

HIV Protease Inhibitors & You

December 1997

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Introduction

This booklet will give you information about new drugs to treat HIV infection, called protease inhibitors. Since these are new medicines, you may have questions about how they work and what to expect when taking them. No booklet can answer all of your questions, or take the place of a doctor in helping you make the important decisions you are facing, but this information will help you understand the basics about HIV protease inhibitors.

The six Department of Health and Human Services agencies that co-sponsor the HIV/AIDS Treatment Information Service (ATIS) provided support for this booklet. ATIS is a free telephone reference service for people who need information about HIV and AIDS treatment. Reference specialists at ATIS answer questions and provide information on federally approved treatments for HIV and AIDS.

You can contact the HIV/AIDS Treatment Information Service at:

1-800-448-0440 (Voice)

1-800-243-7012 (TTY)

1-301-519-6616 (Fax)

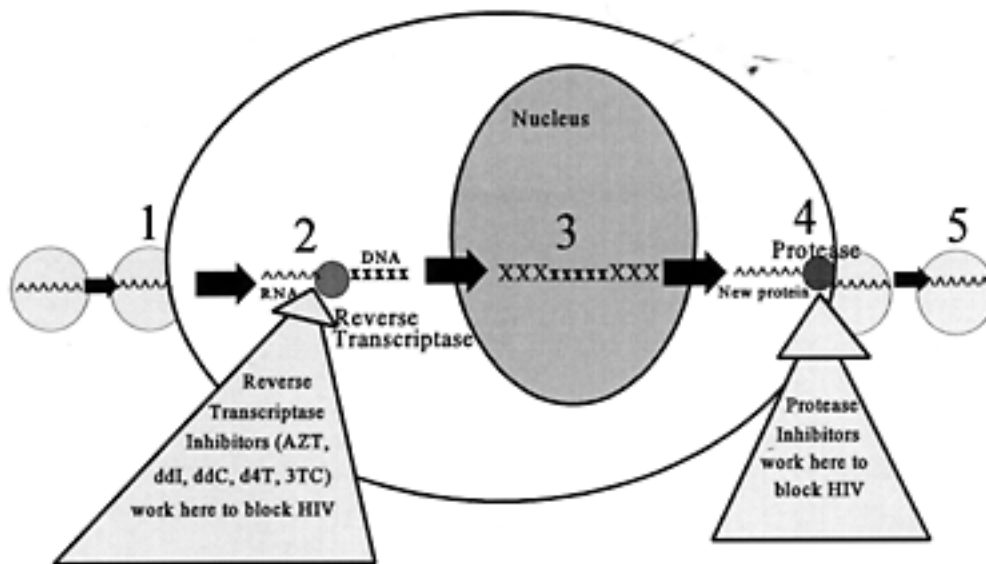
<http://www.hivatis.org>

atis@cdcnac.org

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How do protease inhibitors work?

Protease inhibitors are antiviral drugs. They interrupt the way HIV uses a healthy cell to make more virus. When HIV enters a healthy cell, its only goal is to make more viruses to infect other healthy cells. It does this by making the cell produce certain proteins the virus can use to copy itself. Two of the proteins used by the virus are reverse transcriptase and protease. The goal of the protease inhibitor is to stop the protease from helping to assemble a new virus.



The diagram above shows the virus entering the cell (1), the cell making new proteins (2-3), the proteins forming a new virus (4) and the cell releasing the new virus to infect other cells (5). It also shows some steps in the process that can be interrupted by protease inhibitors and other antiviral drugs (reverse transcriptase inhibitors) that are taken along with protease inhibitors.

What can protease inhibitors do?

Protease inhibitors are the most powerful anti-HIV drugs available so far. Although many different factors affect how well any drug will work for an individual, some people who have taken protease inhibitors have had the following benefits:

- increase in CD4 (t cell) counts, which can help fight infections
- decrease in the amount of virus in the blood (viral load), which may slow down the disease process
- feeling of improved overall health and ability to do more of their usual activities (ie: work, travel, socialize)

Researchers are not sure how long protease inhibitors will work in a person infected with HIV, but they have seen promising results in studies. They are hopeful that people will live longer, healthier lives because of the benefits of these new drugs.

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Is this a cure?

Protease inhibitors are not called a cure because researchers do not yet know how well they will work in different people. Some people have had their viral load drop to a level that is too low for current tests to measure. Even though the virus cannot be found in their blood, doctors believe HIV is still in their bodies and that it would reproduce quickly if they stop taking the protease inhibitor. In other people, protease inhibitors may not work as well or the benefits might not last. Clinical trials are going on to help answer questions about where HIV "hides" and why people have different results with protease inhibitors.

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Which protease inhibitor will I take?

There are five approved protease inhibitors: *ritonavir* (Norvir) and *nelfinavir* (Viracept) are for use by adults and children, while *indinavir* (Crixivan) and the two forms of *saquinavir* (Invirase and Fortovase) are approved for adults only. Invirase was approved in 1995, and Fortovase, a new, stronger form of *saquinavir* was approved in 1997. The company that makes both drugs will continue to make Invirase available to people who already take that form of *saquinavir* through Spring 1998. After that, it will be available to them under a limited distribution program. A decision about which drug to take should be made with a doctor who knows your individual condition, and has medical knowledge of HIV disease. By finding out about the available treatment options, you can talk to your doctor about the risks and benefits of different drug combinations.

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Will I need other medications?

If you take *saquinavir* (Invirase or Fortovase) you will also need to take one or two other antiviral medications, called reverse transcriptase inhibitors. Reverse transcriptase inhibitors such as *AZT* (Retrovir), *ddI* (Videx), *ddC* (Hivid), *d4T* (Zerit), or *3TC* (Epivir) are antiviral drugs that block HIV at a different point in its life cycle than protease inhibitors ([see diagram](#)). Although *indinavir* (Crixivan), *ritonavir* (Norvir), and *nelfinavir* (Viracept) may be taken by themselves, most doctors will also prescribe one or two reverse transcriptase inhibitors along with the protease inhibitor. Research shows that combining two or more antiviral drugs is more effective than taking one drug alone. The HIV/AIDS Treatment Information Service can give you information on all of these anti-HIV drugs.

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How often will I take my protease inhibitor? For how long?

Each of the approved protease inhibitors is taken in a different way. You may take your protease inhibitor two or three times every day, depending on which one you take. It is important to take the protease inhibitor on schedule so the drug will stay at the same level in your body. ***Taking a "drug holiday" or skipping doses is dangerous.*** Missing one or more doses can allow the virus to become resistant, meaning the virus changes itself to avoid the medication and keep making copies of itself.

You should take the protease inhibitor for as long as your tests show it is helpful; your doctor will keep track of your progress based on blood tests that you will have on a regular basis. (see [How will I know if my protease inhibitor is working?](#))

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How will I take my protease inhibitor?

You will take the protease inhibitor orally (by mouth). Whichever protease inhibitor you take, it is important to set a medication routine and stick to it. Some medications work best if taken on an empty stomach, while others must be taken with food, or with a large amount of water. Your doctor or pharmacist should give you specific instructions for taking your medication. The chart below has information about dosage and special instructions for each of the approved protease inhibitors.

Protease Inhibitor	Dosage Information	Special Instructions
nelfinavir (Viracept) (1,2,3)	3 tablets, 3 times a day (9 total tablets each day)	Take with a meal or a snack. Keep at room temperature.
saquinavir (Fortovase) (4)	6 capsules, 3 times a day (18 total capsules each day)	Take within 2 hours of a full meal. Keep refrigerated until the expiration date printed on the label. If capsules reach room temperature, they should be used within 3 months.
saquinavir (Invirase) (4)	3 capsules, 3 times a day (9 total capsules each day)	Take within 2 hours of a full meal. Keep at room temperature.
indinavir (Crixivan)	2 capsules, 3 times a day (6 total capsules each day)	Take on an empty stomach 1 hour before or 2 hours after a meal. Drink at least 1½ liters of liquid every day. Keep at room temperature in original bottle.
ritonavir (Norvir) (1,2,3)	6 capsules, 2 times a day (12 total capsules each day) OR 7.5 mL liquid Norvir, 2 times a day	Take with meals. Keep refrigerated.

1) *Phenylketonurics: Viracept oral powder contains 11.2 mg phenylalanine per gram.*

- 2) *Persons with hemophilia should be monitored for increased bleeding.*
- 3) *Interferes with effectiveness of birth control pills; a different method or backup should be used.*
- 4) *The two forms of saquinavir (Invirase and Fortovase) require different doses and handling. Please refer to the appropriate instructions for each drug.*

NELFINAVIR (VIRACEPT) DOSAGE INFORMATION FOR CHILDREN

Body Weight	Dosage
15.5 lb to <18.5 lb	4 scoops or 1 teaspoon
18.5 lb to <23 lb	5 scoops or 1 ¼ teaspoons
23 lb to <26.5 lb	6 scoops or 1 ½ teaspoons
26.5 lb to <31 lb	7 scoops or 1 ¾ teaspoons
31 lb to <35 lb	8 scoops or 2 teaspoons
35 lb to <39.5 lb	9 scoops or 2 ¼ teaspoons
39.5 lb to <50.5 lb	10 scoops or 2 ½ teaspoons
50.5 lb+	15 scoops or 3 ¾ teaspoons

RITONAVIR (NORVIR) DOSAGE INFORMATION FOR CHILDREN

Body Surface Area	Liquid Dosage
0.25 m(sq)	1.25 mL
0.50 m(sq)	2.5 mL
1.00 m(sq)	5 mL
1.25 m(sq)	6.25 mL
1.50 m(sq)	7.5 mL

Remember that you may be taking other antiviral drugs with the protease inhibitor. Planning when to take several different medications can be tricky, so review the instructions carefully and ask for some help from your doctor or pharmacist if you have trouble staying on schedule.

Are there medications I should not take with protease inhibitors?

Some drugs can cause problems (interactions) when they are taken together. Interactions might make your drugs less effective, or they could make you sick. Even some of the drugs that you might be taking to treat an infection or to keep you from getting an opportunistic illness (prophylaxis) should not be taken with a protease inhibitor. Your doctor may say that taking those drugs together is contraindicated. For example, rifamycin drugs (rifampin and rifabutin) which are used to treat TB (tuberculosis) or MAC (Mycobacterium avium complex) can interact with protease inhibitors. In this interaction, the rifamycin makes the protease inhibitor less effective, and the protease inhibitor increases the chances of rifamycin side effects.

If you have HIV and you also have either TB or MAC, you should talk to your doctor about these options:

- stopping the protease inhibitor during treatment including rifampin and other anti-TB/anti-MAC drugs;
- stopping the protease inhibitor during treatment including rifampin and other anti-TB/anti-MAC drugs, then stopping the rifampin, but continuing the other anti-TB/anti-MAC drugs and the protease inhibitor;
- taking the anti-TB/anti-MAC treatment with rifabutin instead of rifampin (*only if the protease inhibitor is indinavir (Crixivan)*);
- taking one-half the usual dose of rifabutin (*only if the protease inhibitor is nelfinavir (Viracept)*).

Also, if you have not yet started a protease inhibitor, the recommendation is to finish treatment with rifampin and other anti-TB/anti-MAC drugs before starting the protease inhibitor.

Check the table, [Medications That Should Not Be Used With](#), to make sure you are not taking drugs together that are contraindicated. *Be sure to talk to your doctor before stopping or starting any drug.*

Usually, your doctor can prescribe a different drug that will help you avoid an illness or treat a symptom.

How will I know if my protease inhibitor is working?

Your doctor will schedule you for checkups to monitor your blood tests and see how well your treatment plan is working. Some of the tests might include a CD4+ (T cell) count and a test to measure the amount of HIV in your blood (viral load) so that your doctor can tell if the medication is working against the virus. You may also have tests to check how well your liver and kidneys are working, and other measures of your overall health.

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Will I have side effects?

People react to medications in different ways. Some people have mild effects or no symptoms at all, while others may have many side effects or severe symptoms. Even when side effects occur, they can be temporary, or get better over time.

Some of the common side effects are listed on the following pages, but please remember that you may have only some of these or none at all.

ABDOMINAL PAIN

Some medicines can cause pain or discomfort in your abdomen (belly). If you have severe pain, if the pain is also in your back, or if your skin or eyes look yellow (jaundiced) let your doctor know.

BLEEDING PROBLEMS

Some people with hemophilia type A or B have reported increased bleeding problems. It is not known whether this is related to protease inhibitors, but these problems should be reported to the doctor immediately so they can be treated.

BLOOD SUGAR PROBLEMS

Some people taking protease inhibitors have had problems with their blood sugar levels, or have developed diabetes. Symptoms such as increased thirst, hunger, urination or weight loss should be reported to the doctor immediately.

People with diabetes who are considering protease inhibitor therapy should talk with their doctors about carefully monitoring their glucose (blood sugar) level.

DIARRHEA

Medications may cause you to have diarrhea (loose bowel movements). If you have severe cramping, or the problem lasts more than a day, call your doctor to ask about medicines that might help.

FATIGUE

You may have less energy or feel tired more often. This may be the result of the drug reducing the number of red blood cells in your body, which carry oxygen to your tissues and organs. A condition called anemia can occur if there are not enough red blood cells to carry oxygen throughout your body. Let your doctor know if you become dizzy or short of breath. Some of your blood tests will also let the doctor know if the drug is causing anemia.

HEADACHE

If you get severe or long-lasting headaches, ask your doctor which pain reliever you can take to help relieve them.

KIDNEY/BLADDER PROBLEMS

This can especially be a problem if you are taking *indinavir* (Crixivan). Making sure you drink enough liquids can help avoid some kidney or bladder effects. You should watch for signs that might signal a problem, such as:

- urinating, or feeling that you need to, more than usual
- pain or burning feeling when you urinate
- blood or reddish color in urine
- fever or chills
- pain in the back or side

MOUTH PROBLEMS

Some medications may cause mouth ulcers or sores. If it becomes difficult to eat or brush your teeth, or if you think you have signs of an infection, such as dark red or white patches, you should call your doctor.

NAUSEA/VOMITING

There may be occasional nausea or vomiting after taking medication, or it may be severe or long-lasting. If you vomit for more than a day, or have trouble keeping down liquids, call your doctor.

NUMBNESS/TINGLING SENSATIONS

Some common areas that can feel numb or tingle are the fingers/hands, toes/feet and around the mouth. You may also feel some pain in these areas. Your doctor may call it neuropathy. Call your doctor if you have these side effects. Sometimes they get better with time, but they may get worse and may last even after you stop taking the medication.

Your doctor can help you decide how to handle these side effects.

SKIN PROBLEMS

You may have a rash or dry, itchy skin with some drugs. If your skin breaks out in hives or if you have sudden or intense itching, it may mean you are allergic to a drug. Call your doctor immediately to get treatment.

You should also ask your doctor or pharmacist if your medicine can make you

more sensitive to sunlight, since you may sunburn more easily.

TASTE CHANGES

Medication can sometimes leave a taste in your mouth, or make foods or liquids taste odd. You may need to try different foods, or vary your diet if you find that things taste unpleasant.

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How long do side effects last?

Sometimes side effects get worse over time, and other times they get better as your body adjusts to the medication. Any side effects should be reported to your doctor right away, especially if they are sudden, severe or seem to be getting worse. Your doctor may know ways to help ease the problem, or may suggest a change in treatment if it is too bad.

Side effects will often go away after you stop taking a drug, but sometimes they can be long lasting or even permanent after stopping the drug. Also, since protease inhibitors are fairly new, there may be delayed effects that are not yet known.

People taking medications for HIV may get discouraged if they feel sicker after they start a drug treatment than they did before. They may feel that the quality of their life was better before starting their drug.

Talk to your doctor if you feel this way so you can make an informed decision about your treatment. Many experts recommend treating HIV early, before symptoms start to make you feel sick. Your doctor may suggest that you stay on the drug for a certain length of time to see if the side effects improve.

Side effects are a risk of taking any drug that you must weigh against possible benefits.

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What if I still have questions?

You will want to talk about your options with your doctor or other health care provider. It is important to get all of the information you need to make you feel comfortable with your decisions about medical treatment.

Talking to a family member, a friend or a support group might also help in making a decision about treatment. They can help you think of questions to ask your doctor.

Also, reference specialists at the HIV/AIDS Treatment Information Service may be able to answer some of your questions. You can call Monday through Friday from 9 a.m. to 7 p.m. Eastern time at 1-800-448-0440.

If you have specific questions about one of the protease inhibitors, you may want to call the company that makes the drug, listed below:

Crixivan (*indinavir sulfate*)

[Merck Research Laboratories](#), 1-800-379-1332

approved for marketing by FDA: 3/14/96

Fortovase & Invirase (*saquinavir mesylate*)

[Hoffmann-LaRoche Incorporated](#), 1-800-526-6367

Fortovase approved for marketing by FDA: 11/7/97

Invirase approved for marketing by FDA: 12/7/95

Norvir (*ritonavir*)

[Abbott Laboratories](#), 1-800-441-4987

approved for marketing by FDA: 3/1/96 (adults); 3/14/97 (children)

Viracept (*nelfinavir*)

[Agouron Pharmaceuticals](#), 1-888-847-2237

approved for marketing by FDA: 3/14/97 (adults and children)

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Medications That Should Not Be Used With:

SAQUINAVIR (INVIRASE, FORTOVASE)

Drug Category	Potential Alternatives
Antimycobacterial (anti-TB or anti-MAC): rifampin (Rifadin, others), rifabutin	azithromycin (Zithromax), ethambutol (Myambutol)
Sedative/hypnotic: midazolam (Versed), triazolam (Halcion)	very limited clinical experience
Ergot derivatives (anti-migraine):	very limited clinical experience
Cold and allergy antihistamines: astemizole (Hismanal), terfenadine (Seldane)	loratadine (Claritin)
Gastrointestinal: cisapride (Propulsid)	very limited clinical experience

INDINAVIR (CRIXIVAN), NELFINAVIR (VIRACEPT)

Drug Category	Potential Alternatives
Antimycobacterial (Anti-TB or anti-MAC): rifampin (Rifadin, others)	clarithromycin (Biaxin) azithromycin (Zithromax) ethambutol (Myambutol)
Cold and allergy antihistamines: astemizole (Hismanal), terfenadine (Seldane)	loratadine (Claritin)
Gastrointestinal: cisapride (Propulsid)	very limited clinical experience

Sedative/hypnotic

midazolam (Versed)
triazolam (Halcion)

RITONAVIR (NORVIR)

Drug Category	Potential Alternatives
Analgesic (pain reliever): meperidine (Demerol) piroxicam (Feldene) propoxyphene (Darvon, others)	acetaminophen (Tylenol, others) aspirin (Bayer, others) oxycodone (Percocet, others)
Cardiovascular (for the heart): amiodarone (Cordarone) flecainide (Tambocor) propafenone (Rythmol) quinidine (various)	very limited clinical experience
Antimycobacterial (Anti-TB or anti-MAC): rifabutin (Mycobutin)	clarithromycin (Biaxin) azithromycin (Zithromax) ethambutol (Myambutol)
Calcium Channel Blocker (for the heart): bepridil (Vascor)	very limited clinical experience
Ergot Alkaloid (vasoconstrictor): dihydroergotamine (D.H.E. 45) Ergotamine (various)	
Cold and allergy antihistamines: astemizole (Hismanal), terfenadine (Seldane)	loratadine (Claritin)
Gastrointestinal: cisapride (Propulsid)	very limited clinical experience
Psychotropic (antidepressant): bupropion (Wellbutrin)	fluoxetine (Prozac) desipramine (Norpramin)
Psychotropic (neuroleptic): clozapine (Clozaril) pimozide (Orap)	very limited clinical experience

Sedative/hypnotic:

alprazolam (Xanax)
clorazepate (Tranxene)
diazepam (Valium)
estazolam (ProSom)
flurazepam (Dalmane)
midazolam (Versed)
triazolam (Halcion)
zolpidem (Ambien)

Temazepam (Restoril)
Lorazepam (Ativan)

** Please note that alternatives may not be therapeutically equivalent*

References: Product Labeling

Invirase™ (December 6, 1995)

Norvir™ (March 1, 1996)

Drug Interactions: *Physician Guide*

Crixivan™ (March 13, 1996)

Fortovase™ (November 7, 1997)

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Drugs That May Interact With Ritonavir

The following is a list of medications that may potentially interact with ritonavir therapy.

Drug Category	Drugs that may interact with ritonavir (Norvir)
Analgesics, Narcotics (pain relievers)	alfentanil (Alfenta) fentanyl (Sublimaze)
Antiarrhythmics (for the heart)	disopyramide (Norpace) lidocaine (Xylocaine, others)
Anticoagulants (for the blood)	R-warfarin (Coumadin)
Anticonvulsants	carbamazepine (Tegretol) clonazepam (Klonopin) ethosuximide (Zarontin)
Antihistamine	loratadine (Claritin)
Antidepressants, other	nefazodone (Serzone) sertraline (Zoloft) trazodone (Desyrel)
Antiemetics	dronabinol (Marinol) ondansetron (Zofran)
Antimycobacterial (anti-TB or anti-MAC)	rifampin (Rifadin, others)
Antiparasitics	quinidine (various)
Calcium Channel Blockers	amlodipine (Norvasc) diltiazem (Cardizem, Diltiazem) felodipine (Plendil) isradipine (DynaCirc) nicardipine (Cardene) nifedipine (Adalat, Procardia) nimodipine (Nimotop) nisoldipine (Sular) verapamil (Calan, Isoptin)

Cancer chemotherapeutic agents	etoposide (VePesid) paclitaxel (Taxol) tamoxifen (Nolvadex, others) vinblastine (Velban) vincristine (Oncovin)
Corticosteroids	dexamethasone (Decadron, others) prednisone (various)
Hypolipidemics	lovastatin (Mevacor) pravastatin (Pravachol)
Immunosuppressants	cyclosporine (Sandimmune, Neoral) tacrolimus (Prograf)

References: Norvir™ Prescribing information (March 1, 1996)

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Drugs That May Interact With Nelfinavir (Viracept)

The following is a list of medications that may potentially interact with nelfinavir therapy.

Drug Category	Drugs that may interact
Anticonvulsants	carbamazepine (Tegretol) phenobarbital phenytoin (Dilantin)
Anti-HIV protease inhibitors	indinavir (Crixivan) ritonavir (Norvir)
Oral contraceptives (birth control pills)	ethinyl estradiol norethindrone

References: Viracept® Prescribing information (March 14, 1997)

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Questions to ask my doctor:

- What should I do if I miss a dose of medicine, or if I feel too sick to take my medicine?
- What is my CD4+ count? Has it changed?
- What is my viral load? Has it changed?
- What medications are prescribed for me?
- How many times a day do I take them?
- What are their possible side effects?

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Things to tell my doctor

- As soon as I take my medicine, I feel:
- Before my next dose of medicine, I feel:
- Changes in my eating habits:
- Changes in my sleeping habits:
- Side effects I have:
- How often?
- How long do they last?
- What I do that helps reduce the side effects:

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