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## I ANTI-HIV AGENTS

### A. Kaletra approved in Canada

#### Summary

On March 9, 2001, Health Canada granted permission to Abbott Laboratories for the sale of Kaletra (a combination of protease inhibitors lopinavir and ritonavir), formerly known as ABT-378/r, for the treatment of HIV infection in adults and children six months or older. Kaletra was approved for sale in the U.S. in September 2000.

#### Approval Data

The approval of Kaletra is based partly on results from a Phase III study. In that study, subjects received one of two protease inhibitors — Kaletra or nelfinavir (Viracept) — as well as d4T (Zerit) and 3TC (lamivudine). According to the data analysis, Kaletra reduced viral load and raised CD4+ cell counts in significantly more people than did nelfinavir. Regulatory authorities also reviewed data from several small studies. These studies were designed to assess the effect of different doses of Kaletra. Currently there is no data in the public domain about the ability of Kaletra to delay the onset of symptoms of AIDS.

#### Dosing

The recommended adult dose of Kaletra is 400 mg (3 capsules) twice daily with food. In children the dose is adjusted depending on the child's weight.

#### Access

Apart from enrolling in a clinical trial, access to Kaletra in Canada has occurred via an expanded access programme. Since Kaletra is now available for sale, the expanded access programme will no longer be recruiting people.

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There are currently more than 1,400 Canadians with HIV/AIDS receiving Kaletra in the expanded access programme. Abbott Labs has said that it will continue to provide the drug at no charge to these people until such time as payment for Kaletra is covered by provincial/territorial formularies. One month's supply of Kaletra is expected to cost about \$600.

### Storage

At home, Kaletra capsules do not need to be refrigerated if they are used within two months and stored at temperatures not higher than 25°C (77°F). The liquid formulation of Kaletra can be stored at room temperature if used within two months. Refrigerated liquid Kaletra remains effective until the expiration date.

### Side Effects

Side effects that can occur in some people who use Kaletra include the following:

- diarrhea
- frequent stools
- feeling weak or tired
- headache
- nausea
- vomiting

### Warning

Pancreatitis — a painfully swollen pancreas gland — has occurred in people using Kaletra. In some cases, this complication has been fatal. According to the manufacturer, pancreatitis should be considered if the following signs/symptoms occur:

- nausea
- vomiting
- abdominal pain
- high levels in the blood of the enzymes amylase or lipase

### Drug Interactions

Kaletra should not be used with the following drugs:

- heart drugs — Tambocor (flecainide), Rythmol (propafenone)
- antihistamines — Hismanal (astemizole), Seldane (terfenadine)
- ergot drugs — Ergonovine, Ergomar (ergotamine)
- anti-psychotic drugs — Orap (pimozide)
- sedatives/sleeping pills — Versed (midazolam), Halcion (triazolam)
- herbs — St. John's wort
- lipid-lowering drugs — Mevacor (lovastatin), Zocor (simvastatin)

A CATIE Fact Sheet on Kaletra, listing further drug interactions and side effects, is now available at [www.catie.ca](http://www.catie.ca).

## B. Canadian researchers study “immune healing”

### Background

Shortly after entering the body, HIV begins to damage the ability of the immune system to fight microbes in general and HIV in particular. A major focus of AIDS research is to find a way to restore the immune system's ability to fight HIV.

Treating people with HIV/AIDS (PHAs) with highly active antiretroviral therapy (HAART) usually leads to increased CD4+, CD8+ and other cells as viral load falls. These changes persist in people who are able to adhere to and tolerate these drug regimens. As well as increasing the numbers of immune cells, HAART also appears to improve their ability to fight many of the microbes that cause life-threatening complications in PHAs.

Unfortunately, several research teams have found that despite the use of HAART, the immune system does not usually develop the ability to control HIV. Because the immune system does not fully recover despite the use of HAART, some researchers have suggested that immune boosters may also be needed to help with “immune healing.” It may be that one reason for the incomplete immune recovery is the long-term impact of anti-HIV treatment on the immune system. Although HAART has potent anti-HIV activity, it may also suppress some of the immune system's subtle functions. In the short term this may be useful, as parts of the HIV-infected immune system may well be overactive. In the long term, the drugs' interference with the functions of immune cells may not be helpful.

In trying to understand the impact of HAART on the immune system, it may be useful to study the effect of different classes of anti-HIV drugs separately before studying their effects together. For instance, nucleoside analogues, or nukes, such as AZT, may have a different impact on the immune system than do protease inhibitors (PIs). In the report below, researchers in Ottawa conducted a two-year study on PHAs using, in most cases, just two drugs — the PIs ritonavir (Norvir) and saquinavir (Fortovase). (Note: Prescribing this combination is a highly unusual practice that is not considered appropriate treatment. However, these people were part of a carefully planned clinical trial. Do not try this at home.)

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## Study Details

Researchers enrolled 42 subjects who had no previous exposure to PIs and gave them a minimum of ritonavir 400 mg and saquinavir 400 mg, both twice daily. If after 12 weeks of this dual PI combination their viral load was not below the 200 copy mark, then subjects could include the nukes d4T (Zerit) and 3TC (lamivudine) to their regimens. At the start of the study, the profile of subjects was as follows:

- average CD4+ count – 286 cells
- average CD8+ count – 846 cells
- average viral load – 58,000 copies

## Results

After two years of treatment, 35 subjects remained in the study. By this time, their lab values were as follows:

- average CD4+ count – 494 cells
- average CD8+ count – 799 cells
- average viral load – less than 200 copies

After two years of treatment, the proportion of subjects taking the following drugs was:

- two PIs only – 66%
- two PIs and two nukes – 33%

Four subjects had viral loads above the 200 copy mark. In two people, this event occurred because they had temporarily stopped taking their drugs. In the other two, the increased viral loads were only temporary.

## But do they work?

It's one thing to have a lot of CD4+ and CD8+ cells, but a big question is: "Do they work?" Researchers conducted many tests on blood cells taken from the subjects. The purpose of these tests was to find out how well immune cells were able to respond to HIV.

According to their results, at the start of the study only about 5% of subjects had T cells that could recognize and attack HIV. By the end of the second year of the study, this figure had increased to 50%. This may not seem like much, but readers should note that it takes many years for HIV to degrade the immune system, and it is likely that it will take many years to rebuild it.

The research team thinks that the improvement in the immune system's ability to function properly happens because viral load is suppressed by HAART. They found that in cases where viral load was temporarily increased, the immune system's ability

to respond to and attack microbes (in simulated tests) was weakened. This finding of a link between viral load and a weakened immune response is something to bear in mind when thinking about "drug holidays" or strategic treatment interruptions (STIs).

## Who responds best to HAART?

Researchers looked at several factors that could help them identify which of their subjects would develop strong immunologic responses to HIV while receiving HAART. These factors included the following:

- CD4+ count
- viral load
- age
- previous use of nukes

According to their analysis, the researchers could find no link between any of the factors and the development of anti-HIV responses.

In this study, it is interesting that 66% of subjects did not use nukes but relied upon a combination of the two PIs ritonavir and saquinavir for viral suppression. This may be one reason why the immune recovery seen in these subjects was more dramatic than detected in several previous studies. Other researchers have usually included nukes, particularly AZT, in anti-HIV treatment combinations. It may be that the impact of some nukes over the long term weakens the immune response against HIV in some PHAs. Studying this impact of anti-HIV drugs on the immune system is important if safe, effective and long-term therapies are to be developed. There are several studies underway that are comparing regimens containing nukes against regimens containing no nukes. Preliminary results from these studies should be available next year.

## Lipodystrophy

We eagerly look forward to further analysis of the Ottawa study data, specifically information on which regimens were associated with an increased risk of developing certain side effects, such as the following:

- diabetes
- heart disease
- weakened bones
- fat loss
- fatty lumps and humps

Preliminary analysis suggests that those subjects who used nukes were more likely to develop fat wasting in the face and buttocks than subjects who did not use nukes (JB Angel, personal communication, 2001).

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## Important Findings

Drug holidays or STIs have been embraced by some PHAs who welcome relief from HAART side effects or who are simply tired of taking handfuls of pills several times a day for years. But short drug holidays may also be a way for the immune system to become re-exposed to HIV after the virus has been suppressed for long periods of time.

An important message from this study is that rebuilding the immune system takes time and may also depend on the type of therapy used. As well, prolonged suppression of viral load is beneficial. Thus, drug holidays need to be carefully planned, taking into account several factors. More effective and less toxic drugs might be a more useful path to better control of HIV infection.

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## II INFECTION FIGHTERS

### A. St. John's wort extract found not helpful for hepatitis C

#### Background and Summary

The plant St. John's wort (*Hypericum perforatum*) is used for the treatment of mild to moderate depression. Hypericin is a compound found in the stems and petals of the flowers of St. John's wort. Over the past decade, research teams in Canada, the U.S., Israel and Europe have been conducting lab experiments using hypericin and other compounds extracted from St. John's wort. In these experiments, hypericin has shown activity against viruses that cause herpes, AIDS and diseases similar to hepatitis in animals. Based on these results, researchers in New York decided to conduct a study to find out about

hypericin's antiviral effect in people with hepatitis C virus (HCV). According to the results, hypericin taken orally for two months had no detectable anti-HCV activity, but it caused "considerable" temporary side effects.

#### Study Details

Researchers enrolled 19 HCV positive adults (4 female, 15 male), all of whom had high levels of the following in their blood:

- hepatitis C viruses
- liver enzymes (suggesting liver damage)

None of the subjects was pregnant, actively abusing substances or had HIV infection. Twelve subjects received low-dose hypericin – 0.05 mg per kg of body weight per day for two months – and seven subjects received high-dose hypericin – 0.1 mg/kg of body weight/day for two months. As hypericin can make people sensitive to sunlight, all subjects were encouraged to wear hats, gloves and sunscreen when outdoors.

#### Results — side effects

Seven of 12 subjects receiving low-dose hypericin and all seven subjects who received high-dose hypericin developed side effects, usually a photosensitivity reaction associated with the following symptoms:

- burning or tingling after exposure to sunlight
- redness and inflammation
- darkening of the skin
- swollen nodules on the skin

All side effects cleared after subjects stopped taking hypericin. No subject developed any toxicity that was detected by lab tests.

#### Results — effect on HCV

Hypericin had no impact on commonly used blood tests used to assess HCV infection, including the following:

- levels of HCV
- levels of liver enzymes

This is the second study using purified hypericin supplied by VimRx Pharmaceuticals (Wilmington, Delaware) for the treatment of a viral infection in humans. The first study tested hypericin in HIV positive subjects and also found no beneficial effect(s). Some people might argue that the dose of hypericin used in the current study of HCV was not high enough. But in the study with HIV positive subjects, high doses of hypericin were associated with side

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effects, even though the drug in that study was only taken twice or three times weekly.

In the current study on HCV, researchers regularly checked blood samples from subjects to assess levels of hypericin. They found that levels of this compound were high enough to, in theory, have anti-HCV activity. Yet the researchers are not sure why hypericin did not have significant antiviral activity in either study. Several research teams have found that in the lab it is necessary for hypericin to be exposed to light to have significant antiviral activity. It may also be that hypericin requires a great deal of exposure to light to have anti-HIV or anti-HCV activity in people. If this is the case, given the photosensitivity reaction associated with use of hypericin, this product when taken in large doses may not be safe as an antiviral drug in people.

It is worth noting that St. John's wort contains many compounds of which hypericin is merely one. The beneficial effects of the plant may depend on use of several of these compounds, not just one. St. John's wort and its extracts are being tested for their antibacterial and anticancer activity.

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### III TESTING

#### A. Are deaths due to liver damage becoming more common?

##### Background and Summary

After receiving reports of increased deaths due to liver disease in PHAs, a team of doctors in Boston decided to review medical records at its hospital to find out if more PHAs were indeed dying of complications from liver disease. The doctors looked at data from three points in time — 1991, 1996 and 1998-1999. According to their review of 84 deaths, 50% of deaths in 1998-1999 occurred because of complications

from liver damage. The possible reasons for this are discussed later in the report below.

#### Results — causes of death

The proportion of PHAs who died from complications due to liver disease in each time point was as follows:

- 1991 – 12%
- 1996 – 14%
- 1998-1999 – 50%

The remaining proportion of PHAs died from complications due to AIDS. One year before subjects with liver-related disease died, 50% of them had CD4+ counts greater than 200 cells or a viral load below the 500 copy mark.

#### Why liver disease?

The doctors conducting the review were unable to find out from medical records how long the PHAs who died of liver disease had been co-infected with hepatitis C virus (HCV). They did note that the proportion of PHAs who were tested for exposure to HCV increased over time:

- 1991 – 3 of 4 subjects (75%)
- 1996 – 15 of 26 subjects (56%)
- 1998-1999 – 15 of 16 subjects (94%)

In 1998-1999, 11 subjects died from complications due to liver damage; 9 out of 10 of these tested positive for HCV.

#### Looking Forward

Studies reviewing old medical records (retrospective studies) can be helpful as they identify patterns that may have occurred. The results of these findings confirm the suspicions in the AIDS community that there has been an increase in liver-related deaths in the late 1990s in North America. Deaths due to liver disease may be increasing for a number of reasons. For instance, because of highly active antiretroviral treatment (HAART), PHAs are no longer dying in large numbers from formerly common AIDS-related complications such as PCP (*Pneumocystis carinii* pneumonia), CMV (cytomegalovirus) infections and weird bacterial and parasitic diseases. They are living longer, which allows more time for HCV to inflict damage on the liver — damage that has fatal consequences.

Another possible reason for the increase in liver-related deaths is that as people are living longer because of HAART, their exposure to potentially liver-damaging drugs increases compared to the time before HAART.

Studies are needed to determine the following:

- the long-term impact on the liver of HAART and other drugs commonly used by PHAs
- more tolerable and effective anti-HCV therapies

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### **B. St. John's wort found to lower nevirapine levels**

St. John's wort (*Hypericum perforatum*) is a common herbal remedy used to treat mild to moderate depression. About a year ago, we reported findings that St. John's wort may interact with certain drugs used to treat HIV infection. The herb does this by interfering with the liver's ability to break down anti-HIV medications, speeding up the body's elimination of at least one drug — indinavir (Crixivan) — and thus lowering levels of indinavir in the blood. This situation could make it easier for HIV to develop resistance to indinavir and other protease inhibitors, which would limit treatment options for PHAs. Now doctors in Amsterdam have found that St. John's wort can also reduce levels of another anti-HIV drug — the NNRTI nevirapine (Viramune) — in PHAs.

The doctors reported data on patients who were taking nevirapine along with two nucleoside analogues for more than one year. During this time, patients were having their blood tested for levels of nevirapine every three months. The doctors noticed that nevirapine levels were less than normal in five male patients. The five men were also taking St. John's wort for several months, along with nevirapine. The doctors then compared nevirapine levels in the five men to levels in 176 other PHAs. According to this comparison, St. John's wort significantly reduced levels of nevirapine. Less-than-normal levels of nevirapine in the blood could make it easier for HIV to develop resistance to nevirapine, as well as to other NNRTIs such as efavirenz (Sustiva) and delavirdine (Rescriptor). The Dutch doctors therefore warned that St. John's wort should not be taken by PHAs using nevirapine.

There may be at least two ways in which St. John's wort can reduce levels of nevirapine. First, the herb could decrease absorption of nevirapine in the intestine. Second, St. John's wort could also speed up the rate at which the liver breaks down nevirapine.

The findings by the doctors also underscore the importance for patients to tell their doctor(s) about the supplements and herbs they are using. For further information about St. John's wort, please see the CATIE Supplement Sheet at [www.catie.ca](http://www.catie.ca).

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### Disclaimer

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

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