



Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Rilpivirine (RPV, Edurant) (Last updated May 22, 2018; last reviewed May 22, 2018)

For additional information see Drugs@FDA: <http://www.accessdata.fda.gov/scripts/cder/daf>

Formulations

Tablet: 25 mg

Fixed-Dose Combination Tablet:

- [Complera] Emtricitabine 200 mg plus rilpivirine 25 mg plus tenofovir disoproxil fumarate (TDF) 300 mg
- [Odefsey] Emtricitabine 200 mg plus rilpivirine 25 mg plus tenofovir alafenamide (TAF) 25 mg
- [Juluca] Dolutegravir 50 mg plus rilpivirine 25 mg

Dosing Recommendations

Neonate/Infant Dose:

- Not approved for use in neonates/infants.

Children Aged <12 Years:

- Not Food and Drug Administration-approved for use in children aged <12 years. For more information regarding consideration for use in children aged <12 years and weighing ≥ 35 kg, see the Pharmacokinetics section below.

Adolescent (Weighing ≥ 35 kg) and Adult Dose:

- 25 mg once daily in antiretroviral (ARV)-naive patients who have HIV RNA $\leq 100,000$ copies/mL or in patients who are virologically suppressed (HIV RNA <50 copies/mL) with no history of virologic failure or resistance to rilpivirine and other ARV drugs in the new regimen.

Combination Tablets

[Complera] Emtricitabine plus Rilpivirine plus TDF

Adolescent (Weighing ≥ 35 kg) and Adult Dose:

- One tablet once daily in treatment-naive patients with baseline viral load $\leq 100,000$ copies/mL. One tablet once daily can also be used to replace a stable ARV regimen in patients who are currently on their first or second regimen and who have been virologically suppressed (HIV-1 RNA <50 copies per mL) for ≥ 6 months with no history of treatment failure and no known current or past substitutions associated with resistance to the individual components of Complera.

[Odefsey] Emtricitabine plus Rilpivirine plus TAF

Adolescent (Weighing ≥ 35 kg) and Adult Dose:

- One tablet once daily with a meal as initial therapy in treatment-naive patients with

Selected Adverse Events

- Depression
- Insomnia
- Headache
- Rash (can be severe and include Drug Reaction/Rash with Eosinophilia and Systemic Symptoms)
- Hepatotoxicity
- Altered ACTH stimulation test of uncertain clinical significance

Special Instructions

- Do not start rilpivirine in patients with HIV RNA >100,000 copies/mL due to increased risk of virologic failure.
- Patients must be able to take rilpivirine with a meal of at least 500 calories on a regular schedule (a protein drink alone does not constitute a meal).
- Do not use rilpivirine with other non-nucleoside reverse transcriptase inhibitors.
- Do not use rilpivirine with proton pump inhibitors.
- Antacids should only be taken at least 2 hours before or at least 4 hours after rilpivirine.
- Use rilpivirine with caution when co-administered with a drug that has a known risk of Torsades de Pointes (for more information see [CredibleMeds](#))
- When using fixed-dose combination (FDC) tablets, see other sections of the [Drug Appendix](#) for special instructions and additional information about the individual components of the FDC.

HIV-1 RNA \leq 100,000 copies per mL. One tablet once daily can also be used to replace a stable ARV regimen in patients who have been virologically suppressed (HIV-1 RNA $<$ 50 copies per mL) for \geq 6 months with no history of treatment failure and no known current or past substitutions associated with resistance to the individual components of Odefsey.

[Juluca] Dolutegravir plus Rilpivirine

Adult Dose:

- One tablet once daily with a meal as a complete regimen to replace the current ARV regimen in patients who have been virologically suppressed (HIV-1 RNA $<$ 50 copies per mL) on a stable ARV regimen for \geq 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Juluca.
- Not approved for children or adolescents. See Simplification of Treatment section below.

Metabolism/Elimination

- Cytochrome P450 (CYP) 3A substrate

Rilpivirine Dosing in Patients with Hepatic Impairment:

- No dose adjustment is necessary in patients with mild or moderate hepatic impairment.
- Rilpivirine decreases tubular secretion of creatinine and slightly increases measured serum creatinine, but it does not affect glomerular filtration.

Rilpivirine Dosing in Patients with Renal Impairment:

- No dose adjustment is necessary in patients with mild or moderate renal impairment.
- The FDC drugs Complera and Odefsey should not be used in patients with creatinine clearance $<$ 50 or $<$ 30 mL/min, respectively, or in patients who require dialysis.
- Use rilpivirine with caution in patients with severe renal impairment or end-stage renal disease. Rilpivirine concentrations may be increased in patients with severe renal impairment or end-stage renal disease, so monitoring for adverse effects is especially important in these patients.
- When using Complera, see the TDF section of the guidelines; when using Odefsey, see the TAF section.

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

- **Metabolism:** Rilpivirine is a cytochrome P (CYP) 3A substrate and requires dose adjustments when administered with CYP 3A-modulating medications.
- A patient's medication profile should be carefully reviewed for potential drug interactions before rilpivirine is administered.
- Co-administering rilpivirine with drugs that increase gastric pH may decrease plasma concentrations of rilpivirine.
- Antacids should only be taken at least 2 hours before or at least 4 hours after rilpivirine.
- H2-receptor antagonists should only be administered at least 12 hours before or at least 4 hours after rilpivirine.
- Do not use rilpivirine with proton pump inhibitors.
- Rifampin and rifabutin significantly reduce rilpivirine plasma concentrations; co-administration of rifampin with rilpivirine is **contraindicated**. For patients concomitantly receiving rifabutin, rilpivirine dose should be increased (doubled) to 50 mg once daily, taken with a meal.
- In a cohort of adolescent patients, rilpivirine exposure was increased two- to three-fold when administered in combination with darunavir/ritonavir (DRV/r).¹

Major Toxicities

- *More common:* Insomnia, headache, and rash.
- *Less common (more severe):* Depression or mood changes, suicidal ideation.
- In adult studies, 7.3% of patients treated with rilpivirine showed a change in adrenal function identified by an abnormal 250-microgram ACTH stimulation test (peak cortisol level <18.1 micrograms/dL). **In an adolescent study**, 6 out of 30 patients (20%) developed this abnormality.² The clinical significance of these results is unknown.

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.

Pediatric Use

Approval

With the viral load and antiretroviral (ARV) resistance restrictions noted above, rilpivirine (**Edurant**) used in combination with other antiretroviral agents,² the combination tablet rilpivirine/emtricitabine/tenofovir disoproxil fumarate (Complera),³ and the combination tablet rilpivirine/emtricitabine/tenofovir alafenamide (Odefsey) are all Food and Drug Administration (FDA)-approved for use in persons aged ≥ 12 years and weighing ≥ 35 kg.⁴ **The combination tablet of dolutegravir/rilpivirine (Juluca) is not approved for use in pediatric or adolescent patients at the time of this review.**⁵

Efficacy in Clinical Trials

A rilpivirine-containing regimen has been compared to an efavirenz-containing regimen in two large clinical trials in adults, ECHO and THRIVE. In both studies, rilpivirine was demonstrated to be non-inferior to efavirenz. Subjects with pretreatment HIV viral loads $\geq 100,000$ copies/mL who received rilpivirine had higher rates of virologic failure than those who received efavirenz. These findings resulted in licensure for initial therapy with rilpivirine only in patients with HIV viral load $\leq 100,000$ copies/mL.⁶⁻⁹

A study of treatment-naïve adolescents aged 12 to 18 years demonstrated that rilpivirine 25 mg, given once daily in combination with two nucleoside reverse transcriptase inhibitors (NRTIs), was well tolerated over 48 weeks. Among adolescents with baseline viral loads $\leq 100,000$ copies/mL, 86% had a virologic response at 24 weeks and 79% had a virologic response at 48 weeks. Among adolescents with baseline viral loads $> 100,000$ copies/mL, 38% had a virologic response at 24 weeks and 50% had a virologic response at 48 weeks.¹⁰

Patients selected for rilpivirine use need to be able to take the drug on a regular schedule and with a full meal, which may limit its usefulness for some adolescents with irregular schedules. The FDC formulation, Odefsey, is a small pill and can be useful for select patients who might want to switch from a multi-pill regimen and who do not have any drug resistance mutations **to the components of Odefsey.**

A Spanish multicenter observational study enrolled 17 adolescents (aged <18 years of age) who acquired HIV perinatally to receive emtricitabine/tenofovir disoproxil fumarate/rilpivirine (Complera) as part of an off-label medication use program. At the time of enrollment, 12 patients were on a protease inhibitor-based regimen, four were on a non-nucleoside reverse transcriptase inhibitor-based regimen, and one had not received antiretroviral therapy (ART). After a median follow-up of 90 weeks (for participants with undetectable viral loads at baseline) or 40 weeks (for participants with detectable viral loads at baseline), 86% and 89% of patients, respectively, achieved and maintained an undetectable viral load. None of the patients discontinued rilpivirine-based therapy because of adverse effects; no skin rashes or central nervous system (CNS)-related events were observed. In addition, serum lipids improved and two adolescents with a history of insomnia and abnormal dreams while receiving efavirenz-based therapy did not report similar problems while receiving rilpivirine-based therapy.¹¹

Pharmacokinetics

The pharmacokinetics (PK), safety, and efficacy of rilpivirine in children aged <12 years have not been established but are under study in patients aged 6 to <12 years and weighing ≥ 17 kg (*ClinicalTrials.gov* identifier [NCT00799864](https://clinicaltrials.gov/ct2/show/study/NCT00799864)). The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) has decided that that rilpivirine may be appropriate in select children aged <12 years and weighing ≥ 35 kg. However, the Panel advises consulting an expert in pediatric HIV infection prior to use in this age group.

An international (India, Thailand, Uganda, and South Africa) Phase 2 trial, PAINT TMC278, investigated a 25-mg dose of rilpivirine given in combination with two NRTIs in ARV-naive adolescents aged 12 to <18 years, weighing ≥ 32 kg, and who had viral loads $\leq 100,000$ copies/mL.¹⁰ In the dose-finding phase of the study, 11 youth aged >12 to ≤ 15 years and 12 youth aged >15 to ≤ 18 years underwent intensive PK evaluations after an observed dose of rilpivirine taken with a meal. PK were comparable to those in adults; results are listed in the table below.¹²

Table A. Rilpivirine Pharmacokinetics in Adults and in Adolescents Aged 12 to <18 Years²

Parameter	Adults	Adolescents Aged 12 to <18 years
Dose	25 mg once daily	25 mg once daily
Number of Participants Studied	679	34
AUC_{24h} (ng•h/mL)		
Mean \pm Standard Deviation	2,235 \pm 851	2,424 \pm 1,024
Median (Range)	2,096 (198–7,307)	2,269 (417–5,166)
C_{0h} (ng/mL)		
Mean \pm Standard Deviation	79 \pm 35	85 \pm 40
Median (Range)	73 (2–288)	79 (7–202)

Key to Acronyms: AUC = area under the curve; C_{0h} = plasma concentration just prior to next dose

In a PK study of youth aged 13 to 23 years receiving rilpivirine,¹ rilpivirine exposure was comparable to the results from PAINT in patients receiving 25-mg doses rilpivirine without DRV/r and substantially higher in those receiving 25-mg doses rilpivirine with DRV/r (AUC = 6,740 ng•h/mL). No dose adjustments are currently recommended for adults when rilpivirine is used with DRV/r, where a similar two- to three-fold increase in rilpivirine exposure has been reported.²

Rilpivirine has been reported to have fewer CNS adverse effects and has been promoted as a replacement ARV for some patients who experience CNS effects while receiving efavirenz. However, there has been concern that prolonged efavirenz half-life might have an impact on rilpivirine levels after a drug switch. A Thai study evaluated 20 Thai adolescents 4 weeks after switching from efavirenz to rilpivirine. The PK parameters of rilpivirine in this study population were comparable with those in previous pediatric (PAINT) and adult (ECHO/THRIVE) PK substudies. No virologic failure was detected at 12 or 24 weeks and no patients discontinued rilpivirine because of adverse effects.¹³

Simplification of Treatment

Dolutegravir/rilpivirine (Juluca) is a fixed-dose combination tablet that contains dolutegravir 50 mg and rilpivirine 25 mg. The recently reported results from two trials in adults (SWORD-1 and SWORD-2) support FDA approval of dolutegravir/rilpivirine as a complete regimen for treatment simplification or maintenance therapy in selected patients. The two identical SWORD trials enrolled 1,024 patients with suppressed viral replication who had been on stable ART for at least 6 months and had no history of treatment failure or evidence of resistance mutations to dolutegravir or rilpivirine. The participants were randomized to receive dolutegravir/rilpivirine or to continue their suppressive ARV regimen. After 48 weeks of treatment, 95% of

patients in both arms maintained HIV RNA <50 copies/mL.¹⁴ More adverse events (AEs) were reported and more AEs led to discontinuation in the dolutegravir/rilpivirine arm. In a subgroup of SWORD study patients whose original ARV regimen contained tenofovir disoproxil fumarate, small but statistically significant increases in hip and spine bone mineral density were observed.¹⁵ Although dolutegravir/rilpivirine as Juluca is not approved for use in adolescents, the doses of both dolutegravir and rilpivirine in Juluca are approved for use in adolescents as single drugs. The Panel usually endorses adult formulations for use in adolescents, and this product may be appropriate for certain adolescents. However, because the strategy of treatment simplification has not been evaluated in adolescents who may have difficulties adhering to therapy, the Panel **does not currently recommend** the use of Juluca for adolescents and children until more data are available.

Long-Acting, Injectable Rilpivirine

Currently, a long-acting, injectable formulation of rilpivirine is under development as a treatment for adult patients (in combination with a cabotegravir long-acting injectable).¹⁶ An IMPAACT study of the same regimen in adolescents is expected to begin enrolling participants in 2018.

Toxicity

In the PAINT study, the observed AEs were similar to those reported in adults (e.g., somnolence, nausea, vomiting, abdominal pain, dizziness, and headache). The incidence of depressive disorders was 19.4% (7/36 participants) compared to 9% in the Phase 3 trials in adults. The incidence of Grades 3 and 4 depressive disorders was 5.6% (2/36 participants).²

Six out of 30 adolescents (20%) with a normal adrenocotropic hormone stimulation test at baseline developed an abnormal test during the trial. There were no serious AEs, deaths, or treatment discontinuations attributed to adrenal insufficiency. The clinical significance of abnormal adrenocotropic hormone stimulation tests is not known, but **this finding** warrants further evaluation.²

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