

Table 11: Rilpivirine (RPV) Interactions (also see prescribing information)
 The combination CAB/RPV antiretroviral therapy regimen can be used during an oral medication lead-in period and then as monthly long-acting injections; also see Table 6: Cabotegravir (CAB) Interactions.

Class or Drug	Mechanism of Action	Clinical Comments
Macrolides	Coadministration may increase RPV levels.	Consider alternatives. Increased RPV levels when combined with macrolides may lead to increased risk of torsades de pointes.
Proton pump inhibitors (PPIs) [Schafer and Short 2012]	<ul style="list-style-type: none"> PPIs inhibit gastric acid secretion by proton pumps, thereby increasing gastric pH. Oral RPV requires acidic environment for optimal absorption. 	<ul style="list-style-type: none"> Concurrent use of PPIs with <i>oral</i> RPV is contraindicated. Use of PPIs with <i>injectable</i> RPV is acceptable.
Histamine-2 receptor antagonists (H2RAs) [Schafer and Short 2012]	<ul style="list-style-type: none"> H2RAs inhibit gastric acid secretion by proton pumps, thereby increasing gastric pH. Oral RPV requires acidic environment for optimal absorption. Concomitant use may decrease RPV absorption. 	<ul style="list-style-type: none"> Administer H2RA at least 12 hours before or 4 hours after. Use lowest effective dose. Administer with food. Use of H2RAs with <i>injectable</i> RPV is acceptable.
Antacids [Schafer and Short 2012]	<ul style="list-style-type: none"> Antacids increase gastric pH. RPV requires acidic environment for optimal absorption. Concomitant use may decrease RPV absorption. 	Administer antacids 2 hours before or 4 hours after.
Dexamethasone [Welz, et al. 2017]	Dexamethasone is a CYP3A inducer, which is primarily responsible for metabolism of RPV.	Dexamethasone (systemic): <ul style="list-style-type: none"> Concomitant use is contraindicated; consider alternative steroids. If using more than a single oral or IM dose, consider an alternative NNRTI after consultation with experienced HIV care provider (see prescribing information for Cabenuva and Edurant).
Antiarrhythmic medications [Sanford 2012]	Supratherapeutic RPV doses have caused QT prolongation and additive effects may be seen.	Avoid concomitant use (may cause QT prolongation and torsades de pointes).
Long-acting beta agonists (LABAs)	RPV and drugs from LABA class may both theoretically increase QT interval, especially at high doses.	<ul style="list-style-type: none"> No dose adjustments are necessary. Do not use more LABA than recommended; this can increase risk of QT prolongation.
Antipsychotics	No significant interactions reported.	No dose adjustments are necessary, but avoid excess doses of either antipsychotic or RPV because excess doses of both drugs may increase risk of QT prolongation.
Carbamazepine, oxcarbazepine, phenobarbital, phenytoin	Coadministration may significantly reduce RPV concentrations through induction of CYP450, UGT1A, and/or P-gP system.	Concomitant use is contraindicated with oral and injectable RPV (see prescribing information for Cabenuva and Edurant).
Methadone, buprenorphine (BUP)	<ul style="list-style-type: none"> BUP: No significant interactions are expected. Methadone: RPV mildly reduces methadone concentrations. 	<ul style="list-style-type: none"> Methadone: Monitor for signs of methadone withdrawal; increase dose as necessary. Methadone, BUP: Use cautiously with RPV; supratherapeutic RPV doses have been known to cause increase in QT prolongation.

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Rifabutin, rifampin, rifapentine	Coadministration may significantly reduce RPV concentrations through induction of CYP450, UGT1A, and/or P-gP system.	<ul style="list-style-type: none"> • Rifabutin: <ul style="list-style-type: none"> – Oral RPV: Increase RPV dose to 50 mg once daily [DHHS(a) 2024]. – Injectable RPV: Concomitant use is contraindicated. • Rifampin, rifapentine: Concomitant use with oral and injectable RPV is contraindicated [FDA(b) 2025].
Strong inducers or inhibitors of CYP3A	RPV is a CYP3A substrate, and as such, drugs that affect its metabolism affect its concentrations.	<ul style="list-style-type: none"> • Avoid concomitant use if possible. • Dose adjustments of RPV are not recommended. • Consider alternative concomitant agents.
Mpox treatments [a]	Tecovirimat is a weak inducer of CYP3A and a weak inhibitor of CYP2C8 and CYP2C19; use may increase or decrease plasma concentrations of other medications.	Tecovirimat may reduce NNRTI levels, though effects are not likely to be clinically relevant. No dose adjustment in either drug is necessary.
ADHD medications	Modafinil: CYP3A4 induction may reduce NNRTI levels.	Modafinil: Avoid concurrent use due to potential loss of virologic response.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ARV, antiretroviral; AUC, area under the curve; CAB, cabotegravir; CYP, cytochrome P450; IM, intramuscular; NNRTI, non-nucleoside reverse transcriptase inhibitor; P-gP, P-glycoprotein; TDM, therapeutic drug monitoring; VIGIV, vaccinia immune globulin intravenous.

Note:

a. No data are currently available on effects related to concurrent use of tecovirimat and HIV medications. However, [midazolam AUC was reduced by 32% with concomitant tecovirimat use](#), and some experts recommend caution due to the mild CYP3A4 induction associated with tecovirimat. Among them is [University of Liverpool HIV Drug Interactions](#), which makes the following dosing change recommendations, although they are not based on any clinical data: Increase dose to 50 mg daily for the duration of tecovirimat treatment and for 2 weeks after tecovirimat is stopped.

No significant interactions/no dose adjustments necessary (see guideline section [Drug-Drug Interactions by Common Medication Class](#)): Common oral antibiotics; antihypertensive medications; anticoagulants; antiplatelet medications; statins; asthma and allergy medications; antidepressants; benzodiazepines; sleep medications; anticonvulsants not specifically stated above; nonopioid pain medications; opioid analgesics and tramadol; erectile and sexual dysfunction agents; alpha-adrenergic antagonists for benign prostatic hyperplasia; tobacco and smoking cessation products; alcohol, disulfiram, and acamprosate; naloxone and naltrexone; immunosuppressants; COVID-19 therapeutics; gender-affirming hormones.

References

- DHHS(a). Guidelines for the use of antiretroviral agents in adults and adolescents with HIV: drug-drug interactions: role of therapeutic drug monitoring in managing drug-drug interactions. 2024 Sep 12. <https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/overview> [accessed 2018 Jul 6]
- FDA(b). Cabenuva (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension), co-packaged for intramuscular use. 2025 Apr. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/212888s016lbl.pdf [accessed 2021 May 28]
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- Welz T, Wyen C, Hensel M. Drug interactions in the treatment of malignancy in HIV-infected patients. *Oncol Res Treat* 2017;40(3):120-127. [PMID: 28253501] <https://pubmed.ncbi.nlm.nih.gov/28253501>