



## COMBIVIR

### Summary

Combivir is a combination of two antiretroviral drugs, both of which are called nucleoside analogues (“nukes”). Each Combivir tablet contains 300 mg of AZT (Retrovir, zidovudine) and 150 mg of 3TC (lamivudine). The most common side effects of Combivir can include headache, nausea, vomiting, unexpected tiredness, diarrhea, loss of appetite, insomnia and muscle pain. It is usually taken at a dose of one tablet twice daily, with or without food.

### What is Combivir?

**Combivir** is the brand name of two anti-HIV drugs—AZT and 3TC—that are combined together in one capsule. Both of these drugs belong to a class of antiretrovirals (anti-HIV drugs) called nucleoside analogues or “nukes”. Combivir is used in combination with other antiretroviral drugs to treat (but not cure) HIV/AIDS.

### How does Combivir work?

To explain how Combivir works, we need to first tell you some information about HIV. When HIV infects a cell, it takes control of that cell. HIV then forces the cell to make many more copies of the virus. In order to make these copies, the cell uses proteins called enzymes. When the activity of these enzymes is reduced or blocked, production of HIV slows or stops.

Combivir contains two drugs, AZT and 3TC, which belong to a group of drugs called nucleoside analogues. AZT and 3TC interfere with an enzyme called reverse transcriptase (RT), which is used by HIV-infected cells to

make new viruses. Since AZT and 3TC both inhibit, or reduce the activity of this enzyme, Combivir causes HIV-infected cells to produce fewer viruses.

### How do people with HIV/AIDS use Combivir?

Combivir is used in combination with several other antiretroviral drugs, usually including drugs from different classes, such as protease inhibitors and/or non-nukes (non-nucleoside reverse transcriptase inhibitors). Combinations such as this are called highly active antiretroviral therapy, or HAART. For more information on HAART, see CATIE’s *Practical Guide to HAART for People Living with HIV/AIDS* at [www.catie.ca/PG\\_HAART\\_e.nsf](http://www.catie.ca/PG_HAART_e.nsf).

For many people with HIV/AIDS (PHAs), the use of HAART has increased their CD4+ cell counts and decreased the amount of HIV in their blood (viral load). These beneficial effects help to reduce the risk of developing a life-threatening infection. Neither Combivir nor any other antiretroviral medication is a cure for



HIV/AIDS. It is therefore important that you do the following:

- see your doctor regularly so that he/she monitors your health
- continue to practice safer sex and take other precautions so as not to pass HIV on to other people

## Warnings

### 1. Anemia and bone marrow toxicity

The AZT in Combivir can be toxic to the bone marrow—the soft tissue inside bones where blood cells are made. As a result, Combivir can cause **anemia** (lowered red blood cell levels) and **neutropenia** (lowered **neutrophil** or white blood cell counts). In serious cases, this can require blood transfusions, and Combivir must be stopped.

People with abnormally low hemoglobin levels or neutrophil counts should not take Combivir, or other drugs containing AZT. People starting Combivir should have their blood cell counts monitored closely. If anemia occurs at all, it usually happens within the first four to six weeks after starting Combivir. Although it was previously thought to be more common, a recent large-scale review found that only about 1% to 2% of people taking AZT develop anemia. Estimates of neutropenia range from 1.8% to 8%.

### 2. Lactic acidosis and hepatic steatosis

Two related conditions, **lactic acidosis** (a buildup of lactic acid in the blood) and **hepatic steatosis** (excess fat in the liver), have occurred in some people who have used nucleoside analogues. These conditions can be serious or fatal. They have mostly been seen in women and people who are overweight or who have been on nucleosides a long time, and can cause the following symptoms:

- unexpected tiredness or weakness
- nausea and/or vomiting
- persistent abdominal pain

- painful inflammation of the pancreas (**pancreatitis**)

If any of these symptoms occur without apparent reason, call your nurse or doctor right away.

Lactic acidosis is rare (less than one case per year for every thousand patients). If you do develop any of these symptoms, it does not necessarily mean you have lactic acidosis, but you should still let your doctor know right away.

### 3. Hepatitis B

If someone with hepatitis B infection is taking 3TC—a component of Combivir—the hepatitis can “flare up” if the medication is stopped. People with hepatitis B who are taking Combivir should be carefully monitored if they stop taking the drug.

## Side effects

### 1. General

The general side effects that occur in PHAs taking AZT and 3TC separately may also occur in PHAs taking Combivir. These may include: headache, nausea, vomiting, unexpected tiredness, diarrhea, loss of appetite, insomnia, and muscle pain. Other reported side effects include abdominal pain and discomfort, and coughing. Many people find that side effects caused by antiretrovirals improve or go away after the first several weeks of treatment.

Less common, but more serious, side effects include **peripheral neuropathy** (a numbness, tingling or burning sensation in the hands or feet), **neutropenia** (a decrease in the number of white blood cells called neutrophils), **anemia** (a decrease in hemoglobin or red blood cells), and **myopathy**, a weakness or loss of muscle mass, especially with long-term use. Some people of colour have experienced darkening of the skin and/or nails while using AZT.

### 2. Lipodystrophy syndrome

The HIV **lipodystrophy syndrome** is the name given to a range of symptoms that can develop



over time when people use HAART regimens. Some features of the lipodystrophy syndrome include:

- loss of fat just under the skin (subcutaneous fat) in the face, arms, and legs
- bulging veins in the arms and/or legs due to the loss of fat under the skin
- increased waist and belly size
- fat pads at the back of the neck (“buffalo hump”) or at the base of the neck (“horse collar”)
- small lumps of fat in the abdomen
- increased breast size (in women)

Together with these physical changes, lab tests of your blood may detect the following:

- increased levels of fatty substances called **triglycerides**
- increased levels of **LDL-cholesterol** (low-density lipoprotein), or “bad” cholesterol
- increased levels of sugar (**glucose**)
- increased levels of the hormone **insulin**
- decreased sensitivity to insulin (insulin resistance)
- decreased levels of **HDL-cholesterol** (high-density lipoprotein), or “good” cholesterol

The precise causes of the HIV lipodystrophy syndrome are not clear and are difficult to understand because in some PHAs there may be one or more aspects of the syndrome taking place. For instance, some people may experience fat wasting, others fat gain, and others may experience both fat gain and wasting. What is becoming increasingly clear is that unfavourable changes in the lab readings of glucose, cholesterol, and triglycerides over a period of several years increase the risk of diabetes and cardiovascular disease. So far, however, the many benefits of HAART are much greater than the increased risk of cardiovascular disease or other side effects.

Maintaining a normal weight, eating a healthy diet, exercising regularly, and quitting smoking

are all important in helping you to reduce your risk of diabetes, heart disease, and other complications. Regular visits to your doctor for checkups and blood tests are a vital part of staying healthy. If necessary, your doctor can prescribe lipid-lowering therapy.

Researchers are studying the lipodystrophy syndrome to try to discover ways of helping PHAs avoid or reduce this problem. To find out more about options for managing aspects of the lipodystrophy syndrome, see CATIE’s *Practical Guide to HIV Drug Side Effects* at [www.catie.ca/sideeffects\\_e.nsf](http://www.catie.ca/sideeffects_e.nsf).

## Drug interactions

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

Some drugs can interact with the AZT in Combivir, increasing or decreasing its levels in your body. Increased drug levels can cause you to experience side effects or make pre-existing side effects worse. On the other hand, if drug levels become too low, HIV can develop resistance and your future treatment options may be reduced.

It may also be necessary to avoid drugs that do not affect AZT drug levels, but cause similar side effects.

If you must take a drug that has the potential to interact with your existing medications, your doctor can do the following:

- adjust your dose of either your antiretroviral drugs or other medications
- prescribe different antiretroviral drugs for you

## Drug interactions for Combivir

The following drugs interact or have the potential to interact with the AZT in Combivir. These lists are not exhaustive. No significant drug interactions have been reported with 3TC.



Combivir should never be combined with d4T (**Zerit**, stavudine), as AZT and d4T have been proven to interfere with each other.

The following drugs can affect the bone marrow, decreasing the production of white and/or red blood cells. Using Combivir with these or other drugs that affect the bone marrow can increase the risk of infections and/or anemia:

- dapsone (**Avlosulfon**)
- ganciclovir (**Cytovene**)
- interferon-alpha and ribavirin (used as treatment for hepatitis C)
- valganciclovir (**Valcyte**)
- valproic acid (**Depakene**, **Divalproex**, other brand names)

Combivir should be used cautiously with these drugs, or not at all.

For some people, but not all, methadone increases the blood level of AZT. Aspirin, codeine, morphine and a number of other drugs can also affect the metabolism of AZT, so use of these drugs should be discussed with your doctor.

## Resistance and cross-resistance

Over time, as new copies of HIV are made in the body, the virus changes its structure. These changes are called mutations and can cause HIV to resist the effects of antiretroviral drugs, which means those drugs will no longer work for you. Combining Combivir with at least one other antiretroviral drug delays the development of drug resistance.

To reduce the risk of developing drug resistance, all antiretroviral drugs should be taken every day exactly as prescribed and directed. If doses are delayed, missed, or not taken as prescribed, levels of AZT and 3TC in the blood may fall too low. If this happens, resistant virus can develop. If you find you are having problems taking your medications as directed, speak to your doctor and nurse about

this. They can find ways to help you.

When HIV becomes resistant to one drug in a class, it sometimes becomes resistant to other drugs in that class. This is called cross-resistance. Feel free to talk with your doctor about your current and future treatment options. To help you decide what these future therapies might be, at some point your doctor can have a small sample of your blood analysed using resistance testing. Should HIV in your body become resistant to the AZT and/or 3TC in Combivir, your doctor, with the help of resistance testing, can help put together a new treatment regimen for you.

## Dosage and formulations

**Combivir** is available as tablets, each containing 300 mg AZT (zidovudine) and 150 mg 3TC (lamivudine). The usual standard adult dose of Combivir is one tablet, twice a day. Formulations can change, and dosages may need to be customized. All medications should always be taken as prescribed and directed.

## Availability

Combivir is licensed in Canada for the treatment of HIV infection in adults, in combination with other antiretroviral drugs. Your doctor can tell you more about the availability and coverage of Combivir in your region. CATIE's online module, Federal, Provincial and Territorial Drug Access Programs (on CATIE's website at [www.catie.ca/eng/Publications/drugaccess/drugaccessIndex.shtml](http://www.catie.ca/eng/Publications/drugaccess/drugaccessIndex.shtml)) also contains information about Canadian drug coverage.

Also see CATIE's fact sheets on AZT, 3TC and Trizivir.



# Credits

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# References

Antoniou T, Gough K, Yoong D and Arbess G. Severe anemia secondary to a probable drug interaction between zidovudine and valproic acid. *Clinical Infectious Diseases* 2004;38(5):e38-e40.

Canadian Pharmacists Association. *Compendium of Pharmaceuticals and Specialties*. 2006 edition.

Castagna A, Danise A, Menzo S, et al. E-184V study. Lamivudine monotherapy vs treatment interruption in failing HIV-1-infected subjects harbouring the M184V mutation: 48 week final results. *Third International AIDS Society Conference on HIV Pathogenesis and Treatment*, Rio de Janeiro, 2005. Abstract WeFo0204.

Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. *New England Journal of Medicine* 1994;331(18):1173-1180.

Department of Health and Human Services (US). *Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents*. Revision date October 10, 2006.

DeJesus E et al. Once-daily versus twice-daily lamivudine, in combination with zidovudine and efavirenz, for the treatment of antiretroviral-naïve adults with HIV infection: a randomized equivalence trial. *Clinical Infectious Diseases* 2004; 39:411-418.

Edwards MT et al. Characterization of anemia in HIV-infected (HIV+) subjects treated with antiretroviral therapy (ART) with and without zidovudine (+/- ZDV) in 54 clinical trials. *Third International AIDS Society Conference on HIV Pathogenesis and Treatment*, Rio de Janeiro, 2005. Abstract TuFo0106.

Fellay J, Boubaker K, Ledergerber B, et al. Prevalence of adverse events associated with potent antiretroviral treatment: Swiss HIV Cohort Study. *Lancet* 2001;358(9290):1322-1327.

GlaxoSmithKline Shire Biochem. *3TC Canadian Product Monograph*. September 12, 2006.

GlaxoSmithKline. *Combivir Canadian Product Monograph*. September 12, 2006.

GlaxoSmithKline. *Trizivir Canadian Product Monograph*. September 20, 2006.

Health Canada. *Drug Products Database*: [http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index\\_e.html](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index_e.html) Accessed Dec 13, 2006.

Johnson AA, Ray AS, Hanes J, et al. Toxicity of antiviral nucleoside analogs and the human mitochondrial DNA polymerase. *Journal of Biological Chemistry* 2001;276(44):40847-40857.

Havlir DV, Tierney C, Friedland GH et al. In vivo antagonism with zidovudine plus stavudine combination therapy. *Journal of Infectious Diseases*, 2000;182(1):321-325.

Shafer RW, Kantor R, Gonzales MJ. The genetic basis of HIV-1 resistance to reverse transcriptase and protease inhibitors. *AIDS Reviews* 2000; 2:211-228.

US Food and Drug Administration. FDA Approved Drug Products: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm> Accessed Dec 13, 2006.



## 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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