

Rilpivirine (RPV, Edurant)

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Formulations	
<p>Tablet: 25 mg</p> <p>Fixed-Dose Combination Tablets</p> <ul style="list-style-type: none"> • [Complera] Emtricitabine 200 mg/rilpivirine 25 mg/tenofovir disoproxil fumarate 300 mg • [Juluca] Dolutegravir 50 mg/rilpivirine 25 mg • [Odefsey] Emtricitabine 200 mg/rilpivirine 25 mg/tenofovir alafenamide 25 mg <p>When using fixed-dose combination (FDC) tablets, refer to other sections of Appendix A: Pediatric Antiretroviral Drug Information for information about the individual components of the FDC. See also Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets and Co-packaged Formulations: Minimum Body Weights and Considerations for Use in Children and Adolescents.</p> <p>Co-packaged Formulations</p> <ul style="list-style-type: none"> • [Cabenuva Kit] Cabotegravir 400 mg/2 mL (200 mg/mL) and rilpivirine 600 mg/2 mL (300 mg/mL) suspension for intramuscular injection • [Cabenuva Kit] Cabotegravir 600 mg/3 mL (200 mg/mL) and rilpivirine 900 mg/3 mL (300 mg/mL) suspension for intramuscular injection <p>When using the co-packaged formulation, refer to the Cabotegravir section for additional information.</p> <p>For additional information, see Drugs@FDA or DailyMed.</p>	
Dosing Recommendations	Selected Adverse Events
<p>Neonate and Infant Dose</p> <ul style="list-style-type: none"> • Rilpivirine (RPV) is not approved for use in neonates or infants. <p>Children Aged <12 Years</p> <ul style="list-style-type: none"> • RPV is not approved for use in children aged <12 years (for more information, see the Pharmacokinetics section below). <p>Child and Adolescent (Aged ≥12 Years and Weighing ≥35 kg) and Adult Dose</p> <ul style="list-style-type: none"> • RPV 25 mg once daily with a meal in antiretroviral therapy (ART)-naïve patients who have HIV RNA ≤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 RPV and other antiretroviral (ARV) drugs in the new regimen. 	<ul style="list-style-type: none"> • Depression • Insomnia • Headache • Rash, which can be severe and include DRESS (drug reaction [or rash] with eosinophilia and systemic symptoms) • Hepatotoxicity • Altered adrenocorticotrophic hormone stimulation test of uncertain clinical significance

<p>[Complera] Emtricitabine/Rilpivirine/Tenofovir Disoproxil Fumarate (TDF)</p> <p>Child and Adolescent (Aged ≥ 12 Years and Weighing ≥ 35 kg) and <i>Adult Dose</i></p> <ul style="list-style-type: none">One tablet once daily with a meal in ART-naïve patients with baseline viral loads $\leq 100,000$ copies/mL. One tablet once daily also can be used to replace the current ARV regimen in patients who are currently on their first or second regimen and who have been virologically suppressed (HIV RNA < 50 copies/mL) for at least 6 months with no history of treatment failure and no known mutations associated with resistance to the individual components of Complera.	<p>Special Instructions</p> <ul style="list-style-type: none">Do not start RPV in patients with HIV RNA $> 100,000$ copies/mL because of the increased risk of virologic failure.RPV concentrations are significantly increased when either RPV or dolutegravir (DTG)/RPV is administered with a moderate- or high-fat meal.¹ Patients must be able to take RPV (or DTG/RPV) with a meal of at least 500 calories on a regular schedule (a protein drink alone does not constitute a meal).Do not use RPV with other non-nucleoside reverse transcriptase inhibitors.Do not use RPV with proton pump inhibitors (e.g., omeprazole, pantoprazole).Antacids should only be taken at least 2 hours before or at least 4 hours after RPV.H2 receptor antagonists (e.g., cimetidine, famotidine) should only be administered at least 12 hours before or at least 4 hours after RPV.Use RPV with caution when coadministering it with a drug that has a known risk of prolonging the QTc interval or causing Torsades de Pointes (for more information, see CredibleMeds).Screen patients for hepatitis B virus (HBV) infection before using FDC tablets that contain TDF or TAF. Severe acute exacerbation of HBV infection can occur when TDF or TAF are discontinued, see Tenofovir Disoproxil Fumarate and Tenofovir Alafenamide. Therefore, hepatic function and hepatitis B viral load should be monitored for several months after therapy with TDF or TAF is discontinued in patients with HBV.Refer to Cabotegravir for special instructions when using CAB and RPV for IM injection.
<p>[Juluca] Dolutegravir/Rilpivirine</p> <p><i>Adult Dose</i></p> <ul style="list-style-type: none">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 RNA < 50 copies/mL) on a stable ARV regimen for at least 6 months with no history of treatment failure and no known mutations associated with resistance to the individual components of Juluca.Not approved for use in children or adolescents (see the Simplification of Treatment section below).	
<p>[Odefsey] Emtricitabine/Rilpivirine/Tenofovir Alafenamide (TAF)</p> <p>Child and Adolescent (Aged ≥ 12 Years and Weighing ≥ 35 kg) and <i>Adult Dose</i></p> <ul style="list-style-type: none">One tablet once daily with a meal in ART-naïve patients with HIV RNA $\leq 100,000$ copies/mL. One tablet once daily also can be used to replace a stable ARV regimen in patients who have been virologically suppressed (HIV RNA < 50 copies/mL) for at least 6 months with no history of treatment failure and no known mutations associated with resistance to the individual components of Odefsey.	
<p>[Cabenuva] Cabotegravir (CAB) and Rilpivirine (RPV) Kit</p> <p>Child and Adolescent (Aged ≥ 12 Years and Weighing ≥ 35 kg) and <i>Adult Dose</i></p> <ul style="list-style-type: none">Cabenuva is a two-drug co-packaged product for intramuscular (IM) injection that is approved by the U.S. Food and Drug Administration as a complete regimen for the treatment of HIV-1 in patients with HIV RNA levels < 50 copies/mL on a stable ARV regimen with no history of treatment failure and no known or suspected resistance to CAB or RPV.	<p>Metabolism/Elimination</p> <ul style="list-style-type: none">Cytochrome P450 3A substrate.Refer to Cabotegravir for information about the IM CAB and RPV regimen. <p>Rilpivirine Dosing in Patients With Hepatic Impairment</p> <ul style="list-style-type: none">No dose adjustment is necessary in patients with mild or moderate hepatic impairment. <p>Rilpivirine Dosing in Patients With Renal Impairment</p> <ul style="list-style-type: none">RPV decreases tubular secretion of creatinine and slightly increases measured serum creatinine, but it does not affect glomerular filtration.

<ul style="list-style-type: none"> • Oral lead-in dosing for at least 28 days can be used to assess tolerability prior to initiating IM CAB and RPV injections or patients can proceed directly to IM CAB and RPV on the last day of their current ARV regimen. • Refer to Cabotegravir for dosing information. • Long-acting CAB and RPV for IM injection is not approved for children aged <12 years. 	<ul style="list-style-type: none"> • No dose adjustment is necessary in patients with mild or moderate renal impairment. However, RPV should be used with caution in patients with severe renal impairment or end-stage renal disease. These patients should be monitored more frequently for adverse events; renal dysfunction may alter drug absorption, distribution, and metabolism, leading to increased RPV concentrations. • The FDC tablet Complera should not be used in patients with creatinine clearance (CrCl) <50 mL/min, and the FDC tablet Odefsey should not be used in patients with CrCl <30 mL/min. Patients with CrCl <30 mL/min who are taking Juluca should be monitored closely. • When using Complera, see the Tenofovir Disoproxil Fumarate section of the guidelines; when using Odefsey, see the Tenofovir Alafenamide section.
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Drug Interactions

Additional information about drug interactions is available in the [Adult and Adolescent Antiretroviral Guidelines](#) and the [HIV Drug Interaction Checker](#).

- *Metabolism:* Rilpivirine (RPV) is a cytochrome P450 (CYP) 3A substrate, and concentrations may be affected when administered with CYP3A-modulating medications.
- A patient's medication profile should be carefully reviewed for potential drug interactions before RPV is administered.
- Coadministering RPV with drugs that increase gastric pH may decrease plasma concentrations of RPV.
 - Antacids should only be taken at least 2 hours before or at least 4 hours after RPV.
 - H2 receptor antagonists should only be administered at least 12 hours before or at least 4 hours after RPV.
 - Do not use RPV with proton pump inhibitors.
- All the rifamycins significantly reduce RPV plasma concentrations; coadministration of rifampin and oral RPV is **contraindicated**. For patients who are concomitantly receiving rifabutin and oral RPV, the dose of RPV should be doubled to 50 mg once daily and taken with a meal. Intramuscular (IM) RPV given with IM CAB is **contraindicated** with rifampin, rifabutin, and rifapentine.
- In a cohort of adolescent patients, RPV exposure was two to three times greater when RPV was administered in combination with darunavir/ritonavir (DRV/r) than when RPV was administered alone.²

Major Toxicities

- *More common:* Insomnia, headache, rash

- *Less common (more severe):* Depression or mood changes, suicidal ideation

In studies of adults, 7.3% of patients who were treated with RPV showed a change in adrenal function characterized by an abnormal 250-microgram adrenocorticotrophic hormone (ACTH) stimulation test (peak cortisol level <18.1 micrograms/dL). In a study of adolescents, 6 out of 30 patients (20%) developed this abnormality.³ The clinical significance of these results is unknown.

- *Rare:* RPV drug-induced liver injury has been reported.⁴

Resistance

The International Antiviral Society–USA (IAS–USA) maintains a list of updated [HIV drug resistance mutations](#), and the [Stanford University HIV Drug Resistance Database](#) offers a discussion of each mutation.

Transmitted drug resistance to second-generation non-nucleoside reverse transcriptase inhibitors (NNRTIs) may be present in infants and children who have recently received a diagnosis of HIV.

Pediatric Use

Approval

With the viral load and antiretroviral (ARV) resistance restrictions noted above, RPV (Edurant) used in combination with other ARV agents, the fixed-dose combination (FDC) tablet emtricitabine/rilpivirine/tenofovir disoproxil fumarate (FTC/RPV/TDF; Complera), the FDC tablet emtricitabine/rilpivirine/tenofovir alafenamide (FTC/RPV/TAF; Odefsey) and the long-acting regimen of cabotegravir (CAB) and RPV for IM injection (IM CAB and RPV; Cabenuva) are all approved by the U.S. Food and Drug Administration (FDA) for use in persons aged ≥ 12 years and weighing ≥ 35 kg. The FDC tablet dolutegravir/rilpivirine (DTG/RPV; Juluca) is not approved for use in pediatric or adolescent patients at the time of this review.

Efficacy in Clinical Trials

An RPV-containing regimen has been compared to an efavirenz (EFV)-containing regimen in two large clinical trials in adults—ECHO and THRIVE. In both studies, RPV was shown to be non-inferior to EFV. Patients with pretreatment HIV viral loads $\geq 100,000$ copies/mL who received RPV had higher rates of virologic failure than those who received EFV. These findings resulted in FDA approval for initial therapy with RPV only in patients with HIV viral loads $\leq 100,000$ copies/mL.⁵⁻⁸

A study of antiretroviral therapy (ART)-naïve adolescents aged 12 to 18 years demonstrated that RPV 25 mg, given once daily in combination with two nucleoside reverse transcriptase inhibitors (NRTIs), was well tolerated over 48 weeks. In studies of 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. In 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.⁹

Patients must be able to take RPV 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 certain patients who have difficulty swallowing pills and want to switch

from a multipill regimen, and who do not have any drug resistance mutations that are associated with the components of Odefsey.

A Spanish multicenter observational study enrolled 17 adolescents (aged <18 years) who acquired HIV perinatally to receive FTC/RPV/TDF (Complera) as part of an off-label medication use program. At the time of enrollment, 12 patients were on a protease inhibitor-based regimen, 4 were on an NNRTI-based regimen, and 1 had not received 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 RPV-based therapy because of adverse events (AEs); 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 EFV-based therapy did not report similar problems while receiving RPV-based therapy.¹⁰

Another study evaluated 102 virologically-suppressed Thai adolescents who were switched from an EFV- to an RPV-based therapy. Ninety-four of the adolescents remained virologically suppressed through 48 weeks; six experienced virologic failure. Overall, RPV was well tolerated. No improvement in EFV-related symptoms (e.g., sleep, mood, dizziness, headache, concentration) was observed, and no change in quality of life or depression scores could be documented; however, there were significant improvements in some assessments of cognitive and executive function as measured at week 24.¹¹

Pharmacokinetics

The pharmacokinetics (PKs), safety, and efficacy of RPV in children aged <12 years have not been established but are currently being studied in patients aged 6 years to <12 years and weighing ≥ 17 kg ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00799864) identifier NCT00799864). The Panel on Antiretroviral Therapy and Medical Management of Children Living With HIV (the Panel) has agreed that the use of RPV may be appropriate in certain children aged <12 years and weighing ≥ 35 kg. However, the Panel advises consulting an expert in pediatric HIV infection prior to prescribing RPV for a child in this age and weight group.

An international (India, Thailand, Uganda, and South Africa) Phase 2 trial, Pediatric Study in Adolescents Investigating a New NNRTI TMC278 (PAINT), investigated a 25-mg dose of RPV given in combination with two NRTIs in ARV-naïve adolescents aged 12 years to <18 years who weighed ≥ 32 kg and who had viral loads $\leq 100,000$ copies/mL.⁹ In the dose-finding phase of the study, 11 youth aged >12 years to ≤ 15 years and 12 youth aged >15 years to ≤ 18 years underwent intensive PK assessment after they took an observed dose of RPV with a meal. PKs were comparable to those in adults; results are listed in the table below.¹²

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

Parameter	Adults	Adolescents Aged 12 Years to <18 Years
Dose	RPV 25 mg once daily	RPV 25 mg once daily

Parameter	Adults	Adolescents Aged 12 Years to <18 Years
Number of Participants Studied	679	34
AUC_{24h} (ng·h/mL)		
Mean ± SD	2,235 ± 851	2,424 ± 1,024
Median (Range)	2,096 (198–7,307)	2,269 (417–5,166)
C_{0h} (ng/mL)		
Mean ± SD	79 ± 35	85 ± 40
Median (Range)	73 (2–288)	79 (7–202)

Source: Adapted from Rilpivirine [package insert]. Food and Drug Administration. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/202022s014lbl.pdf

Key: AUC_{24h} = area under the curve after 24 hours; C_{0h} = plasma concentration just prior to next dose; RPV = rilpivirine; SD = standard deviation

In a PK study of youth aged 13 to 23 years who received RPV,² RPV exposure was comparable to the exposure observed during the PAINT study in patients who received 25-mg doses of RPV without DRV/r and substantially higher than the exposure observed in those who received 25-mg doses of RPV with DRV/r (RPV area under the curve in this study was 6,740 ng·h/mL). No dose adjustments are currently recommended for adults when RPV is coadministered with DRV/r, where a similar twofold to threefold increase in RPV exposure has been reported.³

RPV has been reported to have fewer CNS AEs than EFV, and it has been promoted as a replacement ARV drug for some patients who experience CNS effects while receiving EFV. However, concern exists that the prolonged half-life of EFV might result in residual drug levels that could have an impact on RPV levels. A Thai study evaluated 20 Thai adolescents 4 weeks after they switched from EFV to RPV. The PK parameters of RPV in this study population were comparable to 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 RPV because of AEs.¹³

Simplification of Treatment

Juluca is an FDC tablet that contains DTG 50 mg and RPV 25 mg. The results from two trials in adults (SWORD-1 and SWORD-2) supported FDA approval of DTG/RPV as a complete regimen for treatment simplification or maintenance therapy in certain 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 that are associated with DTG or RPV. The participants were randomized to receive DTG/RPV (“early switch”) 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 After 52 weeks, the participants who had been randomized to continue their suppressive ARV regimen were switched to DTG/RPV (“late switch”). At 148 weeks of treatment, 84% of the early switch patients and 90% of the late switch patients remained virologically suppressed, and only 11 patients receiving dual therapy (DTG/RPV) met virologic failure criteria. No integrase inhibitor resistance was identified.¹⁵ More AEs were reported, and more AEs led to treatment discontinuation in the DTG/RPV arm during the comparative

randomized phase. In a subgroup of SWORD study patients whose original ARV regimen contained TDF, small but statistically significant increases in hip and spine bone mineral density were observed.¹⁶ Although DTG/RPV as Juluca is not approved for use in adolescents, the doses of both component drugs that make up Juluca are approved for use in adolescents. 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 recommend** using Juluca in adolescents and children until more data are available.

Long-Acting Injectable Rilpivirine

A long-acting IM injectable formulation of RPV has recently been approved for coadministration with IM CAB as a complete ARV regimen for children and adolescents aged ≥ 12 years and weighing ≥ 35 kg and adults with HIV RNA levels < 50 copies/mL, on a stable ARV regimen, with no history of treatment failure, and no known or suspected resistance to CAB or RPV.¹⁷ This formulation has been evaluated in adults as monthly or every-2 month intramuscular injections following an initial oral, lead-in daily dose for 4 weeks to assess toxicity.¹⁸⁻²⁰ These studies in adult patients demonstrated non-inferior efficacy to standard oral therapy and good participant satisfaction and tolerability through 96 weeks. A follow-on study demonstrated that dosing IM CAB and RPV every 2 months in virally suppressed participants provided similar safety and efficacy to monthly injections through 48 weeks.²¹ Additionally, an extension of one study evaluated the benefit of oral lead-in therapy prior to initiating IM CAB and RPV, demonstrating that initial oral therapy can be optional based on the needs and desires of persons initiating treatment.²² [IMPAACT study 2017](#), More Options for Children and Adolescents (MOCHA), is currently evaluating the safety, tolerability, acceptability, and PK profile of this injectable regimen in adolescents weighing ≥ 35 kg ([ClinicalTrials.gov identifier NCT03497676](#)) and has reported acceptable PKs and safety for the single IM products administered monthly and good acceptability by both adolescents and their parents.^{23,24} However, MOCHA has not completed evaluating the dual injectable regimen long term, and clinical experience with IM CAB and RPV remains limited. See the [Cabotegravir](#) section for more information about this regimen.

Toxicity

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

Six out of 30 adolescents (20%) with a normal ACTH stimulation test at baseline developed an abnormal test during the trial. No serious AEs, deaths, or treatment discontinuations were attributed to adrenal insufficiency. The clinical significance of abnormal ACTH stimulation tests is not known, but this finding warrants further evaluation.³

Crushing Tablets for Enteral Administration

Some cases report DTG/RPV tablets' being crushed and successfully administered via an enteral tube.²⁵ If DTG/RPV is administered via enteral tube, care should be taken to disperse the tablets completely and flush the tube to avoid clogging.

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