

Non-nucleoside Reverse Transcriptase Inhibitor–Based Regimens as Initial Antiretroviral Therapy

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Table 8c. Characteristics of Non-nucleoside Reverse Transcriptase Inhibitors That Are Recommended as Initial Antiretroviral Therapy in Certain Clinical Scenarios

Characteristics	DOR	RPV ^a
Dosing Frequency	Once daily	Once daily
Food Requirement	With or without food	With a meal
STR Available as Initial ARV Regimens for Certain Clinical Scenarios	DOR/TDF/3TC	RPV/TAF/FTC
Available as a Single-Drug Tablet	Yes	Yes
Adverse Effects	<ul style="list-style-type: none"> • Skin rash • SJS/TEN (rarely observed) • DRESS (rarely observed) 	<ul style="list-style-type: none"> • Depression • Headache • Skin rash • SJS/TEN (rarely observed) • DRESS (rarely observed) • QTc prolongation
CYP3A4 Drug–Drug Interactions	CYP3A4 substrate	CYP3A4 substrate
Other Significant Drug Interactions	None	RPV oral absorption is reduced with increased gastric pH. Use of RPV with PPIs is contraindicated ; see the Liverpool HIV Drug Interaction Checker for dosing recommendations when RPV is coadministered with an H2 blocker or antacids.

^a See [Optimizing Antiretroviral Therapy in the Setting of Viral Suppression](#) and [Appendix A, Table 6](#) for information regarding injectable RPV.

Key: 3TC = lamivudine; ARV = antiretroviral; CYP = cytochrome P450; DOR = doravirine; **DRESS = drug reaction with eosinophilia and systemic symptoms**; FTC = emtricitabine; H2 = histamine 2; PPI = proton pump inhibitor; QTc = QT corrected for heart rate; RPV = rilpivirine; **SJS = Stevens-Johnson syndrome**; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; **TEN = toxic epidermal necrolysis**

Summary

Non-nucleoside reverse transcriptase (NNRTI)-based regimens have demonstrated virologic potency and durability. Earlier NNRTIs (efavirenz [EFV] and nevirapine [NVP]) have some major disadvantages, including the prevalence of pre-treatment NNRTI resistance,¹ a low barrier for the development of resistance, the potential for drug–drug interactions, and a high rate of toxicities. The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) no longer recommends EFV as initial therapy because of the high incidence of serious toxicities, including neuropsychiatric effects and suicidality. NVP is no longer recommended in adults and adolescents due to a relatively high potential for adverse effects, including serious hepatotoxicity and skin reactions, including Stevens-Johnson syndrome. This section of the guidelines focuses on rilpivirine (RPV) and doravirine (DOR), which are the two NNRTIs currently recommended as part of [Initial Antiretroviral Regimens for Certain Clinical Scenarios](#) (also see [Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios](#)). There is no clinical trial comparing the efficacy of these two NNRTIs as initial antiretroviral regimens.

Resistance testing should be performed before initiation of an NNRTI-based regimen in people without prior antiretroviral therapy (ART) experience. Thus, these regimens are not appropriate for rapid ART initiation when ART is to be started before the results of HIV genotypic resistance testing are available.

Doravirine

DOR is approved for use in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) as initial ART for people with HIV. DOR has a distinct resistance pathway and a potentially higher barrier to resistance than earlier NNRTIs, though not comparable to that of boosted protease inhibitors or second-generation integrase strand transfer inhibitors.² Data suggest that DOR can retain activity in the setting of common, single NNRTI resistance-associated mutations (K103N, V106I, Y181C, G190A).^{3–6}

Efficacy in Clinical Trials

Doravirine Plus Two NRTIs Versus Efavirenz Plus Two NRTIs

In the DRIVE-AHEAD trial, 734 treatment-naïve participants received either DOR/tenofovir disoproxil fumarate (TDF)/lamivudine (3TC) or EFV/TDF/emtricitabine (FTC), both as a daily fixed-dose combination tablet.⁷ At 96 weeks, DOR/TDF/3TC was non-inferior to EFV/TDF/FTC, with 77.5% and 73.6% of participants achieving HIV RNA <50 copies/mL, respectively. Neuropsychiatric side effects and rash were more common in the EFV arm. Virologic rebound and virologic nonresponse were similar in the DOR/TDF/3TC (9.3%) and EFV/TDF/FTC (7.7%) treatment groups. Among participants in the DOR arm who had protocol-defined virologic failure with genotypic resistance testing available at the time of failure, 7 of 21 (33.3%) had NNRTI resistance, and 6 of 21 (28.6%) had NRTI resistance. In the EFV arm, 10 of 15 (66.7%) participants had NNRTI resistance and 5 of 15 (33.3%) had NRTI resistance.

Doravirine Plus Two NRTIs Versus Darunavir/Ritonavir Plus Two NRTIs

In the DRIVE-FORWARD trial, 769 treatment-naïve participants received DOR or darunavir/ritonavir (DRV/r) once daily along with two investigator-selected NRTIs, either abacavir (ABC)/3TC or TDF/FTC.⁸ At 96 weeks, DOR was non-inferior to DRV/r, with 73% versus 66% of study participants achieving HIV RNA <50 copies/mL, respectively. Participants who received DOR plus ABC/3TC (n = 48) and those who received DOR plus TDF/FTC (n = 316) had similar virologic responses.

Treatment-related diarrhea was more frequently reported in the DRV/r arm. Greater increases in fasting low-density lipoprotein cholesterol, triglycerides, non–high-density lipoprotein cholesterol, and total cholesterol were seen in the participants who received DRV/r than in those who received DOR. Protocol-defined virologic failure was similar in the DOR and DRV/r groups (9% vs. 11%). Treatment-emergent resistance was observed in two participants in the DOR group (resistance to both DOR and to FTC/3TC) and one participant in the DRV/r group (FTC/3TC resistance).

In a pooled analysis of DRIVE-AHEAD and DRIVE-FORWARD participants who entered an open-label extension phase following the initial 96 weeks of randomized treatment, 550 participants continued their DOR-based regimen and 502 participants switched to a DOR-based regimen. At 192 weeks, 83% of participants who continued on DOR and 81% of participants who switched to DOR maintained viral suppression.⁹ Additional virologic failures in the open-label extension were uncommon, occurring in 2.7% of participants who continued DOR and 5.2% of those who switched to DOR after Week 96. Treatment-emergent phenotypic resistance to DOR following Week 96 was observed in four participants: three in the delayed switch arm and one in the initial therapy arm.¹⁰

Other Factors and Considerations

- DOR is available as a single-drug 100-mg tablet¹¹ and as part of a three-drug single-tablet regimen (STR) that contains DOR 100 mg/TDF 300 mg/3TC 300 mg.¹² All formulations are dosed once daily, with or without food.
- DOR has not been studied with tenofovir alafenamide (TAF)/FTC in clinical trials as initial ART. However, based on the similar efficacy of TAF and TDF in other clinical trials, DOR plus TAF/FTC is expected to have virologic efficacy comparable to DOR/TDF/3TC.
- DOR is also available as a two-drug STR containing DOR 100 mg/islatravir (ISL) 0.25 mg, which is approved as a switch regimen in people with viral suppression.¹³ Because DOR/ISL has not been approved by the U.S. Food and Drug Administration (FDA) for initial therapy, the Panel cannot recommend it for use in those who are not virally suppressed on ART.
- DOR is primarily metabolized by the cytochrome P450 (CYP) 3A4 enzyme and should not be coadministered with strong CYP3A4 inducers. DOR concentration may increase in the presence of a CYP3A4 inhibitor (see the [Liverpool HIV Drug Interaction Checker](#)). DOR is not a CYP3A4 inducer or inhibitor; thus, it is not expected to affect the concentrations of concomitant CYP3A4 substrates.
- Please refer to the [Perinatal Guidelines](#) for recommendations on the use of DOR in pregnancy.
- Because clinical trial data for the combination of DOR plus ABC/3TC is limited, the Panel is less certain about the efficacy of this regimen.

The Panel's Recommendations

- Based on the clinical trial data discussed above, the Panel classifies DOR/TDF/3TC (**BI**) and DOR plus two NRTIs (**BI** for TDF/FTC and **BIII** for TAF/FTC) as [Initial Antiretroviral Regimens for Certain Clinical Scenarios](#).
- DOR-based regimens are not appropriate for rapid ART initiation when ART is to be started before the results of HIV genotypic resistance testing are available.

Rilpivirine

Oral RPV is approved for use in combination with two NRTIs as initial ART for people with HIV who have pre-treatment viral load $\leq 100,000$ copies/mL.¹⁴ In people treated with RPV, the presence of RPV resistance mutations at virologic failure may confer cross-resistance to other NNRTIs.

RPV is also approved as part of a long-acting injectable regimen combined with cabotegravir (LA CAB/RPV) and as an oral STR combined with dolutegravir (DTG) for use in people with viral suppression (HIV RNA < 50 copies/mL). These two regimens have not been studied in treatment-naïve populations and **are not recommended** as initial ART. See [Optimizing Antiretroviral Therapy in the Setting of Viral Suppression](#) for discussion of LA CAB/RPV and DTG/RPV.

Efficacy in Clinical Trials

Rilpivirine Plus Two NRTIs Versus Efavirenz Plus Two NRTIs

- Two Phase 3 randomized, double-blind clinical trials—ECHO and THRIVE—compared RPV and EFV, each combined with two NRTIs as initial ART.¹⁵ At 96 weeks, RPV was non-inferior to EFV overall. However, among the RPV-treated participants, the rate of virologic failure was higher in those with pre-treatment CD4 T lymphocyte (CD4) cell counts < 200 cells/mm³ and in those with pre-treatment viral loads $> 100,000$ copies/mL. NNRTI and NRTI resistance were more frequently found in RPV-treated participants with virologic failure.
- STaR, a Phase 3b open-label study, compared two STRs—RPV/TDF/FTC and EFV/TDF/FTC—as initial ART in 786 people with HIV. The results at 96 weeks¹⁶ were similar to those reported at 48 weeks.¹⁷ RPV was non-inferior to EFV overall. RPV was superior to EFV in participants with pre-ART viral loads $\leq 100,000$ copies/mL and non-inferior in those with pre-ART viral loads $> 100,000$ copies/mL. Among participants with pre-ART viral loads $> 500,000$ copies/mL, virologic failure was more common in RPV-treated participants than in EFV-treated participants. At Week 96, there were more participants with emergent resistance in the RPV/FTC/TDF arm than in the EFV/FTC/TDF arm (5.3% vs. 1.0%, respectively). The STR of RPV/TAF/FTC was approved by the FDA based on results from a bioequivalence study. In this study, plasma concentrations of RPV, FTC, and TAF 25 mg in participants taking the coformulated drug were similar to those seen in participants who received RPV as the single-drug tablet and TAF/FTC as part of the STR of EVG/cobicistat/TAF 10 mg/FTC.¹⁸

Adverse Effects

- RPV is generally well tolerated. In the ECHO, THRIVE, and STaR trials, fewer instances of central nervous system adverse events (e.g., abnormal dreams, dizziness, psychiatric side effects), skin rash, and dyslipidemia were reported in the RPV arms than in the EFV arms, and fewer people in the RPV arms discontinued therapy due to adverse events. However, up to 9% of clinical trial participants experienced depressive disorders, including approximately 1% of participants who had suicidal thoughts or who attempted suicide. People receiving RPV who have severe depressive symptoms should be evaluated to assess whether the symptoms may be due to RPV and whether the risks of continuing the same regimen outweigh the benefits.

Other Factors and Considerations

- For initial ART, oral RPV is formulated as a single-drug tablet and as an STR in combination with TAF/FTC or TDF/FTC. Among available STRs, RPV/TDF/FTC is no longer recommended by the Panel for initial therapy.
- The STR of RPV/TAF/FTC is given once daily and must be administered with a meal.

- The oral drug absorption of RPV can be significantly reduced in the presence of acid-reducing agents. RPV is **contraindicated** in people who are receiving proton pump inhibitors and should be used with caution in those receiving H2 antagonists or antacids (see the [Liverpool HIV Drug Interaction Checker](#) for dosing recommendations).
- RPV is primarily metabolized in the liver by the CYP3A4 enzyme; its plasma concentration may be affected in the presence of CYP3A inhibitors or inducers (see the [Liverpool HIV Drug Interaction Checker](#)).
- At doses above the approved dose of 25 mg, RPV may cause QTc (QT corrected for heart rate) interval prolongation. RPV should be used with caution when coadministered with a drug known to increase the risk of Torsades de Pointes.

The Panel's Recommendations

- Given the availability of other effective regimens that do not have virologic and immunologic prerequisites to initiate treatment, substantial drug–drug interactions, and a low genetic barrier to resistance, RPV is **not recommended** for initial therapy in most persons with HIV. RPV/TDF/FTC is no longer recommended as part of [Initial Antiretroviral Regimens for Certain Clinical Scenarios](#), largely due to the limitations of RPV and the availability of DOR/TDF/3TC, which has fewer drug–drug interactions and no virologic and immunologic prerequisites. The Panel continues to recommend RPV/TAF/FTC as part of *Initial Antiretroviral Regimens for Certain Clinical Scenarios*, largely to retain an STR option containing an NNRTI and TAF.
- Use of RPV/TAF/FTC (**BII**) should be limited to people with pre-treatment viral load $\leq 100,000$ copies/mL and CD4 count ≥ 200 cells/mm³.
- RPV/TAF/FTC is not appropriate for rapid ART initiation when ART is to be started before the results of HIV genotypic resistance testing are available.
- Data on RPV plus ABC/3TC are insufficient to consider recommending this regimen.

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