

Ritonavir (Norvir)

Summary

Ritonavir is a type of anti-HIV drug called a protease inhibitor. The most common side effects of ritonavir can include unexpected tiredness or lack of energy, nausea, vomiting, diarrhea and changes in your sense of taste. Ritonavir is usually taken to boost levels of a second protease inhibitor. Ritonavir dosage varies depending on the second protease inhibitor.

What is ritonavir?

Ritonavir, sold under the brand name Norvir, is a type of anti-HIV drug (antiretroviral) called a protease inhibitor (PI). Ritonavir is used in combination with other anti-HIV drugs to treat (but not cure) HIV.

How does ritonavir work?

Ritonavir can work in two different ways in managing HIV infection. It can be used as a protease inhibitor or it can be used as a drug 'booster.' Ritonavir may also be useful in the management of other types of infection.

1. Ritonavir as a protease inhibitor

When HIV infects a cell, it takes control of that cell. HIV then forces the cell to make many more copies of the virus. To make these copies, the cell uses proteins called enzymes. When the activity of these enzymes is reduced the production of HIV slows.

Ritonavir belongs to a group or class of drugs called protease inhibitors. This drug interferes with an enzyme called protease, which is used by HIV-infected cells to make new viruses. Since ritonavir inhibits, or reduces the activity of this enzyme, this drug causes HIV-infected cells to produce fewer viruses.

However, ritonavir is almost never prescribed as the only protease inhibitor in a treatment regimen today.

2. Ritonavir as a drug 'booster'

The most common way that ritonavir is used today is as a booster for other protease inhibitors. Ritonavir causes this effect in two ways. First it helps to increase absorption of other protease inhibitors, mainly by inhibiting enzymes in the intestine that degrade this class of drug. Second, it also inhibits the activity of enzymes in the liver that break down protease inhibitors. As a result,

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ritonavir causes prolonged and high levels of other protease inhibitors in the blood, enabling ritonavir–protease inhibitor combinations to be taken once- or twice-daily.

3. Other uses for ritonavir

Ritonavir in combination with other antiviral agents—lopinavir and ribavirin—has been tested as a treatment for SARS (severe acute respiratory syndrome). Very preliminary results suggest that the combination may be useful in managing SARS, although more studies are needed before this can be confirmed.

How do people with HIV use ritonavir?

Ritonavir is used in combination with several other antiretroviral drugs, usually another protease inhibitor (which ritonavir boosts) and also nukes (nucleoside analogues). Sometimes drugs from other classes such as non-nukes (non-nucleoside reverse trans-cryptase inhibitors) are also used. Combinations of antiretrovirals are called antiretroviral therapy, or ART. For more information on ART, see CATIE's *Your Guide to HIV Treatment*.

For many people with HIV, the use of ART has increased their CD4+ cell counts and decreased the amount of HIV in their blood (viral load). These beneficial effects help to reduce the risk of developing a life-threatening infection. Neither ritonavir nor any other antiretroviral medication is a cure for HIV. It is therefore important that you do the following:

- see your doctor regularly so that he/she monitors your health
- continue to practice safer sex and take other precautions so as not to pass HIV on to other people

Side effects

1. General

Common side effects that have been reported by some ritonavir users include the following: unexpected tiredness or lack of energy, nausea,

vomiting, diarrhea, loss of appetite, fatigue, numbness or a tingling sensation around the mouth (circumoral parasthesia), abdominal pain, headache and dizziness. To help prevent or minimize side effects, the manufacturer recommends taking ritonavir with food.

2. Liver enzymes

Because ritonavir is metabolized (processed and broken down) by the liver, blood tests may show increased levels of liver enzymes.

3. Bleeding

Women may experience heavier menstrual periods when using protease inhibitors. Hemophiliacs who use protease inhibitors may experience increased bleeding. If you are a hemophiliac who uses ritonavir and has this problem, let your doctor know about it.

4. Blood sugar

In some people with HIV who use protease inhibitors, levels of sugar (glucose) in the blood become higher than normal. Prolonged bouts of higher-than-normal blood sugar levels may lead to diabetes. At least one study has found that some HIV-positive women, particularly those who are overweight, may be at increased risk for diabetes when they use protease inhibitors. Regular monitoring of your blood to assess sugar levels and other measurements will help you and your doctor be aware of changes that might suggest problems with your blood sugar. Although the risk of developing diabetes is generally low, symptoms that may be related to diabetes (increased thirst, increased urination, unexplained weight loss, fatigue and dry, itchy skin) should be discussed with your doctor.

5. Lipodystrophy syndrome

The HIV lipodystrophy syndrome is the name given to a range of symptoms that can develop over

time when people use ART. Some features of the lipodystrophy syndrome include:

- loss of fat just under the skin (subcutaneous fat) in the face, arms, and legs
- bulging veins in the arms and/or legs due to the loss of fat under the skin
- increased waist and belly size
- fat pads at the back of the neck (“buffalo hump”) or at the base of the neck (“horse collar”)
- small lumps of fat in the abdomen
- increased breast size (in women)

Together with these physical changes, lab tests of your blood may detect the following:

- increased levels of fatty substances called triglycerides
- increased levels of LDL-cholesterol (low-density lipoprotein) or “bad” cholesterol
- increased levels of sugar (glucose)
- increased levels of the hormone insulin
- decreased sensitivity to insulin (insulin resistance)
- decreased levels of HDL-cholesterol (high-density lipoprotein) or “good” cholesterol

The precise causes of the HIV lipodystrophy syndrome are not clear and are difficult to understand because in some people with HIV there may be one or more aspects of the syndrome taking place. For instance, some people may experience fat wasting, others fat gain, and others may experience both fat gain and wasting. What is becoming increasingly clear is that unfavourable changes in the lab readings of glucose, cholesterol, and triglycerides over a period of several years increase the risk of diabetes and cardiovascular disease. So far, however, the many benefits of ART are much greater than the increased risk of cardiovascular disease or other side effects.

Maintaining a normal weight, eating a healthy diet, exercising regularly, and quitting smoking are all important in helping you to reduce your risk of

diabetes, heart disease, and other complications. Regular visits to your doctor for checkups and blood tests are a vital part of staying healthy. If necessary, your doctor can prescribe lipid-lowering therapy.

Researchers are studying the lipodystrophy syndrome to try to discover ways of helping people with HIV avoid or reduce this problem. To find out more about options for managing aspects of the lipodystrophy syndrome, see CATIE’s *A Practical Guide to HIV Drug Side Effects*.

Ritonavir, like some protease inhibitors can cause increased levels of cholesterol and triglycerides in your blood.

6. Pregnancy

The effect of ritonavir on the fetus are not known. The manufacturer notes that this drug should only be used by pregnant women if “clearly needed.”

Drug interactions

Always consult your doctor and pharmacist about taking any other prescription or non-prescription medication, including herbs, supplements and recreational drugs.

Some drugs can interact with ritonavir, increasing or decreasing its levels in your body. Increased drug levels can cause you to experience side effects or make pre-existing side effects worse. On the other hand, if drug levels become too low, HIV can develop resistance and your future treatment options may be reduced.

It may also be necessary to avoid drugs that do not affect ritonavir drug levels, but cause similar side effects.

Ritonavir is known to have strong interactions with many other drugs (both prescription and non-prescription). It is often used as a drug ‘booster’, which means that it is used to increase the amount of other drugs available in the body, especially other anti-HIV drugs.

It is therefore important to always consult your doctor and pharmacist about taking any other medication—prescription and non-prescription—including herbs and supplements, to ensure that

they do not interfere with your ritonavir levels and vice versa. If you must take a drug that has the potential to interact with your existing medications, your doctor can do the following:

- adjust your dose of either your antiretroviral drugs or other medication
- prescribe different antiretroviral drugs for you

Drug interactions for ritonavir

The following drugs interact or have the potential to interact with ritonavir. These lists are not exhaustive.

The manufacturer recommends that the following drugs should not be taken by people using ritonavir because this could lead to serious (or life-threatening) interactions.

- antihistamines – astemizole (Hismanal), terfenadine (Seldane)
- anti-psychotic drugs – pimozide (Orap)
- drugs for abnormal heart rhythms – amiodarone (Codarone), bepridil (Vascor) flecainide (Tambocor), propafenone (Rhythmol), quinidine
- gastrointestinal motility agents – cisapride (Prepulsid)
- herbs – St. John's wort
- lipid-lowering agents – lovastatin (Mevacor), simvastatin (Zocor)
- migraine drugs (ergot derivatives) – dihydroergotamine (Migranal), ergotamine (Ergomar), Ergonovine
- sedatives – midazolam (Versed), triazolam (Halcion)
- drugs to treat erectile dysfunction – sildenafil (Viagra), tadalafil (Cialis), vardenafil (Levitra).

Taking ritonavir with any of these drugs can lead to dangerous side effects and even death. Talk to your doctor if you have erectile dysfunction about how you might use these drugs safely.

The following drugs can *decrease* levels of ritonavir in the blood:

- antibiotics / anti-tuberculosis drugs – rifabutin (Mycobutin)

Ritonavir can *increase* levels of the following drugs:

- protease inhibitors – in general, ritonavir will raise the level of other protease inhibitors in your blood
- anesthetics – meperidine is converted by the body into another compound (normeperidine) and ritonavir raises the level of this drug in the brain
- anti-alcohol drugs – disulfiram (Antabuse)
- antidepressant – desipramine, bupropion, drugs of the SSRI class (such as Prozac, Paxil, Zoloft)
- antifungal agents – ketoconazole (Nizoral)
- antibiotics – clarithromycin (Biaxin), rifabutin (Mycobutin)
- erectile dysfunction – sildenafil (Viagra) and likely other, related drugs such as vardenafil (Levitra) and tadalafil (Cialis)
- lipid-lowering agents – atorvastatin (Lipitor)
- transplant drugs – cyclosporine, tacrolimus, sirolimus
- sedatives – diazepam, flurazepam, zolpidem
- steroids – dexamethasone, fluticasone (Flonase), prednisone
- stimulants – methamphetamine (“crystal meth”)

Ritonavir can *decrease* levels of the following drugs:

- anti-seizure drugs – phenytoin, divalproex, lamotrigine
- anti-parasite drugs – atovaquone (Mepron)
- anti-asthma drugs – theophylline

- narcotics – methadone; your dose of methadone may need to be increased if you are taking ritonavir
- hormones – ethinyl estradiol

Resistance and cross-resistance

Over time, as new copies of HIV are made in the body, the virus changes its structure. These changes are called mutations and can cause HIV to resist the effects of antiretroviral drugs, which means those drugs will no longer work for you. Combining ritonavir with at least two other antiretroviral drugs delays the development of drug resistance.

To reduce the risk of developing drug resistance, all antiretroviral drugs should be taken every day exactly as prescribed and directed. If doses are delayed, missed, or not taken as prescribed, levels of ritonavir in the blood may fall too low. If this happens, resistant virus can develop. If you find you are having problems taking your medications as directed, speak to your doctor and nurse about this. They can find ways to help you.

When HIV becomes resistant to one drug in a class, it sometimes becomes resistant to other drugs in that class. This is called cross-resistance. Feel free to talk with your doctor about your current and future treatment options. To help you decide what these future therapies might be, at some point your doctor can have a small sample of your blood analysed using resistance testing. Should HIV in your body become resistant to ritonavir, your doctor, with the help of resistance testing, can help put together a new treatment regimen for you.

Dosage and formulations

Ritonavir (Norvir) is available as 100 mg capsules and 80 mg/mL liquid.

Shortly after it was licensed, ritonavir was found to raise or boost levels of other protease inhibitors. Because of this effect, ritonavir is often used with other protease inhibitors to boost their levels.

1. Ritonavir as the sole protease inhibitor in a regimen

The recommended and approved dose of ritonavir, when used as the sole protease inhibitor in a regimen, is 600 mg twice daily. However, because of side effects, ritonavir is rarely used as the sole protease inhibitor in a regimen and so this dose is seldom used today.

2. Ritonavir with lopinavir (Kaletra)

Kaletra is the brand name of a combination of two drugs – ritonavir and lopinavir. These two drugs are found together (co-formulated) in one capsule or tablet.

Each *capsule* contains 33.3 mg ritonavir and 133.3 mg of lopinavir. The standard adult dose is 3 capsules (100 mg ritonavir and 400 mg lopinavir) twice daily in treatment-experienced people with HIV and six capsules (200 mg ritonavir and 800 mg lopinavir) once-daily in people with HIV who are new to treatment.

Each *tablet* contains 50 mg of ritonavir and 200 mg of lopinavir. The standard adult dose is two tablets twice daily in treatment-experienced people with HIV and four tablets once-daily in people who are new to treatment.

3. Ritonavir with saquinavir (Invirase)

In this combination, the doses initially used were 400 mg of ritonavir and 400 mg of saquinavir (Invirase), both drugs taken twice daily with food. However, the more commonly used dose today is 100 mg of ritonavir and 1,000 mg of saquinavir, both drugs taken twice daily. This lower dose of ritonavir has less side effects than the 400 mg dose twice daily dose. Still other combinations and schedules of ritonavir-saquinavir, including once-daily, are under study.

4. Ritonavir with atazanavir (Reyataz)

Ritonavir is taken at a dose of 100 mg and atazanavir (Reyataz) 300 mg, each drug once daily.

5. Ritonavir with fosamprenavir (Telzir)

Ritonavir may be taken at a dose of 100 mg with fosamprenavir (Telzir) 700 mg, both drugs taken twice-daily. For PHAs taking this combination once-daily, the manufacturer recommends a dose of 200 mg ritonavir and 1400 mg of fosamprenavir.

6. Ritonavir and darunavir (Prezista)

Ritonavir is taken at a dose of 100 mg and darunavir (Prezista) 600 mg, both drugs twice daily.

7. Ritonavir and tipranavir (Aptivus)

The manufacturer of tipranavir (Aptivus) recommends a dose of ritonavir 200 mg and tipranavir 500 mg be taken twice daily.

8. Ritonavir with indinavir (Crixivan)

The dose of ritonavir used may be 100 or 200 mg, twice daily with 800 mg of indinavir (Crixivan), also twice daily. Other doses of indinavir are being tested but note that in Canada, the use of ritonavir with indinavir is not approved by regulatory authorities.

Storage

Ritonavir capsules should be stored at room temperature below 25° C (or 77° F) if used within a month. For longer periods, keep refrigerated.

Ritonavir liquid should be kept at room temperature and not refrigerated.

Availability

Ritonavir is licensed in Canada for the treatment of HIV infection in adults, in combination with other antiretroviral drugs. Your doctor can tell you more about the availability and coverage of ritonavir in your region. CATIE's online module *Federal, Provincial and Territorial Drug Access Programs* also contains information about Canadian drug coverage.

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Disclaimer

Decisions about particular medical treatments should always be made in consultation with a qualified medical practitioner knowledgeable about HIV- and hepatitis C-related illness and the treatments in question.

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