

<b>RITONAVIR (RTV) (Updated April 2010)</b>	
<b>Trade Name</b>	Norvir
<b>Classification</b>	Protease Inhibitor
<b>Form</b>	100-mg capsules; 100-mg tablets; 600 mg/7.5 mL oral solution
<b>Dosing Recommendations</b>	100 – 200 mg once or twice a day in combination with another PI. RTV is used as a pharmacokinetic booster Separate dosing with didanosine (buffered) by 2.5 hours
<b>Hepatic Impairment Dosing</b>	No dose adjustment for mild hepatic impairment; use with caution for moderate to severe hepatic impairment
<b>Food Effect</b>	<b>Tablets:</b> Tablets must be taken with food and should be swallowed whole, and not chewed, broken, or crushed  <b>Capsules:</b> Take with food that contains both protein and fat. Absorption ↑ 15% with food; take with a meal containing >15 g fat
<b>Oral Bioavailability</b>	When tablets are taken with a high-fat or moderate-fat meal, an approximate 22% ↓ in mean AUC and Cmax were observed relative to fasting conditions
<b>Serum Half-life</b>	3-5 hours
<b>Route of Metabolism</b>	P450 cytochrome 3A4 substrate (3A4 >2D6; potent 3A4 inhibitor)
<b>Storage</b>	<b>Tablets:</b> Room temperature  <b>Capsules:</b> Refrigerate (capsules can be left at room temperature ≤30 days)  <b>Oral solution:</b> Should NOT be refrigerated
<b>Adverse Events</b>	GI intolerance, nausea, vomiting, diarrhea, taste alteration  Paresthesias (circumoral and extremities) associated with high-dose RTV >400 mg twice daily.  Transaminase elevation and hepatitis, pancreatitis (secondary to elevated triglyceride), asthenia, elevated CPK and uric acid, possible increased bleeding episodes in patients with hemophilia  Triglycerides increase >200%, hyperglycemia, <sup>a</sup> fat redistribution and lipid abnormalities <sup>b</sup>  QTc and PR interval prolongation with RTV 400 mg twice daily. First-, second-, and third-degree AV block; right bundle branch block have been reported. Use with caution in patients with structural heart disease, with preexisting or at-risk for conduction system abnormalities
<b>FDA Pregnancy Category</b>	B
<b>Long-Term Animal Carcinogenicity Studies</b>	Positive (rodent, liver adenomas and carcinomas in male mice)
<b>Animal Teratogen Studies</b>	Negative (but cryptorchidism in rodents)

<b>Black Box Warnings</b>	Co-administration of ritonavir with certain non-sedating antihistamines (e.g., terfenadine and astemizole), sedative hypnotics (e.g., midazolam and triazolam), antiarrhythmics, or ergot alkaloids may result in potentially serious and/or life-threatening adverse events due to possible effects of ritonavir on hepatic metabolism of certain drugs
<b>Drugs to Avoid</b>	Alfuzosin, alprazolam, amiodarone, astemizole, bepridil, cisapride, desipramine, ergot derivatives, flecainide, fluticasone, garlic supplements, lovastatin, midazolam, <sup>c</sup> pimozone, propafenone, quinidine, ranolazine, rifampin, rifapentine, salmeterol, high-dose sildenafil, simvastatin, St. John's wort, terfenadine, triazolam, voriconazole <sup>d</sup>
<b>Cautious Use or Dose Adjustment</b>	
<b>Antiretrovirals</b>	<p><b>Atazanavir:</b> ATV AUC ↑ 238% – Use ATV 300 mg + RTV 100 mg once daily</p> <p><b>Darunavir:</b> DRV AUC ↑, C<sub>max</sub> ↑, C<sub>min</sub> ↑. ARV-experienced patients: DRV 600 mg twice daily + RTV 100 mg twice daily ARV-naïve patients: DRV 800 mg once daily + RTV 100 mg once daily</p> <p><b>Delavirdine:</b> RTV AUC ↑, C<sub>max</sub> ↑, C<sub>min</sub> ↑. Combination dosing not established</p> <p><b>Didanosine (buffered):</b> Dosing should be separated by 2.5 hours to avoid formulation incompatibility</p> <p><b>Etravirine:</b> Standard doses</p> <p><b>Fosamprenavir:</b> FPV AUC ↑ 100%, C<sub>min</sub> ↑ 400% when combined with 200 mg RTV ARV-experienced patients should receive RTV-boosted regimen: FPV 700 mg twice daily + RTV 100 mg twice daily PI-naïve patients only: FPV 1400 mg once daily + RTV 100-200 mg once daily</p> <p><b>Indinavir:</b> IDV ↑ 2- to 5-fold – Use IDV 800 mg + RTV 100 mg twice daily; renal events may be increased with higher IDV C<sub>max</sub></p> <p><b>Maraviroc:</b> ↑ MVC AUC – ↓ MVC dose to 150 mg twice daily</p> <p><b>Nelfinavir:</b> NFV ↑ 1.5-fold – Limited clinical data; only a modest benefit with RTV boosting with significant GI intolerance</p> <p><b>Raltegravir:</b> Standard doses</p> <p><b>Saquinavir:</b> SQV ↑ 20-fold – Use SQV 1000 mg + RTV 100 mg twice daily or SQV 400 mg + RTV 400 mg twice daily (higher GI intolerance)</p> <p><b>Tipranavir:</b> TPV AUC ↑, C<sub>max</sub> ↑, C<sub>min</sub> ↑. Use TPV/r 500/200 mg twice daily. Monitor closely for signs of hepatotoxicity</p>
<b>Antialcoholics</b>	<b>Disulfiram/metronidazole:</b> RTV liquid formulations contain alcohol, which can produce disulfiram-like reactions when combined with antialcoholics
<b>Antiarrhythmics</b>	<b>Disopyramide, lidocaine, mexiletine:</b> Therapeutic concentration monitoring of antiarrhythmics recommended. Monitor closely for conduction abnormalities
<b>Anticoagulants</b>	<b>Warfarin:</b> Initial frequent monitoring of the INR during ritonavir and warfarin co-administration is indicated. Increased INR initially, but may require higher warfarin dose after 2 weeks. Monitor closely

<b>Anticonvulsants</b>	<b>Carbamazepine, phenobarbital, phenytoin:</b> May ↑ or ↓ anticonvulsant serum levels; may ↓ RTV – Use with caution; monitor anticonvulsant levels (consider valproic acid or levetiracetam)
<b>Antidepressants</b>	<b>Trazodone:</b> Trazodone AUC ↑ 240%, Cmax ↑ 34% – Use lowest dose; monitor for CNS and CV adverse effects
<b>Antifungals</b>	<b>Itraconazole, ketoconazole:</b> Itra/keto ↑ 3-fold – Use with caution; do not exceed 200 mg itra/keto daily  <b>Voriconazole:</b> RTV (100 mg twice daily used to boost other PIs) decreases voriconazole by 39%. Consider higher voriconazole dose for invasive fungal disease. Monitor voriconazole serum concentrations
<b>Antigout</b>	<b>Colchicine:</b> For treatment of gout flares – 0.6 mg (1 tablet) x 1 dose, then 0.3 mg (½ tablet) 1 h later. Do not repeat dose before 3 days. For prophylaxis of gout flares – adjust dose to ¼ original regimen For treatment of familial Mediterranean fever (FMF) – Max: 0.6 mg daily  Do not co-administer in patients with hepatic or renal impairment
<b>Antimycobacterials</b>	<b>Clarithromycin:</b> CL ↑ 77% – ↓ CL dose for moderate and severe renal impairment (CrCL <30 ml/min: Use 50% Clarithromycin dose)  <b>Rifabutin:</b> RFB ↑ 430% – ↓ RFB dose to 150 mg qod or 3x/wk <sup>e</sup> . Consider monitoring RFB serum concentrations
<b>Beta Blockers</b>	<b>Metoprolol, timolol, carvedilol, propranolol, labetalol:</b> Beta blockers ↑ – Clinical monitoring of patients recommended
<b>Bronchodilators</b>	<b>Theophylline:</b> Theophylline ↓ – May require ↑ in theophylline dosage; consider therapeutic monitoring  <b>Salmeterol:</b> Co-administration not recommended. Consider formoterol
<b>Calcium Channel Blockers</b>	<b>Diltiazem, amlodipine, felodipine, nifedipine, verapamil:</b> Channel blockers ↑ – Consider ↓ dose. Clinical monitoring recommended
<b>Cardiac Glycosides</b>	<b>Digoxin:</b> Digoxin AUC ↑ 49% with RTV/SQV co-administration. Use with close monitoring of digoxin serum concentrations
<b>Corticosteroids</b>	<b>Fluticasone:</b> Fluticasone ↑ – Co-administration not recommended. Consider beclomethasone  <b>Prednisone:</b> Prednisolone AUC ↑ 30-40% with RTV (200 mg twice-daily) co-administration. May require lower prednisone dose with long-term co-administration
<b>Erectile Dysfunction Agents</b>	<b>Sildenafil:</b> Sildenafil ↑ 11-fold – Use cautiously, start with reduced dose of 25 mg q48h and monitor for adverse effects  <b>Tadalafil:</b> Tadalafil ↑ 124% – Start with a 5-mg dose, and do not exceed a single dose of 10 mg in 72 hours  <b>Vardenafil:</b> Vardenafil ↑ 49-fold; RTV ↓ 20% – Start with a 2.5-mg dose, and do not exceed a single 2.5-mg dose in 72 hours
<b>Immunosuppressants</b>	<b>Cyclosporine, tacrolimus, sirolimus:</b> Significant ↑ immunosuppressants – Monitor immunosuppressant concentrations closely with appropriate dose reduction

<b>Lipid-Lowering Agents</b>	<p><b>Atorvastatin:</b> ATO ↑ 450% when combined with SQV/RTV – Use lowest possible starting dose (10 mg) of ATO with careful monitoring</p> <p><b>Rosuvastatin:</b> May ↑ rosuvastatin concentrations. With co-administration, start with rosuvastatin 5 mg/d. Use with close monitoring</p>
<b>Narcotic Analgesics</b>	<b>Meperidine:</b> ↓ meperidine; ↑ normeperidine (metabolite) – Dosage ↑ and long-term use of meperidine with RTV are not recommended
<b>Neuroleptics</b>	<b>Perphenazine, risperidone, thioridazine:</b> ↑ Neuroleptics – Dose ↓ may be necessary
<b>Oral Contraceptives</b>	<b>Ethinyl estradiol:</b> EE ↓ 40% – Use alternative or additional method of contraception
<b>Pulmonary Hypertension Agents</b>	<p><b>High-dose sildenafil:</b> Avoid co-administration</p> <p><b>Bosentan:</b> With all RTV-boosted PI co-administration, significant ↑ in bosentan concentrations likely. Co-administer bosentan only after RTV has reached steady-state. In patients taking RTV &gt;10 days: Start bosentan at 62.5 mg once daily or every other day. In patients already taking bosentan: Discontinue bosentan for &gt;36 hrs prior to initiation of RTV-boosted PIs and restart bosentan at 62.5 mg once daily or every other day after RTV has reached steady-state (after 10 days)</p> <p><b>Tadalafil:</b> In patients already taking RTV for ≥1 wk, co-administer tadalafil at 20 mg once daily; increase to 40 mg once daily based on tolerability. In patients already taking tadalafil, avoid use of tadalafil during initiation of RTV. Stop tadalafil ≥24 h prior to starting RTV. At least ≥1 wk after initiating RTV, resume tadalafil at 20 mg once daily; increase to 40 mg once daily based on tolerability.</p>
<b>Synthetic Narcotics</b>	<b>Methadone:</b> Methadone ↓ 37% – Monitor and titrate dose if needed; S-methadone (inactive) more affected. No withdrawal symptoms observed. Use with caution – may cause prolongation of QTc
<p><sup>a</sup> Cases of worsening glycemic control in patients with preexisting diabetes, and cases of new-onset diabetes including diabetic ketoacidosis have been reported with the use of all protease inhibitors.</p> <p><sup>b</sup> Discontinuation of PIs may be required to reverse fat redistribution. Patients with hypertriglyceridemia or hypercholesterolemia should be evaluated for risks for cardiovascular events and pancreatitis.</p> <p><sup>c</sup> Can be used with caution as a single dose in a monitored situation for procedural sedation.</p> <p><sup>d</sup> RTV (400 mg q12h) decreased voriconazole AUC by 82%. RTV level was not affected by voriconazole. RTV (400 mg q12h) should not be co-administered with voriconazole. RTV (100 mg twice daily used to boost other PIs) decreases voriconazole by 39%. Use with caution. Monitor voriconazole serum concentrations with co-administration.</p> <p><sup>e</sup> Rifabutin 3x/wk is recommended if CD4 count &lt;100 cells/mm<sup>3</sup>.</p>	