

Ritonavir (Norvir)

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What is Norvir?

- Norvir is an anti-HIV medication. It is in a category of HIV medications called protease inhibitors (PIs). Norvir prevents T-cells that have been infected with HIV from producing new HIV.
- Norvir is manufactured by Abbott Laboratories. The U.S. Food and Drug Administration (FDA) approved it for the treatment of HIV infection in 1996.
- Norvir is one of the two drugs in Kaletra®. Kaletra contains the protease inhibitor lopinavir and small amounts of Norvir.

What is known about Norvir?

- The official Norvir dose is six 100mg capsules twice a day. However, this dose is rarely used anymore because it is associated with a number of side effects. However, Norvir is still being usually used at much lower doses (one or two 100mg capsules twice a day) to help boost the levels of other protease inhibitors in the bloodstream.
- Norvir, even if low doses are used with another protease inhibitor, should be taken with a meal or light snack.
- Refrigeration of the Norvir capsules is recommended but is not necessary if they are used within 2 months and stored below 77° fahrenheit (25° celsius).
- All of the protease inhibitors are broken down (metabolized) by the same family of enzymes in the liver. In order for the protease inhibitors to be metabolized by these liver enzymes, they must first either slow down its activity or speed it up. All of the currently approved

protease inhibitors slow down the activity of these liver enzymes. Norvir is the most powerful of all the protease inhibitors in this regard, even when low doses of the drug are used. In turn, Norvir can prevent other protease inhibitors from getting to the enzyme, causing levels of these other protease inhibitors to increase in the bloodstream. This can make the other protease inhibitors more effective against HIV. It also means that lower doses—or less frequent daily doses—of these other protease inhibitors can be taken. This is why low doses of Norvir are often combined with other protease inhibitors: to make them more effective and easier to take.

- Norvir is approved by the FDA for use in combination with the protease inhibitors Agenerase® (amprenavir), Lexiva® (fosamprenavir), Fortovase® (soft gel saquinavir), and Invirase® (hard gel saquinavir). Norvir is also frequently combined with Crixivan® (indinavir) and Reyataz™ (atazanavir).
- Norvir can be given to HIV-positive children. The dose will depend on body weight. As the child gets older and gains weight, the dose will continually need to be increased. The child's doctor can prescribe a liquid formulation of Norvir.
- Early clinical trials determined that Norvir was effective when combined with other drugs, most notably two nucleoside reverse transcriptase inhibitors (NRTIs). After the drug was approved, many people had a difficult time taking the full dose of Norvir to treat their HIV because of side effects. More recently, Norvir has been shown to be very effective in terms of “boosting” the

levels of other protease inhibitors in the bloodstream, thereby making many of them easier to take and all of them more effective.

- The United States Department of Health and Human Services (DHHS) does not recommend full-dose Norvir as a protease inhibitor option, either for HIV-positive people starting therapy for the first time or for those who have failed other protease inhibitors in the past. For HIV-positive patients beginning protease inhibitor therapy for the first time, the DHHS recommends using low-dose Norvir to boost blood levels of specific protease inhibitors, specifically Fortovase® (soft gel saquinavir), Invirase® (hard gel saquinavir), Lexiva® (fosamprenavir), and Crixivan® (indinavir). The protease inhibitor Kaletra®, which contains the protease inhibitor lopinavir and a small dose of Norvir to boost lopinavir levels, is listed as the “preferred” option.
- Many of the currently available protease inhibitors are affected by cross-resistance. This means that, if you’ve tried and failed a drug regimen in the past that contained a protease inhibitor, your virus might be resistant to Norvir. Similarly, if you take an anti-HIV drug regimen that contains Norvir and your virus becomes resistant to the drug, your virus might also be resistant to many of the other protease inhibitors available. However, even if your virus becomes resistant to Norvir, the drug can still be used to boost other protease inhibitors in the bloodstream.

What about drug interactions?

- Norvir is broken down (metabolized) by the liver, like many medications used to treat HIV and AIDS. This means that Norvir can interact with other medications. Norvir, more than most other anti-HIV drugs, can lower or raise the levels of other medications in the body. Similarly, some medications can lower or raise the levels of Norvir in the body. While many interactions are not a problem, some can cause your medications to be less effective or increase the risk of side effects.
- Tell your doctors and pharmacists about all medicines you take. This includes those you buy over-the-counter and herbal or natural remedies, such as St. John’s Wort. Bring all your medicines when you see a doctor, or make a list of their names, how much you take, and how often you take them. Your

doctor can then tell you if you need to change the dosages of any of your medications.

- The following medications should not be taken while you are being treated with Norvir:
 - Acid reflux/heartburn medications:** Propulsid® (cisapride)
 - Antibiotics:** Prifitin® (rifapentine)
 - Antifungals:** Vfend® (voriconazole)
 - Antimigraine medications:** Ergostat®, Cafegot®, Ercaf®, Wigraine® (ergotamine) or D.H.E. 45® (dihydroergotamine)
 - Antihistamines:** Hismanal® (astemizole) or Seldane® (terfenadine)
 - Calcium channel blockers:** Vasacor® (bepridil)
 - Heart arrhythmia medications:** Cordarone® (amiodarone), Tambocor™ (flecainide), Rythmol® (propafenone), or Quinaglute®/Quinidex® (quinidine)
 - Cholesterol-lowering drugs (statins):** Zocor® (simvastatin) and Mevacor® (lovastatin)
 - Antipsychotics:** Orap® (pimozide)
 - Sedatives:** Versed® (midazolam) and Halcion® (triazolam)
- Anticonvulsants, such as Tegretol® (carbamazepine), Luminal® (phenobarbital), and Dilantin® (phenytoin), may interact with Norvir and should be used with caution. Norvir can increase Tegretol levels in the bloodstream.
- Anti-HIV protease inhibitors can interact with Norvir. Norvir can increase the blood levels of all the available protease inhibitors; none of the protease inhibitors have a significant effect on Norvir levels in the bloodstream. If Crixivan® (indinavir) is combined with Norvir, the most common dose is two 400mg Crixivan capsules plus one or two 100mg Norvir capsules, twice a day. If Fortovase® (soft gel saquinavir) or Invirase® (hard gel saquinavir) is combined with Norvir, the usual dose is five 200mg capsules plus one 100mg Norvir capsule, twice a day. If Agenerase® (amprenavir) is combined with Norvir, once-daily dosing is possible (eight 150mg Agenerase capsules and two 100mg Norvir capsules) and so is twice-daily dosing (four Agenerase capsules and one Norvir capsule, every 12 hours). If Lexiva® (fosamprenavir) is combined with Norvir, once-daily dosing is possible (two 700mg Lexiva tablets in combination with two 100mg capsules of Norvir, once a day) and so is twice-daily

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dosing (one 700mg Lexiva tablet in combination with one 100mg capsules of Norvir, twice a day). If Viracept® (nelfinavir) is combined with Norvir, the correct dose is two or three 250mg Viracept tablets plus four 100mg Norvir capsules. And if Reyataz™ (atazanavir) is combined with Norvir, the correct dose is two 150mg Reyataz capsules plus one 100mg Norvir capsule.

- Anti-HIV non-nucleoside reverse transcriptase inhibitors (NNRTIs) can also interact with Norvir. Rescriptor® (delavirdine) and Sustiva® (efavirenz) can increase the amount of Norvir in the bloodstream (similarly, levels of Sustiva can also increase when combined with Norvir). A third NNRTI, Viramune® (nevirapine), does not alter levels of Norvir in the bloodstream.
- Demerol® (meperidine) is a powerful analgesic (painkiller). Norvir can increase the amount of normeperidine, an active byproduct of Demerol, in the bloodstream. In turn, Demerol should be used cautiously if it must be combined with Norvir.
- Another painkiller, methadone, commonly used to treat drug addiction, can interact with Norvir. Methadone levels in the bloodstream can decrease when combined with Norvir. Because of this, it might be necessary to increase the dose of methadone.
- Norpramin® (desipramine) is used to treat depression. Levels of this drug can increase in the bloodstream if it is combined with Norvir. In turn, it might be necessary to reduce the usual dosage of this drug.
- Antabuse® (disulfiram) is a medication taken by people with an alcohol-dependency problem. This medication can make people very sick if they consume even small amounts of alcohol. Because the liquid formulation of Norvir contains small amounts of alcohol, it should not be combined with Antabuse®.
- Flagyl® (metronidazole) is used to treat some types of parasitic infections. People should not drink alcohol—or take medications that contain alcohol—while taking this drug. The combination of alcohol and Flagyl can cause someone to become very ill. In turn, HIV-positive people taking the liquid formulation of Norvir should not take Flagyl.
- Norvir can interact with some medications used to treat TB, MAC, and other bacterial infections. Rifadin® (rifampin) can decrease Norvir levels and Norvir can increase Rifadin levels (these drugs should not be used together). Norvir can increase Mycobutin® (rifabutin) (the Mycobutin dose will need be reduced to 150mg every other day or three-times-weekly). Norvir also raises Biaxin® (clarithromycin) levels in the bloodstream (the Biaxin dose will need to be decreased).
- Norvir can interact with some medications used to treat thrush (candidiasis) and other fungal infections. Norvir can increase Nizoral® (ketoconazole) levels in the bloodstream. In turn, you should be taking no more than 200mg Nizoral daily while on Norvir.
- Norvir decreases the amount of oral contraceptives (taken by women to help avoid pregnancy) in the bloodstream. This means that there may be a higher risk of becoming pregnant if Norvir and oral contraceptives are taken at the same time. To reduce the risk of pregnancy, barrier protection (e.g., condoms) should be used.
- Cholesterol-lowering drugs, also known as “statins,” can interact with Norvir. There are two statins that should not be used with Norvir: Zocor® (simvastatin) and Mevacor® (lovastatin). Levels of these two drugs can become significantly increased in the bloodstream if they are combined with Norvir, which increases the risk of side effects. The two statins that are considered to be the safest in combination with Norvir are Pravachol® (pravastatin) and Lescol® (fluvastatin). It is also possible to take Norvir with Lipitor®, although Norvir can increase the levels of this drug in the bloodstream. If Lipitor is prescribed, it’s best to begin treatment with the lowest possible dose of the drug and then increase the dose if necessary. Little is known about the newest statin, Crestor® (rosuvastatin), although it is not expected to have any serious drug interactions with Norvir or the other protease inhibitors.
- Some patients with asthma or emphysema (chronic obstructive pulmonary disorder) take a drug called theophylline. Norvir can decrease the amount of theophylline in the bloodstream. If these two drugs are taken at the same time, a doctor can order a blood test to check the level of theophylline in the bloodstream. If the theophylline level is too low, the dose can be increased.
- Viagra® (sildenafil), Levitra® (vardenafil) and Cialis® (tadalafil) levels in the bloodstream may increase when combined with Norvir. In turn, it is best to use a lower dose of these drugs in order to reduce the risk of side effects.



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- Herbal products can also interact with Norvir. St. John's wort should not be used with Norvir, since it can greatly reduce the amount of Norvir in the bloodstream. HIV-positive people should also be cautious about using garlic supplements or milk thistle with Norvir—test tube studies suggest that both herbal products can interact with the same liver enzyme system (cytochrome P450 3A4) responsible for metabolizing Norvir. This may alter the amount of Norvir in the bloodstream. These and other herbal products should be used with caution, until further studies are conducted.
- Other drug interactions are possible. Be sure to tell your doctor about all the medications you are taking (or plan to take), including those you buy over-the-counter at your pharmacy or health-food store, while taking Norvir.

What about side effects?

- The most common side effects of Norvir therapy—which are usually more severe if the standard dose (600mg twice-daily) is used—are related to the gut. Nausea, vomiting, diarrhea, and appetite loss are common.
- Another possible side effect of Norvir is numbness/tingling around the mouth (oral paresthesias).
- Anti-HIV drug regimens containing protease inhibitors, including Norvir, can cause increased fat levels (cholesterol and triglycerides) in the blood, abnormal body-shape changes (lipodystrophy; including increased fat around the abdomen, breasts, and back of the neck, as well as decreased fat in the face, arms, and legs), and diabetes.

Who should not take Norvir?

- Before taking this medication, tell your doctor if you have kidney disease or liver disease. You may not be able to take Norvir, or you may require a dosage adjustment or special monitoring during treatment if you have any of these conditions.
- Norvir is classified by the FDA as a pregnancy category B drug. All the FDA-approved anti-HIV drugs are classified as either category B or C. Pregnancy category B means that animal studies have failed to demonstrate a risk to the fetus, but there are no adequate and well-controlled studies in pregnant women. Pregnancy category C means that

animal studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. HIV-positive women who become pregnant should discuss the benefits and possible side effects of anti-HIV treatment to help protect their babies from HIV.

- It is not known whether Norvir passes into breast milk and what effects it may have on a nursing baby. However, to prevent HIV transmission of the virus to uninfected babies, it is recommended that HIV-positive mothers not breast-feed.

Where can I learn more about clinical trials that are using Norvir?

- If you would like to find out if you are eligible for any clinical trials that include Norvir (ritonavir), there is an interactive web site run by amfAR, the American Foundation for AIDS Research.
- Another useful service for finding clinical trials is *AIDSinfo.nih.gov*, a site run by the U.S. National Institutes of Health. They have “health information specialists” you can talk to at their toll-free number at 1-800-HIV-0440 (1-800-448-0440).

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