Brief Communication

Current Evidence on Islatravir Drug Resistance and Implications for Future HIV Treatment

Annemarie M. Wensing, MD, PhD[1]; Vincent Calvez, MD, PhD[2]; Francesca Ceccherini-Silberstein, PhD[3]; Charlotte Charpentier, PharmD, PhD[4]; Huldrych F. Günthard, MD[5]; Roger Paredes, MD, PhD[6]; Robert W. Shafer, MD[7]; Douglas D. Richman, MD[8]

[1]University Medical Center Utrecht, The Netherlands, and Ezintsha Wits Reproductive Health and HIV Institute, University of the Witwatersrand, Johannesburg, South Africa; [2]Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, AP-HP, Hôpitaux Universitaires Pitié Salpêtrière—Charles Foix, Laboratoire de Virologie, and Sorbonne Université School of Medicine, Paris, France; [3]University of Rome Tor Vergata, Rome, Italy; [4]Paris Cité University and Bichat-Claude Bernard Hospital, France; [5]University Hospital Zurich and Institute of Medical Virology, University of Zurich, Switzerland; [6]Hospital Universitari Germans Trias i Pujol, Badalona, Spain, and Universitat Politècnica de Catalunya–BarcelonaTech, Terrassa, Spain; [7]Stanford University Medical School, California; [8]University of California San Diego

Keywords: antiretroviral therapy, drug resistance, HIV, ISL, islatravir, mutation

Background

Islatravir (ISL; MK-8591; 4′-ethynyl-2-fluoro-2′-deoxyadenosine; EFdA) is the first antiviral drug that acts as a nucleoside reverse transcriptase translocation inhibitor (NRTTI). Unlike classic nucleoside and nucleotide analogue reverse transcriptase inhibitors (nRTIs) that terminate viral DNA chain extension upon incorporation because they lack the 3′-hydroxyl group, ISL primarily interferes with reverse transcriptase (RT) translocation. After ISL-triphosphate (ISL-TP) is incorporated into viral DNA, RT has a reduced ability to shift along the template to effectively position the subsequent nucleotide for incorporation, thereby inhibiting further DNA synthesis. In addition, ISL is frequently misincorporated by RT, leading to mismatched primer termini that further reduces productive DNA elongation.[1]

ISL has highly potent antiviral activity against both wild-type HIV-1 (50% effective concentration [EC_{50}], ~0.07–0.20 nM) and a broad panel of nRTI-resistant clinical isolates in vitro.[2,3] It is also active against HIV-2, with an EC_{50} on average 4.8-fold more potent than observed for HIV-1.[4]

Author Correspondence
Write to Annemarie M. Wensing, MD, PhD, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Heidelberglaan 100, Utrecht 3584 CX, The Netherlands, or email A.M.J.Wensing@umcutrecht.nl

In late 2025, a fixed-dose combination of the nonnucleoside reverse transcriptase inhibitor (NNRTI) doravirine (DOR) and ISL (DOR/ISL 100/0.25 mg once daily) was filed with the US Food and Drug Administration for therapy in adults with HIV who are virologically suppressed on their antiretroviral (ARV) regimens and have no known resistance to either drug. In parallel, a once-weekly oral regimen combining ISL with the capsid inhibitor lenacapavir is currently undergoing phase III clinical investigation as maintenance therapy for people with HIV-1 who are virologically suppressed.

People with HIV who are expected to be eligible for combinations with ISL may have been previously exposed to ARV therapy or preexposure prophylaxis, during which resistance mutations may have emerged. In addition, some individuals may have acquired virus containing resistance mutations through the transmission of a resistant strain.

The most recent International Antiviral Society–USA (IAS-USA) mutation chart provides an established framework for interpreting DOR resistance–associated substitutions.[5] In contrast, experience with ISL is currently confined to clinical trial settings, and further data are required to gain more insight into potential resistance selection and the clinical significance of preexisting ISL-associated mutations before a resistance bar can be established in the mutation chart.[5]

This report summarizes available evidence on ISL susceptibility and aims to support clinical decision-making when DOR/ISL is approved, particularly in the presence of previously selected or transmitted resistance mutations (**Table 1**).

Published ahead of issue March 30, 2026 © IAS–USA

Table 1. Overview of In Vitro Resistance Data for Islatravir

Mutation/ pattern	Phenotypic resistance (fold increase compared with wild-type virus)	Subtype	Technique/ assay	Comments	Reference (year)
M184I	4×-6×	B	Clinical isolates/ SDM		Diamond et al (2022)[1] Grobler et al (2018)[3] Cilento et al (2021)[9]
M184V	4×–10×	A, B, C	Clinical isolates/ SDM		Diamond et al (2022)[1] Kawamoto et al (2008)[2] Aulicino et al (2014)[8] Cilento et al (2021)[9] Byun et al (2024)[19]
A114S + M184V	24×-37×	B	SDM		Diamond et al (2022)[1] Cilento et al (2021)[9]
A114S	2×	B	SDM		Diamond et al (2022)[1] Cilento et al (2021)[9]
V90I + M184I	4×	B	SDM		Diamond et al (2022)[1]
V90I	1×	B	SDM		Diamond et al (2022)[1]
L74I + M184I	4×	B	SDM		Diamond et al (2022)[1]
I142V + T165R + M184V	22×	B	SDM		Kawamoto et al (2008)[2]
M41L + A114S + M184V	65×		SDM		Diamond et al (2022)[1]
M184I/V + 1 TAM	<4×	B	Clinical isolates		Giammarino et al (2025)[7]
M184I/V + 2-3 TAMs	2×-21×	B	Clinical isolates		Grobler et al (2018)[3] Giammarino et al (2025)[7]
M184I/V + 4-6 TAMs	2×-38×	B	Clinical isolates		Grobler et al (2018)[3] Giammarino et al (2025)[7]
M184V + 1 or 2 TAMs	4×-10×	C	Clinical isolates	Additive reduction in susceptibility up to 19× with increasing number of TAM-2[a]	Byun et al (2024)[19]
69insert	<4×-10×	B	Clinical isolates	69insert is typically observed in the background of TAMs	Grobler et al (2018)[3]
K65R	<1×	A, B, C	Clinical isolates/ SDM	Increased ISL-TP incorporation; hypersusceptibility	Diamond et al (2022)[1] Kawamoto et al (2008)[2] Grobler et al (2018)[3] Michailidis et al (2013)[20]
K65R + M184I/V	2×	B, C	Clinical isolates		Grobler et al (2018)[3] Byun et al (2024)[19]
M184I	14×-22×	Circulating BF recombinant forms	Clinical isolates		Aulicino et al (2014)[8]
M184V	5×-34×	Circulating BF recombinant forms	Clinical isolates		Aulicino et al (2014)[8]

[a]TAM-2 mutations are D67N + K70R + T215F/Y + K219Q/E.

Abbreviations: ISL, islatravir; SDM, site-directed mutagenesis; TAM, thymidine analogue mutation; TP, triphosphate.

Published ahead of issue March 30, 2026 © IAS–USA

Table 2. Clinical Interpretation of nRTI Mutations

Clinical setting	Recommendation
Adults with virologically suppressed HIV-1; no nRTI or NNRTI resistance history	DOR/ISL is an appropriate switch option
M184I/V only	Clinical data are lacking; consider alternative regimens until more data are available unless the potential benefits of ISL outweigh uncertainty
M184I/V + TAM-2	Impact on efficacy not yet established; avoid use until further data are available
K65R (alone or with M184I/V)	DOR/ISL is an appropriate switch option due to hypersusceptibility induced by K65R
Ambiguous M184I by proviral DNA	Potential APOBEC-induced artifact; confirm with historical RNA genotypes before using ISL

Abbreviations: APOBEC, apolipoprotein B mRNA-editing enzyme catalytic polypeptide; DOR, doravirine; ISL, islatravir; NNRTI, nonnucleoside reverse transcriptase inhibitor; nRTI, nucleoside and nucleotide analogue reverse transcriptase inhibitor; TAM, thymidine analogue mutation.

Phenotypic Testing of Clinical Isolates

No subtype-specific loss of intrinsic potency has been demonstrated.[3,6] In 2025, Giammarino and colleagues analyzed various subtype B isolates from individuals with viruses containing historical nRTI resistance mutations.[7] Although a clinical cutoff for reduced clinical activity has not yet been established, ISL fold-change values in M184V-containing isolates varied but were generally below the threshold associated with loss of potency for other nRTIs and were still below the drug levels achieved in vivo expected to retain substantial activity (**Table 2**). Increasing numbers of thymidine analogue mutations (TAMs) resulted in a higher level of resistance to ISL in the subset of viruses harboring the M184I/V mutation.[3] Notably, one report described greater variability in ISL fold-change values for M184I/V, with increases of up to approximately 34-fold observed in a limited number of clinical isolates of circulating B/F recombinant viruses.[8] In contrast, clinical isolates containing K65R alone generally demonstrated increased susceptibility to ISL. When M184V was present in combination with K65R, susceptibility to ISL was preserved.[1,3]

Mechanisms of Resistance to ISL In Vitro

Resistance to ISL is primarily driven by the emergence of M184I/V. M184I is typically the first mutation selected in vitro and is later replaced by M184V. Other mutations observed more than once in combination with M184I/V include V90I, A114S, and C162Y.[1,9] Based on available in vitro phenotypic data, M184I and M184V confer minimal to modest reductions in ISL susceptibility, whereas the other individual substitutions appear to have minimal or no impact on ISL susceptibility.[1,2,9,10] However, the presence of A114S with M184I/V results in a greater reduction in susceptibility (**Table 1**). Notably, A114S was associated with markedly reduced fitness and was identified rarely in independent passage experiments.[1] Cilento and colleagues[9] reported reduced catalytic efficiency (kcat/Km) compared with wild-type RT: a 2.1-fold decrease for A114S alone and a 6.5-fold decrease for A114S/M184V/A502V. In addition, a structural study[11] has shown that ISL interacts with residues A114, Y115, F160, M184, and D185. These findings indicate that changes at positions A114 and M184 alter the local structure of the binding pocket and are associated with reduced efficiency of the incorporation of ISL-TP.

Importantly, ISL maintains activity against numerous common nRTI resistance mutations selected by other agents. Site-directed mutant viruses containing resistance mutations, such as K65R, L74V, and Q151M, have been associated with hypersusceptibility to ISL. Viral constructs with 3 to 4 TAMs had no or minimal impact on susceptibility in the absence of M184I/V.[1-3]

Impact of Resistance in Clinical Studies

A short-course monotherapy study of doses between 0.5 mg and 30 mg did not result in the emergence of resistance mutations. Individuals who were treatment naive had a decrease of 1.26 $\log_{10}$ copies/mL in HIV-1 RNA level 7 days after a single dose of 0.5 mg ISL.[12] These doses in the monotherapy study were higher than the expected approved dose of 0.25 mg. The phase III studies evaluating the dose of 0.25 mg ISL with DOR (MK-8591A-051 and MK-8591A-052) enrolled adults with HIV-1 RNA levels below 50 copies/mL for 3 months or longer, with no prior virologic failure. Individuals with HIV carrying at least 1 of the following NNRTI mutations were excluded: V106A/M, V108I, Y188L, H221Y, P225H, F227C/L/V, M230I/L, L234I,

Published ahead of issue March 30, 2026 © IAS–USA

P236L, Y318F. At week 48, virologic suppression was maintained in more than 90% of participants receiving DOR/ISL.[13,14] Resistance mutations resulting in reduced susceptibility to DOR/ISL were detected in 2 cases who discontinued their drug regimens because of lack of antiviral efficacy before 48 weeks. The following mutations at resistance-related positions in RT were detected: A98G + V106I + Y188L with M184V and multiple TAMs in one case and V106M + Y188W + F227L with M184T and multiple TAMs in the other case. Of note, these profiles were also detected in proviral DNA samples taken at baseline.

A subsequent phase III study evaluating 0.25 mg ISL with DOR (MK-8591A-053) enrolled adults with HIV-RNA levels higher than 500 copies/mL who had never been treated for HIV.[15] Individuals carrying at least one of the above-listed exclusionary NNRTI mutations or the following nRTI mutations were excluded: K65R/E/N, T69insert, K70E, Q151M, M184I/V, or 3 or more TAMs (M41L, D67N, K70R L210W, T215F/Y, K219E/Q). At week 48, virologic suppression was maintained in more than 90% of participants receiving DOR/ISL. Two individuals with virologic rebound acquired resistance mutations (Y188L with M184I and L74I + V106A + F227L with M184V), resulting in 2.42- and 6.69-fold increases in IC_{50} to ISL, respectively, and maximal increases in IC_{50} to DOR.

Retrospective analyses suggest that M184I/V mutations detected by proviral DNA sequencing are not associated with the loss of virologic control after switching to ISL with DOR.[16,17] However, interpretation of these findings requires caution. Apolipoprotein B mRNA-editing enzyme catalytic polypeptide, which is part of the host innate antiviral immune response, can introduce hypermutations into HIV, resulting in defective proviral genomes that may complicate the interpretation of resistance testing results. In particular, the detection of M184I in proviral DNA does not necessarily indicate clinically relevant resistance. Therefore, results of proviral DNA resistance testing should be interpreted in conjunction with ARV treatment history and prior virologic response, rather than used in isolation to guide clinical decision-making.[18]

Conclusion

Key points for clinicians are summarized in the Box. Current evidence supports the use of ISL in individuals in whom there is no evidence of nRTI resistance. In vitro data suggest only modest susceptibility reductions if the M184I/V mutation alone is present. ISL likely retains substantial activity against these viruses; however, clinical data are yet to be generated. ISL-containing regimens may be used in people with HIV who do not have documented nRTI resistance by RNA testing, recognizing that efficacy in the presence of nRTI-associated drug resistance mutations may well exist but has not yet been demonstrated. Results from drug resistance tests using proviral DNA should be interpreted with caution.

Box. Key Points for Clinicians

- M184I/V results in minor or modest reductions of ISL susceptibility; high-level resistance requires the addition of the A114S mutation, which is rarely observed in clinical isolates (<0.01%).[1,9]
- Phenotypic analysis of clinical isolates indicates that M184V + TAM combinations yield marked fold-change increases in the 50% effective concentration of ISL.
- Available phase III data are derived exclusively from individuals without evidence of relevant nRTI resistance mutations.
- Results from resistance testing using proviral DNA should be interpreted cautiously.[17] APOBEC-mediated hypermutation can generate the M184I mutation.
- Historical RNA genotypic test results, if available, can be applied to confirm archived drug resistance mutations in replication-competent HIV.
- In the absence of historical resistance testing, clinicians could review prior treatment history, including periods of viral rebound or incomplete suppression, to assess whether resistance selection is likely to have occurred.

Abbreviations: APOBEC, apolipoprotein B mRNA-editing enzyme catalytic polypeptide; ISL, islatravir; nRTI, nucleoside and nucleotide analogue reverse transcriptase inhibitor; TAM, thymidine analogue mutation.

The IAS–USA has identified and mitigated ahead of time any possible conflicts of interest that may influence CME activities with regard to exposition or conclusion. All financial relationships with ineligible companies for the authors and planners/reviewers are below.

Financial relationships with ineligible companies within the past 24 months: Dr Calvez reported serving as an advisor or consultant to and receiving research grants from Merck Sharp & Dohme, Inc, ViiV Healthcare, and Gilead Sciences, Inc. (Updated February 2, 2026) *Dr Ceccherini-Silberstein reported serving as a consultant to Gilead Sciences, Inc, and Merck Sharp & Dohme, Inc, and receiving research grants from ViiV Healthcare and Gilead Sciences, Inc.* (Updated January 29, 2026) *Dr Charpentier reported serving as an advisor or consultant for ViiV Healthcare, Gilead Sciences, Inc, and MSD Pty, LTD.* (Updated February 2, 2026) *Dr Günthard reported serving as a consultant to Merck & Co, Inc, participation in a data monitoring committee for Merck & Co., Inc; and receiving research grants from ViiV Healthcare.* (Updated January 29, 2026) *Dr Paredes reported receiving research grants from ViiV Healthcare, Gilead Sciences, Inc, and Merck Sharp & Dohme, Inc, and serving as a consultant for Gilead Sciences, Inc, Pfizer, Inc, Merck Sharp & Dohme, Inc, and ViiV Healthcare.* (Updated February 2, 2026) *Dr Richman*

reported consulting or advisor fees from Generate Biomedicines and Gilead Sciences, Inc. (Updated January 29, 2026) *Dr Shafer reported no financial relationships with ineligible companies. (*Updated February 2, 2026) *Dr Wensing reported advisor or consulting fees to her institution from Merck Sharp & Dohme, Roche Laboratories, Gilead Sciences, Inc, and ViiV Healthcare; grants to her institution from Gilead Sciences, Inc; and noncash provision of medicines, equipment, or administrative support to her institution from ARK.* (Updated January 28, 2026) *All relevant financial relationships with ineligible companies have been mitigated.*

References

1. Diamond TL, Ngo W, Xu M, et al. Islatravir has a high barrier to resistance and exhibits a differentiated resistance profile from approved nucleoside reverse transcriptase inhibitors (NRTIs). *Antimicrob Agents Chemother*. 2022;66(6):e0013322. doi:10.1128/aac.00133-22
2. Kawamoto A, Kodama E, Sarafianos SG, et al. 2'-deoxy-4'-C-ethynyl-2-halo-adenosines active against drug-resistant human immunodeficiency virus type 1 variants. *Int J Biochem Cell Biol.* 2008;40(11):2410-2420. doi:10.1016/j.biocel.2008.04.007
3. Grobler J, Huang Q, Hazuda D, Lai M. Efficacy of MK-8591 against diverse HIV-1 subtypes and nRTI-resistant clinical isolates. *J Int AIDS Soc*. 2018;21.
4. Wu VH, Smith RA, Masoum S, et al. MK-8591 (4'-Ethynyl-2-Fluoro-2'-Deoxyadenosine) exhibits potent activity against HIV-2 isolates and drug-resistant HIV-2 mutants in culture. *Antimicrob Agents Chemother*. 2017;61(8): e00744-17. doi:10.1128/AAC.00744-17
5. Wensing AM, Calvez V, Ceccherini-Silberstein F, et al. 2025 update of the drug resistance mutations in HIV-1. *Top Antivir Med*. 2025;33(2):457-473.
6. Njenda DT, Aralaguppe SG, Singh K, et al. Antiretroviral potency of 4'-ethnyl-2'-fluoro-2'-deoxyadenosine, tenofovir alafenamide and second-generation NNRTIs across diverse HIV-1 subtypes. *J Antimicrob Chemother.* 2018;73(10):2721-2728. doi:10.1093/jac/dky256
7. Giammarino F, Paletti C, Bartolini N, et al. Combined doravirine and islatravir cooperate to inhibit nRTI and NNRTI resistant HIV-1 in vitro. *Antiviral Res*. 2025;239:106157. doi:10.1016/j.antiviral.2025.106157
8. Aulicino PC, Sharma S, Truong K, et al. Variable antiviral activity of islatravir against M184I/V mutant HIV-1 selected during antiretroviral therapy. *J Antimicrob Chemother*. 2024;79(2):370-374. doi:10.1093/jac/dkad390
9. Cilento ME, Reeve AB, Michailidis E, et al. Development of human immunodeficiency virus type 1 resistance to 4'-ethynyl-2-fluoro-2'-deoxyadenosine starting with wild-type or nucleoside reverse transcriptase inhibitor-resistant strains. *Antimicrob Agents Chemother.* 2021; 65(12):e0116721. doi:10.1128/AAC.01167-21
10. Oliveira M, Brenner BG, Xu H, Ibanescu RI, Mesplede T, Wainberg MA. M184I/V substitutions and E138K/M184I/V double substitutions in HIV reverse transcriptase do not significantly affect the antiviral activity of EFdA. *J Antimicrob Chemother*. 2017;72(11):3008-3011. doi:10.1093/jac/dkx280
11. Takamatsu Y, Das D, Kohgo S, et al. The high genetic barrier of EFdA/MK-8591 stems from strong interactions with the active site of drug-resistant HIV-1 reverse transcriptase. *Cell Chem Biol.* 2018;25(10):1268-1278. e3. doi:10.1016/j.chembiol.2018.07.014
12. Schurmann D, Rudd DJ, Zhang S, et al. Safety, pharmacokinetics, and antiretroviral activity of islatravir (ISL, MK-8591), a novel nucleoside reverse transcriptase translocation inhibitor, following single-dose administration to treatment-naive adults infected with HIV-1: an open-label, phase 1b, consecutive-panel trial. *Lancet HIV*. 2020;7(3):e164-e172. doi:10.1016/S2352-3018(19)30372-8
13. Orkin C, Mngqibisa R, Velez JD, et al. Switch to fixed-dose doravirine (100 mg) and islatravir (0.25 mg) once daily in virologically suppressed adults with HIV-1 on oral antiretroviral therapy: 48-week results of a phase 3, multicentre, randomised, open-label, non-inferiority trial. *Lancet*. 2026;407(10528):599-610. doi:10.1016/S0140-6736(25)01945-2
14 Colson AE, Mills AM, Ramgopal MN, et al. Switch to fixed-dose doravirine (100 mg) and islatravir (0.25 mg) once daily in virologically suppressed adults with HIV-1 on bictegravir, emtricitabine, and tenofovir alafenamide: 48-week results of a phase 3, multicentre, randomised, controlled, double-blind, non-inferiority trial. *Lancet*. 2026;407(10528):611-621. doi:10.1016/S0140-6736(25)01948-8
15. Rockstroh JK, Kassim S, Paredes R, et al. Fixed-dose daily doravirine (100 mg) with islatravir (0.25 mg) versus bictegravir, emtricitabine, and tenofovir alafenamide for initial HIV-1 therapy: 48-week results of a phase 3, randomised, controlled, double-blind, non-inferiority trial. *Lancet HIV*. 2026 Feb 25 (online ahead of print). doi:10.1016/S2352-3018(26)00033-0
16. Asante-Appiah E, Joseph S, Cha J, et al. Switching to doravirine/islatravir maintains viral suppression regardless of archived mutations [Abstract 694]. In Special Issue: Abstracts From the CROI 2024 Conference on Retroviruses and Opportunistic Infections. *Top Antivir Med*. 2024;32(1):198-199.
17. Diamond T. Switching to doravirine/islatravir (100 mg/0.25 mg) once daily maintaned viral suppression in the presence of archived M184I/V resistance-associated mutations in proviral DNA. Poster presented at: IAS Conference on HIV Science (IAS 2025); July 13-16, 2025; Kigali, Rwanda.
18. Wensing AM, Charpentier C, Calvez V, et al. Utilizing HIV proviral DNA to assess for the presence of HIV drug resistance. *Clin Infect Dis*. 2025;81(4):e132-e136. doi:10.1093/cid/ciaf161
19. Byun H, Papathanasopoulos MA, Steegen K, Basson AE. Thymidine analogue mutations with M184V significantly decrease phenotypic susceptibility of HIV-1 subtype C reverse transcriptase to islatravir. *Viruses*. 2024;16(12):1888. doi:10.3390/v16121888
20. Michailidis E, Ryan EM, Hachiya A, et al. Hypersusceptibility mechanism of tenofovir-resistant HIV to EFdA. *Retrovirology*. 2013;10:65. doi:10.1186/1742-4690-10-65

Top Antivir Med. 2026 March 30 (ahead of issue).
©2026, IAS–USA. All rights reserved.