

A Practical Guide to

H A A R T

{ Highly Active AntiRetroviral Therapy }

for people living with HIV/AIDS



**Canadian AIDS Treatment
Information Exchange**

**Réseau canadien
d'info-traitements sida**

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first edition



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**A Practical Guide to HAART
(Highly Active AntiRetroviral Therapy)**

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first edition (2002); revised (2003,
2006)

isbn 0-9730715-0-8

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CATIE would like to thank the following people for working with us to help produce this guide. Their time and knowledge were invaluable and much appreciated.

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mission statement The Canadian AIDS Treatment Information Exchange (CATIE) is committed to improving the health and quality of life of all people living with HIV/AIDS (PHAs) in Canada. CATIE provides HIV/AIDS treatment information to PHAs, caregivers, health care providers, and AIDS service organizations who are encouraged to be active partners in achieving informed decision-making and optimal health care.

This Practical Guide to HAART is chock-full of useful information about treating HIV and AIDS. However, because some of the concepts are complex, we encourage readers to read it at their leisure, one section at a time.

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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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H I V a n d A I D S :
t h e b a s i c s

The decisions that people living with HIV and AIDS

(often referred to as PHAs or PWAs) must make about treating the disease can often seem overwhelmingly difficult. In this guide, we hope to provide the latest on what is currently known about the various aspects of treatment, as well as a bit of skepticism about anyone claiming to have definitive answers on this topic. We don't know it all, but we will try to tell you what is known and, sometimes more importantly, what is not known about infection with the Human Immunodeficiency Virus (HIV) and how to treat it.

If someone asks about your HAART medications, they aren't presuming that you have blocked arteries.

If you have only recently been diagnosed as HIV positive — or just want a refresher course on the basics — you may want to start at the top to read our description of the virus, the immune system that fights it, the stages of the disease, the drugs that attack it at each point in its life cycle, and the tests that will be used to assess your health status. Having a basic understanding of all of the above is very useful for anyone living with HIV or AIDS. It will help you understand the HIV information you read, increase the likelihood of effective communication with your doctor(s), and, we hope, assist you in your journey along the path of making treatment decisions.

And when they want to know what's in your cocktail, they aren't trying to find out your secret recipe for the perfect martini.

If you've been around the HIV world for quite some time but are now considering starting or changing drug therapy, you might want to skip down to the section on, you guessed it, "Treating HIV." Because HIV belongs to a group of viruses called *retroviruses*, treatment to fight HIV infection is known as *antiretroviral therapy (ART)* or *anti-HIV treatment*. Because we have learned that the best way to treat HIV effectively is with a combination of at least three antiretroviral drugs, you will most often see this multiple-medication approach referred to as *HAART*, which stands for *Highly Active AntiRetroviral Therapy*, or as a *drug cocktail* or *combination therapy*.

Throughout this guide, we've tried to explain all the basic terms you'll need to know. However, if you're new to the world of HIV, it might be a good idea to also take a glance at an AIDS glossary and learn some of these basic terms. Otherwise, you might sometimes feel that everyone's speaking in a secret code. Here are some HIV/AIDS glossaries available on the Web:

- Gay Men's Health Crisis (GMHC) — *AIDS Medical Glossary*:
<http://www.gmhc.org/health/glossary.html>
- HIV/AIDS Treatment Information Service (ATIS) — *4th edition of the Glossary of HIV/AIDS-Related Terms*:
www.aidsinfo.nih.gov/
- San Francisco AIDS Foundation — *Glossary of HIV/AIDS-Related Terms*:
www.sfaf.org/treatment/glossary/index.html

At the time of this writing, there are more than 20 antiretroviral drugs and drug combinations available in Canada.

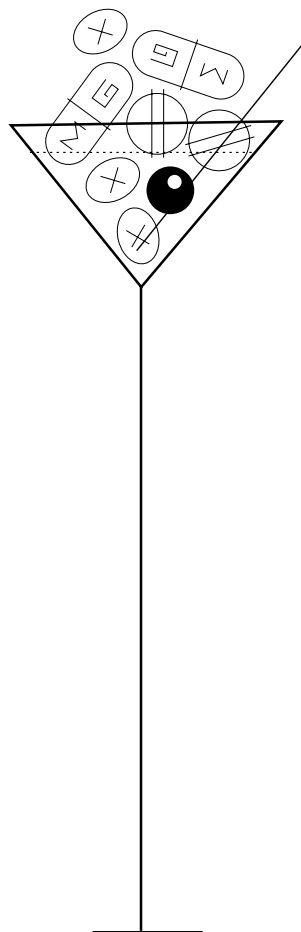
At the time of this writing, there are more than 20 antiretroviral drugs (including the various combinations and formulations) available in Canada. Many other drugs are being studied, and several should become available within the next couple of years. Some of the latter are already options for those willing to enter the clinical trials where they're being studied. This obviously means that there are now a huge number of possible therapeutic combinations.

For many thousands of PHAs, these combinations have extended life and improved health. In many cases, when effective drugs are available, their use can result in significantly restored immune function and the ability to fight off the infections that once would have been fatal. So instead of what many would have once considered an inevitable downhill slide into illness and death, there is now hope that — for those living in parts of the world where the drugs are available — disease progression can be slowed down or even reversed.

But there are downsides that have become more evident the longer people have stayed on HAART:

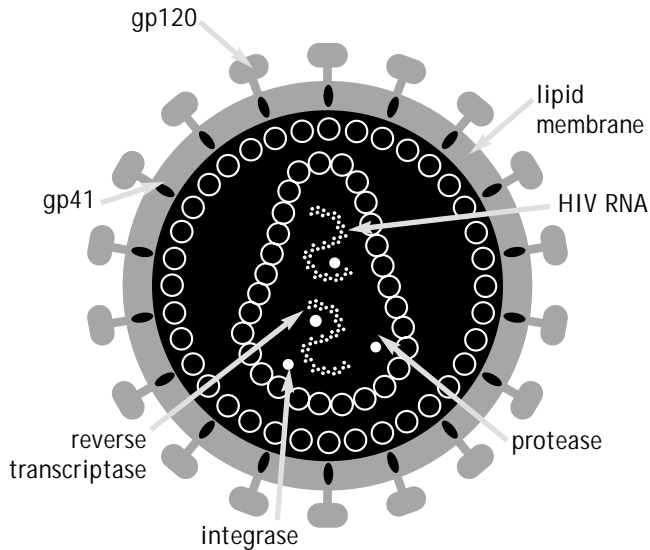
- First, in some people, there are very serious side effects and long-term complications that can result from these powerful drugs. Even a single drug can cause side effects, and using several at the same time means that this risk increases. For many people today, the miserable symptoms that are sometimes caused by drugs are the major issue in their ability to continue taking them.
- In addition, many people have trouble sticking to the scheduling and other requirements of their drug regimens over the long haul. Continuing to take the drugs exactly as directed is called *adherence*. Not doing this, *non-adherence*, is a major cause of drug resistance and, ultimately, drug failure (for a full discussion of what this means, see the “Drug Resistance” section).
- And that leads us to the many people who have been on treatment for a long time for whom the drugs have quit working in the way that is needed. For those people — called the *treatment-experienced* or the *heavily pre-treated* — there may be few or no remaining treatment options.

So, while scientific advances have increased our understanding of HIV disease and provided new weapons in the fight against it, HIV treatment has grown more and more complex. And there are many questions to which we do not yet have definitive answers. Even the opinions of experts in the field often vary on such questions as the best time to start treatment, the best combination of drugs to use and in what order to use them, whether treatment should be continued lifelong or cycled in various ways, and so on. This guide is intended to provide a summary of the current scientific thought on these and other issues. There are no simple answers here, but there is information that may help you make decisions about treating HIV in the most effective and lifestyle-friendly way possible.



Like all viruses, HIV cannot multiply by itself.

It must get inside a cell in order to make copies of itself. When HIV infects a cell, it takes over the cell's control centre. From there, the virus starts to make new copies of itself (it reproduces or replicates). These newly minted viruses then go on to infect other cells. Without treatment, experts estimate that up to 10 billion copies of HIV may be made every day. Understanding how HIV replicates can help you understand how antiretroviral drugs work. All of these drugs interfere with key stages of viral replication.



The HIV Virus

Human immunodeficiency virus (HIV) is made up of two strands of genetic material called RNA. Along with the RNA, HIV contains three key enzymes:

- reverse transcriptase
- integrase
- protease

These enzymes are chemicals that help the virus make copies of itself. The outer surface of the virus is covered with proteins called gp120 and gp41.

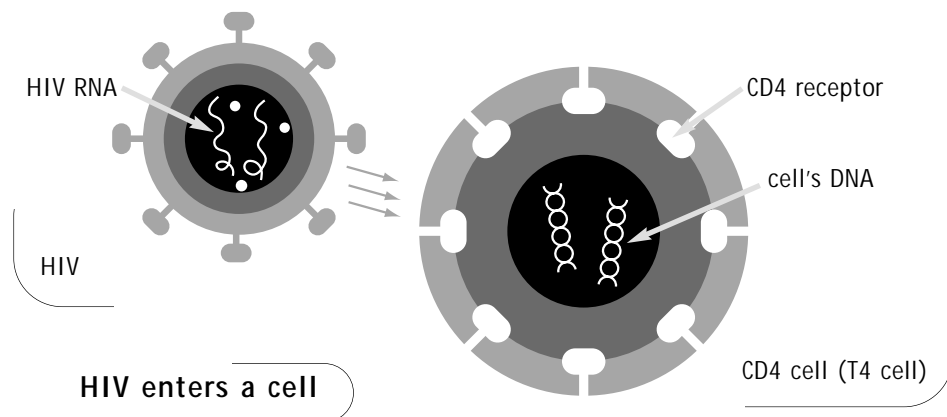
HIV Virus

1. HIV enters a cell

HIV uses the proteins on its surface to lock on to the parts of the cell called the CD4 receptor and the co-receptors, such as CCR5 and CXCR4. Once HIV is attached to the receptors, the virus can fuse with the cell. Then the contents of the virus are inserted into the cell. Not all of the cells in your body have CD4 receptors; the most important cells that do are called *CD4+ T cells* or *T4 cells*.

Drugs known as *entry inhibitors* are being developed to prevent HIV from getting inside cells. Some of these drugs are designed to block the co-receptors while others prevent the virus from fusing with the cell. The first entry inhibitor approved in Canada was T-20 (enfuvirtide, Fuzeon).

See "Appendix A, Antiretroviral Drugs," for a listing of all the drugs now approved in Canada, as well as those currently being studied. This listing includes the names of the drugs and their manufacturers.



2. HIV takes control of the cell

Inside the cell, the *reverse transcriptase* (RT) enzyme converts the viral RNA into DNA. Now the genetic material of the virus matches the genetic material of the cell. Drugs called *reverse transcriptase inhibitors* slow down or stop the action of the RT enzyme. The three types of these drugs are:

- ▮ *nucleoside analogue reverse transcriptase inhibitors* (NRTIs)
- ▮ *non-nucleoside analogue reverse transcriptase inhibitors* (NNRTIs)
- ▮ *nucleotide analogue reverse transcriptase inhibitors* (nucleotide RTIs)

The NRTIs, commonly referred to as *nukes*, were the first drugs approved for the treatment of HIV and continue to be a major part of many PHAs' drug regimens. Currently approved *nukes* are:

- ▮ 3TC (EpiVir, lamuvidine)
- ▮ abacavir (Ziagen)
- ▮ AZT (Retrovir)
- ▮ d4T (Zerit)
- ▮ FTC (Emtriva)
- ▮ ddI (Videx)

There are also combinations of nukes, taken as one pill:

- ▮ AZT/3TC in one pill (Combivir)
- ▮ 3TC/abacavir (Kivexa)
- ▮ AZT/3TC/abacavir in one pill (Trizivir)
- ▮ FTC/tenofovir (Truvada)

Many other nukes are being studied.

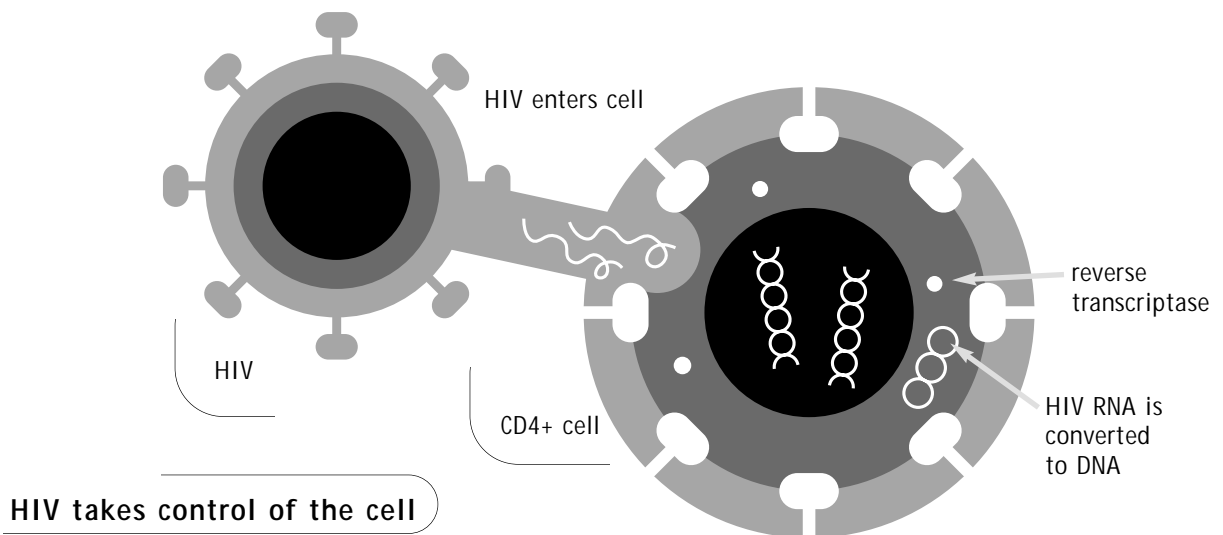
The NNRTIs, or *non-nukes*, were developed later than the nukes, but due to their powerful ability to suppress HIV they have also become an important component of many PHAs' approaches. Currently approved non-nukes are:

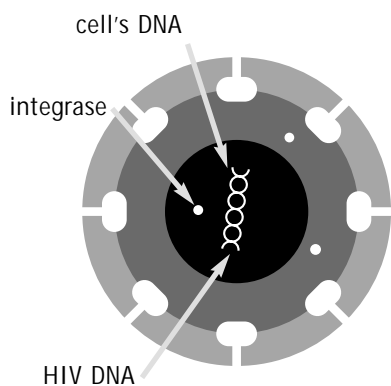
- ▮ delavirdine (Rescriptor)
- ▮ efavirenz (Sustiva)
- ▮ nevirapine (Viramune)

The nucleotide RTIs are very similar to the nukes but require one less processing step to work in the body. The one nucleotide RTI available in Canada is:

- ▮ tenofovir (Viread)

There are several other nucleotide RTIs being studied.





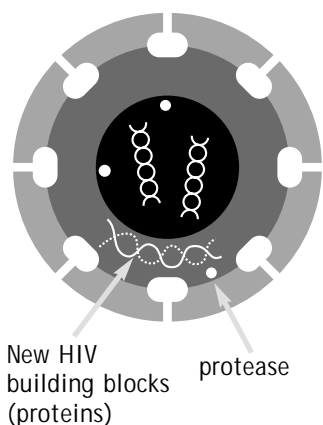
HIV-infected CD4+ cell

3. HIV becomes part of the infected cell

The second viral enzyme, called *integrase*, inserts the newly converted viral DNA into the cell's own DNA. With the viral DNA integrated into the DNA of the cell, the virus has become part of the cell. This process has sometimes been compared to putting a "bug" in a computer software program. Researchers are working to develop drugs that will interfere with the action of integrase. Right now, there are no approved *integrase inhibitors*.

4. HIV tricks the infected cell into making copies of itself

At this point, if the infected CD4+ cell is activated — which happens any time the immune system is called upon to respond to an infection or allergen or cancerous cell — instead of performing its proper functions, it will start making and releasing new virus. The first step is to make long chains of viral protein. The *protease* enzyme works like scissors to cut these protein chains into the smaller pieces that make up HIV. The newly cut pieces are assembled into new virus particles, which then "bud" out from the host cell and can go on to infect other cells.



Infected CD4+ cell creates new HIV

Protease inhibitors (PIs) are drugs that interfere with the action of protease. They prevent the protease enzyme from cutting the long chains of new viral protein. Although new virus can be formed, it is defective and cannot infect new cells. Protease inhibitors have a very powerful ability to suppress the virus and are an important part of many drug combinations.

Currently approved protease inhibitors are:

- amprenavir (Agenerase)
- lopinavir and ritonavir (Kaletra)
- ritonavir (Norvir)
- saquinavir (Invirase)
- fosamprenavir (Telzir)
- indinavir (Crixivan)
- nelfinavir (Viracept)
- tipranavir (Aptivus)
- atazanavir (Reyataz)

Sometimes your doctor may prescribe two PIs together. This is because one PI, usually ritonavir, can "boost" the level of the other PI. Examples of dual-PI or PI-boosted regimens include the following:

- ritonavir/(fos)amprenavir
- ritonavir/atazanavir
- ritonavir/saquinavir
- ritonavir/tipranavir

Many other PIs are being studied.

Another group of drugs that is being studied is called *immune boosters*. These can help raise the level of CD4+ and other cells. An example of an immune booster is IL-2 (interleukin-2). You may also hear about "therapeutic vaccines." These are meant to be used in HIV positive people to help improve their immune system's ability to fight HIV. Many of these products are being tested in clinical trials.

The immune system is the body's defense against

disease. It defends the body from attack by foreign invaders such as bacteria, viruses, fungi and parasites, as well as cancerous cells.

Normally, the immune system can distinguish between what belongs in your body (self) and what doesn't (non-self). It is able to remember previous encounters with foreign invaders and to defend itself. For example, if you had measles or chicken pox as a child, your immune system will remember the organisms that caused these diseases, and during any future encounter should respond to them in a way that is effective in preventing you from again developing those diseases.

Outside the Body The skin is the first line of immune defense. It provides a physical barrier to keep bacteria and viruses from getting inside the body. The mucous membranes that line the body's entrances (such as the mouth, nose, rectum, vagina and penis) and passages (such as the throat and windpipe) form another barrier.

Inside the Body When disease-causing germs (also referred to as pathogens or microbes, including bacteria, viruses, parasites and fungi) get past these outer barriers, the internal part of the immune system comes into play. The immune system's job is to recognize what belongs in the body and attempt to get rid of what doesn't, or at least suppress it so it won't cause harm. The major parts of the immune system include the bone marrow, the thymus, the lymph nodes, the spleen, and the mucosal-associated lymphoid tissue (MALT), which includes the tonsils, the appendix, the Peyer's patches on the outer wall of the intestines, and the lymphoid cells in the inner part of the intestines.

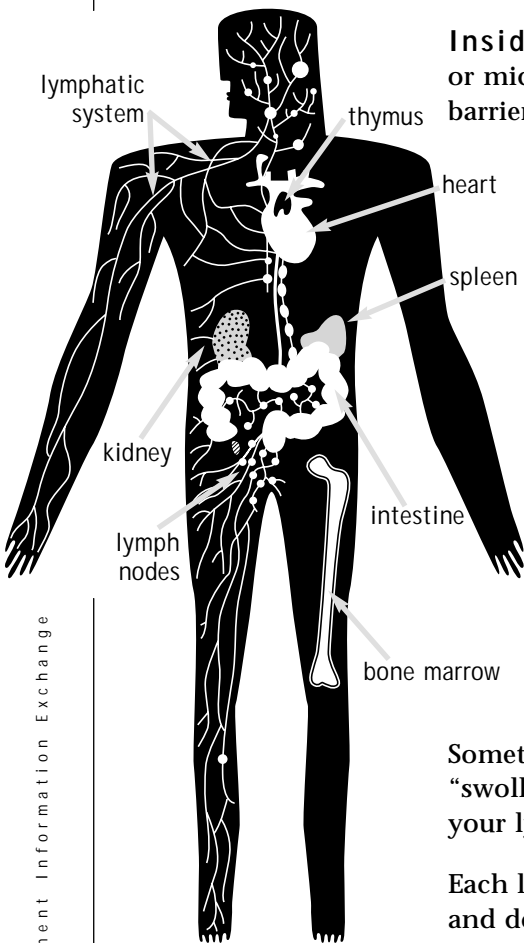
The lymphatic system is made up of vessels — just like the veins, arteries and capillaries that carry blood — that branch out into all parts of the body. Instead of blood, these vessels carry a clear, watery fluid called *lymph*. This fluid carries foreign material away from your body's cells. The lymphatic vessels pass through small bean-shaped tissues called *lymph nodes*. The lymph nodes trap, filter and destroy foreign material, including bacteria, viruses and other microbes.

There are 500 to 1,000 lymph nodes scattered throughout the body.

Large groups of lymph nodes are found in the neck, armpits and groin. Sometimes when you have an infection you can feel what people often call "swollen glands" in your neck. These are not actually glands at all, but rather your lymph nodes responding to the unwanted germs.

Each lymph node is densely packed with millions of immune cells that identify and destroy the microbes that cause disease. These infection-fighting cells are known as white blood cells or leukocytes, and they are the fundamental players in your cellular immune response. Although they are called white *blood* cells, only about 2% of these cells actually circulate in the bloodstream, with the rest found in the lymphatic system.

There are many different kinds of white blood cells, including dendritic cells, granulocytic cells (neutrophils, basophils and eosinophils), mast cells, megakaryocytes, mononuclear cells (monocytes and macrophages). The ones most affected by HIV are the *lymphocytes*.



Immune Cells You Need to Know About

Lymphocytes are very important immune cells. At any given moment, a healthy person has about one trillion lymphocytes in the body. Below is some information about key lymphocytes and macrophages, another group of cells that are strongly affected by HIV disease:

B cells are lymphocytes which make and release antibodies. These are proteins that can lock on to bacteria or viruses. When an antibody locks on to a germ, it acts as a signal for other immune cells to destroy the invader. Each B cell is programmed to make one specific antibody. For example, one B cell will make the antibody that blocks the common cold virus, while another makes an antibody that locks on to the bacteria that cause pneumonia. Antibodies are generally not useful in fighting HIV.

T cells are lymphocytes which carry out a number of different functions, depending on their type. The different T cells can be identified by proteins, called *receptors*, on their surfaces.

CD4+ cells are T cells that have a protein called CD4 on their surface (also referred to as CD4 positive or helper T cells or T4 cells). CD4+ cells lead the attack against infections. They release chemical messengers called cytokines that stimulate other immune cells to make antibodies or to destroy infected cells. CD4+ cells are sometimes compared to the quarterbacks on a football team or the conductors of an orchestra, because they direct the body's immune response.

CD8+ cells are T cells that have a protein called CD8 on their surface (also referred to as CD8 positive). CD8+ cells which recognize a specific antigen (like HIV) differentiate into what are called cytotoxic T lymphocytes (CTLs), often referred to as killer T cells (but not to be confused with natural killer cells, discussed below). These CTLs monitor the cells of the body and kill altered cells (such as virus-infected or cancerous cells) or stop them from producing HIV.

Natural killer (NK) cells are lymphocytes which kill virus-infected and cancerous cells, both in response to CD4+ cell signals and on their own, without direction from other lymphocytes. NK cells are important in the regulation of lymphocytes and other immune cells and, although they have been far less studied by AIDS researchers, may contribute substantially to the body's suppression of HIV. It is thought that they work to check the spread of infection by destroying HIV-infected cells; they also kill opportunistic virus-infected and cancerous cells.

Macrophages are a group of immune cells that perform many functions, including warning the immune system about invading microbes and helping to attack and destroy HIV-infected and cancerous cells. Macrophages can be infected with HIV, and HAART does not work well in HIV-infected macrophages. Researchers are trying to design new drugs that can work in them.

HIV and Your Immune System

In a nutshell, HIV prevents the immune system from working properly. When it infects and destroys CD4+ cells, their ability to direct the body's immune response is compromised. Although the body fights this by constantly producing new cells — up to 2 billion new CD4+ cells daily — over time the virus tends to win out, with the body becoming less and less able to suppress HIV. In addition, as the immune system becomes ever more dysfunctional, the body may become unable to control the organisms that can ultimately cause potentially fatal opportunistic infections. It may also have less ability to control the spread of cancerous cells.

Everyone experiences HIV infection differently.

However, as a general way of describing the disease process, the course of HIV infection can be looked at in four (4) stages. These stages are important because different treatment options may be considered at each stage.

primary or acute infection — the first stage of HIV infection

1. Primary Infection

The first stage of HIV infection is often called *primary* or *acute infection*. During acute HIV infection, the virus makes its way to the lymph nodes, a process which probably takes three to five days. In the lymph nodes, HIV reproduces or replicates very quickly and releases new virus into the bloodstream. This burst of rapid HIV replication usually lasts for two or three months.

Many people experience flu-like symptoms two to 12 weeks after they are first infected with HIV. These can include:

- aching joints and muscles
- fevers
- swollen lymph nodes
- sore throat
- skin rash
- fatigue

During primary infection, the amount of HIV in the body is very high and there is often a sharp drop in the number of CD4+ cells. People with acute infection usually do not test HIV positive because the body has not yet had time to produce antibodies against the virus. And it is this antibody that is detected in the standard tests to see if someone is HIV positive (see below).

During this time, the body begins to produce large numbers of CD8+ cells. These cells produce antiviral chemicals that help shut down or destroy virus-infected cells, thus helping to reduce the amount of virus in the blood (the *viral load*).

Seroconversion means that someone's blood has changed or converted from being negative for HIV antibodies to being positive for HIV antibodies.

As the immune system learns to recognize and fight HIV, B cells start to make the HIV antibodies. When an HIV test is positive, that means that HIV antibodies have been found in the blood sample. *Seroconversion* means that someone's blood has changed or converted from being negative for HIV antibodies to being positive for HIV antibodies. Seroconversion usually happens one to three months after infection.

asymptomatic — the second stage of HIV infection; someone with HIV who is *without* symptoms

2. Asymptomatic Infection

Asymptomatic means *without* symptoms. Many people with HIV may have few or no signs or symptoms of the disease for up to 10 years. However, some people may progress much faster, seeing their CD4+s decline within a few years and experiencing symptoms in the first few years after infection. And some lucky few, called *long-term non-progressors*, may continue to have normal CD4+ cell counts and no symptoms for much longer than the average.

Many factors have been found to affect the speed of disease progression, including the following:

- a person's genes;
- the strength of the virus with which someone is infected;
- the type of immune response that is produced against the virus;
- the nutrient level of the person both at the time of infection and later;
- the person's mental state and stress level (and how well that stress is handled); and
- various lifestyle factors such as smoking.

During the asymptomatic period, the only evidence of HIV infection may come from lab tests. Blood tests may show lower-than-normal numbers of CD4+ cells and moderate levels of HIV. The amount of HIV in the blood is usually called the *viral load*.

Although the immune system is able to fight HIV, it cannot get rid of the virus completely. Gradually, in most people the virus will be able to damage the immune system and they will progress to *symptomatic infection*.

symptomatic — the third stage of HIV infection; someone with HIV who has symptoms of long-term infection

3. Symptomatic Infection

As time passes, the damage to the immune system increases and the body's defenses weaken. At this stage, HIV may cause symptoms of long-term infection, such as chronic fatigue, weight loss, skin problems or diarrhea. This may occur when CD4+ cells are still at reasonable levels, or only after they have dropped to the stage officially called *AIDS*.

4. AIDS

AIDS stands for Acquired ImmunoDeficiency Syndrome.

- *Acquired* means that the condition is not inherited — you acquire (get) it at some point in your life.
- *Immunodeficiency* is a weakness in your immune system.
- *Syndrome* is a combination of symptoms and/or diseases.

An official diagnosis of AIDS in Canada is given when a person with HIV develops one or more *opportunistic infections* or certain cancers.

An official diagnosis of AIDS in Canada is given when a person with HIV develops one or more opportunistic infections (OIs) — infections that take the "opportunity" to cause disease when the immune system is weakened or damaged.

A damaged immune system can leave HIV positive people vulnerable to infections that a healthy immune system could easily control. These infections are called “opportunistic” because they take the opportunity to cause disease when the immune system is weakened. Included among the opportunistic *infections* and other conditions that are considered “AIDS-defining” are:

- bacterial infections — such as *Mycobacterium avium* complex (MAC) or tuberculosis (TB)
- fungal infections — such as *Candida* overgrowth, cryptococcal meningitis or *Pneumocystis carinii* pneumonia (PCP)
- parasitic infections — such as cryptosporidiosis (crypto) or toxoplasmosis (toxoplasma)
- viral infections — such as cytomegalovirus (CMV) or progressive multifocal leukoencephalopathy (PML)
- cancers — such as non-Hodgkin’s lymphoma (NHL), Kaposi’s sarcoma (KS), and anal and cervical cancer

A full list of AIDS-defining conditions can be found on the Web at:

For more info on specific opportunistic infections, check out CATIE’s Fact Sheets at www.catie.ca/facts.nsf or by calling 1-800-263-1638.

- Gay Men’s Health Crisis (GMHC) — list of AIDS-defining illnesses (in the “Treatment” section):
www.gmhc.org/health/treatment.html
- HIV Insite — list of infections associated with HIV (in the “AIDS Knowledgebase” section):
hivinsite.ucsf.edu/InSite.jsp?page=kb-05
- The U.S. Centers for Disease Control and Prevention (CDC) — 1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS among Adolescents and Adults (see Appendix B):
www.cdc.gov/mmwr/preview/mmwrhtml/00018871.htm

Developing any of the infections that are related to AIDS is a clear sign that the immune system is damaged and no longer able to fully protect you from invading organisms. But instead of waiting until someone becomes ill, lab tests can be used to get an idea of how well the immune system is coping with HIV infection.

The most important thing to know about the tests described below is that it is the *trend* of your test results over time that is important, not any single reading. Whether it's a CD4+ count or a viral load that concerns you, making a snap judgment or a treatment change based on any single test would be a very bad idea. At the very least, any significant change should be confirmed with a follow-up test. And always, always consider the pattern over the last few tests in your decision-making.

A complete immune panel reports many test results, as listed below (your doctor will not order all of these tests all of the time):

- I the total number of white blood cells (WBC);
- I the total number of lymphocytes (T cells, B cells and natural killer cells);
- I the number of T lymphocytes, or total T cells (marked as CD3+ on your lab results);
- I the number of CD4+ cells (marked as CD4+ on your lab results; these are mostly helper T cells, but note that although this count is usually discussed as though it refers only to them, it also includes some other cells [monocytes] that are CD4+ positive);
- I the number of CD8+ cells (marked as CD8+ on your lab results; these are the cytotoxic/suppressor T cells);
- I the ratio between CD4+ and CD8+ cells;
- I the number of B lymphocytes (marked as CD19 or CD20); and
- I the number of natural killer cells (marked as CD16 and CD56 on your lab results).

CD4+ Count

CD4+ count or T4 cell count — the single most important indicator of where you are in the course of HIV disease

After an era of emphasis on viral load when many people seemed to forget the importance of CD4+ counts, it now appears that this tried-and-true measure is probably the single most important indicator of where you are in the course of HIV disease. The general advice is to check on these cells every three to six months. However, during and after times of stress or illness — known CD4 destroyers — or at any time when the viral load seems to be rising significantly, it may be important to check them more often.

The test actually calculates the CD4+ count by multiplying the total number of white blood cells times the percentage of white blood cells that are lymphocytes times the percentage of lymphocytes that are CD4+ cells. The CD8+ count is calculated similarly.

The CD4+ count in healthy, HIV negative people has a wide range — from 400 to 1,500 CD4+ cells per cubic milliliter of blood in men, and 400 to 1,800 CD4+ cells per cubic milliliter of blood in women. There is considerable

individual variance in the average count. The lab that does your blood work has a “normal” range, which means that what is “normal” in one lab may not be “normal” in another. However, in most people, repeated test results below 500 CD4+ cells is considered abnormal and a good healthy score would usually be above that range.

It is important to point out that there is a small percentage of people who normally have lower counts and for whom “healthy normal” might be substantially below these counts. Since CD4+ cells are not normally tested until someone is discovered to be HIV positive, most people have no way of knowing what their average count was prior to being infected and, thus, how much decline there may have been prior to their first CD4+ count.

It is only with repeated tests over time that real trends in CD4+ cell count status can be identified.

This may be of comfort for those who know that their time of infection was fairly recent but who already have lower counts than would normally be seen after only a short period of infection. They may be needlessly upset by these initial counts, presuming that they’re crashing downhill faster than normal, when really their healthy normal count was just fairly low and they’re not really decreasing any more rapidly than is common.

CD4+ Percentage

The normal range for percentages of CD4+ cells is from 32% to 50%. It is important to track the changes in this percentage over time because a change of even 3 percentage points in your CD4+ cell percentage is considered significant. It is possible for your CD4+ cell percentage to drop even though your actual CD4+ cell count stays the same, due to changes in the total lymphocyte count.

Remember: The absolute CD4+ count is derived from multiplying the CD4+ percentage by the total number of lymphocytes. Thus, if the total lymphocyte number goes up and the CD4+ percentage goes down, the calculated CD4+ absolute count might stay the same. It is thought that percentages under 20% mean that you may be at risk for *Pneumocystis carinii* pneumonia (PCP), and below 15% that you are probably at risk of other opportunistic infections.

The CD4+ percentage does not vary as much as the CD4+ count does. When used in combination with the CD4+ count, the CD4+ percentage can give you a good idea of how well your immune system is fighting HIV and may better reflect your immune status when your absolute numbers fluctuate, as they tend to do.

CD8+ Count

In HIV positive people, the CD8+ count rises as these cells attempt to bring HIV infection under control. Researchers believe that the CD8+ cells are producing important protective antiviral factors. The normal range for CD8+ cells is between 375 and 1,100 cells. Some have theorized that, in general, CD8+ counts above 500–600 are a good sign, whereas counts below this range are not, and that a rapidly declining CD8+ count is an early warning that the body’s control of HIV is lessening. However, note that CD8+ cell counts usually decline a bit after people start taking potent anti-HIV therapy. This is because the amount of HIV in the blood decreases. Because less HIV is being produced, the immune system reduces the number of CD8+ cells. In addition, it is important to note that one CD8+ cell is not the same as another. There are

certain classes of CD8+ cells (in particular, CD38 positive cells) that have been seen to relate to disease progression. Especially in later disease stages, it appears that some of the increases in CD8+ cells that occur may consist, at least in part, of such cells. Thus, although, in general, an increase in CD8+ cells might be seen as a good, protective thing, there are no absolutes on this.

Interpreting Immune Cell Changes

Regardless of the initial count, it is very important to monitor any changes over time. Without treatment, the overall level of CD4+ cells declines in HIV positive people by an average of around 50 to 100 CD4+ cells each year. The lower the CD4+ count, the more damage HIV has done to your immune system. Generally speaking:

- In HIV positive people not taking treatment, a CD4+ count of about 500 cells suggests mild damage to the immune system.
- A count between 350 and 500 CD4+ cells suggest moderate damage.
- The onset of infections or other symptoms related to immune dysfunction usually occurs when the CD4+ cell count drops below 400.
- Most, but not all, opportunistic infections and conditions occur when the count goes below 200, or the CD4+ percentage falls below 20%. At this point, it is clear that the immune response is seriously compromised.
- The most common opportunistic infection that occurs in people with CD4+ counts between 100 and 200 is *Pneumocystis carinii* pneumonia (PCP).
- Many of the other serious infections, including MAC, CMV and cryptosporidiosis, most commonly occur in those with CD4+ counts under 50.

prophylaxis — treatment to prevent opportunistic infections that can occur when the immune system is weakened or damaged

Any substantial decline in CD4+ absolute count or percentage (in the neighborhood of 50 to 100 cells or more, or 3 or more percentage points) that is confirmed by follow-up testing is worrisome, and particularly so if the decline has occurred in a relatively short period of time. A drop that pushes you down to the point where you become vulnerable to infections (for example, dropping from 240 CD4+ cells to 150) would also be cause for more concern than losing the same number of cells when your counts are still relatively high (for example, dropping from 640 to 550 CD4+ cells). That person with 550 CD4+ cells still has relatively good immune function, good protection from opportunistic illnesses, and time to continue watching for trends that may indicate whether or not treatment is looking like a good idea. But the person who has dropped to 150 CD4+ cells is already vulnerable to opportunistic illness and in more pressing need of considering good treatment options, including not only HAART but also *prophylaxis* (preventive medicine) against the opportunistic infection most likely at this stage — PCP.

Because many factors — such as allergies, infections and stress — can affect immune cell counts on any given day, it is important not to become so CD4+ cell-obsessed that even a minor bouncing around causes undue worry, and to always confirm that a change is “real” with a second test. Again, in the long run, it is the trend of the count over time that is most important. It would never be wise to make decisions about treatment on the basis of a single test. And when any count seems to be out of line with previous tests, consider all the possible factors that might have affected it.

Factors that Affect Immune Cell Counts and Ways to Reduce Variation
First, both CD4+ and CD8+ counts naturally bounce around quite a bit over the course of a day. Usually, the number of CD4+ cells is lowest early in the morning and rises during the day to a high in the evening for people with normal sleep patterns. In people who work night shifts, this pattern reverses. The daily variation is less in HIV positive people than in those who are HIV negative. One study found that between 8 a.m. and 10 p.m., CD4+ counts varied by an average of 506 cells in HIV negative people, but by only 59 cells in HIV positive people. However, even that number of cells could help explain a sudden decrease if you normally have your blood drawn in the late afternoon, and this time you did it first thing in the morning.

Many other factors can affect the CD4+ count:

- | illnesses — even the common cold — can worsen the count, but it is usually a temporary decrease (vaccines can have a similar effect);
- | women's CD4+ counts rise and fall at different times during menstrual cycles;
- | oral contraceptives (birth control pills) may lower CD4+ counts slightly;
- | lack of sleep has been known to temporarily decrease counts;
- | acute stress and periods of depression can also lower CD4+ cell counts;
- | recreational drug use often results in decreased counts, especially for the next few hours, so indulging in a street drug or alcohol might cause a significant decrease;
- | corticosteroid drugs, such as prednisone, can lower counts for many weeks;
- | counts can be temporarily increased after eating or exercise or any time blood pressure is elevated;
- | smokers often have higher counts than non-smokers; and
- | different labs can get different results when they test the same sample of blood.

To help eliminate as many of these test-changing factors as possible, it is best to always try to have your tests done at the same time of day, by the same lab, and, for women, at the same time during the menstrual cycle. The easiest way to avoid some of the likely count variation is to always be tested first thing in the morning, before eating or exercising.

Ask your doctor about rescheduling your blood test, preferably waiting a couple of weeks, if:

- | you have an active infection like a cold or the flu or an outbreak of herpes
- | you've recently stopped or started smoking
- | you've been having trouble sleeping for more than a few days.

If the test can't be rescheduled, make a note of any of these problems. If your test results are unusual, your note may be able to explain them.

Viral Load

viral load — the amount of HIV in the blood

Viral load is the amount of HIV in your blood. Viral load tests measure the amount of HIV in a sample of blood. The results are reported as the number of copies of HIV RNA in a millilitre of blood (copies/ml). Viral load tests can measure as few as 20 or more than 1 million copies in the blood sample. The

standard test in most common use in Canada measures down to 50 copies, below which your virus is considered *undetectable*. The so-called ultrasensitive tests can measure down to as few as 20 copies.

undetectable — a viral load below 50 copies. An undetectable viral load does *not* mean that HIV has been wiped out. Rather, it means that the amount of HIV being produced in your body is so low that it can't accurately be counted.

It is important to note that although viral load may be “undetectable” this does not mean that HIV has been wiped out. Rather, it means that the amount of HIV being produced in your body is very low — so low that it can't accurately be counted. If you stop taking your treatment or if HIV develops resistance to your antiretroviral drugs, your viral load will once again become detectable.

In general, a high viral load is a warning signal that CD4+ cells may be heading for a decline and that the risk of disease progression is elevated. For people using antiretroviral treatment, a change in viral load test results is generally considered to be an important measure of the effectiveness of a drug cocktail. The initial goal of treatment is to reach an undetectable viral load within four to 12 weeks of beginning a HAART regimen — and to keep the reading there long-term. And, on the other end of the treatment spectrum, in someone who has previously been undetectable, an increase in viral load is an indication that the drug combination is no longer working to fully suppress the virus. If several tests confirm that your viral load is staying above detectability, and especially if it has returned to your baseline level (the viral load you had before starting treatment) or is staying above a significant threshold (20,000 to 50,000, more or less), then it may be time to discuss with your doctor why this might be happening. Factors which could cause this problem include:

- lack of adherence to your drug regimen
- malabsorption of drugs
- the inability of today's drugs to fully and permanently suppress the virus in a way that prevents resistance over the long haul

As with the CD4+ count, you can reduce some of the variation in your test results by always having your viral load test done at the same lab and at the same time of day. And ask your doctor about rescheduling the test for a couple of weeks if you have any active infection or have recently been vaccinated.

After talking to your doctor, depending on what you both think may be affecting your viral load, it may be time to consider a treatment change.

However, things are never as easy as we'd like them to be, and these generalities have many exceptions. Without any treatment at all, some people with HIV manage to coexist with a viral load of 100,000 or more for years with no apparent immune decline, as evidenced by their stable CD4+ cells. And on the other side are the less lucky in whom a viral load of a mere 10,000 to 20,000 may be enough to cause a downhill slide in immune function, with CD4+s that drop and drop. Watching the pattern of CD4+ cells over time and comparing it to viral load results is the only way to identify such people.

For those taking treatment, it is equally important to look at individual variables rather than just using some generic rule. For example, consider that 1–3 month time frame after starting HAART or changing treatment for reaching an undetectable reading. If your viral load was really high to begin with (say half a million or higher), it might take six months to reach the magical undetectable mark. For those who have been undetectable but suddenly start to see virus, especially if it's only a very low level, it is important to know that it may be just a viral “blip,” a temporary increase that seems to occur in some people, after which the virus may again disappear with no treatment change. Only repeated tests can distinguish whether the virus is really making a comeback or just briefly poking its head aboveground.

Viral load test results can vary because of changes in your body or in the test procedure. Your viral load can be affected by vaccinations (like a flu shot) or by illnesses because both of these call upon the immune system to respond, and that response activates HIV. As a result, even a cold or sinus infection could cause the viral load to temporarily increase.

Drug Resistance

One of the characteristics of retroviruses like HIV is that they often make mistakes as they make copies of themselves. These mistakes — called *mutations* — are small, subtle changes in the genetic structure of the virus. Sometimes, these mutations are harmful to the virus and make the virus unable to replicate (make new copies of itself). However, other mutations can allow the virus to replicate even when anti-HIV drugs are being used. Virus that is able to multiply when someone is taking HAART is said to be “drug resistant.” In contrast, virus that is stopped by antiretroviral drugs is said to be “sensitive” to those drugs.

The highest likelihood of the development of *drug resistance* occurs when — due to skipping doses or taking them irregularly — you end up with a small amount of drug in the body but not enough to fully suppress the virus. This lets the virus reproduce in the presence of that small amount of drug. And that’s when the virus may accidentally mutate into a form that is resistant to the drug(s) you’re taking. Then, even when you take the drugs as scheduled, that resistant virus will not be suppressed and, furthermore, it will have an advantage in reproducing itself.

The result is that the viruses that the drugs worked on will be replaced by the resistant ones. The end result is *treatment failure* — the drugs will no longer work for you. Because there are a limited number of drugs available, this will limit your future treatment options. This is particularly problematic with drugs that are *cross-resistant* — meaning that the development of resistance to one drug in a particular class results in resistance to the others in that class, too. For example, HIV that is resistant to one non-nuke, such as nevirapine, will probably be resistant to the other two non-nukes (delavirdine and efavirenz). With protease inhibitors, if there is high-level resistance to one protease inhibitor, there likely may be cross-resistance to the others.

It is very important to have a discussion with your doctor about the “all or nothing” approach in the following cases — such as when you have the flu or gastroenteritis or when you are admitted to a hospital. These situations can affect your ability to take your medications (meds) on time as noted below:

- Infections can cause you to vomit your meals, fluids or meds, and have diarrhea.
- When you are admitted to a hospital because certain tests need to be performed, you may have to fast or not eat food for prolonged periods. This can cause you to miss doses of your medications.
- You are in the middle of a difficult or very stressful period of your life.

If you just can’t eat or function properly, it may be better to temporarily completely stop taking all your drugs, in the way directed by your physician, rather than to miss several doses here and there.

drug resistance — the ability of the virus to overcome the suppressive action of the drug(s) used to treat it

drug-resistant HIV — virus that is able to multiply even when someone is taking drugs to treat it

treatment failure — the inability of a drug regimen to suppress viral load below the limit of detection, meaning that the drugs no longer work for you

cross-resistance — this happens when the development of resistance to one drug in a particular class results in resistance to the other drugs in that class too

The obvious sign that drug resistance may have developed is an increase in viral load. But in order to specifically check whether resistance is present and, if so, to which of the drugs being taken, there are two types of *resistance tests* that can be used:

- *Genotypic* tests identify specific mutations in the virus that can lead to resistance to a particular drug.
- *Phenotypic* tests measure the amount of drug it takes to inactivate a sample of virus: the more drug needed, the more resistant the virus is.

Drug resistance tests may be used with people who recently have been infected with HIV (in order to determine if they have been infected with drug-resistant virus) and, more often, for people whose drug cocktail is no longer working (to try to determine which of the drugs is failing). In both cases, the goal is to determine which drugs are most likely to be effective in fully suppressing the virus.

However, it is important to know that the usefulness of these tests is limited. The blood sample that is taken is likely to contain mostly the virus that is currently the dominant population in the body. So, you might receive test results that don't show resistance to X, Y or Z drug, but that's just because the viruses resistant to those drugs didn't end up in the sample. If you then started to take those drugs (X, Y or Z), eventually HIV would develop resistance to them. At some point in the future, your test may then detect some level of resistance to those drugs. In general, a resistance test should be able to rule drugs *out*, not in. So, you can use it to help find out what drugs are *not* likely to be working very well, but not to say with certainty which drugs will work.

The risk of developing drug resistance can be reduced by *taking all your drugs exactly as they are prescribed*. Resistance can only develop when HIV can replicate. The more the virus replicates, the more it can mutate — and the greater the chances of drug resistance developing. On the other hand, if HAART can shut down HIV replication as much as possible, it will be much less likely for mutations to occur, and drug resistance may be prevented.

Taking drugs precisely as directed is crucial for avoiding drug resistance but can be very difficult over the long haul. Even so...

- Always try to follow the instructions you were given for taking your medications (with or without food, with large amounts of liquid, a certain amount of time before or after a meal, etc.).
- Never, ever skip a dose. Don't say to yourself, "Gee, it's Saturday night and I have a date and I don't want to have gas, so I'll just skip that dose." Or "Gosh, I deserve a vacation from all this. I'll just skip taking the meds this weekend and start over on Monday." That kind of thinking will help give the virus a leg up toward replicating and mutating. The end result for you could be drugs that no longer work and, eventually, no remaining treatment possibilities.

The far better answer is to choose from among your available combinations (based on your treatment history and, if available, resistance testing results) the one that causes you the least problems. And then consider all the strategies discussed in CATIE's *Practical Guide to HIV Drug Side Effects* to manage any remaining side effects.

t r e a t i n g H I V

before, during and after starting drug treatment

For a complete discussion of nutrient approaches to side effects, see CATIE's *Practical Guide to HIV Drug Side Effects*. For much more complete info on the nutrient aspects of HIV disease, see CATIE's *Practical Guide to Nutrition*; both are available at www.catie.ca. Also check out CATIE's Supplement Sheets at www.catie.ca or by calling 1.800.263.1638.

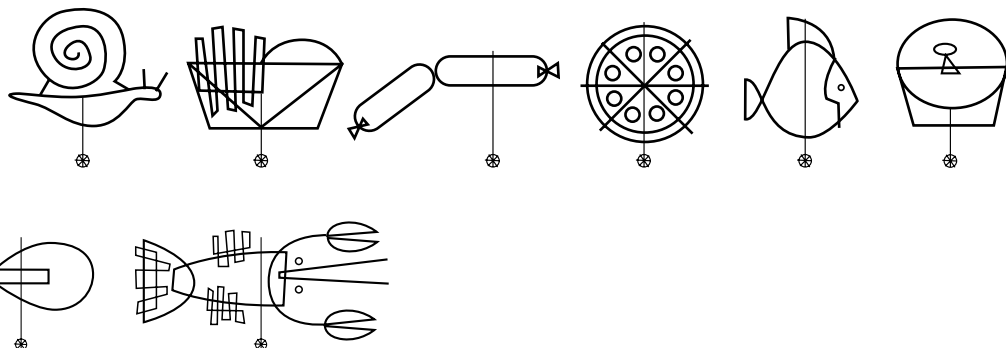
The body's basic elements of health: When most people discuss HIV treatment, they're talking about antiretroviral drugs and all the issues related to their use. However, before we move on to a discussion of HAART, it is very important to know that there are things other than medicines that all PHAs should include in their disease management plan for the best possible results. All of these things should be part of a lifelong plan for living with HIV, whether you are currently on drug therapy or not.

Good Nutrition

First, address the nutrient problems of this disease. There is substantial research showing that multiple nutrient deficiencies begin early in HIV disease — even when CD4+ counts are still high — and that these deficiencies can both speed disease progression and cause many symptoms. Since virtually every known nutrient contributes to some aspect of the immune response, doing everything necessary to maintain optimal levels of nutrients is crucial for managing this disease.

So what does that mean in practical terms? First, eat what's good for you. This means consuming a balanced diet with a variety of foods. This includes:

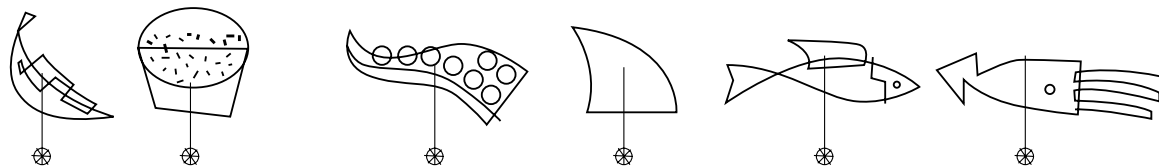
- good levels of protein;
- good levels of mostly unrefined complex carbohydrates (brown rice instead of white; whole grain breads, crackers, cookies and pasta instead of those made with nutrient-poor white flour);
- lots of fresh fruits and vegetables;
- moderate amounts of only the good kinds of fats (use only natural fats and mostly the monounsaturated fats like olive oil; avoid the partially hydrogenated oils — also referred to as “trans” fats — widely found in margarines, shortenings and many baked goods, fried foods and snack foods; read the labels!);
- lots of healthful liquids (water, juices, herbal teas and the like; not chemical and sugar-loaded junk drinks); and
- always make sure the food you eat and the water you drink is safe!



For more info on exercise, see *Built To Survive*, a guide to surviving and thriving with HIV by building well-being, improving lean body mass and increasing your overall health.

It covers lifestyle changes, hormonal therapies and nutrition and dietary supplements, and includes a simple guide to productive exercising.

Available at www.medibolics.com.



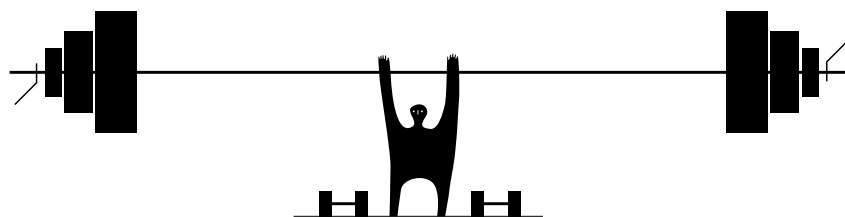
Second, take appropriate nutrient supplements to help ensure that you will always have in your body optimal nutrient levels for slowing disease progression, improving long-term survival, and reducing or eliminating many drug side effects and other symptoms such as fatigue, skin problems, diarrhea, neuropathy, digestive problems, wasting, memory or other mental problems, and others. Start with a high-potency multivitamin/mineral formula that provides not only optimal levels of the basic micronutrients (like vitamin A, B vitamins, vitamin D, minerals and trace minerals), but also especially potent levels of all the antioxidants (such as vitamin E, vitamin C, alpha-lipoic acid, N-acetyl-cysteine, selenium, carotenoids, coenzyme Q₁₀, etc.) that are so crucial for immune system support and body protection.

Hormone Replacement

For all HIV positive people — men and women — it is very important to monitor hormone levels and, when deficiencies are found, to do appropriate hormone replacement therapy. Too-low levels of testosterone are common, and appropriate replacement using the through-the-skin approaches (patches for men, and creams or gels for men or women) that will best achieve normal levels will have many benefits, including maintenance of muscle mass and organ tissue (crucial for long-term survival), as well as restoration of normal sex drive. For women, testing and appropriate replacement of female hormones may also improve overall health and prevent worsening of PMS, perimenopausal or menopausal symptoms. You should note that there are side effects from using these hormones so, as with all medications, discuss the pros and cons with your doctor.

Exercise

Appropriate moderate exercise that combines aerobics (walking, rowing, swimming, running, skating, and all the other heart-pumping exercises) and weight training (the muscle-building exercises like weight lifting that create plenty of the lean tissue you need for survival) is terribly important for all PHAs. It can contribute to both the physical maintenance of the body and to mental well-being. Yoga is another such form of exercise.



For more info on other tools to add to your healing repertoire, see *CATIE's Practical Guide to Complementary Therapies*, available at www.catie.ca.

Program the Mind Toward Healing

The power of the mind to boost the body toward healing is amazing. And the power of hope is one of the best tools you can have for long-term survival. Studies have shown speedier disease progression in those with negative attitudes toward the disease and in those with higher levels of stress. Anything that helps lower stress and create feelings of hope and a positive outlook — including yoga, meditation, positive thinking, affirmations, massage, support groups and absolutely anything else that helps you thrive — can be a powerful tool to add to your healing repertoire.

Last, but definitely not least, we come to the use of antiretroviral therapy. Although even the best HAART combinations cannot cure HIV infection, they can usually help to control the virus, promote significant immune restoration, and slow or even reverse disease progression. When successful treatment combinations can be found, the immune decline that might otherwise continue is often stopped and usually restored to levels that are sufficient to prevent opportunistic infections and otherwise restore good health. However, growing concerns about the long-term toxicity of the drugs and the difficulty of continuing over the long haul to take them perfectly as directed — the absolute requirement for preventing resistance — has made decisions about which therapy to use — and when to begin it, change it, interrupt it, or stop it — ever more difficult.

There are no hard-and-fast rules about beginning HAART.

Deciding when to start drug treatment can be one of the most difficult choices to make. There are no hard-and-fast rules about beginning HAART. When triple-drug cocktails first became widely available in 1996, many experts recommended starting treatment as soon as possible. Their slogan was “hit early, hit hard.” The idea was to use these powerful drugs to protect and preserve the immune system as much as possible. Since that time, expert opinion on starting HIV treatment has been modified to reflect new information about long-term side effects and drug resistance. We might call the new viewpoint “hit later, hit carefully.”

In an attempt to provide guidance, groups of experts from around the world meet regularly and make recommendations for using HIV treatment. These guidelines change as research gives us new insight into HIV. The treatment guidelines are long, complex documents and different expert groups have slightly different opinions. However, their recommendations can be summarized for people considering starting treatment at the various stages of HIV infection:

- I During primary (acute) infection. The idea behind starting treatment at this stage is to protect and preserve the highest level of immune function, and perhaps create a lifelong tendency toward a lower viral load due to the body’s improved ability to control the virus. The benefits to starting treatment at this stage are mostly *theoretical* as there have been only a very few studies of people who have started this early in their infection. However, there is some evidence from the research done so far that this very early use of antiretrovirals for a period of time (and it does not have to be lifelong, although the exact length of the treatment period varies depending on the researcher you listen to) may, indeed, help preserve immune function. It will take considerably more research to know the long-term effectiveness and safety of such approaches.

- During asymptomatic infection when the CD4+ count is between 200 and 500. Some doctors and PHAs prefer to delay treatment at this stage, while others will begin it. The precise point at which physicians will usually urge that treatment be started will vary from doctor to doctor, but it is most often based on their assessment of some combination of:
 - CD4+ count
 - viral load
 - whether or not you have symptoms of HIV-related problems
 - your readiness and ability to handle HAART

You are an important factor in the decision about when to start treatment. Discuss your feelings and situation with your doctor.

Doctors who generally delay starting treatment usually do more frequent testing of viral load and CD4+ counts to watch for new trends. When thinking about treatment at this stage, changes in the CD4+ count are probably more important than viral load (see “Interpreting Immune Cell Changes” section). Most experts would recommend that treatment be delayed if your CD4+ count is greater than 350 cells, particularly if your viral load is fewer than 55,000 copies and you are feeling fine. Some experts suggest treatment for people whose CD4+ counts are between 200 and 350 cells, depending on several factors as outlined in the bullets above.

- During symptomatic infection or when the CD4+ count drops below 200. People who have had an AIDS-defining illness or who have symptoms of long-term infection will still benefit from starting HAART. Even if the immune system has been severely damaged, it can usually rebuild itself substantially.

If you have Internet access, you can review the most recent HIV/AIDS treatment guidelines at these websites:

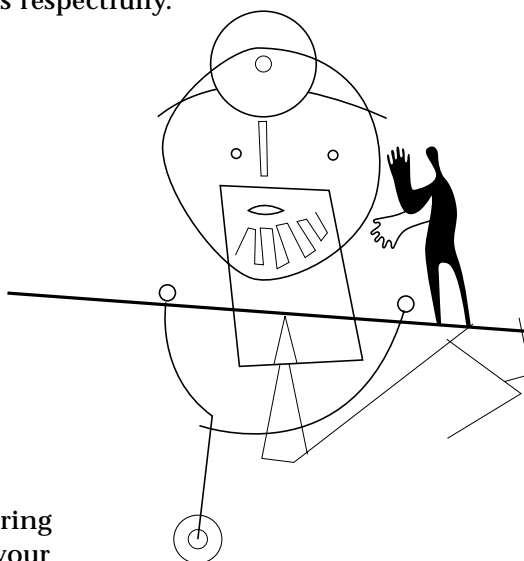
- British Columbia Centre for Excellence in HIV/AIDS — Therapeutic Guidelines for HIV/AIDS and Related Conditions:
<http://www.cfenet.ubc.ca>
- the British HIV Association:
<http://www.bhiva.org>
- the International AIDS Society-USA:
www.iasusa.org/pub/index.html
- the U.S. Department of Health and Human Services:
www.aidsinfo.nih.gov

Now that we've sent you to look at the guidelines, we must strongly state that such documents are written about the "average" patient. With so many individual variables, they are no substitute for good medical judgment. And that makes your choice of doctor — and your relationship with that doctor — of paramount importance. Ideally, you will want to choose a doctor who is very experienced in treating HIV disease and who takes the time to keep up to date on all the latest information. Studies have clearly shown that doctors' levels of experience affect their patients' chances for survival. Feel free to interview any doctor you're considering and ask all the questions that are important to you. You definitely want a doctor with whom you feel comfortable and are able to talk freely, and one who will answer your questions respectfully.

A doctor who has many HIV positive patients and much experience in dealing with their problems — and who keeps up to date on the latest therapy breakthroughs — will be better able to treat you than someone with little experience in the area.

After you find the doctor who seems to be the best choice, remember to keep the communications lines open. Here are some suggestions for working with your doctor:

- Always write down questions as they occur to you and bring them with you to your medical appointments.
- Never think that any question is stupid. If there is something you don't understand, you should ask. If part of your confusion stems from the fact that the doctor has slipped into Med-Speak, then by all means ask her or him to spell things out in layperson's terms. At each point, if something confuses you, say that you don't understand and ask for clarification.
- At any time when recommendations are made for this or that therapy, ask for clear explanations of why it's being recommended, exactly what it will entail, what any possible side effects might be, and so on. This will almost certainly work best if you can ask for all this in a way that leaves the doctor feeling that you are just politely asking for full information on anything that's being recommended to you, rather than being hostile.
- Because the amount of information may sometimes seem overwhelming, bringing a tape recorder along may be useful. Most doctors don't object to that and you may find that they'll be even more thorough if you're taping the conversation. Or, you may want to bring along a family member, partner or friend.



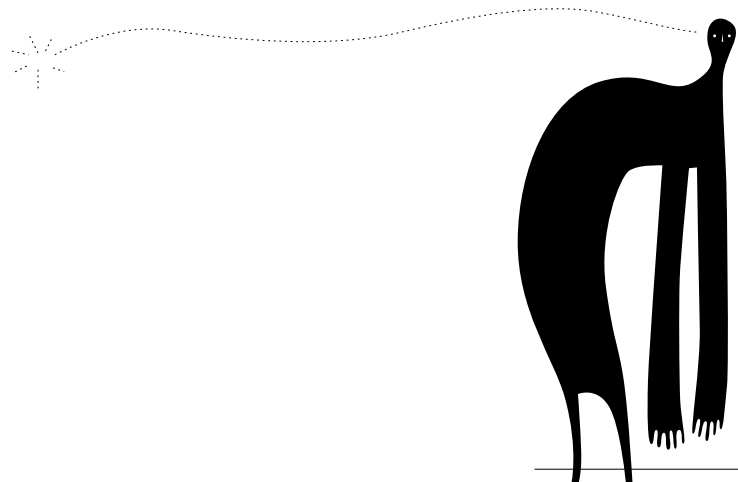
Once you've found a good doctor, but before

starting treatment, there are many issues — both medical and non-medical — that you may want to consider. By taking the time to think about these before you swallow the first dose of your HAART medication, you may greatly increase your chances that the drugs will continue to work well for you over time and that you will be able to live well while taking them.

- **Check your CD4+ count and your viral load.** Don't ever make a decision based on the results of a single test; instead, always watch for trends. Review your previous test results with your doctor. Have your test results stayed about the same? Have your CD4+ cells significantly dropped over the past year? Has your viral load significantly gone up?
- **Assess your general health.** Have you had symptoms of long-term infection, such as chronic fatigue, weight loss, skin problems or diarrhea? Have you had infections that keep coming back even though you've taken treatment? Have you had an AIDS-related illness, such as PCP?
- **Do you have other health conditions that could complicate your HIV treatment?** For example, hepatitis causes liver damage that could be made worse by some drugs. Depression, anxiety, or alcohol or recreational drug use can sometimes affect your ability to stick to a strict medication schedule.
- **How do you feel about taking medication on an absolutely precise and regular schedule?** Are you able to make that commitment? The drugs only work when you take them. To keep your drug cocktail working, you must be able to very consistently stick to the schedule. Skipping doses can lead to drug resistance that will cause treatment failure (see "Drug Resistance" section), so you must be ready to make a firm commitment to taking the drugs precisely as directed in order to avoid this.
- **What are your own feelings about anti-HIV drugs?** Some people have strong feelings of skepticism or fear about taking them. It is very important to discuss such feelings with your doctor and work through them before beginning to take medication. If you're looking at each pill thinking "Ewww, it's a poison," the result is not likely to enhance your ability to stick to a regimen and may create immune-damaging stress.
- **Have you taken the time to understand all aspects of the treatment regimens you are considering and to think carefully about how each will affect you?** Taking medication daily will have an effect — and sometimes a very dramatic one — on your life and your lifestyle. While most drugs can be taken with food, a couple of them must be taken on an empty stomach. Some drugs are taken only once a day, while others must be taken two or three times a day. Is your life fairly structured, and do you enjoy keeping to a routine every day? If so, then a drug cocktail that requires three doses per day might work well for you. If your lifestyle is more unpredictable or your schedule often erratic, then a cocktail that you take once or twice a day with meals may suit you better.

- I Don't forget about work or social situations. Is your HIV status unknown to your coworkers or friends or those who share your living space? Is that a huge concern to you? If so, you will have to decide if you are willing to begin a demanding drug regimen despite concerns in this area. Once you have decided to do so, you should also consider whether some regimens may be preferable to others in this regard. For example, you may prefer a regimen that allows for less frequent dosing or fewer pills as a way to help ensure that your pill-popping remains a private affair. You may also need to strongly consider likely side effects. Let's be blunt: If diarrhea or stinky gas is a common effect of one or more of the drugs you're considering, you'll have to look at your work and home situations to see if such things are likely to be noticed. Although there is much that can be done to address many of the drug side effects (see CATIE's *Practical Guide to HIV Drug Side Effects*), there are no guarantees that you will be able to eliminate all of them, and the likelihood is that one or more of the effects might cause you problems that are noticeable to others.
- I There are other important reasons to consider possible drug side effects of both the short- and long-term variety. Not everyone will have much in the way of side effects, and for some they may be mild or barely noticeable. However, for many others, side effects may be much more severe and may interfere with daily life. You should consider practical realities. If reaching your workplace requires a long commute with no possibility of bathroom stops, medications that cause diarrhea might be particularly difficult for you. If your job requires long hours on your feet, neuropathy might be harder for you than for someone who can sit down on the job. In general, it is crucial to learn as much as you can about side effects and how to cope with them before starting treatment. As discussed in CATIE's *Practical Guide to HIV Drug Side Effects*, there may be nutritional and other remedies that may help prevent side effects or at least greatly lessen their severity.

By considering these issues before starting treatment, you will give yourself the best chance of living *well* with HIV, not just longer.



choosing treatment: with what

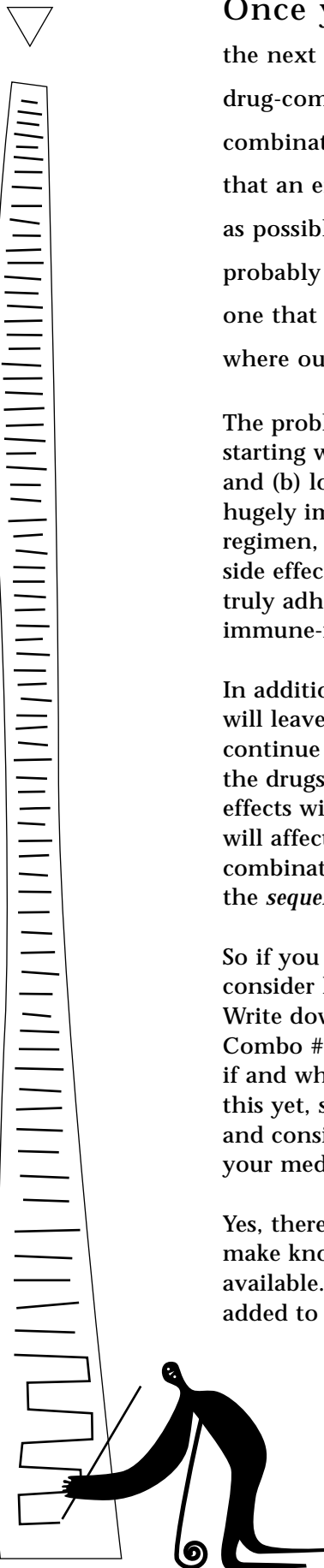
Once you have made the decision to start treatment, the next challenge is choosing the drugs in the combination. Despite any drug-company-generated hype you may have read, there is no single best combination of drugs and no best starting combination. We can all agree that an effective combination is one that will drop your viral load as low as possible and raise your CD4+ count as high as possible. And we could probably get most people to agree that, for you, the best combination is one that meets those goals but also works for you and your lifestyle. That's where our consensus will most likely end.

The problem is that there is no clear-cut, long-term data that proves that starting with X, Y and Z drugs gives you: (a) the best chance for initial success, and (b) lots of remaining treatment choices down the line. And both are hugely important. Since most people have their best response to their first regimen, it is obviously important to choose one that has proven potency, side effects that you can tolerate, and a dosing schedule that you can really, truly adhere to. This will give you the best possible chance for getting the immune-restoring benefits that any first regimen should aim for.

In addition, you want to strongly consider whether this first combination will leave you with many future options. Sadly, you're not likely to be able to continue with the same regimen forever. Eventually, there is a possibility that the drugs may fail (due to resistance or other problems) or that long-term side effects will become too difficult. Each choice you make with your first regimen will affect what treatment choices will be available to you when this initial combination fails. This concern means that you need to strongly consider the *sequencing* of your drug combinations.

So if you haven't already started treatment, before you even start Combo #1, consider how it will affect your possible downstream treatment choices. Write down a plan that considers which options will be available to you for Combo #2 when #1 goes by the wayside, and for Combos 3, 4, 5 and so on if and when you need them. If you're already on HAART and haven't done this yet, start now to plan as carefully as possible. Pick up that pen and paper and consider where you've been and what is still available to you, based on your medication history.

Yes, there may be future options that are not even known yet, but you need to make knowledgeable decisions *now*, based on everything currently known and available. Later, you can revise this plan as more is known and future drugs are added to the list of possibilities. For now, your choices are fundamentally these:



For details on the ways in which the different HIV drugs work, see “Viral Life Cycle” section; for drug names and manufacturers, see “Appendix A, Antiretroviral Drugs.”

For more info on specific HIV drugs, check out CATIE’s Fact Sheets at www.catie.ca/facts.nsf or by calling 1-800-263-1638.

A protease inhibitor–based regimen

Most commonly, this will mean a combination of one protease inhibitor (PI) with two drugs from the earliest class of anti-HIV drugs, the nucleoside analogue reverse transcriptase inhibitors (nukes or NRTIs). Other possibilities that some have used successfully include the use of two PIs with either a single nuke or a single non-nuke (NNRTI,) or two PIs and two nukes.

The one-PI/two-nuke combination is the oldest version of HAART, and thus the one for which we have the best long-term data. Prior to the development of PIs most people were already on two nukes. When this new class became available (and it became clear that PIs would lead to quick development of drug resistance when used alone), the PI was just added to what was already being taken. This approach has a long track record of successful use, and its power as a treatment combination is well proven. However, currently available PIs have many possible side effects.

If you find the prospect of certain side effects particularly troubling or you have difficulty with scheduling and food issues or large numbers of pills, you might want to consider one of the other possible regimens. Alternately, you can also consider PI-boosting. This involves the use of ritonavir (Norvir) taken in low doses (usually 100–200 mg) with another protease inhibitor in order to slow down the breakdown of the other PI in the liver, and thus increase its level in the bloodstream to make it more effective. Ritonavir has this effect because it inhibits certain liver enzymes. This ritonavir/2nd PI combo often reduces dosing frequency and the total number of pills that need to be taken, and sometimes eliminates certain food requirements, making PI-based regimens more user-friendly. However, it does not usually eliminate side effects.

A protease-sparing regimen

The most common of these regimens uses a combination of a non-nuke with two nukes (just as in the PI-based combo, but substituting a non-nuke for the PI). When protease-sparing regimens have been compared to PI-based regimens in clinical trials, they have generally appeared to be similar in their effectiveness. These regimens may require fewer pills. And they will, indeed, eliminate some of the troubling PI-caused side effects; but use of non-nukes can cause a different set of side effects in some people.

A two-class-sparing all-nukes regimen

This approach uses all nukes all the time, most commonly Glaxo’s Trizivir (AZT/3TC/abacavir). This only requires a single pill taken twice daily, so it makes sticking to your treatment schedule easier. And it will eliminate the side effects that are only likely with PIs or non-nukes; but, of course, nukes have side effects of their own. However, current guidelines do not recommend this approach as a preferred regimen for initial therapy.

rescue or salvage therapy — treatment used when a person no longer responds to most available drugs, which involves the use of drugs from all three classes of antiretrovirals

The kitchen-sink regimen

Seldom used for initial treatment unless the patient absolutely demands it, but more common for those seeking *rescue* or *salvage therapy* when multiple earlier regimens have failed, this involves the use of drugs from all three classes — often one or two PIs combined with one or two nukes and a non-nuke. The obvious idea is high potency combined with hitting the virus in three different ways, with the hope that this will make it much more difficult for the virus to effectively mutate to become drug resistant. But even if this approach worked perfectly in these ways, it would have the strong disadvantage of a much higher likelihood of drug toxicity and side effects — not to mention all those pills.

And last, but definitely not least, there is the possibility of using up all three currently available classes of drugs. If resistance to such an approach develops, there could be no place left to look for another combination until whole new classes of drugs become readily available or at least until drugs within the current classes that are not cross-resistant are developed.

A kinder, simpler regimen: once-daily therapy

The complexity of most of the earlier generation HAART regimens — especially the requirement to take large numbers of pills several times per day and schedule them perfectly, often with stringent dietary restrictions — has led to increasing interest in the possibility of simplifying regimens. There are now several approaches that would allow all the medications to be taken in just one or two doses daily. Both research and many reports from clinicians seem to indicate that such approaches greatly increase the likelihood of adherence, and thus of long-term drug effectiveness. And, for obvious reasons, most PHAs greatly prefer these simplified regimens.

However, there are significant potential drawbacks that should be considered. If drugs are only being taken once a day, skipping even one dose means that for quite a lengthy period there will be suboptimal (inadequate) amounts of the drug in the bloodstream, increasing the chance of developing drug resistance. Overall, this means that although adherence to such drugs will be easier — you only have to remember to take them at one particular time every day — you will need to be absolutely consistent in always taking that one dose. In addition, if the goal is having only one time every day when drugs are taken, your options will be limited to drugs that can be taken at the same time (some drugs have interactions that require them to be taken at different times) and with the same food requirements (with food or on an empty stomach). This will somewhat limit your treatment possibilities.

Below is a list of several drugs that are options for once-daily therapy; note that not all of these drugs may be covered in your province or territory:

- efavirenz (Sustiva) — a non-nuke which is taken either as three 200-mg tablets, or one 600-mg capsule, usually at bedtime; and
- a delayed-release formulation of ddl (didanosine, Videx EC) — a nuke which is taken as one 400-mg capsule, either one hour before or two hours after a meal to improve absorption.

For more information on specific HIV drugs, check out CATIE's Fact Sheets at www.catie.ca or by calling 1.800.263.1638.

- 3TC (lamivudine, Epivir) — a nuke now approved for dosing at 150 mg twice daily or 300 mg once per day;
- ABC (abacavir, Ziagen) — a nuke currently approved for dosing at 300 mg twice daily; researchers are testing 600 mg once daily;
- tenofovir (Viread) — a nucleotide reverse transcriptase inhibitor taken in a dose of one 300-mg tablet, once daily with food;
- atazanavir (BMS-232632, Reyataz) — a protease inhibitor, taken once daily with food;
- FTC (emtricitabine, Emtriva) — a nuke taken once daily.

Any of these once-daily drugs must, of course, still be taken with other drugs to create an effective combination. Thus, in order to create a truly once-daily regimen, it will be necessary to choose workable combinations from these once-daily candidates.

When choosing the drugs that will make up your HAART combination, it will be very important to look at the possibility of drug interactions. Interactions can occur when one medication affects how another is absorbed, broken down (metabolized), distributed or flushed out of the body. This can work either well or badly.

Here is an example of a combination that works well: Ritonavir (Norvir), a protease inhibitor (PI), tends to slow down (inhibit) the breakdown of certain other protease inhibitors in the liver, boosting their levels in the blood. The effect of a boosted-PI regimen is a positive one, with some of the following advantages:

- Ritonavir raises levels of the boosted PI to higher than normal, resulting in an increase in anti-HIV activity.
- Ritonavir also prolongs the time that the boosted PI remains in the blood, resulting in a twice- or even once-daily regimen.

The opposite effect can also happen. One drug may speed up the breakdown of another, with the result being that the second drug's effectiveness is diminished, often leading to the development of viral resistance to that drug.

Interactions can also change the effect that drugs have, sometimes worsening them. For example, if two drugs both have a tendency to cause the same type of toxicity, using them together may greatly increase the chances that a serious side effect will occur. For example, the nucleoside analogue “d” drugs — ddC, ddI and d4T — are all likely to cause neuropathy. Combining them makes the risk much higher, something to bear in mind if any of these drugs are used together.

It is important to always check for interactions between *all* the drugs that you are taking, not just the antiretrovirals. With so many different medications being used for antiretroviral therapy *and* for treatment or prevention of opportunistic infections *and* for treatment of drug side effects or other symptoms, the chances for interactions seem to increase all the time. And, as though that's not complicated enough, interactions can occur not only among prescription medications but also between a medication and an over-the-counter agent, an herb, a food, or a recreational drug.

Drug interactions may not always be obvious. They can take various forms, with some occurring immediately after you first combine the drugs, and others not causing any noticeable problem for weeks or longer. In some cases, there are drugs which absolutely cannot be used together. In other cases, it may be possible to use certain drugs together as long as certain adjustments (timing of when they're taken, dosages, etc.) are made.

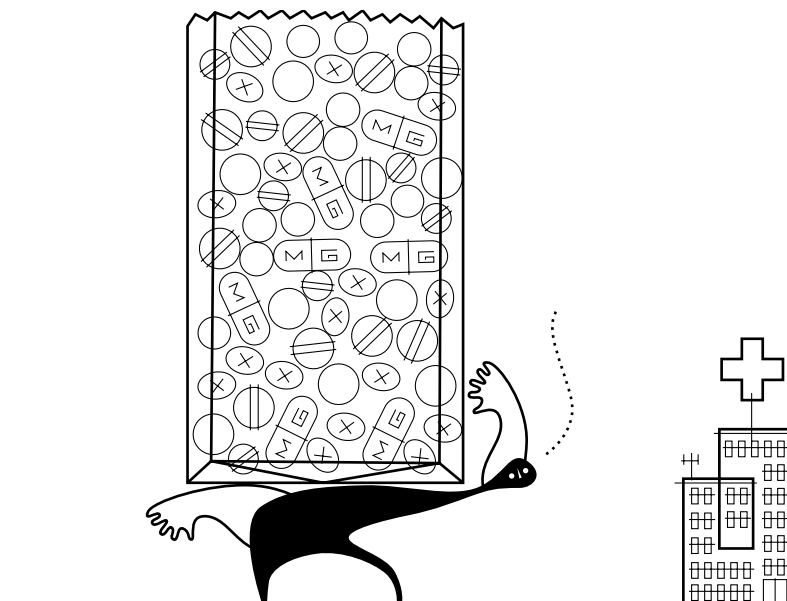
Drug interactions

can occur not only among prescription medications, but also between a med and an over-the-counter agent, an herb, a food, or a recreational drug.

There are no perfect ways to prevent all possible drug interactions because we don't have perfect knowledge on this. Most studies have only looked at the interactions between two drugs at a time, and many people are taking far more than that. Adding in the possibility of interactions between multiple drugs and foods and herbs and, well, we think you get the picture. There may always be some risk that an interaction won't be predicted.

However, there are several steps you can take to try to ensure that it is safe to combine all the things you're taking:

- First and foremost, make sure that your doctor is aware of every single thing you're taking — whether it's a prescription drug, an over-the-counter therapy, an herb, a nutrient or anything else. The simplest way to do this is to do a "brown bag" checkup — each time you see your doctor, put all your medications, including over-the-counter and complementary products, in a bag and have him or her conduct a personalized review of your medicine for safety, appropriateness, compatibility and instructions for use. If you know your medical visits are often too rushed for this, be sure to request the extra time when you make your appointment. You can do the same kind of visit with your pharmacist, who may, in some cases, be better informed of all the latest news on drug interactions than other health care providers. And many pharmacies now have computerized drug interaction programs that will warn of any interactions if they have a complete list of all agents being taken.
- Second, every time you are prescribed a new medication, or decide that you wish to add an herb or an over-the-counter agent of any kind to the list of things you're taking, discuss with your doctor whether it can be combined safely with your other therapies. And don't count on your doctor knowing your whole history by heart. That chart may be five inches thick, and your doctor may have seen 400 patients since your last visit. So remind her or him of your brown-bag list.
- Third, you can do some checking on your own with a great website resource available at www.aidsmeds.com. At this site, click on "Check Your Meds." It will allow you to enter all your drugs plus nutrients plus herbs plus various foods (like garlic or grapefruit, both known causes of certain interactions), and then give you information on all the possible interactions known between all these things. It is a great resource.

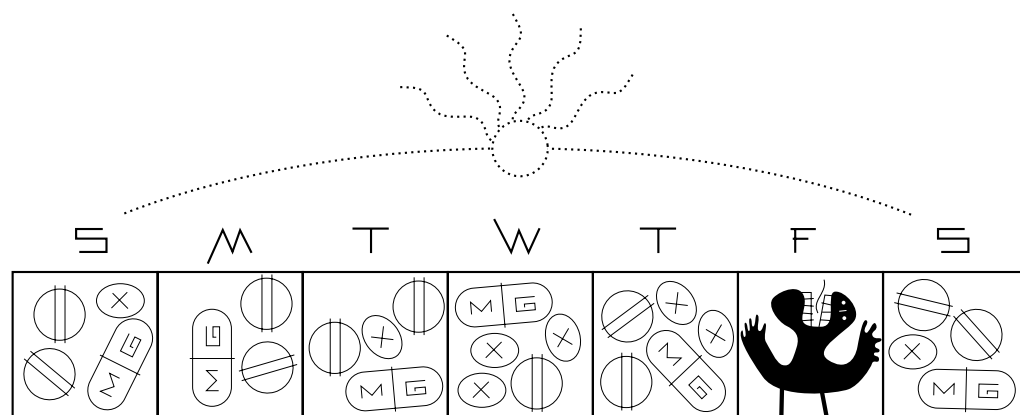


continuing treatment: making it work long-term

adherence — sticking to the pill-taking schedule and taking your drugs exactly as prescribed and directed; also sometimes called **compliance**

drug level — the amount of drug in your blood after it is taken. Too low drug levels can allow the virus to replicate, which could cause drug resistance; too high drug levels can increase the risk of side effects and toxicity.

Regardless of the particular drugs you choose for your cocktail, there is one important rule to remember: Your drugs will only work when you take them. Duh, you say, but remembering to take your pills at the right times every day isn't always easy. And sticking to the pill-taking schedule (also known as *adhering* or *complying*) is very important because these drugs get broken down and removed from the blood very quickly. The pill-popping schedule makes sure that the amount of the drug in your blood stays above the level required to suppress the virus. Missing even one dose means the *drug levels* can drop too low to control the virus. HIV replicates rapidly, and low drug levels can allow it to make many thousands of copies that will go on to infect new cells. Even more important, those low drug levels can allow for the development of drug resistance. In order to get the most out of your cocktail — and avoid drug resistance — you must take all of your pills as scheduled and directed. Even missing a dose or two per week could sabotage your long-term success in using these drugs.



Your doctor and pharmacist may have practical tips to help improve your adherence to your regimen, so be sure to discuss this with them before starting your pills. Here are possibilities that some have found useful:

- Many doctors and pharmacists recommend practicing with candy (Smarties or jellybeans) or mints for a couple of weeks before starting the real drug cocktail. Choose one practice pill for each drug you'll be taking and follow the schedule you'll need for the real drugs.
- Divide your pills into appropriate doses for each day (and each time of day) at the beginning of the week. Use plastic pill boxes (sometimes called "dosettes") with separate compartments for storing the pills. Or use small plastic baggies that can be marked for this. This advance preparation can save time opening multiple bottles every day and ensure that there's a pre-prepared dose ready to take with you any time you're in a rush to leave the house.

- ▮ Before starting a new regimen, consider all aspects of what it will require in order to ensure that it fits your lifestyle.
- ▮ Wear a watch with an alarm or carry a small medication “beeper” (talk to your pharmacist about getting one) to remind you when to take your next dose.
- ▮ Keep your medications where you can clearly see them — in the bathroom, near your bed, near the TV, or any other place that you will be likely to see them and remember to take them on time.
- ▮ Keep a supply of medication at places you frequently visit — family or friend’s house, work, a clinic, etc. Ask your nurse or pharmacist for directions on how to store your pills — some may need to be refrigerated. Be sure to check the expiry date on the bottles from time to time.

If all the tricks in the world don’t keep you on schedule with the drugs in your current cocktail, you may need to consider changing it. In order to choose a new regimen that may work better, it will be very important for you to honestly consider what kept you from sticking to your current approach. For example, if you were supposed to take your drugs three times a day but found that your busy mid-day schedule meant that you would often miss your second dose, you might want to consider switching to a simpler, once- or twice-a-day regimen (see discussion in “A kinder, simpler regimen: once-daily therapy”). If the fact that you often experienced smelly gas or diarrhea or any other side effect that you found particularly problematic after taking a particular drug caused you to skip doses when you were going to a meeting or out on a date, you might want to consider substituting a drug less likely to cause that problem.

Before you use up more drug options by switching at the first sign of side effects, do consider all the possibilities for eliminating the problematic symptoms discussed in CATIE’s *Practical Guide to HIV Drug Side Effects*.

Even with careful planning and sticking to the schedule perfectly, you may have to change your drug cocktail. Sometimes the combination doesn't work to control HIV. At other times, it just doesn't work for you.

As discussed previously, monitoring viral load is the best way to know whether your current drug combination is successful in maintaining viral suppression (for a full discussion on interpreting viral load results, see “Viral Load” section). Any time you plan on starting therapy or making a change, it will be important to make advance appointments with your doctor so that viral load tests can be done at the appropriate intervals. You don't want to be two days away from the time your next blood draw should be performed when you discover that your doctor has no openings for several weeks. Carefully discuss this issue with your doctor before any changes are made and get those appointments on the books.

If viral load results point to treatment failure, it will be time to talk to your doctor about changing your drug combination. It's a good idea to explore with your doctor why your treatment did not work. If you still have plenty of treatment options, a whole new combination of drugs you've never used before is probably best. That's what is most likely to give you powerfully effective viral suppression. If you are among the many with much more limited options because of extensive previous drug use, consider doing resistance testing to check the possibility that only one of your drugs is actually failing. If this is the case, it might be possible to just find a substitute for the medicine that is no longer working. Another possibility for those experiencing drug failure with their standard three-drug regimen is the “kitchen-sink” approach, discussed previously.

If the problem with your drug regimen is not viral control failure but rather side effects, it is terribly important to discuss with your doctor ideas about obtaining therapy that might help counter them. Consider the possible remedies for the most common side effects that are discussed in CATIE's *Practical Guide to HIV Drug Side Effects*, and then talk with your doctor and perhaps see a naturopathic doctor or nutritionist. By implementing an integrated approach to HIV — combining the best available drugs with the remedies that help eliminate side effects and other symptoms — you give yourself the best long-term chance for happily staying on your drugs, instead of miserably. This will mean that you can gain all the benefits that drug therapy can offer, while eliminating the problems that might have sabotaged your ability to adhere to the drugs and compromised your quality of life. If all the possible remedies fail to eliminate side effects that you find unbearable, then it will be time to discuss with your doctor changing your cocktail to one that you may find more tolerable.

Until the recent past, HAART was generally considered to be a lifelong necessity. However, there is now considerable research looking at the consequences of interrupting treatment for varying lengths of time and in varying ways.

- Structured treatment interruption (STI) is a term used to describe an approach in which HIV treatment is stopped, with your doctor's support and guidance, for a planned period of time or until certain pre-planned milestones (often, an increase to a certain level of viral load) are reached, after which treatment is restarted.
- Structured intermittent therapy (SIT, also called "pulsed therapy") is a slight variation of an STI, in which therapy occurs in pre-planned intervals, with breaks in between each treatment period.

You may also hear people refer to "drug holidays," which may be their name for an STI or SIT, or may just mean that they take occasional unstructured breaks. The latter is definitely not a good idea.

Unfortunately, treatment interruptions may cause serious problems, such as the development of drug resistance limiting future treatment options, and, in some cases, the development of life-threatening complications. Researchers strongly recommend that treatment interruption only be done within the setting of supervised clinical research, not on your own at home.

An effective HAART cocktail can almost completely shut down HIV replication. With medication controlling the virus, the immune system can start to rebuild itself. However, with almost no virus in circulation to keep them on their guard, immune cells don't always recognize that the enemy is still there, so the natural anti-HIV response may fade.

When treatment is stopped, the virus will replicate freely, and immune cells will be exposed to it once again. In theory, structured treatment interruptions (STIs) might, therefore, encourage the immune system to control HIV.

Researchers studying this have theorized that after each interruption of therapy, the body's ability to control HIV might increase, ultimately allowing drug therapy to be stopped.

This theory has been tested in several clinical trials and the results have been quite different depending on the disease stage in which the interruption of therapy is begun. Improvement of immune responses has definitely been seen in some people doing STIs during the *acute* HIV infection stage (immediately after initial infection). The trials have not been ongoing for long enough to know how long-lasting the improved viral control will be or the ultimate clinical benefit to the trial participants, but for now some researchers are encouraged by the results they've seen. However, the same cannot be said for the results so far seen with attempts to boost immune control of the virus in those in later disease stages (the "chronically infected"). Most people with longer-term infection who stopped their treatment had a very rapid rise in their viral loads and had to start their cocktails again. Even with multiple repetitions of the STIs, most PHAs have been unable to regain sufficient immune control to discontinue drug therapy for a lengthy period. Researchers are now considering the possibility that for those with chronic infection, a combination of STIs with therapeutic vaccines that are aimed at further boosting the immune response to HIV might have a better effect. Clinical trials to assess this possibility are ongoing.

drug-sensitive or wild-type virus — virus (HIV) that can be attacked or suppressed by treatment; drug-sensitive virus is the opposite of drug-resistant virus

I To make drug-resistant virus sensitive to treatment

Many people who have used multiple anti-HIV drugs for lengthy periods have virus that is resistant to most or all of the current drugs. Taking a break from treatment would mean that the virus in their bodies would no longer be under pressure from the drugs. As a result, drug-sensitive virus (also called "wildtype") is able to replicate. After a few months without treatment, most of the virus will again be "wildtype," as wildtype usually replicates faster than drug-resistant virus. This could mean that such people could start treatment again, even with drugs they've previously used. Because much of the virus in their bodies is once again sensitive to the effects of the drugs, they may get good control of their HIV for at least some period of time. Unfortunately, in the research done to date, it appears that this effect may only last for a few months in some HIV positive people. Eventually, the drug-resistant virus, which had faded away but not completely disappeared, may return in some people.

I To improve quality of life

Sometimes a drug holiday can improve your quality of life. Side effects and toxicities, high numbers of pills, difficulties in sticking to the drug schedule over time, treatment as a constant reminder of HIV infection, and simply being tired of downing the drugs every day can make taking a break look very attractive. Taking a drug holiday may also reduce the risk of long-term complications of the drugs.

There are many concerns that have been expressed about the possible negative results of interrupting therapy. The most-often mentioned is the fear that going on and off drugs could create resistance. However, it appears so far that in people whose virus is fully suppressed — meaning that their viral load is undetectable — there may not be much risk of resistance.

It's simply a matter of the biology of resistance. The viral mutations that can create resistance occur as a function of viral load — the more viruses that are present, the more chances there are for one of them to accidentally develop a mutation that allows it to resist a drug's antiretroviral effect. Then, since it's not being affected by the drug, it can replicate and eventually become the dominant population of HIV in the body. This is particularly likely when low drug levels are present (because someone is skipping doses or not taking drugs as directed or because an unexpected drug interaction lowers HAART medication levels).

With a planned therapy interruption, the drugs are taken properly during the treatment interval, and then stopped cold turkey. Thus, the low drug levels that would be problematic are not present except for a very brief interlude immediately following the cessation (stopping). If the virus is fully suppressed prior to the drug cessation, that means that there should be very little chance of developing resistance to the drugs. This also means that when the virus reappears during the drug holiday, the re-populating virus should be wild-type and sensitive to most drugs. Data from the STI studies so far done suggest that this is, indeed, the case in people with undetectable viral loads prior to a treatment interruption.

In the beginning there was a great deal of excitement about the possibilities for structured treatment interruptions. Disappointing results from more recent studies, however, have tempered this enthusiasm.

Cautions on Stopping Therapy

Unfortunately, research into structured treatment interruptions has been disappointing. There are still many risks, so stopping anti-HIV medications on your own is not recommended. Some of the potential hazards of taking treatment interruptions include:

- Stopping treatment will likely reverse the benefits you've had from anti-HIV medications.
- During a treatment interruption, the viral load will likely rise and the CD4 count will likely fall. This can increase the risk of developing AIDS-related infections.
- Stopping and restarting medications may make it easier for the virus to develop resistance to anti-HIV drugs.
- Some PHAs who restart their treatment after stopping may find their viral load does not drop to previous low or undetectable levels.
- Some PHAs experience flu-like symptoms during an increase (rebound) in their viral load.
- Some PHAs may find it harder to re-develop the habit of taking medications regularly after stopping medications for a while.

As well, we don't know if there might be certain negative consequences that have so far been little studied. For example, researchers have reported that during treatment interruptions there was a rebound of virus in the cerebrospinal fluid, suggesting a possible negative consequence for the central nervous system (brain).

If, however, despite all these unknowns and cautions, you're thinking about taking a drug holiday, it will be very important to plan it carefully with your doctor.

- Review your overall health and lab tests with your doctor. Talk about your reasons for taking a break and find out about the possible risks and benefits to your own health.
- Have viral load and CD4+ count tests done more frequently.
- Decide on the guidelines for restarting your cocktail. For example, you may want to take a break of a certain amount of time, or plan to re-start when your viral load or CD4+ count hits a certain level.
- If your CD4+ count drops, you may need to consider taking medication to prevent opportunistic infections.
- Plan ahead of time the specifics of the cocktail that you will start back on. If your viral load was below 50 copies when you stopped, you could re-start the same combination. If it was higher, and there were signs of drug resistance, you would probably want to start a new combination when your drug holiday ends.
- Talk with your doctor and pharmacist about which drug(s) to stop first. Some drugs remain in your blood longer than others. For example, the non-nuke efavirenz (Sustiva) can stay at fairly high levels for many weeks after your last dose. The other drugs in the cocktail may be gone from your body but some

A drug with a long half-life is one that is broken down by the body slowly, thus leaving it linger in the body after one stops taking it.

efavirenz remains and, for a time, it will be the only drug the virus is exposed to. Exposure to just that one drug may be enough for HIV to build up resistance to it — and to the related drugs nevirapine and delavirdine. Such resistance would rule out these non-nukes as future options.

What to Expect if you Take a Break

- I** Be prepared for your viral load to rise. Eventually it can climb back up to the pre-treatment level or even higher. The rise in viral load may happen fairly quickly after stopping treatment.
- I** Be prepared for your CD4+ count to drop. If your treatment interruption is long enough, your CD4+ count may return to its pre-treatment level or go even lower. If it falls below 200, you could be at risk for serious illnesses, especially PCP.
- I** Some drug side effects may decrease. For example, peripheral neuropathy (PN) — the nerve damage that causes pain, tingling or numbness in the hands and feet — may improve after a number of weeks or months off the causative drugs. Elevated levels of blood fats (cholesterol and triglycerides) may decrease. Drug-induced diarrhea or intestinal gas will probably disappear. However, be aware that in some people there may be little or no improvement with certain side effects. For example, if the nerve damage is too far advanced, the PN may not improve.
- I** If you had HIV-related symptoms (such as skin problems, chronic fatigue, neurologic problems, weight loss or diarrhea) before you started treatment, they may come back.
- I** Some people may experience what is called a “retroviral syndrome,” the combination of flu-like symptoms that many people experience during acute infection.

We hope we've answered many of your HIV

treatment questions, but we'll finish with one strong warning: HIV treatment information changes daily. If you are reading this more than 10 minutes after the writer completed it, there may be new information that is important for you to know in making your treatment decisions. So always, always, always reach out for the very latest information — via treatment newsletters (CATIE offers *TreatmentUpdate* and *CATIE News*), the Internet (check us out at www.catie.ca), your local treatment counsellor and, most importantly, your doctor — before you choose the path you'll follow.

Your doctor may also be interested in some of CATIE's services for health care professionals, such as *Innovations*, which provide leading-edge developments in the clinical treatment of HIV/AIDS. You may wish to encourage your doctor to tap into these resources which are both available at www.catie.ca.

With that, we hope you'll make the best possible treatment decisions, in which effort we wish you good luck and long-lasting good health.

This section includes charts of the different classes of antiretroviral drugs, including experimental drugs. Don't be confused by the multiple names for each drug. When a new drug is first developed, the maker gives it a code name. Reports of the earliest test-tube experiments almost always use the code name of the new drug. Often, people hear about new drugs by the code names or a shortened version of the code name, like DMP-266. As development continues, the drug gets a generic name, in this case, efavirenz. Finally, when the maker is ready to sell the new drug, it is given a brand name. Sometimes the brand name varies from one country to another. For example, in North America, the brand name for efavirenz is Sustiva. In other parts of the world, efavirenz is sold as Stocrin. After about 20 years, the company that developed the drug will lose its patent (exclusive rights to make the drug) and other companies are allowed to make their own generic versions of the drug. You'll notice that in most CATIE publications, we use the generic name. In some cases, however, the brand name is more commonly used by people.

Entry Inhibitors and Fusion Inhibitors

Drugs known as entry inhibitors and fusion inhibitors are being developed to prevent HIV from getting into cells. Entry inhibitors are designed to block the receptors HIV uses to attach itself to cells. Fusion inhibitors prevent the virus from fusing with the cell. Many of these drugs are highly experimental.

- T-20 (enfuvirtide, Fuzeon) is the only fusion inhibitor approved in Canada. T-20 attaches to gp41 — one of the proteins on the outer shell of HIV — and prevents the virus from fusing with the cell. T-20 is taken as a twice-daily injection subcutaneously (under the skin).

Reverse Transcriptase Inhibitors

Reverse transcriptase inhibitors (RTIs) inhibit (slow down or stop) the action of the reverse transcriptase enzyme. These drugs work to prevent the viral RNA from being converted into DNA. If the viral RNA is not converted to DNA, it cannot become part of the cell. There are three classes of RTIs:

- nucleoside analogue reverse transcriptase inhibitors are often called “nukes” for short. You may also see them called “NRTIs” or just “nucleosides.”
- nucleotide analogue reverse transcriptase inhibitors are referred to as “nucleotide RTIs.” These drugs work the same way as nukes, but they require one less processing step (called phosphorylation) in the body.
- non-nucleoside reverse transcriptase inhibitors are usually called “non-nukes” or “NNRTIs.”

All three classes of drugs target the same enzyme, but their molecular structure is very different and they work in different ways.

Nukes or NRTIs (approved in Canada)

Common name	Generic name	Brand name	Manufacturer
AZT or ZDV	zidovudine	Retrovir	GlaxoSmithKline
ddI	didanosine	Videx	Bristol-Myers Squibb
ddI (enteric coated)		Videx EC	
3TC	lamivudine	Epivir	GlaxoSmithKline
d4T	stavudine	Zerit	Bristol-Myers Squibb
FTC	emtricitabine	Emtriva	Gilead Sciences
ABC	abacavir	Ziagen	GlaxoSmithKline
AZT/3TC in one pill		Combivir	GlaxoSmithKline
AZT/3TC/ABC in one pill		Trizivir	GlaxoSmithKline
3TC/ABC in one pill		Kivexa	GlaxoSmithKline
FTC/tenofovir in one pill		Truvada	Gilead Sciences

Nucleotide RTI (approved in Canada)

Common name	Brand name	Manufacturer
tenofovir	Viread	Gilead Sciences

Non-nukes or NNRTIs (approved in Canada)

Common name	Brand name	Manufacturer
nevirapine	Viramune	Boehringer-Ingelheim
delavirdine	Rescriptor	Pfizer
efavirenz	Sustiva	Bristol-Myers Squibb

Integrase Inhibitors

Integrase goes to work after the reverse transcriptase enzyme has converted viral RNA into DNA. The integrase enzyme inserts the new viral DNA into the DNA of the host cell. For several years, scientists have been trying to develop drugs block the action of this enzyme. So far, they have had little success.

Protease Inhibitors

Protease inhibitors interfere with the action of the protease enzyme. These drugs prevent protease from cutting the newly made viral proteins into functional parts.

Protease Inhibitors (approved in Canada)

Generic name	Brand name	Manufacturer
saquinavir	Invirase	Hoffmann-La Roche
indinavir	Crixivan	Merck & Co.
nelfinavir	Viracept	Pfizer
ritonavir	Norvir	Abbott Laboratories
amprenavir	Agenerase	GlaxoSmithKline
lopinavir / ritonavir	Kaletra	Abbott Laboratories
atazanavir	Reyataz	Bristol-Myers Squibb
tipranavir	Aptivus	Boehringer-Ingelheim
fosamprenavir	Telzir	GlaxoSmithKline

This Practical Guide is part of a series and is meant to be used in conjunction with the other guides. The other titles are:

A Practical Guide to Complementary Therapies for People Living with HIV/AIDS
A Practical Guide to Herbal Therapies for People Living with HIV/AIDS
A Practical Guide to Nutrition for People Living with HIV/AIDS
A Practical Guide to HIV Drug Side Effects

All Practical Guides are available on the CATIE website, in French and English.

To be kept up to date on the latest treatment information, become a member of CATIE by calling 1.800.263.1638 or through our website at www.catie.ca

Funding has been provided by the Public Health Agency of Canada



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Bristol-Myers Squibb

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Pharmaceutical Group

CATIE thanks the Public Health Agency of Canada, as well as Bristol-Myers Squibb and GlaxoSmithKline in partnership with Shire BioChem for funding this guide, particularly their respective representatives, Ruth Pritchard and Lorne Fox.



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Funding has been provided by the
Public Health Agency of Canada.