

Non-Nucleoside Reverse Transcriptase Inhibitor–Based Regimens

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Table 8c. Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) That Are Recommended as Initial Therapy for People with HIV

Characteristics	DOR	EFV	RPV ^a
Dosing Frequency	Once daily	Once daily	Once daily
Food Requirement	With or without food	On an empty stomach	With a meal
STR Available for ART-Naive Patients	DOR/TDF/3TC	<ul style="list-style-type: none"> • EFV 600 mg/TDF/FTC • EFV 600 mg/TDF/3TC • EFV 400 mg/TDF/3TC 	<ul style="list-style-type: none"> • RPV/TAF/FTC • RPV/TDF/FTC
Available as a Single-Drug Tablet	Yes	Yes	Yes
Adverse Effects	Generally well tolerated	<ul style="list-style-type: none"> • CNS side effects, including dizziness, abnormal dreams, headache, depression, suicidality, insomnia, somnolence • Skin rash • QTc prolongation 	<ul style="list-style-type: none"> • Depression, headache • Skin rash • QTc prolongation
CYP3A4 Drug–Drug Interactions	CYP3A4 substrate	CYP3A4 substrate, mixed inducer/inhibitor	CYP3A4 substrate
Other Significant Drug Interactions	None	CYP2B6 and 2C19 inducer	RPV oral absorption is reduced with increased gastric pH. Use of RPV with PPIs is not recommended; see Drug–Drug Interactions for dosing recommendations when RPV is coadministered with H2 blocker or antacids.

^a See [Optimizing Antiretroviral Therapy](#) section and [Appendix B, Table 4](#) for information regarding injectable RPV.

Key: 3TC = lamivudine; ART = antiretroviral therapy; CNS = central nervous system; CYP = cytochrome P; DOR = doravirine; EFV = efavirenz; FTC = emtricitabine; H2 = histamine 2; PPI = proton pump inhibitor; QTc = QT corrected for heart rate; RPV = rilpivirine; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Summary

Five NNRTIs—delavirdine (DLV), doravirine (DOR), efavirenz (EFV), etravirine (ETR), nevirapine (NVP), and rilpivirine (RPV) are currently approved by the Food and Drug Administration (FDA) for the treatment of HIV when used in combination with other antiretroviral (ARV) drugs. **This section of the guidelines will focus on DOR, EFV, and RPV, the three NNRTIs recommended by the Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) as part of an initial antiretroviral therapy (ART) regimen for people with HIV in certain clinical scenarios (see [Table 6](#) and [Table 7](#)).**

NNRTI-based regimens have demonstrated virologic potency and durability. The major disadvantages of currently available NNRTIs (especially EFV and RPV) are the prevalence of NNRTI-resistant viral strains in ART-naive patients¹ and the drugs' low barrier for the development of resistance. Resistance testing should be performed before initiation of an NNRTI-based regimen in ART-naive patients. High-level resistance to all NNRTIs (except ETR or DOR) may occur with a single mutation. In RPV-treated patients, the presence of RPV resistance mutations at virologic failure may confer cross-resistance to other NNRTIs, including ETR.^{2,3} DOR-, EFV-, and RPV-based regimens are now categorized as *Recommended Initial Regimens in Certain Clinical Situations* for ART-naive patients. More details about these NNRTI are provided below.

Doravirine (DOR)

Efficacy in Clinical Trials

The efficacy of DOR-based therapy for treatment of HIV in ART-naive individuals was demonstrated in two randomized, double-blind, placebo-controlled trials.

DOR-Based Regimen versus EFV-Based Regimen

- In the [DRIVE-AHEAD](#) trial 734 participants received either DOR/tenofovir disoproxil fumarate (TDF)/lamivudine (3TC) or EFV/TDF/emtricitabine (FTC), both as a daily fixed-dose tablet.⁴
 - At 96 weeks, DOR/TDF/3TC was noninferior to EFV/TDF/FTC, with 77.5% of participants who received DOR/TDF/3TC and 73.6% of those who received EFV/TDF/FTC achieving HIV RNA <50 copies/mL. Although virologic responses to ART overall were lower in participants with pre-treatment HIV RNA >100,000 copies/mL or pre-treatment CD4 counts of ≤200 cells/mm³, there was no difference between the DOR-treated and EFV-treated participants.
 - Virologic rebound and virologic nonresponse were similar in the DOR/TDF/3TC (9.3%) and EFV/TDF/FTC (7.7%) treatment groups. At 96 weeks, genotype resistance results were reported for 21 participants with protocol defined virologic failure in the DOR arm and 15 participants in the EFV arm. For the DOR arm, 7 out of 21 participants had NNRTI resistance and 6 out of 21 had NRTI resistance. For EFV, 10 of 15 participants had NNRTI resistance and 5 of 15 had NRTI resistance.
 - More participants in the EFV arm discontinued their assigned ART due to adverse events than in the DOR arm (6.6% vs. 3.0%). Neuropsychiatric side effects and rash were more common in the EFV arm.
 - Low-density lipoprotein (LDL) cholesterol and non-high-density lipoprotein (HDL) cholesterol did not change with DOR use, whereas both increased with EFV use.

DOR-Based Regimen versus Darunavir/Ritonavir (DRV/r)-Based Regimen

- In the [DRIVE-FORWARD](#) trial, 769 participants received DOR or DRV/r once daily along with two investigator-selected nucleoside reverse transcriptase inhibitors (NRTIs), either abacavir (ABC)/3TC or TDF/FTC.⁵
 - At 48 weeks, DOR was found to be noninferior to DRV/r with 84% of study participants receiving DOR versus 80% of those receiving DRV/r achieving HIV RNA <50 copies/mL at

48 weeks. Participants who received DOR plus ABC/3TC (n = 48) and those who received DOR plus TDF/FTC (n = 316) had similar virologic responses.

- At Week 96, DOR was superior to DRV/r in terms of virologic suppression (73% vs. 66%).⁶ Treatment responses were similar regardless of baseline characteristics.
- Virologic failure by Week 96 was low and similar in the DOR and DRV/r groups (9% vs. 11%). Genotype resistance results were reported for 11 and 14 participants with virologic failure in the DOR and DRV/r arms, respectively. Treatment-emergent resistance to any study drug occurred in 2 (1%) of 383 participants in the DOR group and 1 (<1%) of 383 participants in the DRV/r group.
- Treatment-related diarrhea was more frequently reported in the DRV/r arm, and greater increases in fasting LDL cholesterol, triglycerides, non-HDL cholesterol, and total cholesterol were seen in the participants who received DRV/r than in those who received DOR.

Other Factors and Considerations

- DOR is available as a single-drug, 100-mg tablet⁷ and as part of a single-tablet regimen (STR) that contains DOR/TDF/3TC 100 mg/300 mg/300 mg⁸ and is dosed once daily, with or without food.
- DOR-based regimens have not been directly compared to integrase strand transfer inhibitor (INSTI)-based regimens in clinical trials, and has not been studied with tenofovir alafenamide (TAF) in clinical trials.
- A post hoc analysis of three randomized controlled trials examined weight gain among ART-naïve participants receiving DOR versus DRV/r or EFV. At week 96, mean weight gain was similar in the DOR group (2.4 kg), the DRV/r group (1.8 kg), and the EFV group (1.6 kg). No significant differences between treatment groups were found in the proportion of participants whose BMI class increased to overweight or obese at Week 48 or Week 96.⁹
- DOR is primarily metabolized by the CYP3A4 enzyme and should not be coadministered with strong CYP3A4 inducers. DOR concentration may increase in the presence of a CYP3A4 inhibitor (see [Table 24b](#)). DOR is not a CYP3A4 inducer or inhibitor, so it is not expected to affect the concentrations of concomitant CYP3A4 substrates.
- Treatment-emergent resistance mutations to DOR may confer cross-resistance to certain other NNRTIs. Most isolates with DOR mutations remain susceptible to ETR.¹⁰
- There are currently no data on the safety of DOR use during pregnancy.
- There are limited clinical trial data with the combination of DOR + ABC/3TC so the Panel is less certain about the efficacy of this regimen.

The Panel's Recommendations

- On the basis of 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 *Recommended Initial Regimens in Certain Clinical Situations*.

Efavirenz (EFV)

Efficacy of EFV 600-mg Daily Dose in Clinical Trials

- Large randomized controlled trials and cohort studies in ART-naive patients have demonstrated potent and durable viral suppression in patients treated with EFV plus two NRTIs. EFV-based regimens have demonstrated superiority or noninferiority to a number of comparator regimens in ART-naive patients in several randomized controlled trials.
- In the AIDS Clinical Trials Group (ACTG) 5202 study, EFV was comparable to ATV/r when each was given with either TDF/FTC or ABC/3TC.¹¹
- In the Evidence for Contraceptive Options in HIV (ECHO) and Targeting HIV Retention and Improved Viral Load Through Engagement (THRIVE) studies, EFV was noninferior to RPV, with less virologic failure. However, EFV caused more discontinuations due to adverse events. The virologic advantage of EFV was most notable in participants with pre-ART viral loads >100,000 copies/mL, and NRTI and NNRTI resistance occurred more frequently in patients who experienced failure on a regimen that included RPV.¹²
- In the Gilead Sciences (GS) 102 study, EFV/TDF/FTC was noninferior to elvitegravir/cobicistat [EVG/c]/TDF/FTC.¹³
- The DRIVE-AHEAD study compared EFV/TDF/FTC to DOR/TDF/3TC in ART-naive patients. At 96 weeks, DOR/TDF/3TC was found to be noninferior to EFV/TDF/FTC, as discussed in the DOR section. Neuropsychiatric side effects were more common in the EFV arm.⁴
- ADVANCE, an open-label, noninferiority trial conducted in South Africa, compared TDF/FTC/EFV 600 mg with dolutegravir (DTG) combined with either TDF/FTC or TAF/FTC. At Week 96, the DTG regimens were noninferior to the EFV regimen based on the proportion of participants with HIV-RNA levels <50 copies/mL (79% in DTG/TAF/FTC vs. 78% in DTG/TDF/FTC vs. 74% in EFV/TDF/FTC arms). More participants in the EFV group discontinued the trial regimen than in the DTG group. Mean weight gain was 7.1 kg in the DTG/TAF/FTC group, 4.3 kg in the DTG/TDF/FTC group, and 2.3 kg in the EFV/TDF/FTC, and was greater among women than men¹⁴

In clinical trials, some regimens have demonstrated superiority to those with EFV, based primarily on fewer discontinuations because of adverse events:

- In the SINGLE trial, a DTG-based regimen was superior to an EFV regimen at the primary endpoint of viral suppression at Week 48.¹⁵
- In the STARTMRK trial, raltegravir (RAL) was noninferior to EFV at 48 weeks,¹⁶ but RAL was superior to EFV at 4 and 5 years,^{17,18} in part because of more frequent discontinuations due to adverse events in the EFV group than in the RAL group.
- In the open-label Single-Tablet Regimen (STaR) trial, participants with baseline viral loads ≤100,000 copies/mL had higher rates of treatment success on RPV than on EFV.¹⁹

Efficacy of Low-Dose Efavirenz (EFV 400 mg Daily) in Clinical Trials

- ENCORE 1, a multinational, randomized, placebo-controlled trial, compared two once-daily doses of EFV (combined with TDF/FTC): EFV 600 mg (standard dose) versus EFV 400 mg

(reduced dose). At 96 weeks, EFV 400 mg was noninferior to EFV 600 mg for rate of viral suppression.²⁰ While the frequency of overall adverse events was not different between groups, EFV-related adverse events and treatment-related discontinuations occurred less frequently in the EFV 400 mg group than in the EFV 600 mg group. Although there were fewer self-reported central nervous system (CNS) events in the 400 mg group, the groups had similar rates of psychiatric events. The 400-mg dose of EFV is now approved in the United States for initial treatment of HIV infection and is coformulated with TDF and 3TC in a fixed-dose combination (FDC) tablet.

- NAMSAL ANRS 12313, an open-label, multicenter randomized noninferiority trial conducted in Cameroon, compared EFV 400 mg with DTG, both combined with TDF/3TC. At Week 96, EFV 400 mg was noninferior to DTG based on percentage of participants with viral suppression to HIV RNA <50 copies/mL (72% in EFV group vs. 74% in DTG group). Virologic suppression was reached more rapidly in the DTG group. Among nine virologic failures in the DTG arm, there were no acquired DTG resistance mutations through Week 96. A total of 19 virologic failures occurred in the EFV arm, with 17 having resistance mutations to EFV. Median weight gain was 5.0 kg in the DTG group versus 3.0 kg in the EFV group.^{21,22}
- In an open label trial, 25 pregnant women with HIV and HIV RNA <50 copies/mL while on an EFV-based regimen were switched from EFV 600 mg to EFV 400 mg daily (the TDF and FTC or 3TC components of the regimen did not change). Participants were monitored closely with EFV concentrations measured weekly and viral loads biweekly during pregnancy and postpartum. Stopping criteria were HIV RNA >50 copies/mL on two consecutive occasions or random EFV concentration <800 ng/mL on three consecutive occasions. All participants maintained viral load suppression to HIV RNA <50 copies/mL throughout the study.²³
- A pharmacokinetic (PK) study enrolled 22 people with HIV (without tuberculosis) who were on an EFV-based regimen and had HIV RNA levels <50 copies/mL. Participants were switched from EFV 600 mg to EFV 400 mg. Fourteen days after the switch, isoniazid and rifampin were started for 12 weeks. The combination resulted in only minimal reduction in EFV 400 mg PK parameters, which were within the range of concentrations seen in the ENCORE 1 trial. HIV RNA levels <50 copies/mL were maintained in all participants during the study.²⁴

Adverse Effects

- EFV can cause CNS side effects (e.g., abnormal dreams, dizziness, headache, depression) that resolve over a period of days to weeks in most patients. However, subtler, long-term neuropsychiatric effects can occur.
- EFV use has also been associated with suicidality; however, evidence for this association has differed among various large studies. An analysis of four ACTG comparative trials showed a higher rate of suicidality (i.e., reported suicidal ideation or attempted or completed suicide) among EFV-treated patients than among patients taking comparator regimens (lopinavir/ritonavir [LPV/r], atazanavir (ATV), atazanavir/cobicistat (ATV/r), or ABC-based regimens).²⁵ Similarly, a subgroup analysis of the START trial revealed higher risk of suicidal or self-injurious behavior among participants in the immediate ART group who took EFV than among ART-naïve controls; the risk increased for those with previous psychiatric diagnoses.²⁶ This association, however, was not found in analyses of three large observational cohorts^{27,28} or in a retrospective cohort study that used U.S. administrative pharmacy claims data.²⁹ A prospective observational cohort study among people with HIV in Uganda revealed no evidence that EFV carried a greater risk of suicidal ideation or depression than NVP.³⁰

- Delayed onset neurotoxicities, including ataxia and encephalopathy, have been reported months to years after EFV use.^{31,32}
- EFV may cause elevation in LDL cholesterol and triglycerides.
- QTc interval prolongation has been observed with EFV use.^{33,34} Consider an alternative to EFV in patients taking medications known to increase the risk of Torsades de Pointes, or in patients at higher risk of Torsades de Pointes.

Other Factors and Considerations

- EFV is formulated both as a single-drug, 600-mg tablet and in an FDC tablet of EFV/TDF/FTC that allows for once-daily dosing.
- EFV is also available as a generic single-drug, 600-mg tablet and as a generic once-daily FDC tablet that includes 3TC, TDF, and either 600 mg or 400 mg of EFV; the lower-dose EFV/TDF/3TC tablet is approved for treating adults and children weighing ≥ 35 kg.^{35,36}
- EFV is a substrate of CYP3A4 and an inducer of CYP3A4 and 2D6, and therefore, may potentially interact with other drugs that use the same pathways (see Tables [24b](#), [25a](#), and [25b](#)).
- EFV has been associated with CNS birth defects in nonhuman primates, and cases of NTDs have been reported after first-trimester exposure in humans.³⁷ A link between EFV and birth defects in humans has not been supported in meta-analyses or data on more than 7,900 periconception exposures from Botswana (see the [Perinatal Guidelines](#)).^{38,39}
- People with HIV who are taking a regimen that includes EFV should be screened for depression and suicidality.

The Panel's Recommendations

- Given the availability of regimens with fewer treatment-limiting adverse events and noninferior or superior efficacy, the Panel classifies EFV 600 mg/TDF/FTC or EFV 600 mg/TDF/3TC (**BI**) or EFV 600 mg plus TAF/FTC (**BII**) as *Recommended Initial Regimens in Certain Clinical Situations*.
- Randomized clinical trial data have demonstrated the noninferiority of EFV 400 mg compared with EFV 600 mg²⁰ and to DTG.^{21,22} This dose has not been studied in a U.S. population. The Panel classifies EFV 400 mg/TDF/3TC as a *Recommended Initial Regimen in Certain Clinical Situations (BI)*.

Rilpivirine (RPV)

RPV is an NNRTI where the [oral](#) formulation is approved for use in combination with two NRTIs for ART-naïve patients with pretreatment viral loads $< 100,000$ copies/mL. RPV is also approved as an extended-release injectable suspension as part of a long acting injectable complete ARV regimen when used with cabotegravir (CAB), an INSTI. This regimen is approved to replace oral ART in patients with virologic suppression and no history of resistance to RPV or INSTIs (see the [Optimizing Antiretroviral Therapy in the Setting of Viral Suppression](#) section for discussion of long-acting CAB/RPV).

Efficacy in Clinical Trials

- Two Phase 3 randomized, double-blind clinical trials—ECHO and THRIVE—compared RPV and EFV, each combined with two NRTIs.¹² At 96 weeks, the following findings were reported:
 - RPV was noninferior to EFV overall.
 - Among participants with pre-ART viral loads >100,000 copies/mL, more RPV-treated participants than EFV-treated participants experienced virologic failure. NNRTI and NRTI resistance were more frequently identified in participants with virologic failure in the RPV group.
 - Among the RPV-treated participants, the rate of virologic failure was greater in those with pretreatment CD4 counts <200 cells/mm³ than in those with CD4 counts ≥200 cells/mm³.
- STaR, a Phase 3b, open-label study, compared the FDCs of RPV/TDF/FTC and of EFV/TDF/FTC in 786 treatment-naive patients. The results at 96 weeks⁴⁰ were similar to those reported at 48 weeks.¹⁹
 - RPV was noninferior to EFV overall.
 - RPV was superior to EFV in patients with pre-ART viral loads ≤100,000 copies/mL and noninferior in those with pre-ART viral loads >100,000 copies/mL. Among patients with pre-ART viral loads >500,000 copies/mL, virologic failure was more common in RPV-treated patients than in EFV-treated patients.
 - There were more participants with emergent resistance in the RPV/FTC/TDF arm than in the EFV/FTC/TDF arm (4% vs. 1%, 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/c/TAF 10 mg/FTC.⁴¹

Adverse Effects

- RPV is generally well tolerated. In the ECHO, THRIVE, and STaR trials, fewer instances of CNS 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 patients 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. Patients receiving RPV who have severe depressive symptoms should be evaluated to assess whether the symptoms may be due to RPV and if the risks of continuing the same regimen outweigh the benefits.

Other Factors and Considerations

- Oral RPV is formulated both as a single-drug tablet and in STRs with TAF/FTC with TDF/FTC and with DTG. Among available STRs, RPV/TAF/FTC is the smallest tablet.
- RPV is also available as part of a long-acting injectable ARV regimen for use in combination with long-acting CAB in patients who are virologically suppressed and do not have resistance to these drugs (see [Optimizing Antiretroviral Therapy in the Setting of Viral Suppression](#)).

- RPV/TAF/FTC and RPV/TDF/FTC are given once daily and must be administered with a meal (containing at least 390 kcal).
- RPV is also coformulated as a once-daily FDC tablet with DTG that is used as continuation therapy for people with HIV who have achieved viral suppression.⁴² However, this combination has not been studied in ART-naive individuals, and it **is not recommended** for initial therapy (see [Optimizing Antiretroviral Therapy in the Setting of Viral Suppression](#)).
- The oral drug absorption of RPV can be significantly reduced in the presence of acid-lowering agents. RPV is **contraindicated** in patients who are receiving proton pump inhibitors (PPIs), and should be used with caution in those receiving H2 antagonists or antacids (see [Drug–Drug Interactions](#) for dosing recommendations).
- RPV is primarily metabolized in the liver by the CYP3A enzyme; its plasma concentration may be affected in the presence of CYP3A inhibitors or inducers (see [Drug–Drug Interactions](#)).
- At doses above the approved dose of 25 mg, RPV may cause QTc 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, the Panel recommends RPV/TDF/FTC and RPV/TAF/FTC as *Recommended Initial Regimens in Certain Clinical Situations*.
- Use of RPV with TAF/FTC (**BI**) or TDF/FTC (**BI**) should be limited to ART-naive patients with pretreatment viral loads <100,000 copies/mL and CD4 counts >200 cells/mm³.
- Data on RPV plus ABC/3TC are insufficient to consider recommending this regimen.

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