Table S1: Details on participants with Baseline INSTI RAMs and no treatment failure.

ID	INSTI RAMs	Treatment Group	Treatment Outcome at Week 48
1	T66T/A E92E/Q S147S/G Q148Q/R N155N/H	BIC+LEN 25 mg	Virologic Suppression
2	R263R/K	BIC+LEN 25 mg	Virologic Suppression
3	T66T/A	BIC+LEN 25 mg	Virologic Suppression
4	G140G/S Q148Q/H	BIC+LEN 25 mg	Virologic Suppression
5	Q148Q/H	BIC+LEN 25 mg	Virologic Suppression
6	Q148Q/R	Complex ART	Virologic Suppression
7	N155N/H	BIC+LEN 25 mg	Participant's decision to discontinue (Virologic Suppression at last visit)
8	N155N/H	BIC+LEN 25 mg	Virologic Suppression
9	N155N/H	BIC+LEN 25 mg	Virologic Suppression
10	G140G/R	BIC+LEN 25 mg	Virologic Suppression

BIC = bictegravir; INSTI = integrase strand-transfer inhibitor; LEN = lenacapavir; RAM = resistance-associated mutation.

SUPPLEMENTARY MARTERIALS AND METHODS

Structural modeling and rotamer analysis

The CA-LEN complex from PDB 6V2F served as the template. Side-chain rotamers at residue 74 (N74N/WT, N74T, N74D) were sampled in UCSF ChimeraX using the Dunbrack 2010 backbone-dependent rotamer library[1, 2] with standard probapility cutoffs. Potential steric clashes with LEN were evaluated using ChimeraX clash detection with default settings; rotamers with predicted prevalence >1% were retained for visualization, and clashes are depicted in the figure as dashed purple annotations.

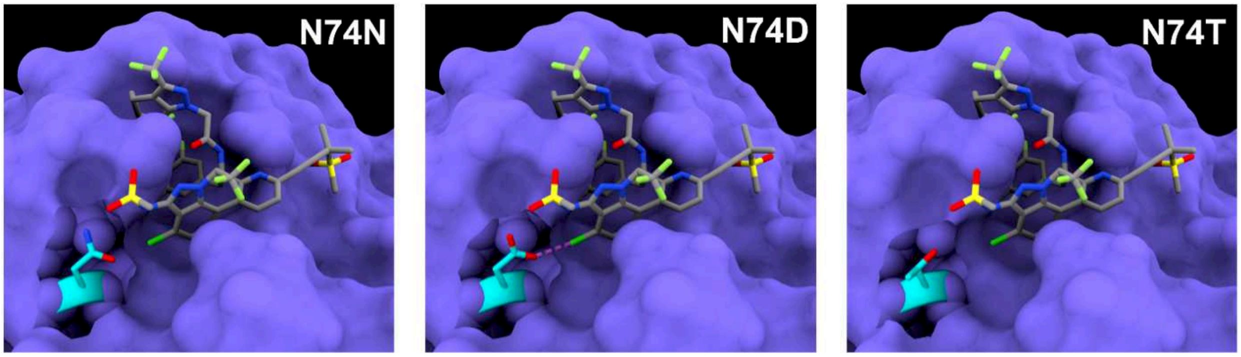

Figure S1. N74 rotamer analysis and steric compatibility with LEN (PDB 6V2F).

Representative side-chain rotamers of residue 74 were modeled in ChimeraX for WT (N74N), N74T, and N74D using the standard rotamer probability cutoffs and visualized in the LEN-binding pocket from PDB 6V2F. The protein is shown as a dark blue surface; LEN is in gray sticks with heteroatoms colored by element; residue-74 side chains are in cyan sticks. In WT and N74T, samples rotamers (>1% prevalence) do not exhibit steric clashes with LEN. In contrast, the highest-probability N74D rotamer shows steric overlap with LEN, indicated by dashed purple lines (ChimeraX clash annotations). Rotamers and potential molecular clashes of mutant amino acids were evaluated in ChimeraX using the Dunbrack 2010 backbone-dependent rotamer library.

D = aspartic acid; LEN = lenacapavir; N = asparagine; PDB = protein database; T = threonine; WT = wild-type;

REFERENCES in SUPPLEMENTARY MATERIAL

1. Meng EC, Goddard TD, Pettersen EF, Couch GS, Pearson ZJ, Morris JH, et al. **UCSF ChimeraX: Tools for structure building and analysis**. *Protein Science* 2023; 32(11):e4792.

2. Shapovalov Maxim V, Dunbrack Roland L, Jr. **A Smoothed Backbone-Dependent Rotamer Library for Proteins Derived from Adaptive Kernel Density Estimates and Regressions**. *Structure* 2011; 19(6):844-858.