	48 (8)	14 (5)	20 (6)
Arthralgia	43 (7)	14 (5)	15 (5)
Diarrhea	38 (6)	19 (6)	9 (3)
Nausea	32 (5)	15 (5)	9 (3)
Influenza	30 (5)	12 (4)	14 (4)
Dizziness	29 (5)	7 (2)	5 (2)

No clinically meaningful differences in adverse event rates were observed between ISL/LEN and B/F/TAF or SOC through Week 48

^aOccurring in ≥ 2% of participants in the Pooled ISL/LEN group. Two incident cases of HBV infection were reported across the two studies, one in ISLEND-1 and one in ISLEND-2. AE, adverse event; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; ISL/LEN, islatravir/lenacapavir; SOC, standard of care.

Adverse Events by Treatment Group and Subgroup

AEs – any grade, n/N (%)		Pooled ISL/LEN (n = 618)	B/F/TAF (n = 303)	SOC (n = 312)
Assigned sex at birth	Male	364/446 (82)	190/245 (78)	160/206 (78)
	Female	126/172 (73)	48/58 (83)	81/106 (76)
Age, years	< 65	411/519 (79)	205/263 (78)	206/270 (76)
	≥ 65	79/99 (80)	33/40 (83)	35/42 (83)
Race ^a	Black	141/183 (77)	77/100 (77)	70/99 (71)
	White	230/278 (83)	105/128 (82)	107/134 (80)
	Other ^b	97/130 (75)	42/58 (72)	53/68 (78)
Ethnicity ^a	Hispanic or Latine	112/135 (83)	71/87 (82)	44/61 (72)
	Not Hispanic or Latine	355/456 (78)	156/202 (77)	185/239 (77)
Geographic region	US	272/344 (79)	141/183 (77)	119/162 (73)
	Non-US	218/274 (80)	97/120 (81)	122/150 (81)
Baseline CD4 ⁺ T-cell count, cells/μL	< 500	99/123 (80)	43/63 (68)	44/66 (67)
	≥ 500	391/495 (79)	195/240 (81)	197/246 (80)
Baseline eGFR, mL/min	30-60	26/39 (67)	15/17 (88)	14/19 (74)
	60-90	146/188 (78)	68/92 (74)	81/109 (74)
	> 90	318/391 (81)	155/194 (80)	146/184 (79)

Incidence of adverse events was similar between treatment groups across subgroups, including age and race

Conclusions

- In the integrated analyses of ISLEND-1 and ISLEND-2, switching to once-weekly ISL/LEN maintained virologic suppression at Week 48 at rates similar to those observed with daily B/F/TAF or SOC across the evaluated subgroups, including age, sex, race, geographic region, presence of M184V/I mutation, baseline CD4+ T-cell count, and baseline eGFR
- No clinically meaningful differences in CD4+ T-cell count changes were observed between treatment groups, supporting immunologic stability following switch to ISL/LEN; there were no discontinuations due to decline in CD4+ T-cell or lymphocyte counts
- Once-weekly oral ISL/LEN was well tolerated, and the incidence of AEs was generally consistent across subgroups

These results support the potential of ISL/LEN to be the first complete once-weekly oral single-tablet regimen for PWH

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