Indinavir (Crixivan)

FACT SHEET

Published
2014

Summary

Indinavir is a type of anti-HIV drug called a protease inhibitor. The most common side effects of indinavir can include nausea, headache, diarrhea, vomiting, and weakness. Indinavir can also cause kidney stones, but drinking a minimum of 1.5 litres of water daily, in addition to your regular intake of other fluids, can help reduce this complication.

What is indinavir?

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

How does indinavir work?

To explain how indinavir works, we need to first tell you some information about HIV. 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.

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

How do people with HIV use indinavir?

Indinavir is used in combination with several other anti-HIV drugs, usually nukes (nucleoside analogues), and sometimes including drugs from other classes such as non-nukes (non-nucleoside reverse transcriptase inhibitors). Combinations such as this 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.

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Neither indinavir nor any other anti-HIV medication is a cure for HIV. It is therefore important that you do the following:

- See your doctor regularly so that he/she can monitor your health.
- Continue to practise safer sex and take other precautions so as not to pass HIV on to other people.

Warnings

1. Kidney stones

The most dangerous side effect associated with indinavir is kidney stones (nephrolithiasis). In one long-term study, as many as 13% of indinavir users developed this complication. Pain in the lower back and sides (flanks), with or without blood in the urine, is a symptom of kidney stones. Urinating may be difficult or painful. These symptoms should be reported to your doctor immediately. To reduce the risk of developing kidney stones, people using indinavir should drink at least 1.5 litres extra of healthful liquids (water, caffeine-free teas, juices) every day, in addition to what they normally drink. Some researchers suggest higher amounts of these liquids – up to 2.0 litres/day.

You should be aware that alcohol and caffeine can dehydrate your body. This means that beverages containing these substances increase your need for water. So alcohol- and caffeine-containing drinks don't count towards the extra 1.5 to 2.0 litres that you need each day.

Under the following conditions, your need for water also increases:

- in hot weather
- when dancing or exercising
- if you have diarrhea
- if you have been vomiting

Of course, if you have persistent diarrhea or vomiting, you should contact your doctor.

2. Other kidney concerns

Because indinavir can affect your kidneys, you may wish to be cautious about using other medications which have the potential to cause kidney damage. The following list of drugs, which is not exhaustive, can cause kidney dysfunction or damage:

- aminoglycoside antibiotics – amikacin (Amikin), gentamicin, paromomycin (Humatin), streptomycin, tobramycin
- other antibiotics – Septra (Bactrim, co-trimoxazole, trimethoprim-sulfamethoxazole)
- antifungals – amphotericin B (Fungizone)
- antivirals – acyclovir (Zovirax), adefovir (Hepsera), cidofovir (Vistide), foscarnet (Foscavir), tenofovir (Viread), tenofovir co-formulated with FTC (emtricitabine, Emtriva) in Truvada, valacyclovir (Valtrex)
- antiparasitic drugs – intravenous pentamidine
- NSAIDs (non-steroidal anti-inflammatory drugs) – acetaminophen (Tylenol), ibuprofen (Advil, Motrin), indomethacin (Indocid), naproxen (Naprosyn)

Side effects

1. General

Common side effects that have been reported by some indinavir users can include nausea, vomiting, abdominal or flank pain, headache, diarrhea, fatigue or weakness, and difficulty falling asleep.

2. Bilirubin

Lab tests on samples of your blood may detect higher-than-normal levels of bilirubin, a substance produced by the liver. Bilirubin levels often return to normal after a few months, but they should be monitored. High levels of bilirubin can sometimes cause the skin to darken slightly, giving the appearance of a tan or mild sunburn.

3. Skin, hair and nails

Some indinavir users have reported thinner hair or temporary loss of hair. Dry skin, dry or cracked lips, and ingrown toenails have also been reported by indinavir users. These symptoms are sometimes referred to as ectodermal dysplasia. For more information about options to help manage this please see CATIE's *A Practical Guide to HIV Drug Side Effects*.

4. Bleeding

Hemophiliacs may experience spontaneous bleeding episodes, including bruising and bleeding into joints. It is not clear if, or how, protease inhibitors cause bleeding. Any such episodes should be closely monitored.

5. 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, although for the average person, the risk of developing this complication is low. 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.

6. 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*.

Drug interactions

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

Some drugs can interact with indinavir, 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 indinavir drug levels, but cause similar side effects.

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 anti-HIV drugs or other medications
- prescribe different anti-HIV drugs for you

Drug interactions for indinavir

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

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

- antibiotics/anti-tuberculosis drugs – rifampin (Rifadin, Rifater)
- antihistamines – astemizole (Hismanal), terfenadine (Seldane)
- anti-psychotic drugs – pimozide (Orap)
- gastrointestinal motility agents – cisapride (Prepulsid)
- herbs – St. John's wort
- lipid-lowering drugs – lovastatin (Mevacor), simvastatin (Zocor).
- migraine drugs (Ergot derivatives) – dihydroergotamine (Migranal), ergotamine (Ergomar), Ergonovine
- sedatives – midazolam (Versed), triazolam (Halcion)

The following drugs can *increase* levels of indinavir in your body:

- anti-HIV drugs – delavirdine (Rescriptor): your dose of indinavir may have to be reduced if you are taking delavirdine. Ritonavir (Norvir): your dose of indinavir will be reduced if you also take ritonavir.
- anti-fungal drugs – itraconazole (Sporanox), ketoconazole (Nizoral): your dose of indinavir may have to be reduced if you are taking these medications

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

- anti-HIV drugs – efavirenz (Sustiva): your dose of indinavir may need to be increased if you are taking efavirenz.
- antibiotics/anti-tuberculosis drugs – rifabutin (Mycobutin): your dose of indinavir may need to be increased. As well, your dose of rifabutin may need to be decreased.

The following supplements may *decrease* levels of indinavir in your blood:

- Milk thistle: one study has found decreased indinavir levels in some users, while another study has not.
- Vitamin C: one small, short-term study has found a small but significant decrease in indinavir levels when 1 gram/day of vitamin C was also taken.

In both sets of studies (milk thistle and vitamin C) subjects were taking indinavir as the sole PI in their regimen. Results may be different when indinavir is taken in combination with other PIs, such as ritonavir.

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 anti-HIV drugs, which means those drugs will no longer work for you. Combining indinavir with at least two other anti-HIV drugs delays the development of drug resistance.

To reduce the risk of developing drug resistance, all anti-HIV drugs should be taken every day exactly as prescribed and directed. If doses are delayed, missed, or not taken as prescribed, levels of indinavir 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 indinavir your doctor, with the help of resistance testing, can help put together a new treatment regimen for you.

Dosage and formulations

Because of the complex regimens and side effects associated with the use of indinavir, this drug is rarely used in Canada and other high-income countries. Still, if indinavir is prescribed in Canada, here is some information.

Indinavir is available as 200 mg and 400 mg capsules.

1. Indinavir as the sole protease inhibitor in a regimen

The recommended dose of indinavir, when used as the sole protease inhibitor in a regimen, is 800 mg every eight hours. When indinavir is used as the only protease inhibitor in a regimen, for best absorption, this drug should be taken with water on an empty stomach, that is, either one hour before or two hours after a meal. Alternatively, it can be taken with a light meal: corn flakes with sugar and skim milk, or dry toast with jam, juice, and coffee. Fats and proteins decrease the amount of indinavir that can be absorbed and used by the body.

2. Indinavir and other protease inhibitors

Some specialists prescribe indinavir in combination of with another protease inhibitor called ritonavir (Norvir). With this combination, ritonavir acts as a "booster" for indinavir, meaning that ritonavir increases or boosts levels of indinavir in the blood when both drugs are taken together. When indinavir is taken with ritonavir, both drugs need only be taken on a twice-daily schedule to maintain high levels of indinavir in the blood. A combination of both drugs that is sometimes used is 800 mg of indinavir with 100 mg of ritonavir, both drugs taken every 12 hours. If your doctor has prescribed this "boosted" indinavir regimen, you still have to drink a minimum of 1.5 litres of extra fluid each day. Unlike the case when indinavir is the only protease inhibitor, indinavir in combination with ritonavir can be taken with or without meals. Another dose combination being studied is indinavir 400 mg and ritonavir 100 mg, twice-daily. However, this and other dose combinations of indinavir and ritonavir are experimental.

There may be other combinations of protease inhibitors that can be prescribed together with indinavir. Discuss these possibilities with your doctor.

Availability

Indinavir is licensed in Canada for the treatment of HIV infection in adults, in combination with other anti-HIV drugs. Your doctor can tell you more about the availability and coverage of indinavir 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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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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Production of this document has been made possible through a financial contribution from the Public Health Agency of Canada. The views expressed herein do not necessarily represent the views of the Public Health Agency of Canada.

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