

Doravirine (DOR, Pifeltro)

(Last updated April 7, 2021; last reviewed April 7, 2021)

Formulations

Tablet: 100 mg

Fixed-Dose Combination Tablet:

- [Delstrigo] Doravirine 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg

When using fixed-dose combination (FDC) tablets, refer to other sections of the [Drug Appendix](#) for information about the individual components of the FDC. See also [Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents](#).

For additional information, see [Drugs@FDA](#) or [DailyMed](#).

Dosing Recommendations

Child and Adolescent Dose:

- Doravirine (DOR) is not approved for use in children or adolescents aged <18 years.

Adult (Aged ≥18 Years) Dose:

- DOR 100 mg once daily in antiretroviral (ARV)-naive patients and ARV-experienced patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen with no history of treatment failure and no known mutations associated with resistance to DOR.

[Delstrigo] Doravirine (DOR)/Lamivudine (3TC)/Tenofovir Disoproxil Fumarate (TDF)

Adult (Aged ≥18 Years) Dose:

- One tablet once daily in ARV-naive patients and ARV-experienced patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen with no history of treatment failure and no known mutations associated with resistance to DOR.

Selected Adverse Events

- Nausea
- Abdominal pain
- Diarrhea
- Abnormal dreams
- Insomnia, somnolence

Special Instructions

- DOR can be taken with or without food.
- **Do not use** DOR with other non-nucleoside reverse transcriptase inhibitors.
- When DOR is coadministered with rifabutin, the dose should be increased from DOR 100 mg once daily to DOR 100 mg twice daily. When DOR/3TC/TDF (Delstrigo) is coadministered with rifabutin, an additional 100-mg dose of freestanding DOR needs to be administered approximately 12 hours later.
- Screen patients for hepatitis B virus (HBV) infection before using Delstrigo, which contains 3TC and TDF. Severe acute exacerbation of HBV can occur when 3TC or TDF are discontinued; therefore, hepatic function and hepatitis B viral load should be monitored for several months after halting therapy with 3TC or TDF.

Metabolism/Elimination

- DOR is metabolized by the enzyme cytochrome P450 3A.
- DOR has multiple interactions with several drugs (see Drug Interactions section below).

Doravirine Dosing in Patients with Hepatic

Impairment:

- Dose adjustment is not required in patients with mild or moderate hepatic impairment. DOR has not been studied in patients with severe hepatic impairment.

Doravirine Dosing in Patients with Renal Impairment:

- Dose adjustment is not required when using DOR in patients with mild, moderate, or severe renal impairment. DOR use has not been studied in patients with end-stage renal disease or in patients on dialysis.
- DOR administered with 3TC and TDF as components of Delstrigo **is not recommended** in patients with estimated creatinine clearance <50 mL/min.

Drug Interactions (see also the [Adult and Adolescent Antiretroviral Guidelines](#) and the [HIV Drug Interaction Checker](#))

- Doravirine (DOR) is a cytochrome P450 (CYP) 3A substrate that is associated with several important drug interactions with drugs that are strong CYP3A enzyme inducers. Coadministration with these drugs may cause significant decreases in DOR plasma concentrations and potential decreases in efficacy and may lead to the development of resistance. Before DOR is administered, a patient's medication profile should be carefully reviewed for potential drug interactions with DOR.^{1,2}
- DOR **should not be coadministered** with the CYP3A inducing non-nucleoside reverse transcriptase inhibitors (NNRTIs) efavirenz (EFV), etravirine, and nevirapine.^{3,4} In a Phase 1 trial (described below under Efficacy in Clinical Trials), DOR plasma exposure transiently decreased by 62% when DOR was started immediately after stopping EFV. However, a post-hoc analysis of the Phase 3 DRIVE-SHIFT study (described below under Efficacy in Clinical Trials) showed that, at Week 4, DOR plasma levels in patients who had switched from an EFV-based regimen to a DOR-based regimen were similar to DOR plasma levels in patients who switched from a protease inhibitor (PI)-based regimen to a DOR-based regimen (all the regimens in the study used a backbone of lamivudine [3TC] plus tenofovir disoproxil fumarate [TDF]).⁵
- DOR **should not be coadministered** with the following drugs: the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, and phenytoin; the androgen receptor inhibitor enzalutamide; the antimycobacterials rifampin and rifapentine; the cytotoxic agent mitotane; or St. John's wort.^{3,4}
- Drug interactions between DOR and rifabutin induce the metabolism of DOR and require an additional dose of DOR 100 mg to be administered 12 hours later.^{2,4}

Major Toxicities

- *More common:* Nausea, headache, fatigue, diarrhea, abdominal pain, abnormal dreams.
- *Less common (more severe):* Neuropsychiatric adverse events (AEs), including insomnia, somnolence, dizziness, and altered sensorium. Immune reconstitution inflammatory syndrome may occur.

Resistance

The International Antiviral Society-USA (IAS-USA) maintains a [list of updated resistance mutations](#) and the [Stanford University HIV Drug Resistance Database](#) offers a discussion of each mutation.

DOR is expected to have activity against HIV with isolated NNRTI resistance that is associated with substitutions at positions 103, 181, or 190. Some single mutations and combinations of viral mutations have been shown to significantly decrease the susceptibility to DOR. Specifically, clinical HIV isolates containing the Y188L substitution alone or in combinations with K103N or V106I; combinations of V106A with G190A and F227L; or combinations of E138K with Y181C and M230L have shown ≥ 100 -fold reduction in susceptibility to DOR.^{3,4} In patients with multiple NNRTI mutations, consult an HIV expert and a resistance database to evaluate the potential efficacy of DOR.

Pediatric Use

Approval

DOR is not approved by the Food and Drug Administration for use in children or adolescents aged < 18 years. An ongoing Phase 1/2 study ([IMPAACT 2014](#)) is evaluating the pharmacokinetics (PKs), safety, and tolerability of DOR and DOR/3TC/TDF in children and adolescents with HIV.

Efficacy in Clinical Trials

The efficacy of DOR was evaluated using data from four randomized adult clinical trials. The first study was a Phase 2b dose-selection, double-blind trial that enrolled treatment-naive adults with HIV.⁶ The efficacy trials included two randomized, multicenter, double-blind, active-controlled Phase 3 trials ([DRIVE-FORWARD](#) and [DRIVE-AHEAD](#)) in treatment-naive adults^{7,9} and one open-label, active-controlled, randomized, noninferiority trial that enrolled virologically suppressed adults on antiretroviral therapy (DRIVE-SHIFT).¹⁰

The dose-selection trial enrolled treatment-naive adults stratified by HIV RNA level at screening ($\leq 100,000$ copies/mL or $> 100,000$ copies/mL) and randomized participants to receive one of four different doses (25 mg, 50 mg, 100 mg, or 200 mg) of once-daily DOR or EFV 600 mg with open-label emtricitabine (FTC) 200 mg/TDF 300 mg. After dose selection at Week 24, all participants were switched to DOR 100 mg and, with additional enrollment, 216 participants were randomized to receive once-daily DOR 100 mg ($n = 108$) or EFV 600 mg ($n = 108$) for 96 weeks with FTC/TDF. At Week 24, 72.9% of participants on DOR 100 mg and 73.1% of participants on EFV 600 mg had HIV RNA < 40 copies/mL.⁶

In DRIVE-FORWARD, adult subjects received either DOR 100 mg ($n = 383$) or darunavir 800 mg/ritonavir 100 mg (DRV/r; $n = 383$) once daily, each in combination with FTC/TDF or abacavir/3TC.⁷ In DRIVE-AHEAD, adult subjects received either coformulated DOR/3TC/TDF ($n = 364$) or EFV/FTC/TDF ($n = 364$) once daily.⁸ An integrated efficacy analysis from both trials (DRIVE-FORWARD and DRIVE-AHEAD) at Week 48 demonstrated that 84.1% of patients who were treated with the DOR-based regimen achieved HIV RNA < 50 copies/mL, compared with 79.9% of patients who were treated with the DRV/r-based regimen and 80.8% of patients who were treated with EFV/FTC/TDF. Results were similar across different baseline viral loads, genders, races, and HIV-1 subtypes.⁸ **At Week 96 in the DRIVE-FORWARD trial, 277 (95%) of 292 participants who remained on DOR maintained viral suppression (that is, 73% of the overall 383 participants), whereas 248 (91%) of 273 participants who remained on DRV/r maintained viral suppression (that is, 66% of the overall 383 participants).**⁹

In the DRIVE-SHIFT study, adult subjects with HIV who were virologically suppressed for ≥ 6 months on two nucleoside reverse transcriptase inhibitors plus a boosted PI, boosted elvitegravir or on an NNRTI were randomized to switch to a once-daily, single-tablet regimen of DOR 100 mg/3TC 300 mg/TDF 300 mg or to continue their current therapy (baseline regimen). At Weeks 24 and 48, 93.7% and 90.8% of participants on the DOR/3TC/TDF regimen, respectively, had HIV RNA < 50 copies/mL, demonstrating the noninferiority of this regimen compared with the baseline regimen at Week 24.¹⁰

Pharmacokinetics

The PKs of DOR have been evaluated in treatment-naive adults aged ≥ 18 years. A Phase 2 trial evaluated DOR over a dose range of 0.25 times to two times the recommended dose in treatment-naive participants with HIV who also received FTC/TDF. No exposure-response relationship for efficacy was reported for DOR.⁸

Toxicity

In trials that compared DOR-based regimens and EFV-based regimens, central nervous system (CNS) AEs (dizziness, sleep disorder and disturbances, and altered sensorium) occurred less frequently among the patients who received DOR than among those who received EFV. In the dose-finding trial, CNS AEs were reported in 26.9% of patients on DOR-based regimens, compared with 47.2% of patients on EFV-based regimens at Week 24.⁶ In the integrated safety analysis from the DRIVE-FORWARD and DRIVE-AHEAD trials, 25.5% of patients on DOR-based regimens experienced CNS AEs at Week 48, compared with 55.9% of patients on EFV-based regimens.^{8,11} Neither DRIVE-FORWARD nor DRIVE-AHEAD included an integrase strand transfer inhibitor-based regimen as an active control. Fewer participants who received DOR-based regimens experienced diarrhea compared with those treated with DRV/r-based regimens (12.4% vs. 22.5%, respectively). In the DRIVE-SHIFT study, among adults who were receiving a ritonavir-boosted PI at study entry, mean reductions in fasting low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol at Week 24 were significantly greater in people who received DOR/3TC/TDF compared with the baseline PI-based regimen with 3TC/TDF ($P < 0.0001$).¹⁰ Similarly, the 96 weeks data from the DRIVE-FORWARD trial supported greater mean reductions in low-density lipoprotein cholesterol (−14.6 mg/dL [95% confidence interval, −18.2 to −11.0]) and non-high-density lipoprotein cholesterol (18.4 mg/dL [95% confidence interval, −22.5 to −14.3]) among participants in the DOR arm than among those in the DRV/r arm.⁹

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