

Doravirine and Islatravir (IDVYNZO) in HIV-1 Infection

National Drug Monograph

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VA Pharmacy Services and National Formulary Committee

The purpose of VA National Formulary Committee drug monographs is to provide a focused drug review for making formulary decisions. Product Information or other resources should be consulted for detailed and most current drug information.

FDA PRESCRIBING INFORMATION¹

Description / MOA	IDVYNZO is a fixed-dose combination of doravirine (DOR) – a non-nucleoside reverse transcriptase inhibitor (NNRTI), and islatravir (ISL) – a nucleoside analog reverse transcriptase translocation inhibitor (NRTTI). DOR competitively inhibits HIV-1 reverse transcriptase and ISL blocks translocation and induces structural changes in viral DNA to prevent further nucleotide incorporation.
Indication	Treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen with no history of virologic treatment failure and no known substitutions associated with resistance to DOR. IDVYNZO is indicated as a complete regimen and co-administration with other antiretroviral agents is not recommended.
Under Review	
Dosage Regimen	One tablet (100mg DOR/0.25mg ISL) orally once daily with or without food If co-administered with rifabutin, take one tablet of IDVYNZO once daily followed by one tablet of DOR 100mg approximately 12 hours later.
Dosage Forms Under Review	Film-coated oral tablets containing 100mg DOR and 0.25mg ISL
Pretreatment Procedures	☐ If switching from strong CYP3A inducers, a minimum 4-week cessation period is recommended prior to initiation.
Treatment Monitoring	☐ Patients with Hepatitis B virus (HBV) co-infection should be closely monitored for potential liver injury if switching from an antiretroviral regimen with activity against HBV. Specific anti-HBV therapy should be considered and initiated, as clinically appropriate.

EFFICACY CONSIDERATIONS

Trial	Trial 051²
Design	Phase 3, randomized, active-controlled, open-label, non-inferiority trial
Population	N=551 virologically suppressed (HIV-1 RNA <50 copies/mL) adults on any oral 2-drug or 3-drug antiretroviral (ART) regimen for at least 3 months with no history of treatment failure or DOR resistance. <u>Key Exclusions:</u> Active AIDS-defining opportunistic infection within 30 days before screening; active HBV infection; chronic hepatitis C virus (HCV) infection; any prior use of long-acting HIV therapy (e.g., cabotegravir or lenacapavir); any previous exposure to islatravir; CD4 of <50 cells/μL <u>Demographics:</u> Median age: 51 years; 60% male; 39% White; 45% Black or African American; 5% Asian; median CD4 count: 706 cells/μL. At enrollment: 64% on INSTI, 30% on NNRTI, 5% on PI
Intervention	Switch to DOR 100mg and ISL 0.25mg once daily (n=366)
Comparator	Continue baseline ART regimen (n=185)
Results	<ul style="list-style-type: none"> Non-inferiority concluded if upper bound of 2-sided 95% CI for treatment difference was <4%.

Primary and Key Secondary Efficacy Endpoints

Outcome (Week 48)	DOR + ISL (n/N)	Baseline ART (n/N)	Treatment Difference (95% CI)
HIV-1 RNA ≥50 copies/mL ^a	1.4% (5/366)	4.9% (9/185)	-3.6% (-7.8, -0.8)
HIV-1 RNA <50 copies/mL ^b	95.6% (350/366) *	91.9% (170/185) *	3.8% (-0.3, 8.9)
HIV-1 RNA <200 copies/mL ^b	95.6% (350/366)	95.7% (177/185)	-0.1% (-3.5, 4.2)
Mean change in CD4 count (cells/μL) from baseline ^b	+5.4	+18.2	

^a Primary endpoint ^b Secondary endpoint

* 11 patients in DOR + ISL group and 6 patients in Baseline ART group did not have virological data available at Week 48.

Safety

- Treatment-emergent adverse effects were more common in DOR + ISL group (12%) compared to baseline ART group (4.9%); rates of serious adverse events and discontinuation due to adverse events were similar between groups.
- No adverse effects on CD4 count or total lymphocyte count observed in either group.
- No treatment-emergent resistance to either DOR or ISL was detected.

Trial	Trial 052³
Design	Phase 3, randomized, active-controlled, double-blind, double-dummy, non-inferiority trial
Population	N=513 virologically suppressed (HIV-1 RNA <50 copies/mL) adults on bicitegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) for at least 3 months with no history of treatment failure or DOR resistance. <u>Key Exclusions:</u> Same as Trial 051

Demographics: Median age: 47 years; 79% male; 61% White; 31% Black or African American; 6% Asian; median CD4 count at baseline: 691 cells/ μ L

Intervention

Switch to DOR 100mg and ISL 0.25mg once daily (n=342)

Comparator

Continue BIC/FTC/TAF once daily (n=171)

Results

- Non-inferiority concluded if upper bound of 2-sided 95% CI for treatment difference was <4%.

Primary and Key Secondary Efficacy Endpoints

Outcome (Week 48)	DOR + ISL (n/N)	BIC/FTC/TAF (n/N)	Treatment Difference (95% CI)
HIV-1 RNA $\geq$ 50 copies/mL ^a	1.5% (5/342)	0.6% (1/171)	0.9% (-1.9, 2.9)
HIV-1 RNA <50 copies/mL ^b	91.5% (313/342) *	94.2% (161/171) *	-2.6% (-7.1, 2.6)
HIV-1 RNA <200 copies/mL ^b	91.8% (314/342)	94.2% (161/171)	-2.3% (-7.1, 1.9)
Mean change in CD4 count (cells/ μ L) from baseline ^b	+30.4	+28.2	

^a Primary endpoint ^b Secondary endpoint

* 24 patients in DOR + ISL group and 9 patients in BIC/FIC/TAF group did not have virological data available at Week 48.

Safety

- No adverse effects on CD4 count or total lymphocyte count observed in either group.
- No treatment-emergent resistance to either DOR or ISL was detected.
- No clinically significant changes in lipids, kidney function (creatinine/cystatin C), bodyweight, homeostatic model assessment-insulin resistance (HOMA-IR), or bone mineral density seen in either group.

SAFETY CONSIDERATIONS^{1,2,3}**Boxed Warnings**

None

Contraindications

Co-administration with strong CYP3A inducers due to potentially significant decreases in DOR concentrations.

Co-administration with lamivudine (3TC) or emtricitabine (FTC) due to potentially significant decreases in ISL concentrations.

Other Warnings

Skin and Hypersensitivity Reactions: Severe reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) have been reported. Discontinue IDVYNSO, monitor clinical status, and initiate appropriate therapy, as indicated. **Drug Interactions:** Concomitant use of IDVYNSO and certain other drugs may result in potentially significant drug interactions, leading to loss of efficacy, possible development of resistance, and adverse reactions. Evaluate potential for drug interactions prior to and during IDVYNSO therapy and monitor for adverse reactions.

Top AEs

Diarrhea, dizziness, fatigue, abdominal distension, headache, increased weight

Drug Interactions

DOR: Primarily metabolized by CYP3A – strong inducers are contraindicated; inhibitors may increase DOR concentrations.

ISL: Primarily metabolized by adenosine deaminase (ADA) – co-administration with ADA inhibitors (e.g., pentostatin) may result in increased ISL concentrations and is not recommended. ISL also requires phosphorylation by deoxycytidine kinase (dCK) – co-administration with other dCK substrates (e.g., 3TC/FTC, cytarabine, gemcitabine) may decrease ISL concentrations and is contraindicated/not recommended. Refer to IDVYNSO prescribing information for additional information.

Pregnancy

Insufficient human data. No developmental effects observed in animal reproduction studies.

The Antiretroviral Pregnancy Registry is encouraged to be utilized to monitor exposures and outcomes in individuals exposed to IDVYNSO.

Lactation

Insufficient human data. DOR and ISL concentrations have been detected in milk of lactating animals.

Potential risks of breastfeeding include HIV-1 transmission, development of viral resistance, and serious adverse reactions.

Renal Impairment

No dosage adjustment required for estimated glomerular filtration rate (eGFR) $\geq$ 30 mL/min.

Not recommended for patients with eGFR <30 mL/min. IDVYNSO has not been studied in patients on dialysis.

Hepatic Impairment

No dosage adjustment required for mild or moderate impairment (Child-Pugh Class A or B).

Not recommended for severe hepatic impairment (Child-Pugh Class C) as IDVYNSO has not been studied in this population.

THERAPEUTIC ALTERNATIVES ⁴		
DRUG	VANF	Clinical Guidance
DOR + ISL (IDVYNSO)	PA-F	
INSTI-based STR		
BIC/FTC/TAF (BIKTARVY) tab	PA-F	Also active against HBV
DTG/ABC/3TC (TRIUMEQ) tab	PA-F	
EVG/c/FTC/TAF (GENVOYA) tab	PA-F	Also active against HBV
DTG/3TC (DOVATO) tab	PA-F	
DTG/RPV (JULUCA) tab	PA-F	
NNRTI-based STR		
DOR/TDF/3TC (DELSTRIGO) tab	PA-F	Also active against HBV
EFV/TDF/3TC (SYMFI) tab	PA-F	Also active against HBV
RPV/TAF/FTC (ODEFSEY) tab	PA-F	Also active against HBV
PI-based STR		
DRV/c/FTC/TAF (SYMTUZA) tab	PA-F	Also active against HBV

STR: single-tablet regimen

POTENTIAL PLACE IN THERAPY^{5,6,7}

1. Continued advances in ART and numerous available treatment options have made it possible for patients who are effectively virologically suppressed to switch to a different regimen.
2. When a regimen switch is indicated, potential considerations include prevention of adverse effects and toxicities, decreased pill burden, potential pregnancy, comorbidities, stigma, regimen simplification, and costs. Maintaining viral suppression following a regimen switch remains of paramount importance.
3. IDVYNSO was shown to be non-inferior to BIC/FTC/TAF and other currently available single-tablet regimens in maintaining virological suppression in patients who were already on effective treatment for at least 3 months and can serve as another potential ART option for patients whom a regimen switch is clinically indicated or desired.
4. For patients with HIV/HBV co-infection, switching to IDVYNSO would require use of an additional medication with anti-HBV activity and would not be generally recommended in these circumstances to avoid increased pill burden and regimen complexity.
5. Close monitoring to assess tolerability, viral suppression, adherence, and safety is recommended during the first 3 months after a regimen switch.

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References

- 1 IDVYNSO (doravirine and islatravir) tablets, for oral use [prescribing information online]. Rahway, NJ: Merck & Co., Inc. April 2026.
- 2 Orkin, Chloe, 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." *The Lancet*, vol. 407, no. 10377, 7 Feb. 2026, pp. 599–610.
- 3 Colson, Amy E., 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." *The Lancet*, vol. 407, no. 10377, 7 Feb. 2026, pp. 611–621.
- 4 Panel on Antiretroviral Guidelines for Adults and Adolescents. "Drug Characteristics Tables." *Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV*, U.S. Department of Health and Human Services, 25 Sept. 2025, clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/drug-characteristics-tables.
- 5 Panel on Antiretroviral Guidelines for Adults and Adolescents. "Optimizing Antiretroviral Therapy in the Setting of Viral Suppression." *ClinicalInfo.HIV.gov*, U.S. Department of Health and Human Services, 11 Sept. 2024, clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/optimizing-antiretroviral-therapy.
- 6 European AIDS Clinical Society. "Switch Strategies." *EACS Guidelines for the Management of People Living with HIV in Europe*, version 13.0, Oct. 2025, eacs.sanfordguide.com/en/eacs-hiv/art/eacs-switch-strategies.
- 7 World Health Organization. *WHO Updated Recommendations on HIV Clinical Management: Recommendations for a Public Health Approach*. World Health Organization, 2025.