Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Doravirine (DOR, Pifeltro) *(Last updated April 14, 2020; last reviewed April 14, 2020)*

**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.

**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 doravirine/lamivudine/TDF (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 text below).
### Drug Interactions

(see also the [Adult and Adolescent Antiretroviral Guidelines](https://aidsinfo.nih.gov/guidelines) and the [HIV Drug Interaction Checker](https://aidsinfo.nih.gov/interact))

- 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.

- DOR **should not be coadministered** with the CYP3A inducing non-nucleoside reverse transcriptase inhibitors (NNRTIs) efavirenz (EFV), etravirine, and nevirapine. In a Phase 1 trial (see below), 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 (see below) 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]).

- 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.

- 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.

### 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. However, 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. 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. The efficacy trials included two randomized, multicenter, double-blind, active-controlled Phase 3 trials (DRIVE-FORWARD and DRIVE-AHEAD) in treatment-naive adults and one open-label, active-controlled, randomized, noninferiority trial that enrolled virologically suppressed adults on antiretroviral therapy (DRIVE-SHIFT).

The dose-selection trial enrolled treatment-naive adults stratified by HIV RNA level at screening (<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.

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. In DRIVE-AHEAD, adult subjects received either coformulated DOR/3TC/TDF (n = 364) or EFV/FTC/TDF (n = 364) once daily. 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 to 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. There were similar results across different baseline viral loads, genders, races, and HIV-1 subtypes.

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 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 to the baseline regimen at Week 24.

**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.


toxicity

In trials that compared DOR-based 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 compared to those who received EFV. In the dose-finding trial, CNS AEs were reported in 26.9% of patients on DOR-based regimens compared to 47.2% of patients on EFV-based regimens at Week 24. 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 to 55.9% of patients on EFV-based regimens. 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 to 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 to the baseline PI-based regimen with 3TC/TDF (P < 0.0001).

References


