Non-Nucleoside Reverse Transcriptase Inhibitor-Based Regimens

(Last updated June 3, 2021; last reviewed June 3, 2021)

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	• EFV 600 mg/TDF/FTC • EFV 600 mg/TDF/3TC • EFV 400 mg/TDF/3TC	• RPV/TAF/FTC • RPV/TDF/FTC
Available as a Single-Drug Tablet	Yes	Yes	Yes
Adverse Effects	Generally well tolerated	• CNS side effects, including dizziness, abnormal dreams, headache, depression, suicidality, insomnia, somnolence • Skin rash • QTc prolongation	• 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.

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; RPV = rilpivirine; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

[a] See Optimizing Antiretroviral Therapy in the Setting of Virologic Suppression and Appendix B Table 4 for information regarding injectable RPV.

Summary

Five NNRTIs—delavirdine (DLV), doravirine (DOR), efavirenz (EFV), etravirine (ETR), nevirapine (NVP), and rilpivirine (RPV)—currently are 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 patients[1] 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 NNRTIs 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/mm^3, no difference was observed 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 because of 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% versus 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% versus 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 of 383 (1%) participants in the DOR group and 1 of 383 (<1%) 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 tablet[7] and as part of a single-tablet regimen (STR) that contains DOR/TDF/3TC 100 mg/300 mg/300 mg[8] and is dosed once daily, with or without food.
- DOR-based regimens have not been compared directly to INSTI-based regimens in clinical trials and have not been studied with tenofovir alafenamide (TAF) in clinical trials.

- A post hoc analysis of three randomized controlled trials examined weight gain among ART-naive 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 metabolized primarily 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]
- No data are currently available on the safety of DOR use during pregnancy.
- Clinical trial data on the combination of DOR + ABC/3TC are limited, 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.[14]
- ADVANCE, an open-label, noninferiority trial conducted in South Africa, compared TDF/FTC/EFV 600 mg to 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 versus 78% in DTG/TDF/FTC versus 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 men.[15]

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.[16]
- In the STARTMRK trial, raltegravir (RAL) was noninferior to EFV at 48 weeks,[17] but RAL was superior to EFV at 4 and 5 years,[18, 19] 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.[20]

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.[21] Although 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 fewer CNS (central nervous system) events were self-reported 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 to 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 versus 74% in DTG group). Virologic suppression was reached more rapidly in the DTG group. Among 9 virologic failures in the DTG arm, none 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.[22, 23]
- 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 mg/mL on three consecutive occasions. All participants maintained viral load suppression to HIV RNA <50 copies/mL throughout the study.[24]
- A pharmacokinetic (PK) study enrolled 22 people with HIV (and 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.[25]

Adverse Effects

- EFV can cause CNS side effects (e.g., abnormal dreams, dizziness, headache, and depression) that resolve over a period of days to weeks in most patients. However, subtler, long-term neuropsychiatric effects can occur.
- EFV use also has 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).[26] 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-naive controls; the risk increased for those with previous psychiatric diagnoses.[27] This association, however, was not found in analyses of three large observational cohorts[28, 29] or in a retrospective cohort study that used U.S. administrative pharmacy claims data.[30] 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.[31]
- Delayed onset neurotoxicities, including ataxia and encephalopathy, have been reported months to years after EFV use.[32, 33]
- EFV may cause elevation in LDL cholesterol and triglycerides.
- QTc interval prolongation has been observed with EFV use.[34, 35] 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 once-daily dosing.
- EFV also is 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.[36, 37]
- EFV is a substrate of CYP3A4 and an inducer of CYP3A4 and 2D6 and, therefore, potentially may 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 neural tube defects have been reported after first-trimester exposure in humans.[38] 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).[39, 40]
- 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 mg[21] and with DTG.[22, 23] 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 whose oral formulation is approved for use in combination with 2-NRTIs for ART-naive patients with pretreatment viral loads <100,000 copies/mL. RPV also is approved as an extended-release injectable suspension as part of a long-acting injectable complete ARV regimen when used with cabotegravir (CAB), an integrase strand transfer inhibitor (INSTI). This regimen is approved to replace oral ART in patients with virologic suppression and no history of resistance to RPV or INSTIs (see Optimizing Regimen 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 identified more frequently 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/mm^3 than in those with CD4 counts ≥200 cells/mm^3.
- 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 weeks[41] were similar to those reported at 48 weeks.[20]
  - 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.
  - A greater percentage of participants experienced emergent resistance in the RPV/FTC/TDF arm than in the EFV/FTC/TDF arm (4% versus 1%, respectively).
- The STR of RPV/TAF/FTC was approved by 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.[42]

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 because of 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 also is 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 Virologic 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 also is coformulated as a once-daily FDC tablet with DTG that is used as continuation therapy for people with HIV who have achieved viral suppression.[43] 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 reduced significantly 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 histamine 2 antagonists or antacids (see Drug–Drug Interactions for dosing recommendations).
- RPV is metabolized primarily 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 greater than 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 **(BII)** or TDF/FTC **(BI)** should be limited to ART-naive patients with pretreatment viral loads <100,000 copies/mL and CD4 counts >200 cells/mm^3.
- Data on RPV plus ABC/3TC are insufficient to consider recommending this regimen.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

References

1. Günthard HF, Calvez V, Paredes R, et al. Human Immunodeficiency Virus Drug Resistance: 2018 Recommendations of the International Antiviral Society–USA Panel. *Clinical Infectious Diseases*. 2018;68(2):177-187. Available at: https://academic.oup.com/cid/article/68/2/177/5055715.

2. Cohen CJ, Molina JM, Cahn P, et al. Efficacy and safety of rilpivirine (TMC278) versus efavirenz at 48 weeks in treatment-naive HIV-1-infected patients: pooled results from the phase 3 double-blind randomized ECHO and THRIVE Trials. *J Acquir Immune Defic Syndr*. 2012;60(1):33-42. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22343174.

3. Edurant package insert [package insert]. Janssen Therapeutics. 2017. Available at: https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/EDURANT-pi.pdf.

4. Orkin C, Squires KE, Molina JM, et al. Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate (TDF) Versus Efavirenz/Emtricitabine/TDF in Treatment-naive Adults With Human Immunodeficiency Virus Type 1 Infection: Week 96 Results of the Randomized, Double-blind, Phase 3 DRIVE-AHEAD Noninferiority Trial. *Clin Infect Dis*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33336698.

5. Molina JM, Squires K, Sax PE, et al. Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 48-week results of a randomised, double-blind, phase 3, non-inferiority trial. *Lancet HIV*. 2018;5(5):e211-e220. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29592840.

6. Molina JM, Squires K, Sax P, et al. Doravirine (DOR) versus ritonavir-boosted darunavir (DRV+r): 96-week results of the randomized, double-blind, phase 3 DRIVE-FORWARD Noninferiority trial Presented at: 22nd International AIDS Conference (AIDS 2018); 2018. Amsterdam, Netherlands. Available at: https://www.natap.org/2018/IAC/IAC_10.htm.

7. Pifeltro prescribing information [Type]. 2018.

8. Delstrigo prescribing information [Type]. 2018.

9. Orkin C, Elion R, Thompson M, et al. Changes in weight and BMI with first-line doravirine-based therapy. *AIDS*. 2021;35(1):91-99. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33048879.

10. Lai MT, Xu M, Ngo W, et al. Characterization of doravirine-selected resistance patterns from participants in treatment-naive Phase 3 clinical trials. Presented at: 22nd International AIDS Conference (AIDS 2018); 2018. Amsterdam, Netherlands. Available at: https://www.natap.org/2018/IAC/IAC_54.htm.

11. Daar ES, Tierney C, Fischl MA, et al. Atazanavir plus ritonavir or efavirenz as part of a 3-drug regimen for initial treatment of HIV-1. *Ann Intern Med*. 2011;154(7):445-456. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21320923.

12. Cohen CJ, Molina JM, Cassetti I, et al. Week 96 efficacy and safety of rilpivirine in treatment-naive, HIV-1 patients in two Phase III randomized trials. *AIDS*. 2013;27(6):939-950. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23211772.

13. Wohl DA, Cohen C, Gallant JE, et al. A randomized, double-blind comparison of single-tablet regimen elvitegravir/cobicistat/emtricitabine/tenofovir DF versus single-tablet regimen efavirenz/emtricitabine/tenofovir DF for initial treatment of HIV-1 infection: analysis of week 144 results. *J Acquir Immune Defic Syndr*. 2014;65(3):e118-120. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24256630.

14. Orkin C, Squires KE, Molina JM, et al. Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate is Non-inferior to Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate in Treatment-naive Adults With Human Immunodeficiency Virus-1 Infection: Week 48 Results of the DRIVE-AHEAD Trial. *Clin Infect Dis*. 2019;68(4):535-544. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30184165.

15. Venter WDF, Sokhela S, Simmons B, et al. Dolutegravir with emtricitabine and tenofovir alafenamide or tenofovir disoproxil fumarate versus efavirenz, emtricitabine, and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection (ADVANCE): week 96 results from a randomised, phase 3, non-inferiority trial. *Lancet HIV*. 2020;7(10):e666-e676. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33010240.

16. Walmsley SL, Antela A, Clumeck N, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. *N Engl J Med*. 2013;369(19):1807-1818. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24195548.

17. Lennox JL, DeJesus E, Lazzarin A, et al. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. *Lancet*. 2009;374(9692):796-806. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19647866.

18. DeJesus E, Rockstroh JK, Lennox JL, et al. Efficacy of raltegravir versus efavirenz when combined with tenofovir/emtricitabine in treatment-naive HIV-1-infected patients: week-192 overall and subgroup analyses from STARTMRK. *HIV Clin Trials*. 2012;13(4):228-232. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22849964.

19. Rockstroh JK, DeJesus E, Lennox JL, et al. Durable efficacy and safety of raltegravir versus efavirenz when combined with tenofovir/emtricitabine in treatment-naive HIV-1-infected patients: final 5-year results from STARTMRK. *J Acquir Immune Defic Syndr*. 2013;63(1):77-85. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23412015.

20. Cohen C, Wohl D, Arribas JR, et al. Week 48 results from a randomized clinical trial of rilpivirine/emtricitabine/tenofovir disoproxil fumarate vs. efavirenz/emtricitabine/tenofovir disoproxil fumarate in treatment-naive HIV-1-infected adults. *AIDS*. 2014;28(7):989-997. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24508782.

21. ENCORE Study Group, Carey D, Puls R, et al. Efficacy and safety of efavirenz 400 mg daily versus 600 mg daily: 96-week data from the randomised, double-blind, placebo-controlled, non-inferiority ENCORE1 study. *Lancet Infect Dis*. 2015;15(7):793-802. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25877963.

22. NAMSAL ANRS Study Group, Kouanfack C, Mpoudi-Etame M, et al. Dolutegravir-based or low-dose efavirenz-based regimen for the treatment of HIV-1. *N Engl J Med*. 2019;381(9):816-826. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31339676.

23. Calmy A, Tovar Sanchez T, Kouanfack C, et al. Dolutegravir-based and low-dose efavirenz-based regimen for the initial treatment of HIV-1 infection (NAMSAL): week 96 results from a two-group, multicentre, randomised, open label, phase 3 non-inferiority trial in Cameroon. *Lancet HIV*. 2020;7(10):e677-e687. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33010241.

24. Lamorde M, Wang X, Neary M, et al. Pharmacokinetics, pharmacodynamics, and pharmacogenetics of efavirenz 400 mg once daily during pregnancy and post-partum. *Clin Infect Dis*. 2018;67(5):785-790. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30124823.

25. Cerrone M, Wang X, Neary M, et al. Pharmacokinetics of efavirenz 400 mg once daily coadministered with isoniazid and rifampicin in human immunodeficiency virus-infected individuals. *Clin Infect Dis*. 2019;68(3):446-452. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30084943.

26. Mollan KR, Smurzynski M, Eron JJ, et al. Association between efavirenz as initial therapy for HIV-1 infection and increased risk for suicidal ideation or attempted or completed suicide: an analysis of trial data. *Ann Intern Med*. 2014;161(1):1-10. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24979445.

27. Arenas-Pinto A, Grund B, Sharma S, et al. Risk of Suicidal Behavior With Use of Efavirenz: Results from the Strategic Timing of Antiretroviral Treatment Trial. *Clin Infect Dis*. 2018;67(3):420-429. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29538636.

28. Smith C, Ryom L, Monforte A, et al. Lack of association between use of efavirenz and death from suicide: evidence from the D:A:D study. *J Int AIDS Soc*. 2014;17(4 Suppl 3):19512. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25394021.

29. Napoli AA, Wood JJ, Coumbis JJ, Soitkar AM, Seekins DW, Tilson HH. No evident association between efavirenz use and suicidality was identified from a disproportionality analysis using the FAERS database. *J Int AIDS Soc*. 2014;17:19214. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25192857.

30. Nkhoma ET, Coumbis J, Farr AM, et al. No evidence of an association between efavirenz exposure and suicidality among HIV patients initiating antiretroviral therapy in a retrospective cohort study of real world data. *Medicine (Baltimore)*. 2016;95(3):e2480. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26817882.

31. Chang JL, Tsai AC, Musinguzi N, et al. Depression and Suicidal Ideation Among HIV-Infected Adults Receiving Efavirenz Versus Nevirapine in Uganda: A Prospective Cohort Study. *Ann Intern Med*. 2018;169(3):146-155. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29946683.

32. Cross HM, Chetty S, Asukile MT, Hussey HS, Lee Pan EB, Tucker LM. A proposed management algorithm for late-onset efavirenz neurotoxicity. *S Afr Med J*. 2018;108(4):271-274. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29629676.

33. Variava E, Sigauke FR, Norman J, et al. Brief Report: Late Efavirenz-Induced Ataxia and Encephalopathy: A Case Series. *J Acquir Immune Defic Syndr*. 2017;75(5):577-579. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28520619.

34. Sustiva package insert [package insert]. Bristol-Myers Squibb. 2016. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020972s049-021360s038lbl.pdf.

35. Abdelhady AM, Shugg T, Thong N, et al. Efavirenz inhibits the human ether-a-go-go related current (hERG) and induces QT interval prolongation in CYP2B6*6*6 allele carriers. *J Cardiovasc Electrophysiol*. 2016;27(10):1206-1213. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27333947.

36. Symfi prescibing information [Type]. 2018.

37. Symfi Lo prescribing information [Type]. 2018.

38. Fundaro C, Genovese O, Rendeli C, Tamburrini E, Salvaggio E. Myelomeningocele in a child with intrauterine exposure to efavirenz. *AIDS*. 2002;16(2):299-300. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11807320.

39. Ford N, Calmy A, Mofenson L. Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis. *AIDS*. 2011;25(18):2301-2304. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21918421.

40. Zash R, Holmes L, Diseko M, et al. Neural-Tube Defects and Antiretroviral Treatment Regimens in Botswana. *N Engl J Med*. 2019;381(9):827-840. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31329379.

41. van Lunzen J, Antinori A, Cohen CJ, et al. Rilpivirine vs. efavirenz-based single-tablet regimens in treatment-naive adults: week 96 efficacy and safety from a randomized phase 3b study. *AIDS*. 2016;30(2):251-259. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26684822.

42. Zack J, Chuck S, Chu H, et al. Bioequivalence of the rilpivirine/emtricitabine/tenofovir alafenamide single-tablet regimen. *J Bioequiv Availab*. 2016;8(2):49-54. Available at: http://www.omicsonline.org/open-access/bioequivalence-of-the-rilpivirineemtricitabinetenofovir-alafenamidesingletablet-regimen-jbb-1000266.pdf.

43. Juluca prescribing information [Type]. 2017.