

contents

- 3 *Retrovir*
- 6 *Videx*
- 8 *Hivid*
- 10 *Zerit*
- 13 *Epivir*
- 15 *Ziagen*
- 17 *Viread*
- 19 *Emtriva*
- 20 *Combivir*
- 21 *Trizivir*
- 22 *Viramune*
- 24 *Rescriptor*
- 25 *Sustiva*
- 27 *Invirase/Fortovase*
- 30 *Norvir*
- 32 *Crixivan*
- 34 *Viracept*
- 36 *Agenerase/Lexiva*
- 38 *Kaletra*
- 40 *Reyataz*
- 42 *Fuzeon*
- 44 *Glossary of Terms*
- 47 *ACRIA News*

fall 2003/
winter 2004

Drugs! Drugs! Drugs!

An Overview of the Approved Anti-HIV Medications

This double issue of *ACRIA Update* includes discussions of each of the currently approved anti-HIV medications (antiretrovirals). Depending on whether you count new formulations of existing drugs, there are now between nineteen and twenty-one antiretrovirals available in the U.S., including four that were approved in 2003 alone.

Looking at each drug individually is helpful, but it's important to consider them in the context in which they're used – as components of combination therapy. Keeping this in mind, the overviews in this issue include: background on each drug's development and approval process; significant clinical trial results; possible short and long-term side effects; interactions with other drugs; resistance profiles; safety during pregnancy; dosing; availability for pediatric use; and when the drug might be most beneficial as part of a combination.

Organizationally, the issue groups the drugs by class and discusses the individual drugs in order of their FDA approval within that class. A sense of the history of the development and clinical use of anti-HIV treatment lies within the content and subtext of this issue. We've come a long way since the days when a drug was considered beneficial if there were fewer deaths in the group of people taking it alone than in the group taking another drug.

This issue of *ACRIA Update* is intended for people who are considering treatment in the future as well as those who are already on treatment. If

you're not on treatment, we hope that the overviews offer a sense of the pros and cons of individual drugs and combinations as you consider what might work best for you if the time comes to begin treatment. If you are on treatment, we hope that these overviews provide you with helpful information about the drugs you're taking. If this issue helps one person suffering from peripheral neuropathy realize that they don't have to stay on a drug that contributes to that debilitating condition, our efforts have been worthwhile.

We don't expect most people to read through the entire issue – certainly not in one sitting. If you do, let us know and we'll give you some sort of medal. Rather, use it as a reference guide. You may choose to look at only the background of some of the drugs or maybe just the side effects and drug interactions. If you feel overwhelmed or discouraged as you read the side effect and interaction sections, it's important to remember that we've listed the *possible* side effects – no one experiences every possible side effect of a drug. And many people don't experience *any*.

We dedicate this double issue of *ACRIA Update* to the individuals who have participated in – and continue to participate in – clinical trials that give us all a better understanding of HIV disease and its treatments. Thanks to their participation in research, we're able to provide this overview of nineteen to twenty-one antiretrovirals, a far cry from what we would have been able to provide in 1987 when the first antiretroviral was approved.

This issue of *ACRIA Update* was a collaborative effort, researched and written by:

James Learned, ACRIA's Director of Treatment Education and Editor of *ACRIA Update*; Mark Milano, treatment educator at ACRIA and longtime AIDS treatment activist; and Donna M. Kaminski, ACRIA's Associate Director of Treatment Education.

Special thanks to Tim Horn for his editorial review of some of the contents of this issue.

Editor in Chief

J Daniel Stricker

Editor

James Learned

Medical Editor

Jerome A. Ernst, MD

Publications Manager

Mark Milano

ACRIABoard of Directors

Ross Bleckner, *President*
 Donald Kotler, MD, *Vice President*
 Vincent Wm. Gagliostro, *Secretary*
 Charles Franchino, DC, *Treasurer*
 Marisa Cardinale
 Bob Colacello
 Douglas Dieterich, MD
 Tiffany Dubin
 Reinaldo Herrera
 Kevin Krier
 Adam Lippes
 Martha Nelson
 Maer Roshan
 Dolores Witherspoon-Cozier

In Memoriam

Gary Bonasorte
 Kiki Mason
 David Seidner
 George N. Stathakis

Medical Director

Jerome A. Ernst, MD

Executive Director

J Daniel Stricker

ACRIA is an independent, non-profit, community-based AIDS medical research and treatment education organization dedicated to rapidly improving the length and quality of life for people living with HIV/AIDS. Bulk copies of *ACRIA Update* are available free to agencies that provide services to people living with HIV/AIDS. For more information, call 212-924-3934 ext. 121.

Copyright © 2003

AIDSCommunity Research Initiative of America. All rights reserved. Non-commercial reproduction is encouraged provided appropriate credit is given.

ACRIA

230 West 38th St., 17th Floor
 New York, NY 10018
 Phone: (212) 924-3934
 FAX: (212) 924-3936
 www.acria.org

Standard of Care Treatment vs. ZEST Once-Daily Regimen
 This trial will study whether people on their first HAART regimen who take their drugs two or more times a day can switch to a once-daily regimen. People in the trial will either remain on their current medications, or switch to Zerit XR, Epivir and Sustiva (ZEST) taken once daily. They will visit ACRIA 9 times over 11 months. All blood tests, study visits, and study medications (Zerit XR, Epivir & Sustiva), as well as medications from the Standard Of Care arm that are manufactured by the sponsor, will be provided at no charge to the participants. Prescriptions will be written for any other anti-HIV drug. You are eligible if you are HIV-positive, age 18 or over, and on an initial HAART regimen (one or more NRTIs, at least one agent must have a twice-daily dosing schedule, and no NNRTI in the past or in current regimen) with a viral load below 50. Study participants will be reimbursed \$25 for each visit.

To enroll, contact Dr. Douglas Mendez at 212-924-3934 ext. 126 or Dr. Yuriy Akulov at 212-924-3934 ext. 124

RESIST 1: Tipranavir in Multi-Drug Resistant Patients
 This trial, which is closed to new enrollment, continues to study the safety and efficacy of tipranavir (a protease inhibitor) boosted with low-dose ritonavir in people who have taken multiple antiretrovirals. All patients must have taken drugs from each of the three antiretroviral classes, have taken at least two protease inhibitors, have a viral load over 1,000, and must currently be taking a protease inhibitor.

Social Networks Study
 We have completed the first phase of enrollment for this study. Results from this study will be available soon on our website.

HIV Over 50 Database ACRIA is currently establishing a large cohort to conduct research on HIV+ people over 50. If you would like to be included in this database, please contact Salone Howard at 212-924-3934 x105 or email showard@acria.org.

Using Complementary Treatments to Manage HIV/AIDS
 People in this study were interviewed about treatments other than antiretrovirals, such as supplements, exercise, acupuncture, herbal remedies, as well as who provides the treatments, how often they use them, and if they feel they are helpful. To qualify, people must have been HIV+, using HAART for at least a year, and be using other treatments for HIV/AIDS. If you are interested in participating in future studies, contact Salone Howard at 212-924-3934 x105 or email showard@acria.org.

Web Research Study This internet survey studies the extent to which HIV service providers may benefit from HIV prevention programs or programs designed to assist them in other areas of their job. Visit www.acria.org to participate.

Editor's Notes

- All material in *ACRIA Update* is presented for educational and informational purposes only, and is not intended as medical advice. All decisions regarding one's personal treatment and therapy choices should be made in consultation with a physician.
- *ACRIA Update* refers to most drugs by both their commercial and scientific names upon their first reference in an article. Thereafter in the article, they will be identified with the name by which we feel they are most commonly known, either commercial or scientific.

NRTIs : Nucleoside and Nucleotide Reverse Transcriptase Inhibitors

The NRTIs are also called nucleoside/nucleotide analogs or “nukes” for short. Once HIV has entered a cell, usually a CD4 cell, it uses an enzyme called *reverse transcriptase* to change its genetic material, RNA, into DNA. The viral DNA is then integrated into the human DNA in the nucleus of the cell. This programs the cell to make new copies of HIV. Once the cell is activated, the DNA in the nucleus creates pieces of HIV.

HIV's reverse transcriptase enzyme uses nucleotides – the building blocks of DNA – to translate its RNA into DNA. As the name says, NRTIs inhibit (slow down) reverse transcriptase. Simply put, NRTIs are defective versions of the nucleotides. HIV is fooled into inserting the NRTI in the place of one of the nucleotides, preventing the viral DNA from being fully formed. The viral DNA is a mess. It can't be integrated into the nucleus of the cell, and this stops – or at least slows down – the reproduction of new HIV.

Since NRTIs are incorporated into cells to interfere with HIV's replication process, they can also damage other human cells. This is called mitochondrial toxicity. Mitochondria, the power plants of our cells, turn nutrients into energy for the cells. The NRTIs that inhibit reverse transcriptase can also inhibit an enzyme that mitochondria use to reproduce. The result is the production of fewer mitochondria as well as mutations in the mitochondria that *are* produced.

Mitochondrial damage may be responsible for some of the long-term side effects of the NRTIs: myopathy (inflammation of muscle tissue), peripheral neuropathy (nerve damage in the feet and hands), pancreatitis (inflammation of the pancreas), and low levels of certain blood cells. It may also play a role in the redistribution of body fat, especially fat loss (lipoatrophy).

Two rare but particularly serious related conditions can also result from mitochondrial damage – lactic acidosis and hepatic steatosis (fat in the liver). Our bodies usually clear excess lactate. Mitochondrial damage can cause very high levels of lactate to build up in the blood, sometimes leading to lactic acidosis, a potentially fatal condition. It's more common in women than in men and is tied to the use of some NRTIs more than others – particularly Retrovir (AZT), Zerit (d4T), Videx (ddI), and Hivid (ddC). Symptoms of lactic acidosis are subtle and difficult to recognize. They can include shortness of breath, abdominal pain, nausea, vomiting, fatigue, and weight loss. If you experience these symptoms while on NRTIs, see your healthcare provider right away.

Anti-HIV combinations usually include two NRTIs and a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI).

Retrovir (AZT, azidothymidine, ZDV, zidovudine) has been studied more than any other antiretroviral used for the treatment of HIV. It was the first anti-HIV drug approved by the FDA (March 1987) and has been used in clinical trials of almost every new antiretroviral since that time.

Background: AZT was discovered in 1964 as a possible cancer drug by a researcher working under a grant from the National Cancer Institute, part of the National Institutes of Health (NIH). The drug was never approved as an anti-cancer agent, but once HIV appeared in the early '80s, Burroughs Wellcome (later GlaxoWellcome, now GlaxoSmithKline), which owned the rights to AZT, took another look at it. Test tube (*in vitro*) studies showed that it slowed down HIV replication, and clinical trials, including pivotal ones at the NIH, were quickly designed to test its safety and efficacy in humans.

The first thing that many people think of when Retrovir is mentioned is the enormous hope, followed by crushing disappointment, when it was first introduced as “close to a cure” in 1986. In the early trials, people took 1,200-1,500/mg a day – two to three times the current dose. A phase II study conducted in 1986 (ACTG 002) compared Retrovir to placebo in 282 patients with

less than 200 CD4 cells or a history of PCP (pneumocystis pneumonia). At the end of six months, one person taking Retrovir had died compared to 19 taking the placebo. The placebo arm was closed, and everyone in the study was given the opportunity to go on Retrovir. Unfortunately, the death rates evened out the longer people stayed on Retrovir, meaning that the drug helped extend survival a relatively short period of time, not indefinitely.

Later large trials looking at Retrovir in people with higher CD4 counts and no symptoms – particularly the Concorde study results published in 1993 – showed that the benefits of Retrovir taken alone (increases in CD4 counts and slower disease progression) diminished within one year of being on the drug. And during the second year of Retrovir treatment, disease progression sped up, even surpassing that of patients who weren't treated at all. At the time, it wasn't possible to understand why this was happening. Viral load tests weren't available yet. If they had been, the trial investigators would have seen that, although Retrovir decreased viral loads as people began the drug, within six months to a year, viral loads would rise again, perhaps to even higher levels than before people started the drug. HIV had developed resistance, and within a year of taking Retrovir alone, people were taking a drug that continued to cause side effects but did little or nothing to slow down HIV.

(continued on next page)

Retrovir *(continued from previous page)*

The side effects were significant – feeling (and looking) sick, debilitating fatigue, headache, muscle weakness, discolored nails, and bone marrow toxicity, including life-threatening anemia (low red blood cells) and neutropenia (low neutrophils, a kind of white blood cell). Some of these side effects caused or contributed to illness and even death. Retrovir was not the lifesaver – let alone the cure – that many had hoped. Some people who don't remember or never knew the history of the drug think of AZT as the “poison” that killed rather than cured. For some, the idea of AZT as poison extends to all antiretrovirals and poses a considerable barrier to accessing treatment.

In the early '90s, Retrovir was studied as part of two-drug combinations as other nucleoside reverse transcriptase inhibitors (NRTIs) were developed. These studies showed greater clinical benefit when people took two drugs together as opposed to Retrovir alone. The development of protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) in the mid-'90s showed that three-drug combinations that included Retrovir dramatically decreased the rates of opportunistic infections and deaths even further. These studies confirmed Retrovir as an effective treatment, but showed that it needs to be combined with other anti-HIV drugs to delay the onset of resistance and to prolong the effects on viral load, CD4 cell counts, and survival.

Because of its track record, we probably know more about how Retrovir works – its efficacy, safety, and side effects – than any other antiretroviral currently in use. Yet precisely because it was the first anti-HIV drug approved, it comes with a lot of baggage. The early, roller coaster history of Retrovir in many ways anticipated the ups and downs that have characterized the epidemic – the battles between industry and people with HIV over pricing and access issues, controversies over data, the hopes raised, dashed, then raised again. Despite the memories and myths that the drug invokes, Retrovir remains a useful treatment option with plenty of data to support its inclusion in a variety of combinations. Retrovir is part of nine (43%) of the 21 regimens that the recently revised Department of Health and Human Services (DHHS) treatment guidelines recommend for people who have never taken antiretrovirals before.

Side Effects: The side effects seen in the early days of Retrovir can still occur at today's lower dose, although less often and to a much lesser degree. The most common short-term side effects include headache, fatigue, nausea, loss of appetite, and vomiting. These are more likely to occur during the first few weeks on the drug, although some people experience them for longer. The gas-

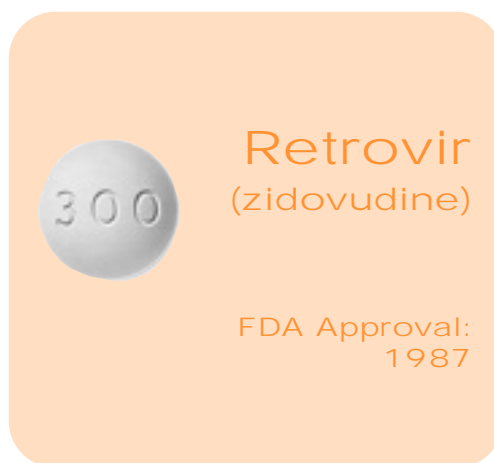
trointestinal side effects (nausea and vomiting) may be lessened if you have some food in your stomach before taking the drug. Long-term use of Retrovir can lead to anemia and neutropenia, so regular blood work is important to catch these irregularities before serious problems develop.

A rare side effect of long-term Retrovir use is myopathy (inflammation of muscle tissue). The symptoms are painful or tender muscles, usually in the thighs, hips, and butt. If you've been on Retrovir for a year or more and experience these symptoms, myopathy is a possibility. There's some evidence that people who experience Retrovir-associated myopathy already have underlying myopathy caused by HIV disease itself. A physical exam will reveal normal muscle reflexes, so the primary way to diagnose myopathy is by having your blood CPK (creatine phosphokinase) levels checked. If the blood level of this enzyme is elevated, it could mean that too many muscle fibers are breaking down. It's important to note, though, that myopathy may not be the only reason for an elevated CPK. There's no specific treatment for myopathy, but Retrovir-associated myopathy is usually reversible if the drug is stopped early. CPK levels and symptoms often improve within one to three months.

Drug Interactions: Although Retrovir has fewer drug interactions than many other antiretrovirals, particu-

larly the protease inhibitors, there are some important ones to be aware of. Retrovir shouldn't be used with Zerit (d4T) because the two drugs work against each other in the body, resulting in less anti-HIV activity. Methadone can increase Retrovir levels so much that some people need to cut their Retrovir dose in half. Other opiates such as morphine, heroin, codeine, and Demerol (meperidine) can have the same effect. If you're on ribavirin as part of combination therapy for hepatitis C, Retrovir shouldn't be part of your HIV regimen. Taking ribavirin and Retrovir together may make each less effective. And since anemia is a possible side effect of each drug, taking both increases the likelihood of developing the condition.

When To Consider It: When someone is thinking about antiviral treatment, the issue of which drugs to use first is an important consideration, since what you start with can affect your future choices. If you develop high-level resistance to Retrovir, you're also likely to be resistant to all of the NRTIs – Eпивir (3TC), Videx (ddI), Zerit, Hivid (ddC), Ziagen (abacavir), and, probably, Emtriva (emtricitabine). Previous use of Retrovir, Zerit, and Videx can make Eпивir less effective. Resistance to Retrovir and Eпивir may mean resistance to Ziagen. Sounds complicated, and it can be. But it's not necessarily a reason to avoid a combination that includes Retrovir. The trick is to choose your regimen carefully, adhere to it, and, as much as possible, avoid the development of resistance.



The backbone of an HIV regimen is usually a pair of NRTIs, combined with a third or fourth drug – most often an NNRTI or PI. Over the years, many studies have compared various dual NRTI combinations, and recent research tends to favor Retrovir/Epivir over other combinations. The current DHHS treatment guidelines recommend Retrovir/Epivir as the dual nucleoside combination “of choice” based on its effectiveness, safety, few interactions with other drugs, the probability of developing resistance mutations, and dosing convenience compared to other dual nucleoside combinations.

Either Retrovir or Zerit are often part of a first-line combination (though not both). In 2000, researchers looked at the CD4 counts and viral loads of patients who used Retrovir as part of their first regimen compared to those who used Zerit first. People who took Retrovir before Zerit had greater viral load drops, more often reaching undetectable levels, than those who took the medications in the reverse order. There was no difference in CD4 counts between the groups. These results suggest that going from Retrovir to Zerit may work better than the reverse. Our growing understanding of Zerit’s long-term side effects makes it a less-than-ideal choice for first-line therapy (see page 10), so the issue of which of the two to use first may be less important now than it was only a few years ago.

Good To Know:

- Retrovir is one of only a few antiretrovirals with the ability to cross the blood-brain barrier. This makes the drug effective against HIV in the brain and central nervous system and may help prevent neurological disease like dementia. It’s important to include at least one antiretroviral that crosses the blood-brain barrier in your combination.
- If your virus has become resistant to Retrovir, using Epivir with Retrovir can sometimes make HIV that’s resistant to Retrovir sensitive to Retrovir again.
- So many people have used Retrovir over such a long period of time that the transmission of Retrovir-resistant virus may make up more than 10% of new HIV infections in the United States.
- Barring any lawsuits (which are likely), generic AZT could be available in 2005, when Glaxo’s patent on the drug as a treatment for HIV expires.

Mother-To-Child Transmission: Retrovir’s ability to reduce transmission of HIV from positive mothers to their children was discovered in 1994 with the release of the results of PACTG 076. This trial, conducted in France and the United States, compared two groups of HIV-positive pregnant women, all with CD4 counts above 200 and none of whom had taken any antiretroviral therapy at the start of their pregnancy. One group of women took Retrovir alone beginning 14 weeks or later in their pregnancies and intravenously during labor. Their babies were given Retrovir for six weeks immediately follow-

ing their birth. The other group of women and their children were given placebo (no Retrovir). Of the newborns evaluated in the study, 8% in the Retrovir group were HIV-positive compared to 25% in the placebo group. Later trials confirmed Retrovir’s ability to reduce mother-to-child transmission. Even with the use of combination therapy in women during pregnancy, the Retrovir protocol continues to be recommended to reduce the risk of transmission.

There was, and continues to be, much concern about possible negative effects of Retrovir when used in this way. Thankfully, no dangerous short-term side effects were observed in either the women or the newborns in PACTG 076 or in subsequent similar studies. The children continue to be monitored for long-term side effects; having been followed for up to six years, researchers have found no differences between those infants who were exposed to the Retrovir regimen and those who received placebo. Early in 2003, researchers published the results of PACTG 288, a follow-up study of women who participated in PACTG 076. Three to six years after the women gave birth, no differences in HIV disease progression, CD4 counts, viral load, opportunistic infections or death were observed in the women who had taken Retrovir during their pregnancies compared to those who took placebo.

Pregnancy: Ironically, Retrovir is still classified as an FDA pregnancy category C drug. Despite the short- and long-term data from PACTG 076, the FDA still considers its safety in human pregnancy to be unproven. This is probably because some studies using very high doses in pregnant rodents resulted in fetal tumors. Aside from the encouraging results of PACTG 076 and PACTG 288, the Antiretroviral Pregnancy Registry has found that, when Retrovir has been used during the first trimester, the prevalence of birth defects was 2.8%, compared to an overall prevalence of 3.1% in the U.S. population.

Dose: 600 mg a day, usually taken as one 300-mg tablet twice a day, with or without food. Also available as 100-mg capsules, as a flavored syrup that contains 50 mg per teaspoonful, and as part of the combination pills, Combivir and Trizivir (see pages 20 and 21). The pediatric dose (ages 6 weeks to 12 years) is 160 mg per meter squared (m²) of body surface area every 8 hours (480 mg/m² daily up to a maximum of 200 mg every 8 hours). Children over 12 take the usual adult dosage. Interestingly, although 600 mg is the recommended daily dose for adults and adolescents in the United States, Retrovir is available as 250-mg tablets in many countries, including the United Kingdom, with a recommended dose of 500 mg a day.

FDA Approval: 1987

Manufacturer: GlaxoSmithKline

Patient Assistance Program: 866-728-4368

Videx, Videx EC (ddl, didanosine, dideoxyinosine) – Videx was the second anti-HIV drug approved by the FDA. Its approval in October 1991 was unique in that it was the first time that a drug was approved based on surrogate markers such as lab results (in this case, increased CD4 cells) rather than on clinical endpoints such as disease progression or survival. Much has been learned about Videx since then, including data from trials that looked at clinical endpoints. The drug has been researched in various combinations and populations and gone through many formulations and dosing schedules. There's much to say both for and against it, but it remains useful for many people and in a variety of triple-drug combinations.

Formulations: People have put up with Videx for years – chewing the huge, horrible tasting tablets, crushing them and mixing them in water, or dissolving a powdered version into water twice a day. Videx has to be taken on an empty stomach because the drug can't be absorbed properly in an acidic setting, including stomach acid. The original versions of Videx (the tablets and powder) contain a buffer to reduce stomach acid, which means that they can't be taken with many other anti-HIV medications that require acid in the stomach to be absorbed properly. The approval of Videx EC (enteric coated) time-release capsules in October 2000, was a big improvement – once-a-day dosing (although still on an empty stomach) and no buffer, which cut down on the diarrhea that the buffer caused and allowed Videx to be taken at the same time as other medications. Most people who use the drug now take Videx EC.

Background: Researchers at the National Cancer Institute (NCI) first identified Videx's potential as a treatment for HIV in 1985. The NCI began the first clinical trial of Videx in 1988, and then licensed the drug to Bristol-Myers Squibb on an exclusive basis. Early studies showed that taking Videx alone was slightly better than taking Retrovir (AZT) alone, particularly for people who had already taken Retrovir.

The first study to show that Videx had a positive effect on slowing disease progression was ACTG 116-B/117. The study assigned 913 people who had taken Retrovir alone for at least four weeks (an average of 13 1/2 months) to continue Retrovir or to switch to one of two doses of Videx (500 or 750 mg a day). After 55 weeks, those who switched to the lower dose of Videx had significantly lower rates of opportunistic infections or death (32%) compared to those who switched to the higher dose of Videx (37%) or those who stayed on Retrovir (41%). People in the trial who took Videx lost fewer CD4 cells than those who stayed on Retrovir. These results, reported in the *New England Journal of Medicine* in August 1992, led the FDA to recommend that Videx be prescribed at lower doses than had originally been approved.

Throughout the early '90s, many studies showed the effectiveness of Videx as monotherapy and as part of two-drug combinations

(see discussions of ACTG 175 and the Delta study in the Hivid section on page 8). Lots of people began to use Videx instead of Retrovir as monotherapy, switched back and forth between the two, or started two-drug combination therapy with both. As trials were designed to study protease inhibitors and non-nucleosides in three-drug combinations, it became more difficult to assess the comparative effectiveness of the individual NRTIs.

In the mid to late '90s, there was a lot of excitement about the possibility of combining Videx (and sometimes Zerit [d4T] or both) with hydroxyurea to boost the activity of Videx. Hydroxyurea has been around for over thirty years and is used to treat certain cancers and sickle cell anemia at higher doses than were used in the HIV research. Hydroxyurea itself doesn't slow down HIV replication, but changes a cellular enzyme in such a way that HIV's reverse transcriptase enzyme can't transcribe its RNA into DNA.

In test tube (*in vitro*) and small human studies, hydroxyurea seemed to enhance the antiviral activity of Videx, even against HIV that was resistant to Videx. Unfortunately, larger studies, particularly ACTG 5025, which involved 200 participants, showed that adding hydroxyurea to a combination increased toxic side effects (more peripheral neuropathy and, particularly, pancreatitis) without increasing CD4 cells. The study was shut down prematurely in September 1999 because of two deaths from pancreatitis in the arm of the study that

added hydroxyurea. Research into hydroxyurea as a way to boost the effectiveness of Videx essentially stopped, and hydroxyurea is rarely used in clinical practice today.

Confusion about the dosage of Videx was complicated further in October 1999 when the FDA approved a version of buffered Videx to be taken as two tablets once a day. The new version made Videx the first nucleoside analog approved for once-daily use. Unfortunately, in August 2000 Bristol-Myers Squibb (BMS) had to send a letter to healthcare providers saying that Videx should be taken twice a day after all. The once-a-day dose was called into question when a study of over 750 people who had never taken anti-HIV therapy before indicated that, after a year, the people on the combination that included once-a-day Videx had significantly higher viral loads than those on the other regimen. The approval in 1999 had been based on six-month results of the same trial. Videx EC, the capsule formulation, was approved for once-a-day use only a few months after BMS' letter went out, so Videx still became the first nucleoside analog approved for once-daily use.

Videx EC capsules are at least as effective and have fewer side effects and interactions with other drugs than the old Videx buffered tablets taken either once or twice a day.

Side Effects: Less serious side effects of Videx include diarrhea (especially with the tablet and powder forms), chills or fever, rash, abdominal pain, weakness, headache, nausea, vomit-



ing, decreased appetite, dry mouth, and dry eyes. Unfortunately, Videx can also cause far more serious side effects – peripheral neuropathy (tingling, pain, and numbness in the feet and hands), pancreatitis (inflammation of the pancreas), and vision changes.

Peripheral neuropathy occurs in as many as 20% of people who take Videx. If the drug isn't stopped, the neuropathy can be irreversible, resulting in permanent nerve damage. Videx-related pancreatitis occurs in 1-7% of patients and usually takes a few months to develop. Symptoms of pancreatitis can include nausea, vomiting, diarrhea, blood in the urine, and sharp pain in the back or upper abdomen. If you experience these symptoms while on Videx, contact your healthcare provider immediately. Pancreatitis can be fatal. If you have to stop taking Videx because of pancreatitis, don't take the drug again. Very rarely, Videx can affect the nerves in the eyes, especially in children. If you're on Videx, getting an exam by an HIV-experienced ophthalmologist (eye doctor) every four to six months is an important part of your care.

The risk of peripheral neuropathy or pancreatitis can be increased by other factors, including advanced HIV disease and a history of either condition. If you're on another drug that also has peripheral neuropathy as a possible side effect, such as Zerit, amphotericin B, Foscavir (foscarnet), dapson, or vincristine, be sure that you're monitored closely for symptoms.

Heavy alcohol use can increase the risk of pancreatitis, so if you're a heavy drinker, avoid either alcohol or Videx. Other drugs that may increase the risk of pancreatitis include Cytovene (oral ganciclovir), rifampin, and Mycobutin (rifabutin).

Drug Interactions: In addition to drugs that can increase the likelihood of side effects, many other drug interactions are possible with Videx. The older tablet and powder versions have more drug interactions because of the buffer.

Tablets or Powder: Nizoral (ketoconazole), Sporanox (itraconazole), dapson, and other drugs that are affected by stomach acid should be taken at least two hours before Videx. Videx shouldn't be taken within two hours of the antibiotics tetracycline, doxycycline, or minocycline because Videx lowers the amount of antibiotic that gets into your system. Videx should be taken at least two hours after or six hours before Cipro (ciprofloxacin). Be careful with other quinolone antibiotics as well. Videx and the protease inhibitor Crixivan (indinavir) need to be taken at least one hour apart and both on an empty stomach. The NNRTI Rescriptor (delavirdine) should be taken one hour before taking Videx. Antacids that contain magnesium or aluminum (Rolaids, Maalox, Milk of Magnesia, and others) may cause more serious side effects if taken with Videx.

Capsules: Many of the interactions that are caused by the buffer in the tablet and powder formulations aren't a problem with the Videx EC capsules. These include the interactions with Nizoral, Sporanox, Crixivan, dapson, Cipro, and other antibiotics. Videx EC can be taken at the same time as these medications.

All Formulations: Methadone decreases Videx levels by as

much as 40%, so the amount of Videx getting into your system may not be enough to do its job. Increasing your Videx dose may be necessary. Videx doesn't decrease methadone levels.

Viread (tenofovir) significantly increases levels of Videx in the blood, which could cause more severe side effects. If Viread is combined with Videx, some research suggests that the Videx dose should be reduced to one 250-mg Videx EC capsule once a day. This dose is still experimental and hasn't been recommended for use in combination with Viread by the FDA.

Ribavirin, used for the treatment of hepatitis C, should not be used with Videx. People taking both drugs have a much greater likelihood of developing Videx-related side effects, particularly pancreatitis.

When To Consider It: The challenge of taking Videx on an empty stomach and the possibility of serious side effects make it less-than-ideal when faced with choosing the best nucleoside analogs for a first combination. Videx is included in only two of the 21 preferred or alternative regimens that the recently revised Department of Health and Human Services treatment guidelines recommend for people who have never taken antiretrovirals before. Recent research has shown promising results using Videx as part of a first-line regimen, particularly in combination with Epivir (3TC), so that recommendation may change in the future. Videx's once-daily dosing gives the drug an advantage over many other nucleoside analogs if you're trying to come up with an entire once-a-day regimen. Videx resistance takes a long time to develop and is unlikely to cause cross-resistance to Retrovir or Zerit, another plus for early use.

But Videx may be more useful later, after earlier regimens have failed. Resistance testing, particularly phenotypic testing, may be helpful in such situations since the resistance profile of Videx is complicated and not entirely clear. Videx is active against HIV that's resistant to Epivir, another argument for saving Videx for later use.

Good To Know:

- Because of the empty stomach requirement, many people find that taking Videx just before going to bed works best.
- Avoid the combination of Videx and Hivid (ddC). Both can cause neuropathy and pancreatitis, they have similar resistance profiles, and they don't work well together anyway.
- Your Videx dose may need to be reduced if you have kidney problems.

Pregnancy: Videx is classified as an FDA pregnancy category B drug, meaning that animal reproduction studies don't show a risk to the fetus and adequate, well-controlled studies of pregnant women haven't been conducted. High doses of Videx given to pregnant rats, mice, and rabbits haven't resulted in problems to the development of the fetus. A small study (PACTG 249) of fourteen HIV-positive pregnant women who took Videx during their third trimester and for six weeks after giving birth showed no negative effects on the women or their fetuses. But the FDA and Bristol-Myers Squibb issued a warning that pregnant women may be at increased risk of fatal lactic acidosis when prescribed

(continued on next page)

Videx *(continued from previous page)*

a combination that includes Videx and Zerit. These drugs should only be prescribed together for pregnant women if the potential benefit clearly outweighs the potential risk.

Dose: Because of its many formulations, Videx dosing is arguably the most complicated of any antiretroviral. The adult dose of both the original buffered version and the newer capsules is based on weight. *All formulations of Videx need to be taken on an empty stomach. For best absorption, take your dose at least 1/2 hour before or 2 hours after eating.* Absorption of Videx can be decreased by as much as 50% if the drug is taken with food, which would leave you with too little drug in your system to do its job.

- **Videx EC capsules** are taken once a day. Capsules are available in 125, 200, 250, and 400 mg versions. People who weigh 60 kg (132 pounds) or more take one 400-mg capsule once a day; those who weigh less than 132 pounds take one 250-mg capsule once a day. After studying the research, the United Kingdom's HIV Pharmacy Association expanded the food restriction, recommending that you not eat anything (or drink anything but water) 2 hours before *and* 2 hours after taking Videx EC.
- **Videx tablets** are available in 25, 50, 100, 150, and 200 mg versions. They are chewed or crushed and mixed in an ounce or more of water (adding apple juice or using apple juice instead of water can help relieve the awful taste). People who weigh 132 pounds or more take 200 mg twice a day; those who weigh less than 132 pounds take 125 mg twice a day. To achieve the required buffering, take at least two but no more than four tablets to make up your necessary dose – for example, if your dose is 200 mg twice a day, use two 100 mg or four 50 mg tablets each time. The 200-mg tablets are only for once-a-day dosing, which is not generally recommended. If an unusual situation warrants once-daily use of this formulation, the dose is 400 mg for people who weigh 132 pounds or more and 250 mg for those who weigh less than 132 pounds.
- **Videx buffered powder** comes in single-dose packets of 100, 167 and 250 mg. The powder is mixed in four ounces of water – water only, don't add apple (or any other) juice! People who weigh 132 pounds or more take 250 mg twice a day; those who weigh less than 132 pounds take 167 mg twice a day. The powder can't be used for once-daily dosing.
- The **pediatric dose** of Videx for children ages 2 weeks to 8 months is 100 mg per meter squared (m²) of body surface area twice a day; the dose for children older than 8 months is 120 mg/m² twice a day. A pharmacist, mixing Videx powder with purified water and antacid, prepares the pediatric formulation. Videx EC is not approved for pediatric use.

FDA Approval: Videx 1991; Videx EC 2000

Manufacturer: Bristol-Myers Squibb

Patient Assistance Program: 877-758-7877

Hivid (ddC, zalcitabine, dideoxycytidine) is rarely used anymore, but, as with most new drugs, its approval by the FDA in June 1992 was eagerly anticipated. Now, its three-times-a-day dosing, poor showing in clinical trials, multiple drug interactions, and potentially serious side effects combine to make it the least prescribed nucleoside analog.

Background: Hivid was the first drug to receive accelerated approval, meaning that it was approved by the FDA very quickly, supported by limited but promising data. Hivid was also the first antiretroviral to be approved for use only as a component of combination therapy, specifically with Retrovir (AZT). This wasn't due to any particular foresight, but because early data from clinical trials that were ongoing showed that people who started treatment with Hivid plus Retrovir had greater increases in CD4 cells than people who started treatment with Retrovir alone. Retrovir plus Hivid was widely used as a two-drug combination in the early to mid-'90s.

Unfortunately, Hivid was far weaker individually than either of the antiretrovirals approved at the time, Retrovir and Videx (ddI). Many early trials showed Hivid to be less effective both alone and as part of a two-drug combination than the other two drugs. ACTG 114, for example, which involved more than 600 participants, showed that Retrovir was far superior to Hivid in people who had advanced HIV disease and little or no experience with antiretrovirals. The full study results weren't published until 1995, but the outcome was well known before then. The trial was stopped a year earlier than planned, in late 1991, when the study's Data and Safety Monitoring Board found a significantly higher percentage of deaths in the people taking Hivid compared to those taking Retrovir.

ACTG 175, which started in early 1992, enrolled almost 2,500 people, 40% of whom had never taken antiretrovirals before; among those who had, Retrovir alone was the most common treatment. Trial participants took Retrovir alone, Videx alone, Retrovir plus Videx, or Retrovir plus Hivid. After three years, people taking Retrovir alone had the worst results whether or not they had been on therapy before. For people who had never taken antiretrovirals before joining the study, the Retrovir plus Hivid combination did slightly better than Videx alone or Retrovir plus Videx in people who had never taken antiretrovirals before. For those who *had* taken antivirals before, Videx alone or Retrovir plus Videx produced the best results. The modest benefit seen for Hivid in people who had never been on treatment was crucial to its FDA approval.

Another trial that included Hivid was the Delta study, which also began in 1992. The Delta study was highly influential in our understanding of HIV treatment and how antiretrovirals came to be used in clinical practice. It enrolled over 3,200 participants in Europe and Australia. Some had never taken Retrovir before, while others had taken it alone for at least three months. Participants took Retrovir plus Videx, Retrovir plus Hivid, or Retrovir plus placebo.

After two and a half years, the results for people who had taken Retrovir before joining the trial were not encouraging. Adding

Videx to Retrovir improved survival compared to staying on Retrovir alone, but adding Hivid showed no benefit.

The participants who *hadn't* taken Retrovir before joining the Delta study experienced much more positive results; compared to people who took Retrovir alone, the death rate for those on Retrovir/Videx was reduced by 42% and for those on Retrovir/Hivid it was reduced by 32%. The results of the Delta study strongly suggested the benefit of using more than one drug to treat HIV and helped to establish both Videx and Hivid as useful components of what would come to be called combination therapy.

Early data from these trials, particularly ACTG 175, contributed to Hivid's approval. Unfortunately, once the trials were completed and the final results were available, it was clear that Hivid's role in the treatment of HIV was less promising than people had originally hoped.

Because of the availability of stronger, less toxic nucleoside analogs, Hivid has rarely been used in large trials of triple-drug combinations; therefore, there's little information comparing the effectiveness of Hivid to that of other NRTIs as part of various three-drug combinations.

Side Effects: The most common serious side effect of Hivid is peripheral neuropathy (tingling, pain, and numbness in the feet and hands), which occurs in 10-30% of people who take the drug. If the drug isn't stopped, the neuropathy is often irreversible, resulting in permanent nerve damage. Other side effects of Hivid can include rash, headache, fever, nausea, fatigue, sores in the mouth or esophagus, and rash. Another possible serious side effect is pancreatitis (inflammation of the pancreas). Symptoms of pancreatitis can include nausea, vomiting, diarrhea, and sharp pain in the back or upper abdomen. If you experience these symptoms while on Hivid, contact your healthcare provider immediately. Pancreatitis can be fatal.

Drug Interactions: Antacids that contain magnesium or aluminum (Rolaids, Maalox, Milk of Magnesia and others) decrease levels of Hivid in the blood, so don't take them together. Other drugs, such as amphotericin B (Amphocin, Fungizone and others), foscarnet (Foscavir), probenecid, and Tagamet (cimetidine) can *increase* levels of Hivid in the blood.

Hivid shouldn't be combined with Videx, Zerit (d4T), Epivir (3TC), or any other drug that has peripheral neuropathy as a possible side effect. Similarly, any drug that lists pancreatitis as a possible side effect should not be used with Hivid.

When To Consider It: It's probably best to avoid Hivid unless your umpteenth combination has failed you and you're trying to put together a rescue regimen. Hivid is no longer included in any



regimens recommended by the Department of Health and Human Services treatment guidelines for people who have never taken antiretrovirals before. In fact, one of the only times that the guidelines mention Hivid is to state that it "should rarely if ever be recommended."

You're unlikely to benefit from Hivid if your virus is already resistant to many of the NRTIs, including Videx, Zerit, Epivir and, probably, Retrovir. With the availability of drugs that are less toxic,

better studied, and easier to take – compounded by the risk of cross-resistance to other NRTIs – it's hard to know when to consider Hivid, if ever. Even as a component of a rescue regimen, cross-resistance to previously used NRTIs severely limits the benefits of the drug.

Good To Know:

- Your Hivid dose may need to be reduced if you have kidney problems.
- Rare cases of liver failure have been reported among people with hepatitis B infection who were taking Hivid. Anyone with liver problems should probably avoid Hivid or at least consider it with extreme caution.
- Avoid alcohol if you're taking Hivid, since alcohol can also cause pancreatitis.
- A study called HIVBID was designed to compare twice-a-day Hivid to twice-a-day Epivir, each combined with Retrovir and Viracept (nelfinavir). Perhaps not surprisingly, the study was unable to recruit the 100 participants it needed to move forward.

Pregnancy: Hivid is classified as an FDA pregnancy category C drug. No studies of Hivid have been conducted in pregnant women or children less than a month old. Certain cancers have occurred in rodents given very high doses of Hivid, and abnormalities including low birth weight and skeletal defects have been seen in offspring born to rodents given moderate to high doses. Hivid shouldn't be used during pregnancy unless the potential benefit outweighs the potential risk to the mother and fetus.

Dose: 2.25 mg a day, taken as one .75-mg tablet every eight hours, with or without food (although taking it on an empty stomach may improve absorption). Hivid also comes in .375-mg tablets. No liquid formulation is commercially available, although you can get it through a compassionate use program. Hivid is not recommended for pediatric use.

FDA Approval: 1992

Manufacturer: Hoffmann-La Roche

Patient Assistance Program: 800-282-7780

Zerit, Zerit XR (d4T, stavudine) – Zerit became the fourth drug available for the treatment of HIV when it was approved by the FDA in June 1994. The drug’s initial approval was only for people with advanced HIV disease who no longer responded to or who couldn’t tolerate the three drugs available at the time – Retrovir (AZT), Hivid (ddC) and Videx (ddI). Although the drug can cause serious side effects, it continues to be used in a variety of regimens. The original version was dosed every twelve hours, but once-a-day Zerit XR was approved in December 2002. Once Zerit XR is actually available in pharmacies, the drug will be able to be used as a part of complete once-daily regimens.

Background: The compound that would later be called Zerit was discovered in 1966 by a researcher working under a grant from the National Cancer Institute, part of the National Institutes of Health (NIH). In 1986, researchers at Yale University, also working under a grant from the NIH, discovered that the drug had activity against HIV in the test tube (*in vitro*) and filed for a patent. In early 1988, Yale licensed the marketing rights to Bristol-Myers Squibb (BMS). Within a few months, the first trial of Zerit began, conducted jointly by BMS and the NIH. Five years later, Zerit was approved by the FDA. Many people felt that Zerit was a more promising drug than Videx and were angry that BMS had put Zerit on the back burner as the company moved forward with its development of Videx.

Zerit was granted accelerated approval based on early, partial results from an ongoing BMS study called AI455-019 (019 for simplicity’s sake) and some data from the drug’s parallel track program (similar to expanded access programs used today). 019 was a double-blind study that began enrolling in May 1992. The 822 participants had been on Retrovir for at least six months (many for much longer) and had never taken Hivid or Videx. They either continued taking Retrovir alone or switched to Zerit. The FDA looked at data on 359 people who had been in 019 for at least four months. Most of the people who had stayed on Retrovir had a CD4 count drop within two weeks of starting the study, while those who switched to Zerit had CD4 cell increases through five months, after which CD4 counts began to decrease. CD4 counts were available for some participants who had been in the study for over a year and a half – those on Zerit had an average decrease of 18 CD4 cells compared to an average decrease of 70 in those on Retrovir. In addition, the people on Zerit showed some weight gain compared to those on Retrovir who showed weight loss.

Final results of 019 were reported at a conference in mid-1995 and published in 1997. They confirmed that the preliminary results indicating Zerit’s ability to raise CD4 counts translated to clinical benefit. After a little over two years of treatment, people on Zerit did better than those on Retrovir in almost every way measured,

including higher CD4 counts, fewer new or recurrent opportunistic infections, less deaths, and better quality of life. In the end, not surprisingly, the trial showed that it was better to switch to Zerit monotherapy than to continue Retrovir monotherapy.

Moving on to combination regimens containing Zerit, the six-month French ALBI (ANRS 070) trial conducted in 1999 compared the combinations of Zerit plus Videx to Retrovir plus Efavir to a strategy that alternated the two combinations in 151 people who had never taken antiretrovirals before. The Zerit plus Videx combination was far superior in raising CD4 counts and lowering viral loads compared to the other two arms of the trial. As a result,

Zerit plus Videx was widely prescribed for a while as the dual-nucleoside backbone to many three-drug combinations. Other research has found less positive results for this particular nucleoside pair.

ACTG 384, for example, was a complex trial that began enrolling participants in 1998. The trial studied either Zerit plus Videx or Retrovir plus Efavir in combination with the protease inhibitor Viracept (nelfinavir), the non-nucleoside Sustiva (efavirenz), or both as starting regimens in 960 people who had never been on antiretrovirals. Overall, Sustiva/Retrovir/Epivir was

the most beneficial triple-drug combination studied in the trial, and people taking Sustiva/ Retrovir/Epivir had a better treatment response and fewer side effects than those taking Sustiva/Zerit/Videx.

START I and START II were sister trials that compared three different pairs of nucleoside analogs, each in combination with the protease inhibitor Crixivan (indinavir). The nucleoside pairs were Zerit plus Videx, Zerit plus Epivir, and Retrovir plus Epivir. Most of the 409 participants in the START trials had never been on anti-HIV treatment (some had been on treatment for less than four weeks), and none of the participants had ever taken a protease inhibitor or Epivir. After three years of follow-up, there were no significant differences between how well the three regimens worked. The three groups had similar results in terms of CD4 cell increases and the percentage of participants with viral loads below 500 copies.

Since ACTG 384 and the START trials began to enroll, it has become clear that combining Zerit with Videx should be avoided because of overlapping toxicities – peripheral neuropathy (tingling, pain, and numbness in the feet and hands) and pancreatitis (inflammation of the pancreas). It has also become increasingly clear in recent years that Zerit is specifically associated with lipodystrophy (fat loss in the arms, legs, face, and butt) and increased lipid levels (cholesterol and triglycerides).

A sub-study of about a third of the ACTG 384 participants used DEXA scans to measure changes in body fat in people on Zerit plus Videx compared to those on Retrovir plus Epivir. DEXA



(Dual Energy X-ray Absorptiometry) scans measure body composition in terms of fat and fat-free mass in the arms, legs, trunk, and whole body. The sub-study (ACTG 5005s) found that, on average, the Zerit/Videx regimen caused a greater loss of fat in the arms and legs than the Retrovir/Epivir regimen. People taking Zerit plus Videx had lost significantly more limb fat than people taking Retrovir plus Epivir after 48, 64, and 80 weeks on treatment. In fact, by week 80 (more than a year and a half on treatment), people on Zerit plus Videx had about 15% less limb fat than when they joined the study, compared to a 7% loss in people taking Retrovir plus Epivir.

Similarly, results of a sub-study of CPCRA 058 (also called the FIRST study) were presented in July 2003. CPCRA 058 is a large trial comparing various combinations in people who are just starting anti-HIV treatment. Most participants used Zerit plus Videx or Epivir plus Ziagen (abacavir) as their dual nucleoside backbone. Using bioelectric impedance analysis (BIA) and physical measurements, the sub-study of 182 trial participants showed that people taking Zerit plus Videx as the backbone of their three-drug regimen were significantly more likely than those taking Epivir plus Ziagen to experience fat loss after almost three years on treatment.

These sub-studies aren't able to tell us whether Videx also contributed to the loss of body fat since it was paired with Zerit in both trials, but numerous other studies have shown that Zerit is particularly associated with the loss of body fat.

The TARHEEL study (ESS40010) was designed to see if people with lipoatrophy who were doing well on regimens that included Zerit might benefit by switching from Zerit to either Retrovir or Ziagen. The 118 trial participants had been on Zerit for at least six months, most of them (82%) for more than two years. 75% switched to Ziagen and 25% to Retrovir. After 48 weeks, people had average fat increases of 25% in their arms, 15% in their legs, and 23% in their trunks compared to when they entered the study. The increases were more significant in people who switched to Ziagen than in those who switched to Retrovir. This small study shows that switching from Zerit to another nucleoside analog helps some people regain some of the fat they lost while on the drug – without sacrificing anti-HIV activity.

Gilead Sciences' study 903 compared their nucleotide analog, Viread (tenofovir), to Zerit in 600 people who had never been on antiretrovirals before. Trial participants took the non-nucleoside Sustiva, Epivir, and either Viread or Zerit. After almost two years on treatment, both groups did equally well in terms of CD4 counts and viral loads. But there were statistically significant differences in triglycerides, total cholesterol, LDL (bad) cholesterol, and HDL (good) cholesterol between the groups, and the differences were all in Viread's favor. People on Viread also had significantly more limb fat than those on Zerit.

In 2002, with the momentum shifting toward simpler, more convenient dosing, BMS received FDA approval for Zerit XR, extended release capsules that are taken once a day. Zerit's origi-

nal formulation had to be taken every twelve hours. Data from clinical trials show the two versions to be equivalent in terms of effectiveness and side effects. Unfortunately, Zerit XR has not reached pharmacy shelves yet. According to BMS, the complex process required to manufacture Zerit XR has delayed the release of the once-a-day formulation. Hopefully, it will be available soon.

Side Effects: The most common side effect of Zerit is peripheral neuropathy, which occurs in 15-20% of people on the drug and ranges in severity from mild to severe. If neuropathy occurs and Zerit isn't stopped, it can become irreversible, resulting in permanent nerve damage. Although peripheral neuropathy usually goes away if Zerit is stopped early enough, the symptoms often get worse for a couple of weeks before they get better. Factors that contribute to the likelihood of experiencing peripheral neuropathy while on Zerit include advanced HIV disease, higher doses of Zerit, pre-existing neuropathy, and other drugs that have peripheral neuropathy as a possible side effect such as Videx, Hivid, amphotericin B, Foscavir (foscarnet), dapsone or vincristine.

Less serious possible side effects of Zerit include nausea, vomiting, chills, fever, diarrhea, headache, rash, and elevated liver enzymes. If you experience any of these side effects, they usually go away after the first few weeks on the drug.

A rare but potentially dangerous side effect of Zerit is pancreatitis, which is more likely to occur if Zerit is taken with Videx. Symptoms of pancreatitis can include nausea, vomiting, diarrhea, blood in the urine, and sharp pain in the back or upper stomach. If you experience these symptoms while on Zerit, contact your healthcare provider immediately.

Various aspects of lipodystrophy are at least partly caused by the nucleoside analogs, but many studies have specifically linked lipoatrophy (fat loss) and, to a lesser degree, increased lipid levels to the use of Zerit (see above).

Lactic acidosis is another possible side effect of all of the nucleoside analogs, but Zerit seems to increase the risk. Some pregnant women on regimens that included both Zerit and Videx have had fatal cases of lactic acidosis. The combination of these two drugs should be avoided during pregnancy.

Drug Interactions: Zerit has relatively few drug interactions. The main drugs to avoid are those that may contribute to Zerit's side effects, such as those listed above that also have peripheral neuropathy as a possible side effect. Drugs that may increase the risk of pancreatitis, such as Cytovene (oral ganciclovir), rifampin, and Mycobutin (rifabutin), should also be avoided, especially if you're taking Videx with Zerit. Taking ribavirin for the treatment of hepatitis C while on Zerit may increase the risk of lactic acidosis and lipoatrophy. Test tube (*in vitro*) studies indicate that ribavirin and Doxil (doxorubicin), used to treat some cancers including Kaposi's sarcoma, may lower levels of Zerit in the body, reducing the drug's anti-HIV effect. Zerit shouldn't be used with Retrovir because the two drugs work against each other in the body, resulting in less anti-HIV activity.

(continued on next page)

Zerit *(continued from previous page)*

When To Consider It: The question of when it's best to use Zerit while developing a strategy for sequencing antiretrovirals has often been somewhat controversial. As described in the section on Retrovir, the backbone of an HIV regimen is usually a pair of NRTIs, combined with a third or fourth drug – most often an NNRTI or PI. Either Retrovir or Zerit are often part of a first-line combination (though not both), and researchers have tried to figure out which of the two is better to use first (see page 5).

The current Department of Health and Human Services (DHHS) treatment guidelines recommend Retrovir/Epivir as the dual nucleoside combination “of choice” based on its effectiveness, safety, few interactions with other drugs, the probability of developing resistance mutations, and dosing convenience. Yet the DHHS guidelines recommend Zerit as part of many regimens for people who have never taken antiretrovirals before. The language in the guidelines is vague and confusing about the use of Zerit, frustrating community activists and healthcare providers – the drug is strongly recommended in some prominent sections, while its potential dangers are only occasionally mentioned or almost hidden in secondary sections. The bottom line is that Retrovir/Epivir really is the preferred dual nucleoside combination.

The DHHS recommendations are in stark contrast to those of the British HIV Association (BHIVA). Because of the risks of lipodystrophy and increased lipids, the July 2003 BHIVA treatment guidelines strongly recommend against using Zerit as part of a first regimen. Of course, not everyone on Zerit experiences fat loss or increased lipid levels, even after being on it for years. These are just two of many factors to take into account when considering the potential risks and benefits of the drug.

When Zerit was first approved, it wasn't believed that resistance was as much of a problem with this drug as with other NRTIs. In recent years, however, researchers have come to recognize that Zerit's resistance profile is very similar to that of Retrovir. HIV that becomes resistant to Zerit will probably be resistant to Retrovir – and vice versa. And as with Retrovir, HIV that has become resistant to Epivir is often more sensitive to Zerit. Some of the mutations (called thymidine analogue mutations) that arise during therapy with either Zerit or Retrovir can cause cross-resistance to almost all of the available NRTIs. But this seems to happen rarely, and most HIV that's resistant to Zerit (or Retrovir) is still sensitive to NRTIs like Ziagen and Videx.

Good To Know:

- HIV reproduces in many parts of the body, including the brain. Zerit is one of only a few antiretrovirals with the ability to cross the blood-brain barrier. This makes the drug effective against HIV in the brain and central nervous system and may help prevent neurological disease like dementia.
- Because of overlapping toxicities, including peripheral neuropathy, the combinations of Zerit plus Videx and Zerit plus Hivid should be avoided if possible.

- Heavy alcohol use can increase the risk of pancreatitis and liver damage. If possible, avoid alcohol while taking Zerit.
- Your Zerit dose may need to be reduced if you have kidney problems.
- Taking Zerit and Viramune (nevirapine) at the same time could increase the risk of severe liver toxicity, especially in women. If both drugs are included in a combination, careful and regular monitoring of liver function is particularly important.
- The Zerit XR capsules, once they become available, can be opened up and their contents mixed with some yogurt or applesauce. Swallow the mixture whole – no chewing or you'll crush the beads. Consume the tasty mixture right away – don't save it for later!

Pregnancy: Zerit is classified as an FDA pregnancy category C drug. When high doses of Zerit were given to pregnant rats, some developmental problems to the fetus were seen. According to the Antiretroviral Pregnancy Registry, when Zerit has been used during the first trimester, the prevalence of birth defects was 2.2%, compared to an overall prevalence of 3.1% in the U.S. population. But the FDA and Bristol-Myers Squibb issued a warning that pregnant women may be at increased risk of fatal lactic acidosis when prescribed a combination that includes Zerit and Videx. These drugs should only be prescribed together for pregnant women if the potential benefit clearly outweighs the potential risk to the mother and fetus.

Dose:

- **Zerit** is taken twice a day (every twelve hours), with or without food. Capsules are available in 15, 20, 30, and 40-mg versions. The dosage is based on weight. People who weigh 60 kg (132 pounds) or more take 80 mg a day (40 mg every twelve hours); those who weigh less than 132 pounds take 60 mg a day (30 mg every twelve hours). The pediatric dose (ages two weeks and older) is 1 mg/kg every twelve hours. Children who weigh 30 kg (66 pounds) or more take the recommended adult dosage. Zerit is also available as a fruit-flavored powder that your pharmacist mixes with purified water, providing 1 mg of drug per mL of solution.
- **Zerit XR** capsules, once they're available, will be taken once a day, with or without food. The capsules will come in 37.5, 50, 75, and 100-mg versions. The dosage is based on weight. People who weigh 60 kg (132 pounds) or more will take one 100-mg capsule once a day; those who weigh less than 132 pounds will take one 75-mg capsule once a day. There is no pediatric version of Zerit XR.

FDA Approval: Zerit 1994; Zerit XR 2002 (not yet available)

Manufacturer: Bristol-Myers Squibb

Patient Assistance Program: 877-758-7877

Epivir (3TC, lamivudine) is a powerful drug with minimal side effects, an easy dosing schedule, and few drug interactions. It may be one of the most useful nucleoside analogs available, particularly if it's used strategically. By the time it received accelerated approval from the FDA in November 1995, close to 30,000 people had already received Epivir through the largest expanded access program ever. To qualify for the expanded access program, you had to have a CD4 count less than 300 and have already failed or be unable to tolerate the four approved anti-HIV therapies. The large number of people who were eligible for the program is a reminder of how very few treatment options were available at the time – and how desperately new treatments were needed.

Background: In the early '90s, clinical trials were designed to study what happened when people took a two-drug combination compared to taking one drug alone – usually Retrovir (AZT). When the results of these studies, particularly ACTG 175 and the Delta study (described in the discussion of Hivid on page 8), were released in late 1995, the message was clear – combination therapy was dramatically more effective at slowing HIV disease progression and prolonging survival than taking only one drug (monotherapy).

Although there have been many trials to determine the safety and effectiveness of Epivir, perhaps the most influential was the large, international CAESAR study, named for the regions in which it was conducted – Canada, Australia, Europe, and South Africa. In July 1996, this trial was stopped early when a planned interim analysis showed that adding Epivir to other antiretroviral treatments cut HIV disease progression and death in half. The study had enrolled 1,892 people with CD4 counts between 25 and 250. Upon entry, almost all of the participants were taking Retrovir alone, Retrovir plus Videx (ddI), or Retrovir plus Hivid (ddC). Some had never taken any antiretrovirals before. The participants were then randomly assigned to add placebo, Epivir, or Epivir plus loviride (an experimental non-nucleoside reverse transcriptase inhibitor that was never approved) to their current treatment.

After about a year of follow-up, the rate of disease progression to a new AIDS-defining condition or death was 17% in the group that added placebo to their treatment, 9% in the group that added only Epivir, and 8% in the group that added Epivir plus loviride. In other words, adding Epivir (with or without loviride) showed a 54% reduction in the risk of disease progression or death compared to people who remained on their current treatment alone (those who were given placebo). Changes in CD4 cell counts and viral load levels in a small group of study participants were consistent with the clinical results. When the trial was stopped in mid-'96, all participants were offered Epivir with or without loviride. The CAESAR study also found that adding Epivir to the other

medications caused no additional side effects. While highlighting the positive impact of Epivir on slowing disease progression, these results also provided further evidence of the effectiveness of combination therapy.

Many later studies of protease inhibitors, NNRTIs, and triple-nucleoside regimens have included Epivir as part of their comparative combinations and shown it to be an effective component of many different regimens.

Side Effects: The most common side effects of Epivir include headache, fatigue, nausea, and vomiting. Rare side effects include trouble sleeping, nasal congestion, cough, and, for a very few people, mild hair loss. Peripheral neuropathy (tingling, pain and numbness in the feet and hands) has been associated with Epivir, but is nowhere near as common or severe as that seen with Videx, Hivid, or Zerit (d4T). Pancreatitis (inflammation of the pancreas) is a rare but possible side effect of Epivir, particularly in children.

Drug Interactions: Epivir has fewer problematic drug interactions than just about any other approved antiretroviral. It shouldn't be taken with Hivid because the two drugs interfere with each other. Blood levels of Epivir may

increase when taken with TMP/SMX (Bactrim, Septra), which is used to prevent PCP (pneumocystis pneumonia). These increased levels usually don't require changing the dose of either drug.

When To Consider It: As you develop a treatment plan, figuring out when and how to use Epivir is important. It can be useful for people just starting treatment as well as for those who have had experience with a lot of antiretrovirals.

If Epivir were taken alone, complete resistance to the drug would develop very quickly, usually within a few weeks. It only takes one mutation (change) in HIV's reverse transcriptase enzyme to make HIV completely resistant to Epivir. It's important to consider this rapid development of resistance when putting together a regimen. If adherence is likely to be a problem, it might not be a great idea to include Epivir in your combination since you're likely to become resistant to the drug very quickly if you miss doses.

Even if your virus is resistant to Epivir, it's possible to keep the drug as part of your three- or four-drug combination and still maintain a low viral load and high CD4 count. HIV that's resistant to Epivir usually can't reproduce as readily as HIV that doesn't have that particular mutation. Also, HIV that's resistant to Epivir is often more sensitive to other anti-HIV drugs, particularly Retrovir, Zerit, and Viread (tenofovir). It's not unusual to stay on an Epivir-containing regimen even when resistance to Epivir has been documented through resistance testing.

(continued on next page)



Epivir *(continued from previous page)*

But resistance to Epivir isn't always a blessing. If your HIV is resistant to Epivir, for example, it will also be resistant to Emtriva (emtricitabine), which is called cross-resistance. Epivir resistance can also affect HIV's sensitivity to Videx, Hivid, and Ziagen (abacavir).

As described in the section on Retrovir (page 3), the backbone of an HIV regimen is usually a pair of nucleosides, combined with a third or fourth drug – most often an NNRTI or PI. Recent research tends to favor Retrovir/Epivir over other nucleoside pairs. The current Department of Health and Human Services (DHHS) treatment guidelines recommend Retrovir/Epivir as the dual nucleoside combination “of choice.” Epivir also figures as part of the two dual-nucleoside pairs described in the DHHS guidelines as alternatives: Epivir/Zerit or Epivir/Viread.

Epivir's efficacy, minimal side effects, few drug interactions, and relatively easy dosing schedule support its inclusion in many combinations. It has the singular distinction of being a component of all 21 regimens that the DHHS guidelines recommend as possibilities for people who have never taken antiretrovirals before.

Hepatitis B: Epivir is also approved for the treatment of chronic hepatitis B (HBV) infection under the brand names Epivir HBV in the United States and Zeffix in most other countries. Before beginning an HIV regimen that includes Epivir, it's a good idea to be tested for chronic HBV, since your use of the drug could change depending on the results. The usual dose to treat HBV is 100 mg a day, one-third the dose used in HIV. People co-infected with HIV and chronic HBV should take the higher HIV dose – if they take Epivir at all. Chronic HBV is sometimes treated using a combination of therapies, and combination therapy for chronic HBV is likely to be the norm in the future. Using Epivir as part of your anti-HIV combination could mean single-drug therapy for your HBV and cause your hepatitis B to become resistant to the drug. The result could be fewer treatment options for your HBV in the future. Including Viread, another anti-HIV drug with activity against HBV, in your combination with Epivir is another choice.

If you've been taking Epivir, are co-infected, and plan to stop Epivir, your HBV may flare-up once the Epivir is removed, possibly causing liver damage. Be sure to have your liver enzyme levels checked regularly if you stop taking Epivir and have chronic HBV. Even if your HIV becomes resistant to Epivir, it might be worthwhile to stay on the drug to help keep your HBV in check.

Good To Know:

- GlaxoSmithKline is developing an Epivir/Ziagen combination tablet to be taken once a day that contains 600 mg of Ziagen and 300 mg of Epivir.

- If you have any kidney problems, be sure to let your health-care provider know before taking Epivir. Your dose may need to be lowered.

Pregnancy: Epivir is classified as an FDA pregnancy category C drug. Its safety in human pregnancy hasn't been determined and animal studies haven't shown fetal risk, but the drug shouldn't be used during pregnancy unless the potential benefit outweighs the potential risk to the mother and fetus. According to the Antiretroviral Pregnancy Registry, when Epivir has been used during the first trimester, the prevalence of birth defects was 3.0%, compared to an overall prevalence of 3.1% in the U.S. population. In other words, using Epivir during the first three months of pregnancy – the time when a fetus is most susceptible to birth defects caused by toxic chemicals and medications – doesn't seem to have any serious effects.

Dose: 300 mg a day, taken as one 300-mg tablet once a day or one 150-mg tablet twice a day with or without food. For adults who weigh less than 110 pounds (50 kg), the dose should be adjusted to 2 mg/kg twice a day. Epivir is also available as a flavored syrup that contains 10 mg/mL and as part of the combination pills Combivir and Trizivir (see pages 20 and 21). Someone who weighs 90 pounds (41 kg) would need to take 82 mg of Epivir twice a day, not an easy trick considering the formulations. The pediatric dose (ages 3 months to 16 years) is based on weight: 4 mg/kg twice a day up to a maximum of 150 mg twice a day.

FDA Approval: 1995. Once-a-day dosing approved in 2002.

Manufacturer: GlaxoSmithKline

Patient Assistance Program: 866-728-4368

HIV Service Providers: We Want You for an Important Web Research Study

ACRIA is collaborating with researchers from Indiana University on a study of issues facing those who work or volunteer for HIV organizations. If you work in an HIV prevention or HIV care program, we invite you to participate in this exciting study. The purpose of this study is to better understand the extent to which HIV service providers may benefit from HIV prevention programs or programs designed to assist them in other areas of their job.

Participation is completely anonymous and voluntary. Completion of the survey will occur via the internet and will take approximately 20 minutes. Visit the ACRIA website if you want to participate, www.acria.org.

Ziagen (abacavir sulfate, ABC), approved by the FDA in December 1998, was the first new NRTI to become available in the era of Highly Active AntiRetroviral Therapy (HAART). As such, it had to compete for a special place in combination therapy. Initial studies of Ziagen had shown it to be as powerful as a protease inhibitor at lowering viral load when taken alone, so the drug's manufacturer, GlaxoSmithKline, positioned (and priced) it as an alternative to a protease inhibitor or non-nucleoside as part of a three-drug combination. Two serious obstacles have kept that strategy from working as well as the company might have hoped: the dangerous allergic reaction that Ziagen can cause, and the failure of triple-nucleoside regimens to work as well as predicted.

Background: Before Ziagen's approval, many studies compared various two-drug combinations to two- or three-drug combinations that contained Ziagen. In most cases, Ziagen-containing regimens were better at lowering viral loads and raising CD4 counts than regimens without the drug. To understand how Ziagen might best be used today, we need to look at clinical trials that compare three-drug combinations, at least one of which includes Ziagen. Two such trials – CNA3005 and CNA3014 – compared Ziagen to the protease inhibitor Crixivan (indinavir), both taken with Combivir (Retrovir [AZT] plus Epivir [3TC]). The trial participants had never taken antiretrovirals before.

CNA3005 was double-blind and placebo-controlled for dosing and number of pills, meaning that neither the 562 participants nor the investigators knew which combination individual participants were taking. These precautions tried to ensure that adherence issues wouldn't cloud the results since Crixivan is dosed every eight hours without food and requires drinking a lot of water while Ziagen is dosed every twelve hours with no food restrictions. By the end of 48 weeks, there was no significant difference in the percentage of people taking Ziagen with viral loads below 50 copies (40%) and those taking Crixivan (46%). But when the researchers looked at those trial participants whose viral loads were above 100,000 before starting treatment, they found that the Ziagen regimen was significantly less likely than the Crixivan regimen to bring viral loads down to below 50 copies (31% compared to 45%). These results suggest that the combination of Ziagen, Retrovir, and Epivir (and perhaps any triple-NRTI combination) is not for someone with a high viral load, particularly if it's above 100,000.

CNA3014 compared the same two regimens, but this trial was open-label, meaning that the 342 participants knew what they were taking. After 48 weeks, the two groups had similar results in terms of reducing viral load to below 50 copies regardless of

whether the participants' viral loads were above or below 100,000 before starting treatment. In fact, the Ziagen group tended to do better than the Crixivan group in almost all respects. This may have been because adherence was much better in the Ziagen group – 78% of the people taking the Ziagen/Combivir regimen reported being completely adherent compared to only 48% of those taking the much more complicated Crixivan/Combivir regimen. Although difficult to measure, the difference between the results of this trial and those of CNA3005 could be attributed to the discrepancies in adherence.

Unfortunately, early results from a large clinical trial called ACTG 5095 confirmed the results of CNA3005. In March 2003, the Data and Safety Monitoring Board (DSMB) for ACTG 5095 stopped the Ziagen/Retrovir/Epivir arm of the study when participants on that regimen experienced pre-defined virologic failure earlier and more often than participants on the two study regimens that didn't include Ziagen. ACTG 5095 involved 1,147 participants and was designed to compare Ziagen/Retrovir/Epivir (taken as Trizivir) to the non-nucleoside, Sustiva (efavirenz), taken with Retrovir and Epivir to a regimen of all four drugs. This study, too, was for people who had never taken antiretrovirals before. It was double-blind and placebo-controlled for dosing and number of pills.



When the DSMB reviewed the results at 32 weeks, they found that 21% of the participants in the Trizivir arm had experienced virologic failure compared to 11% of the participants on the two Sustiva-containing regimens combined, a highly significant difference. This difference was seen in people who began treatment with viral loads above and below 100,000. Virologic failure was defined as having a viral load greater than 200 at least four months after starting treatment. The Trizivir arm of the trial was stopped and participants in that group were offered other treatment. The closing of this arm of the study doesn't necessarily mean that the combination of Ziagen/Retrovir/Epivir (or Trizivir) doesn't have an important role in HIV treatment, but its role might be more limited than initially thought.

Glaxo's focus on making Ziagen work as a part of the combination pill, Trizivir, has resulted in less attention to the study of Ziagen for other purposes. But Ziagen works well with many other anti-HIV medications and can be used effectively in a number of situations.

One possibility is to add Ziagen to a regimen that's working relatively well to get a better antiviral response – a strategy called intensification. The CNA3002 study included 185 people who had been on treatment for at least three months and as long as three years. They had viral loads between 400 and 50,000 and an

(continued on next page)

Ziagen *(continued from previous page)*

average CD4 count of 410. Most of the participants were on two-drug combinations before joining the trial. Everyone continued on their current regimens and added either Ziagen or a placebo. After 48 weeks, 25% of the participants on Ziagen had viral loads less than 400 copies compared to 6% of those on placebo. Looking just at the people who took Ziagen, 41% of those who started the trial with viral loads below 5,000 had viral loads less than 400 copies at the end of 48 weeks compared to 9% of those who started the trial with viral loads above 5,000.

There's also evidence that switching from a protease inhibitor (PI) to Ziagen may help reduce high lipid levels (triglycerides and cholesterol) caused by many PIs while still keeping virus levels low. CNA30017, a trial of 211 people on PI regimens, compared those who stayed on their regimens to those who switched their PI for Ziagen. At the beginning of the trial, everyone had viral loads below 50. After 48 weeks, more people who stayed on their PI experienced treatment failure than those who switched to Ziagen (23% vs. 12%, a statistically significant difference). Treatment failure was defined as having two consecutive viral loads above 400 or leaving the study for any reason, including side effects. The people who switched to Ziagen also experienced statistically significant decreases in triglycerides and cholesterol levels and improvements in lipoatrophy (fat loss) and central fat accumulation. Overall, in this trial, the switch to Ziagen provided some benefit without sacrificing the virologic success achieved by starting treatment with a protease inhibitor.

Ziagen may also be useful as a replacement for Zerit (d4T) in the regimens of people who are experiencing lipoatrophy, an increasingly recognized side effect of Zerit. A number of small studies have shown that replacing Zerit with Ziagen may slow down the rate of fat loss – or even reverse it – while maintaining low or undetectable viral loads.

Side Effects: The side effects of Ziagen are usually relatively mild and can include nausea, vomiting, fatigue, headache, fever, rash, diarrhea, and loss of appetite.

Hypersensitivity Reaction: The most serious side effect of Ziagen is a life-threatening hypersensitivity reaction (a severe allergic reaction) that occurs in about 5% of people who take the drug (the numbers vary a lot from study to study, ranging from 1.5% to 10%). Symptoms usually appear within the first two to six weeks on the drug, although the reaction can occur even after you've been on Ziagen for a while. A series of symptoms generally builds up, often getting worse as more doses are taken. Symptoms include a skin rash or two or more other symptoms such as fever, nausea, vomiting, diarrhea, abdominal pain, severe tiredness, or aching muscles or joints. Respiratory symptoms (cough, shortness of breath, and/or sore throat) sometimes occur, but are almost always accompanied by nausea, vomiting, and/or diarrhea. If you suspect that you may be experiencing Ziagen hypersensitivity, call your doctor immediately. If it's determined

that you're experiencing a hypersensitivity reaction, you'll need to stop the drug and must not start it again. If you restart the drug, the allergic reaction can reoccur within hours, be much more severe than the first time, and may be extremely dangerous, even fatal.

Some people may experience a hypersensitivity reaction without recognizing it, either because they stopped the drug for some other reason before symptoms of the reaction occurred or were diagnosed or because the initial symptoms were diagnosed as something else such as an acute respiratory disease (even the flu). For these reasons, if you took Ziagen once for even a short time and suffered no noticeable hypersensitivity reaction, be aware if you decide to start the drug again – it could be the same as restarting the drug after experiencing a hypersensitivity reaction.

Starting Ziagen at the same time as you start another drug that can cause a rash or other similar systemic reaction may make it more difficult to diagnose a hypersensitivity reaction to Ziagen. Examples of such drugs include sulfa-based antibiotics such as Bactrim and Septra, used to prevent and treat PCP (pneumocystis pneumonia), the non-nucleosides Sustiva (efavirenz) or Viramune (nevirapine), and the protease inhibitor Agenerase (amprenavir).

Drug Interactions: There are very few significant drug interactions associated with Ziagen. Alcohol can increase the amount of Ziagen in the blood by as much as 40%, but the increase doesn't require a reduction in your Ziagen dose. You may experience more side effects if you're a heavy drinker and taking Ziagen, so you might want to avoid combining the two. High doses of Ziagen can reduce methadone levels. A very small number of people on methadone maintenance may require an increase in their methadone dose if they're also taking Ziagen at the usual dose.

When To Consider It: As part of a triple-NRTI regimen when you're just starting treatment, Ziagen may not be as useful as originally hoped – but it can still be useful in many other situations. Recent trials, for example, have shown promising results for people beginning treatment with regimens that included a protease inhibitor or non-nucleoside and the NRTI backbone of Ziagen and Efavirenz.

The mutations required to make your virus resistant to Ziagen are complex. If you took Retrovir for a long time by itself, later took Efavirenz, and developed resistance to both, it's unlikely that you'll benefit from Ziagen. Efavirenz resistance combined with high-level Retrovir resistance (three or more resistance mutations) makes Ziagen ineffective. People who have resistance to Efavirenz but not to Retrovir may still benefit from Ziagen, though. If you develop a particular mutation (K65R) that makes your virus resistant to Ziagen, you probably won't benefit from Viread (tenofovir), Videx (ddI), or Hivid (ddC) because of cross-resistance.

Ziagen is a strong drug with lots of potential. It may be useful as one of the two NRTIs in a starting regimen, particularly with

Epivir. It may be useful as an addition to a regimen that's already working well, to intensify the anti-HIV effect and decrease viral loads further. And it may be useful as a replacement for a protease inhibitor, the NRTI Zerit, or even a non-nucleoside, once viral load is under control. Preliminary data suggest that these uses offer some benefit, but more and larger studies are needed to better understand when it's most valuable.

Good To Know:

- Ziagen is one of only a few antiretrovirals with the ability to cross the blood-brain barrier. This makes the drug effective against HIV in the brain and central nervous system and may help prevent neurological disease like dementia. It's important to include at least one antiretroviral that crosses the blood-brain barrier in your combination.
- In July 2003, a study comparing the combination of Viread, Epivir, and Ziagen to the combination of Sustiva, Epivir, and Ziagen found that the people receiving Viread responded very poorly compared to those receiving Sustiva. The Viread arm of the trial was stopped. Another study was stopped early in October 2003 due to poor results in people taking Viread, Epivir, and Videx. The reasons for these poor results are unclear, but until they're better understood, it may be best to avoid using Viread as part of a triple-NRTI regimen, including one that contains Ziagen.
- GlaxoSmithKline is developing an Epivir/Ziagen combination tablet to be taken once a day that contains 600 mg of Ziagen and 300 mg of Epivir.
- A once-a-day formulation of Ziagen is now in clinical trials.

Pregnancy: Ziagen is classified as an FDA pregnancy category C drug. No studies of Ziagen have been conducted in pregnant women or children less than a month old. Some animal studies have shown risk to the fetus and others are ongoing. Ziagen shouldn't be used during pregnancy unless the potential benefit outweighs the potential risk to the mother and fetus.

Dose: 600 mg a day, taken as one 300-mg tablet twice a day with or without food. Ziagen is also available as a flavored liquid that contains 20 mg/mL and as part of the combination pill, Trizivir (see page 21). The pediatric dose (ages 3 months to 16 years) is based on weight: 8 mg/kg twice a day up to a maximum of 300 mg twice a day.

FDA Approval: 1998

Manufacturer: GlaxoSmithKline

Patient Assistance Program: 866-728-4368

Viread (tenofovir disoproxil fumarate, TDF) was approved by the FDA in October 2001 and is still the only *nucleotide* analog available. Nucleotide analogs work like nucleoside analogs (Retrovir [AZT], Videx [ddI], Zerit [d4T], etc.) but need one less chemical step to interfere with HIV replication. Once inside a cell, they work just like nucleosides and can have the same side effects.

Background: Viread is Gilead Sciences' second attempt to enter the HIV market. Their first nucleotide, adefovir, was denied FDA approval in 1999 due to its kidney toxicity. A lower dose of adefovir was later approved for hepatitis B and is marketed under the brand name Hepsara. Viread was in a much earlier stage of development at the time, but Gilead decided to drop adefovir for HIV and concentrate instead on Viread.



It was a smart move. Viread has not shown the same level of kidney problems as adefovir, although they can still occur. And it has been shown to be more effective, lowering viral load significantly (1.2 logs, or 94%) in people who have never taken anti-HIV drugs.

The major study of Viread in people who have not taken anti-HIV drugs was Study 903, a trial of 600 people taking the non-nucleoside Sustiva (efavirenz) and Epivir (3TC), along with either Viread or Zerit. Since Sustiva plus Epivir plus Zerit was a popular combination when the study opened in March 2000, this was an important comparison. Viread did well, showing similar efficacy to Zerit but causing smaller increases in cholesterol and triglycerides. After 96 weeks, LDL (bad) cholesterol increased 20 mg in the Zerit group compared to an 11 mg increase in the Viread group, a significant difference. Triglycerides increased 103 mg with Zerit but only 5 mg with Viread. And so far, Viread seems to do better in terms of body fat redistribution – doctors reported lipodystrophy in 12% of people on Zerit, but in only 1% of people on Viread.

The most closely watched trial, and the one that led to Viread's FDA approval, was Study 907. In this trial, 550 people who were already taking anti-HIV drugs but who had viral loads between 400 and 10,000 added either Viread or a placebo to their current regimen for six months. After six months, over 40% of people taking Viread had viral loads below 400, compared to only 11% of those taking placebo. Of course, since people stayed on their original drugs, some of which their virus was probably resistant to, they may have been on virtual monotherapy with Viread. It's best to change two or three of your drugs when switching, and, in that situation, Viread could be a potent part of a new regimen.

(continued on next page)

Viread *(continued from previous page)*

Since its introduction two years ago, Viread has become a popular drug due to its convenience and potency – New York State’s AIDS Drug Assistance Program reports that its use more than doubled in the last year. But Gilead has received two warning letters from the FDA regarding the company’s promotion of its drug. The first, in March 2002, said that Gilead representatives had “made false or misleading representations by describing Viread as ‘extremely safe,’ ‘no toxicities’... and characterizing it as a ‘miracle drug.’” Gilead promised to correct these practices, but the FDA had to send another letter in July 2003 saying that Gilead representatives had once again wrongly said that “because Viread is a nucleotide, not a nucleoside, it is ‘more potent,’ has ‘fewer side effects,’ and is ‘safer.’” Since the FDA feels these statements have not been proven, they are asking Gilead to retrain its sales force.

In addition, new data have questioned whether Viread should be used as the backbone of a HAART regimen. Two recent studies reported poor results when using Viread with two other NRTIs. In July 2003, a study comparing the combination of Viread, Epivir, and Ziagen (abacavir) to the combination of Sustiva, Epivir, and Ziagen found that close to 50% of people taking Viread either didn’t have a significant drop in viral load or saw it rise compared to only 5% of those taking Sustiva. The Viread arm of the trial was stopped. And in October 2003, another study was stopped early due to poor results in people taking Viread, Epivir, and Videx. We don’t know whether these results are due to some interaction inside the cell between Viread and the other drugs, or whether triple-NRTI combinations just aren’t strong enough in general. Until the reasons for these results are understood, it may be best to avoid using Viread as part of a regimen containing only two other NRTIs.

Side Effects: Viread’s most common side effects are gastrointestinal (nausea, diarrhea, vomiting, gas) and dizziness.

Viread carries the same toxicity concerns as all of the nucleoside analogs since it acts in the same way they do. The particular warnings that the FDA requires in the drug’s label are for lactic acidosis and liver enlargement. But Study 903 showed that people taking Viread had significantly less mitochondrial damage (which can lead to lactic acidosis) than those taking Zerit. This may be why Viread increased cholesterol and triglycerides less than Zerit and also raises hopes that Viread may lead to less lipodystrophy. We won’t know this for a while, though.

One of the major concerns when Viread was first being tested was kidney toxicity, since this had been the biggest problem with its cousin, adefovir. The studies of Viread didn’t show this to be a significant problem, but now that Viread is more widely used, reports of kidney failure are surfacing, especially among people who have some level of kidney damage before starting the drug. Gilead recently revised the package insert for Viread to add new dosing guidelines that reduce the dose for people with kidney impairment. Anyone taking Viread should closely monitor their kidney function, including creatinine levels, especially if they have more advanced HIV disease.

High doses of Viread caused bone problems in animals, so Study 903 was analyzed to see if this happened in humans. While people using Viread had more bone loss than those taking Zerit, they were still within normal ranges, and bone loss stabilized by the end of the first year on the drug. People who have a history of bone fractures or who are at particular risk for osteopenia should consider bone monitoring and possibly supplement with calcium and vitamin D.

Drug Interactions: Since Viread is eliminated mainly through the kidneys instead of the liver, it does not interact with most HIV drugs. Two exceptions are Videx and Reyataz (atazanavir). Viread can double the amount of Videx in the body, so these two drugs should only be taken together with caution, perhaps by taking only one 250-mg Videx EC capsule a day. On the other hand, Viread *decreases* the amount of Reyataz in the body by 25-40%. But one study (ANRS 107) found that when Reyataz (300 mg) was taken with Norvir (ritonavir) (100 mg) and Viread, the amount of Reyataz was higher than normal. More studies are planned to verify these data – in the meantime, anyone taking Reyataz with Viread should boost it with Norvir.

Any drugs that are cleared through the kidneys will compete with Viread and increase blood levels of these drugs, as well as the risk of kidney damage. These include Zovirax (acyclovir), Valtrex (valacyclovir), Cytovene (ganciclovir), Valcyte (valganciclovir), Foscavir (foscarnet), Vistide (cidofovir), amphotericin, and Vancocin (vancomycin). Mix these drugs with caution.

When To Consider It: The recently revised Department of Health and Human Services treatment guidelines put Viread on equal footing with Retrovir and Zerit as part of a “preferred regimen” with Epivir and Sustiva for people who have not taken anti-HIV drugs before. And they note that Viread caused less lipodystrophy and lipid abnormalities than Zerit. If this holds up in real-world use, Viread will be a major competitor with Zerit when it comes to picking a first regimen.

The mutation most linked to Viread resistance is K65R. People whose HIV has this mutation will most likely also be resistant to Videx, Epivir, and Hivid (ddC). But Study 908 showed that even people who are resistant to these and other drugs can get some benefit from Viread – so Viread may be useful in this situation, especially if you can replace your old drugs with one or two new ones.

Good To Know:

- Gilead recently received FDA approval for Emtriva (emtricitabine), an Epivir-like drug that is taken once a day. They are developing a Viread/Emtriva combination pill that they hope to release in 2005. That could be a useful combination and, with its once-daily dosing, would give Combivir some stiff competition. People who take it with Sustiva will take just two pills once a day – the most convenient regimen to date.
- Viread is also active against chronic hepatitis B (HBV) infection. People should be tested for chronic HBV before starting Viread, since there have been reports of disease flare-ups in people with HBV when they stop the drug.

(continued on next page)

Emtriva (emtricitabine, FTC), the most recently approved nucleoside analog, probably caused less excitement when it was approved in July 2003 than any anti-retroviral so far. Many people viewed it simply as a “me-too” drug because its chemical structure and activity are so similar to Efavirenz (EFV). Even Emtriva’s once-a-day dosing had lost its novelty by the time of its approval since a slew of other drugs, including Efavirenz, had been approved for once-a-day use by then.

Background: Emtriva has had a long development history involving several companies and two publicly announced brand names – Coviracil was the first. Initially discovered at Emory University in Atlanta, the drug was licensed to Triangle Pharmaceuticals in 1996. Triangle, a small company, continued to develop the drug until reaching an agreement with Abbott Laboratories in June 1999 which would have allowed Abbott to bring the drug to market. Three years later, Triangle bought back marketing rights to the drug from Abbott. Then in January 2003, Gilead Sciences purchased Triangle. Throughout all of this corporate drama, clinical trials of Emtriva (florocytidine, usually referred to more simply as FTC) continued.

The results of two relatively large clinical trials led to Emtriva’s approval. FTC-301 involved 571 people who had never been on antiretroviral treatment before. The trial was designed to compare Emtriva to Zidovudine, with everyone taking Zidovudine and Sustiva as well. It was a double-blind trial, meaning that neither the participants nor the researchers knew who was taking which drug. In July 2002, the Data and Safety Monitoring Board stopped the trial early after finding significantly fewer side effects and better efficacy in the group taking Emtriva. The study was unblinded and all participants were offered Emtriva. A 48 week analysis showed that 78% of the group taking Emtriva had viral loads less than 50 copies compared to only 59% of those taking Zidovudine. And the average increase in CD4 cells was significantly higher in the Emtriva group (168) compared to the Zidovudine group (134). Since Zidovudine and Zidovudine have overlapping toxicities, their combined side effects may have contributed to the poor results in the Zidovudine arm of the trial and made Emtriva seem particularly impressive.

FTC-303 was designed to compare Emtriva to Efavirenz in people who had been on three-drug combinations that included Efavirenz for

at least three months and had viral loads below 400. Two-thirds of the 440 study participants switched from Efavirenz to Emtriva, and the remaining third stayed on their Efavirenz-containing regimen. All of the combinations included Zidovudine or AZT and either a protease inhibitor or a non-nucleoside. At the end of 48 weeks, both groups did equally well in terms of side effects (nothing severe) and keeping their viral loads below undetectable levels.

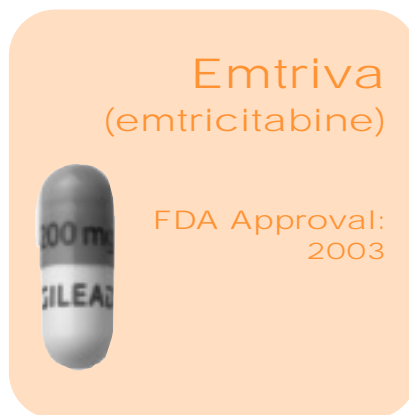
There’s almost no information available yet as to how Emtriva might work for people who have experienced virologic failure on a regimen. Emtriva’s similarity to Efavirenz includes its resistance pattern. As with Efavirenz, Emtriva requires only one change in HIV’s reverse transcriptase enzyme (the M184V mutation) to make HIV completely resistant to Emtriva. So if you’re resistant to Efavirenz, Emtriva won’t work. Further studies are needed to figure out whether Emtriva offers any real advantage over Efavirenz.

Side Effects: Emtriva has very few side effects, although more may be discovered as the drug is used in clinical practice. The side effects seen in clinical trials – headaches, diarrhea, nausea, and rash – were no more frequent or severe in people taking Emtriva than in those on other treatment regimens. The only unusual side effect is skin discoloration (extra pigmentation) on the palms of the hands and/or soles of the feet, which occurred primarily in non-Caucasians. Nobody knows the cause.

Drug Interactions: So far, no drug interactions have been identified with Emtriva. Then again, very few interaction studies have been performed. Some interactions may be discovered through further research and real-life experience, but since Emtriva’s chemical structure is so similar to that of Efavirenz, it may be reasonable to expect that Emtriva will have as few drug interactions as Efavirenz does.

When To Consider It: Emtriva doesn’t fill any desperately needed place in the antiretroviral toolbox. Figuring out how and when best to use it will develop as we learn more about the drug’s long-term safety and effectiveness. There probably won’t be many surprises because of its similarity to Efavirenz, and most of the same considerations that go into deciding when to use Efavirenz probably hold true with Emtriva. One significant difference between the two drugs is that Emtriva stays in the blood much longer than Efavirenz.

(continued on next page)



- A microbicide gel that contains Viread is being studied to prevent vaginal HIV transmission. Studies in monkeys were successful even when the gel was given 24 hours after exposure.

Pregnancy: Viread is classified as an FDA pregnancy category B drug. It has not caused birth defects when studied in animals, but hasn’t been studied in pregnant women. It should be used during pregnancy only if clearly needed.

Dose: 300 mg a day, taken as one 300-mg tablet once a day, with or without food. Viread is not yet approved for pediatric use.

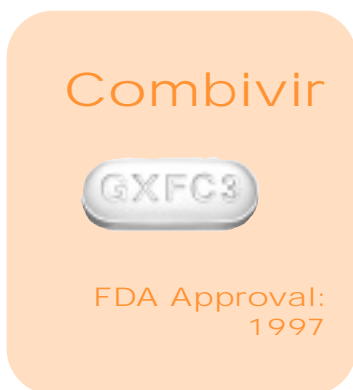
FDA Approval: 2001

Manufacturer: Gilead Sciences

Patient Assistance Program: 800-445-3235 #6

Combivir is a formulation of two drugs – Retrovir (AZT) and Epivir (3TC) – into one tablet. The two have long been used together, originally as a two-drug combination, and then as the backbone of many three-drug regimens. Retrovir has been available separately since 1987 and Epivir since 1995. When the tablet combining the two drugs was approved by the FDA in September 1997, it was a major step toward simpler dosing. Combivir allows people who are on Epivir and Retrovir to take fewer pills – two a day instead of the four if you use the individual formulations of each drug. Simpler dosing often leads to better adherence, and therefore may lead to a better antiviral response.

Background: Epivir and Retrovir are both owned by the same company, GlaxoSmithKline. Combivir's introduction in 1997 was the latest in a series of smart marketing moves by Glaxo that helped simplify treatment regimens for people with HIV. Just a year before, in October 1996, the company introduced a 300-mg version of Retrovir to be taken twice a day. The 300-mg tablets essentially replaced the original 100-mg capsules, which at first called for taking one capsule five times a day, then two capsules three times a day, and finally three capsules twice a day. The simplified 300-mg capsule put Retrovir on the same twice-a-day dosing schedule as Epivir (although Epivir can now be taken once a day) and its main competitor, Zerit (d4T). Combining the company's two nucleoside analogs into a single tablet took things one step further. People using Retrovir and Epivir can now take one tablet twice a day for that part of their regimen.



See the *Retrovir* and *Epivir* entries (pages 3 and 13) for information about *side effects*, *drug interactions*, and *when to consider Combivir*.

Good To Know:

- Some physicians may prescribe Combivir because of its easy dosing, even if Retrovir plus Epivir may not be the best two nucleosides for a particular individual.
- Since Combivir is a fixed-dose formulation, people who need a different dose of either drug for whatever reason can't use it.
- People who weigh less than 110 pounds shouldn't take Combivir, since their dose of Epivir needs to be reduced.
- You may not be able to take Combivir if you've had any kidney problems. The dose of Epivir sometimes needs to be lowered in people with kidney problems.
- Combivir shouldn't be taken with Hivid (ddC) because of the interaction between Hivid and Epivir. Nor should it be taken with Zerit because of the interaction between Zerit and Retrovir.
- Epivir, one of the drugs in Combivir, is also used as a treatment for chronic hepatitis B (HBV), although at a lower dose than that used for HIV. People co-infected with HIV and chronic HBV need to bear that in mind when considering Combivir (see the Hepatitis B section in the discussion of Epivir on page 14).

Dose: One tablet twice a day, with or without food. Each tablet contains 300 mg of Retrovir (AZT) and 150 mg of Epivir (3TC).

FDA Approval: 1997

Manufacturer: GlaxoSmithKline

Patient Assistance Program: 866-728-4368

Emtriva *(continued from previous page)*

Because of this, it may take longer for resistance to Emtriva to develop, but there isn't any data from clinical trials to confirm this. The most recent Department of Health and Human Services treatment guidelines don't discuss Emtriva in any detail or include it in any preferred or alternative regimens. That doesn't mean that the drug couldn't be useful in a first combination – it's just that it was approved shortly before the revised guidelines were released.

Good To Know:

- Gilead, which also markets Viread (tenofovir), is developing a Viread/Emtriva combination pill that they hope to release in 2005. That could be a useful combination and, with its once-daily dosing, would give Combivir some stiff competition. People who take it with Sustiva will take just two pills once a day – the most convenient regimen to date.
- Like Epivir and Viread, Emtriva is also active against chronic hepatitis B (HBV) infection. Studies are underway for Emtriva's use in this disease. People should be tested for chronic HBV

before starting Emtriva, since there have been reports of disease flare-ups in people with HBV when they stop the drug.

- It's recommended that people with severe kidney problems use a lower dose of Emtriva.

Pregnancy: Emtriva is classified as an FDA pregnancy category B drug. Extremely high doses of Emtriva given to pregnant mice and rabbits haven't caused problems to the development of the fetus, but adequate, well-controlled studies of pregnant women haven't been conducted.

Dose: 200 mg a day, taken as one 200-mg capsule, with or without food. Emtriva is not yet approved for pediatric use, although studies in children are ongoing.

FDA Approval: 2003

Manufacturer: Gilead Sciences

Patient Assistance Program: 800-445-3235 #6

Trizivir is not a single drug, but a formulation of three drugs into one tablet. All three drugs – Retrovir (AZT), Efavirenz (EFV), and Ziagen (abacavir) – continue to be available separately.

Background: The FDA approvals of Combivir (Retrovir and Efavirenz in one tablet) in 1997 and Ziagen in 1998 paved the way for Trizivir’s approval in November 2000. Retrovir, Efavirenz, and Ziagen are all owned by GlaxoSmithKline, so it made sense from a commercial viewpoint to combine the drugs into one tablet.

Based on study results (see CNA3005 and, especially, ACTG 5095 described under Ziagen on page 15), using Trizivir – at least without a fourth drug – might not be a good idea for people who are just starting HIV therapy. This triple-nucleoside regimen doesn’t lower viral load as much or for as long as a regimen that combines two nucleosides with a protease inhibitor (PI) or non-nucleoside (NNRTI); people with viral loads greater than 100,000 don’t respond well to this regimen; and there’s the potential for a Ziagen hypersensitivity reaction. On the positive side, Trizivir offers easy dosing, has few interactions with other drugs, saves PIs and NNRTIs for future use, and avoids some of the side effects associated with PIs and NNRTIs. So it may still be a useful option for people with HIV who face adherence difficulties. But the potential benefits may be outweighed by the potential risks.

The recently revised Department of Health and Human Services treatment guidelines list Trizivir as an alternative to a PI- or NNRTI-based regimen for people who have never taken antiretrovirals before, but caution that it should not be used by people with viral loads greater than 100,000. The July 2003 British HIV Association (BHIVA) treatment guidelines go even further, stating that Trizivir should *not* be considered for initial therapy and that it should only be used with an additional drug in a four-drug combination.

As Trizivir’s role is re-evaluated in people who are just starting therapy, it remains useful for some people who have run out of treatment options and are faced with the prospect of taking four, five or more antiretrovirals, including some that they’ve developed at least partial resistance to in the past. Using Trizivir in a mega-combination adds three drugs to the regimen without adding too much to the pill burden. Other people who are doing well on a PI or NNRTI regimen may benefit by switching to Trizivir, hopefully maintaining low viral loads and

high CD4 counts and reducing – or at least not increasing – some of the metabolic changes associated with the PIs and NNRTIs.

*See the Retrovir, Efavirenz, and Ziagen entries (pages 3, 13, and 15) for information about **side effects**, **drug interactions**, and other particulars.*

Good To Know:

- Some physicians may prescribe Trizivir based on assumptions about an individual’s inability to adhere to a more complex regimen even though another regimen may be more beneficial. Trizivir still requires twice-daily dosing, and almost all regimens can now be taken twice a day or once a day. Trizivir isn’t necessarily any less challenging to adhere to than other, more powerful regimens.
- Because Trizivir is a fixed-dose formulation, it can’t be used by people who require a different dose of any of the three drugs it contains.
- People who weigh less than 110 pounds shouldn’t take Trizivir, since their dose of Efavirenz needs to be reduced.
- You may not be able to take Trizivir if you’ve had any kidney problems. The dose of Efavirenz sometimes needs to be lowered in people with kidney problems.
- People starting Trizivir may not be aware of the potentially life-threatening hypersensitivity reaction that occurs in about 5% of people who take Ziagen. Some may not be aware that Trizivir contains Ziagen. Educate yourself about the symptoms of a hypersensitivity reaction (see Ziagen entry on page 15). If you suspect that you’re experiencing Ziagen hypersensitivity, call your doctor immediately. Some people who took Ziagen in the past may have experienced a hypersensitivity reaction without recognizing it. If they take Trizivir, they should be aware that it’s the same as re-starting Ziagen.
- Efavirenz, one of the drugs in Trizivir, is also used as a treatment for chronic hepatitis B (HBV), although at a lower dose than that used for HIV. People co-infected with HIV and chronic HBV need to bear that in mind when considering Trizivir (see the Hepatitis B section in the discussion of Efavirenz on page 14).

Dose: One tablet twice a day, with or without food. Each tablet contains 300 mg of Retrovir (AZT), 150 mg of Efavirenz (EFV), and 300 mg of Ziagen (abacavir).

FDA Approval: 2000

Manufacturer: GlaxoSmithKline

Patient Assistance Program: 866-728-4368



NNRTIs : Non-Nucleoside Reverse Transcriptase Inhibitors

The NNRTIs are also called non-nucleosides or “non-nukes” for short. These drugs interfere with HIV’s reproduction process at the same point as the NRTIs but in a different way. The NNRTIs attach themselves to the *reverse transcriptase* enzyme, changing its shape and preventing it from functioning properly. Reverse transcriptase can’t translate HIV RNA into DNA. If there’s no viral DNA to integrate into the nucleus of the cell, HIV reproduction is slowed down.

Rash is a common side effect of all three NNRTIs, but otherwise their side effects are very different. The NNRTIs are broken down by a partic-

ular system of enzymes in the liver (cytochrome P450) and can interact with other drugs that are broken down by this same system. These include some of the protease inhibitors, methadone, St. John’s wort, and many other medications.

The biggest challenge with the NNRTIs is cross-resistance. It only takes one mutation (change) in HIV’s reverse transcriptase enzyme for HIV to become completely resistant to an NNRTI. If HIV develops this mutation (K103N), it will be resistant to all three currently available NNRTIs, eliminating an entire class of anti-retrovirals as a treatment option.

Two of the NNRTIs, Sustiva (efavirenz) and Viramune (nevirapine), each have a long half-life - it takes the body a long time to clear them. If you were to stop taking all of your drugs at the same time, low levels of the NNRTI might still be in your blood after the other drugs have cleared. This could be like taking only the one drug for a few days, putting you at risk of developing NNRTI resistance. If you are stopping a combination that includes Sustiva or Viramune, talk to your healthcare provider about whether it might be best to stop the NNRTI a few days before you stop taking the other drugs in your combination.

Viramune (nevirapine, NVP) was the first non-nucleoside reverse transcriptase inhibitor (NNRTI) approved by the FDA, but has taken a back seat to Sustiva (efavirenz) due to the latter NNRTI’s impressive results in clinical trials. New data could change that, as we find that Viramune’s “poor cousin” status may more likely be the result of unfortunate research decisions rather than a lack of strength.

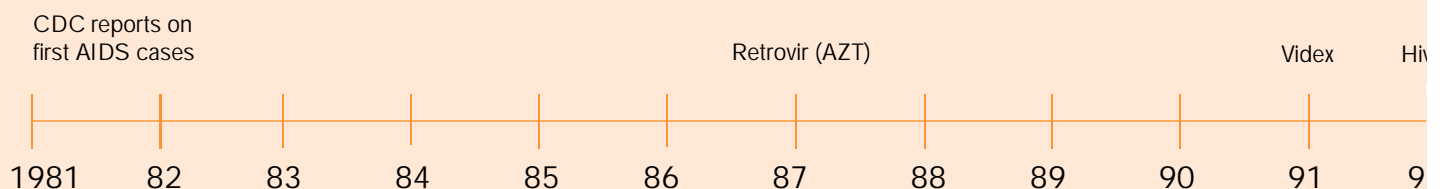
Background: Long before its approval in June 1996, Viramune entered the scene with a big splash in early 1993 when a Harvard medical student, Yung-Kang Chow, published an article in *Nature* magazine describing effects of various two- and three-drug combinations against HIV *in vitro* (in the test tube). Chow said that certain drug combinations – Retrovir (AZT)/Videx (ddI)/Viramune among them – forced the virus to mutate so much that it became unable to reproduce. The press jumped on the bandwagon and “convergent combination therapy” – hitting the virus with multiple drugs targeted at the same point in its life-cycle – became the buzz of the day.

Unfortunately, the experiment didn’t hold up. Chow had to retract his results after it was discovered that he had inadvertently constructed a virus with mutations that made it non-infectious. Worse

than that, the trial designed to test this three-drug combination in people (ACTG 241) was only open to people who had already taken Retrovir, Videx, or Hivid (ddC) for at least six months. Since many of them were resistant to these drugs, the results were not impressive – people taking three drugs saw steeper drops in viral load than those taking only two drugs, but they all returned to starting levels within a year. The first trial of what would years later be called HAART was a disappointment. If a trial had also been done in people who had never taken antiretrovirals before, HAART might have become the standard of care in 1994 rather than in 1996. Who knows how many lives might have been saved?

One of the studies that led to Viramune’s approval was BI 1046, also called the INCAS trial (Italy, Netherlands, Canada and Australia Study). Started in 1994, this trial of 151 people compared two-drug combinations to the three-drug combination of Retrovir, Videx, and Viramune. The study found that 51% of people on the three-drug combination had viral loads below 20 (a tough standard) after a year of treatment compared to 12% of those taking a Retrovir/Videx combination. But when later studies showed that about 70% of people on Sustiva combinations could maintain viral loads below 50, Viramune was viewed as second best for many years.

Timeline of FDA Drug Approvals



That changed with the results of the 2NN study, reported early in 2003. This was a head-to-head comparison of Viramune to Sustiva (or both drugs together) when combined with Efavir (3TC) and Zerit (d4T) in 1,216 people from 17 countries who had never taken any anti-HIV drugs. After a year, the two drugs were equal in potency – 70% of people taking either Viramune or Sustiva once a day had viral loads below 50. (65% of people taking twice-daily Viramune and 63% of those taking both drugs were below 50.) Because of this study, some treatment guidelines now place Viramune on equal footing with Sustiva as a “preferred” first regimen drug. But one study can’t prove that the drugs are equally effective – more data for longer periods of time are needed.

Side Effects: The most common side effects of Viramune are rash and liver problems. Most rashes occur during the first six weeks on therapy. In clinical trials, 17-24% of people developed a rash, and serious rashes occurred in 7% of people. Women have a higher risk of rash, as do people who are allergic to sulfa drugs such as Bactrim. To minimize the possibility of rash, people take Viramune at half-dose for the first two weeks, building up to the full dose. If a rash develops within those first two weeks, the Viramune dose shouldn’t be increased until the rash goes away. People who get a rash while taking Viramune should call their healthcare provider right away and may need to stop the drug. Since Ziagen (abacavir) can also cause a rash, it’s best not to start both drugs at the same time.

In November 2000, Boehringer Ingelheim, Viramune’s manufacturer, sent a letter to physicians stating that the drug’s warning label had been "strengthened in response to continued reports of severe, life-threatening, and, in some cases, fatal hepatotoxicity." A company-sponsored analysis of studies found that only 12% of people had any liver side effects, but other studies have found rates of severe liver problems ranging from 15-20%.

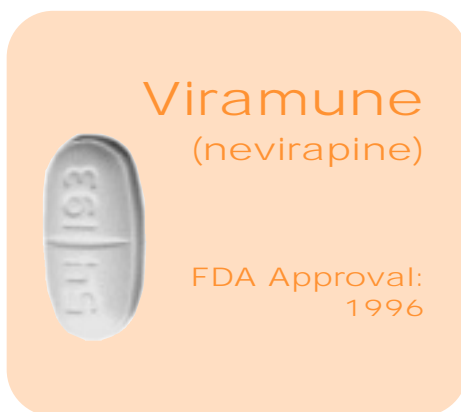
Most liver problems caused by Viramune happen within the first four months on the drug, whereas liver problems caused by other antiretrovirals usually occur later. So people starting Viramune should watch their liver function tests carefully during the first four months and continue to monitor them regularly after that. Women, people with chronic hepatitis B or C, and those with

higher CD4 counts or elevated liver enzymes have a greater chance of developing liver problems. If you get any of the following symptoms, call your healthcare provider right away: flu-like symptoms; dark urine; tiredness; pale stools; nausea; lack of appetite; pain, ache, or sensitivity to touch on the right side below the ribs; yellowing of the skin or eyes (jaundice).

Finally, Viramune can cause a severe allergic reaction called Stevens-Johnson syndrome in about 1% of people. Those who have this reaction should not restart Viramune, since that could be life threatening.

Drug Interactions: Viramune can lower levels of the protease inhibitors Fortovase (saquinavir) and Crixivan (indinavir), but this can be addressed by adding low-dose Norvir (ritonavir). Viramune should not be taken with Nizoral (ketoconazole), since it can lower

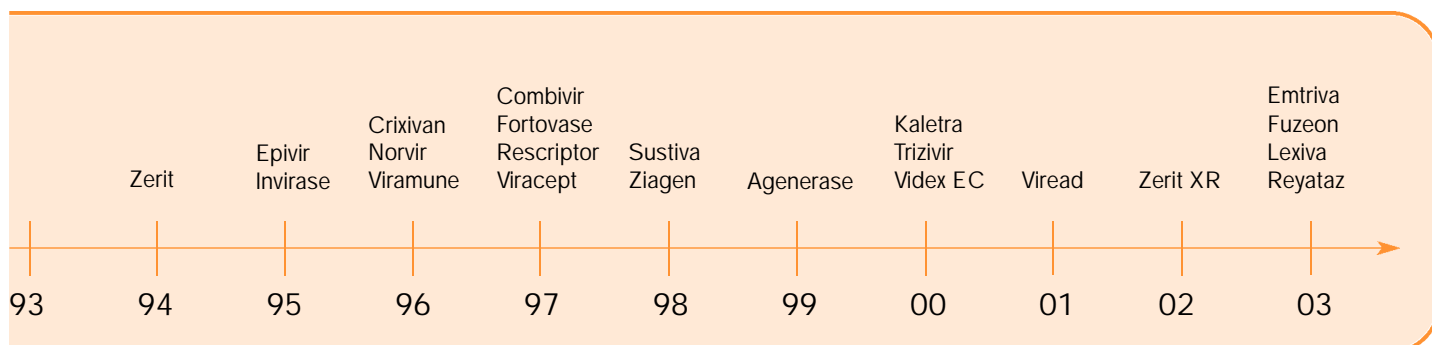
levels of Nizoral significantly. It can also lower levels of methadone up to 36% and lead to symptoms of withdrawal, so people taking methadone may need a dose increase if they take Viramune. Viramune can also lower levels of Viagra (sildenafil), so the Viagra dose may need to be increased to achieve the same result. St. John's wort (hypericum) can lower levels of Viramune, so they should not be taken together. Viramune can lower levels of the oral contraceptives norethindrone and ethinyl estradiol, so other methods of birth control should be used.



When To Consider It: Because of the results of the 2NN study, the British, French, and New York State HIV treatment guidelines place it on an equal footing with Sustiva as a first-line therapy (the U.S. Department of Health and Human Services guidelines do not). The very different side effects of these two drugs may be the main factor in making a personal choice if you’re considering a starting regimen that includes an NNRTI.

A number of studies have shown that people can switch to Viramune from a protease inhibitor and keep their viral load below detection, but only if they are not already resistant to other NNRTIs. Most studies have found that people who switch to Viramune from a protease inhibitor see cholesterol and triglyceride levels improve. It’s questionable if switching to Viramune will improve body shape changes – some trials have reported improvement, but most have not.

(continued on next page)



Viramune *(continued from previous page)*

Good To Know:

- Viramune is one of only a few antiretrovirals with the ability to cross the blood-brain barrier. This ability makes the drug effective against HIV in the brain and central nervous system and may help prevent neurological disease like dementia. It's important to include at least one antiretroviral that crosses the blood-brain barrier in your combination.
- Once-a-day Viramune has been studied with good results, but has not yet been reviewed by the FDA.
- Viramune is not recommended for post-exposure prophylaxis (after a needlestick or unprotected sex) because the risk of short-term liver problems outweighs the potential benefit.

Mother-to-Child Transmission: Viramune made big news in 1999 with the HIVNET 012 study in Uganda, which gave a single dose of Viramune to HIV-positive pregnant women during labor and a single dose to infants immediately after birth. The study found that this lowered the risk of transmission by half. That's not as good as PACTG 076, which showed that Retrovir taken during pregnancy lowered the risk by two-thirds, but it's still impressive, especially since this approach is very cheap. Unfortunately, almost 20% of the women in HIVNET 012 developed resistance to Viramune, and other studies have found that up to 75% of women and 46% of infants will develop resistance to Viramune. Some people have questioned the ethics of using Viramune this way since it may impact future treatment options for both mother and child. A recent commentary in *The Lancet* suggests adding other antiretrovirals in the hopes of avoiding widespread resistance to all of the NNRTIs. A trial adding single-dose Viramune to standard Retrovir treatment during pregnancy did not show any additional benefit.

Pregnancy: Viramune is classified as an FDA pregnancy category C drug. No damage to the fetus was seen when the drug was given to pregnant rats and rabbits. But its safety in pregnant women has not been studied long-term, so it should be used during pregnancy only if the benefit justifies the risk to the mother and fetus. The Antiretroviral Pregnancy Registry has not reported an increase in the prevalence of birth defects when Viramune was used during the first trimester. In fact, the prevalence of birth defects was only 2%, compared to an overall prevalence of 3.1%.

Dose: 400 mg a day taken as one 200-mg tablet twice a day, with or without food. For the first two weeks, the dose is one 200-mg tablet once a day. There is a liquid form of Viramune for pediatric use, which is dosed according to weight. For children ages 2 months to 8 years, the dose is 7 mg/kg twice a day (4 mg/kg once a day for the first two weeks). Over 8 years old, the dose is 4 mg/kg twice a day (once a day for the first two weeks). No one should take more than 400 mg a day.

FDA Approval: 1996

Manufacturer: Boehringer Ingelheim Pharmaceuticals

Patient Assistance Program: 800-274-8651

Rescriptor (delavirdine, DLV) received FDA approval in April 1997, becoming the second non-nucleoside reverse transcriptase inhibitor (NNRTI) available. Mixed results from clinical trials and a difficult dosing schedule (two pills three times a day) combine to make it one of the least-prescribed antiretrovirals.

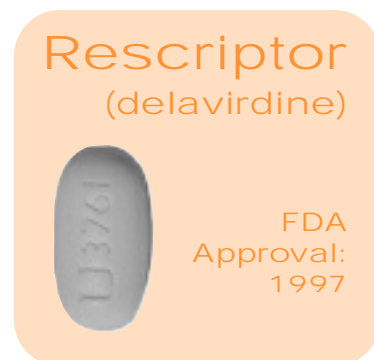
Background: Rescriptor certainly didn't wow the FDA Advisory Panel that reviewed it back in 1996. The vote was a tie – four for approval and four against – due to the drug's lackluster performance in the trials that were submitted for review. At that time, trials were still being designed that added one new drug to a failing regimen, inevitably leading to unimpressive results. One trial (0017) comparing Rescriptor plus Videx (ddI) to Videx alone was stopped early when the number of deaths was nearly equal in both groups. Another trial, ACTG 261, showed a trend toward better CD4 increases in people taking Rescriptor with Videx and Retrovir (AZT) compared to those taking only Videx and Retrovir, but no viral load results were reported at the hearing.

Faced with a non-recommendation from its advisory panel, the FDA decided to wait for the viral load results from ACTG 261. When those results showed that viral loads went down slightly more in people taking the three-drug combination than in people taking only two drugs, the FDA granted approval. (Follow-up results found that there was no real difference between the groups, however.)

Later trials have also questioned Rescriptor's staying power. In a study of 373 people who had taken few or no antiretrovirals (Study 0021 Part II), 82% of those taking Rescriptor with Retrovir and Epivir (3TC) had viral loads below 400 after three months, but only 45% were below 400 after a year on the combination. Similarly, 345 people in another trial (13C) had poor results – after a year, only 29% of people taking Rescriptor with two nucleoside analogs had viral loads below 400.

So the picture seems clear – poor efficacy combined with difficult dosing make Rescriptor a drug to be avoided, right? Well, as always with HIV, nothing is simple. Rescriptor may not be strong enough with nucleoside analogs, but the situation changes with protease inhibitors. In ACTG 370, 63 people who were taking Epivir either switched to Rescriptor or stayed on Epivir. Everyone also added the protease inhibitor Crixivan (indinavir) and Retrovir. After a year, 83% of those who switched to Rescriptor had viral loads below 200 compared to only 48% of those who stayed on Epivir. This may be due to the fact that Rescriptor raises blood levels of Crixivan. While that may be a good thing, it can also increase the risk of Crixivan side effects such as kidney stones.

Now that there are a number of drugs available to fight HIV, Rescriptor's ability to boost Crixivan levels isn't as needed as it once was, especially since it has to be taken three times a day. Viramune (nevirapine) and Sustiva (efavirenz), the other avail-



able NNRTIs, have proven their effectiveness when combined with two nucleosides, so most people don't want to risk starting treatment with Rescriptor since resistance to one NNRTI usually means resistance to all three. While most HIV treatment guidelines recommend the other NNRTIs as a part of preferred first regimens, none put Rescriptor in the "preferred" category, and the drug has never even been approved for sale in Europe.

Side Effects: As with the other NNRTIs, Rescriptor's most common side effect is rash, which occurred in about 35% of people in clinical trials. In most people, it went away within two weeks while still on the drug, but the rash was severe in 4% of people in the trials. There have been two reported cases of Stevens-Johnson syndrome, which is a severe allergic reaction.

Drug Interactions: Another challenge for Rescriptor is the long list of drugs that cannot be taken with it, including certain antihistamines, antiarrhythmics, calcium channel blockers, sedatives, cholesterol-lowering drugs, and many more. Because the list is so long, it's probably best to check the package insert that comes with the drug and talk with your healthcare provider about any other medications you're taking. As with all of the NNRTIs and protease inhibitors, St. John's wort (hypericum) should be avoided, since it may lower the levels of these drugs. Rescriptor may increase levels of Viagra (sildenafil), so the dose of Viagra may need to be lowered.

Viramune and Agenerase (amprenavir) lower levels of Rescriptor, but Rescriptor raises levels of Crixivan, Viracept (nelfinavir), Norvir (ritonavir), and Fortovase (soft-gel saquinavir). Taking Rescriptor at the same time as Videx buffered tablets lowers levels of both drugs – they should be taken at least one hour apart. Rescriptor should also be taken at least one hour apart from antacids.

When To Consider It: Rescriptor is usually not recommended as part of a first regimen since the risk of developing resistance is significant and usually leads to cross-resistance to the other NNRTIs. People who need to boost the level of a protease inhibitor (PI) and don't want to use Norvir may find it useful, however. Rescriptor can still be used to boost PI levels in the bloodstream even if your HIV is resistant to Rescriptor.

Pregnancy: Rescriptor is classified as an FDA pregnancy category C drug. Controlled studies of pregnant women haven't been conducted. Of ten infants known to have been exposed to Rescriptor in the womb, nine had no birth defects and one, born prematurely, had a heart defect that wasn't unusual and resolved after birth. Rescriptor shouldn't be used during pregnancy unless the potential benefit outweighs the potential risk to the mother and fetus.

Dose: 1,200 mg a day, taken at a dose of 400 mg three times a day. Each dose usually consists of two 200-mg tablets. Rescriptor is also available in 100-mg tablets, which can be dissolved in water (the 200-mg tablets will not dissolve). The dissolved form was tried in children, but most of them switched to tablets. Rescriptor can be taken with or without food. It has not been approved for pediatric use.

FDA Approval: 1997

Manufacturer: Agouron Pharmaceuticals (subsidiary of Pfizer)

Patient Assistance Program: 888-777-6637

Sustiva (efavirenz, EFV) – Its FDA approval in September 1998 made Sustiva the third available NNRTI. Since then, it has become one of the most popular antiretrovirals and is often recommended for a person's first regimen because of its effectiveness and once-a-day dosing. While its nervous system side effects can be a problem, many people have found them to be temporary or at least manageable.

Background: Sustiva might be called the "little drug that could." After the less-than-impressive results seen with the first two NNRTIs, Viramune (nevirapine) and Rescriptor (delavirdine), few people expected Sustiva to perform any better. But DuPont Pharma, the company that first developed the drug, had different ideas – they had the nerve to pit Sustiva against Crixivan (indinavir), the protease inhibitor that was then the "gold standard" for treatment.

In 1997, DuPont began the trial (DMP 266-006) that would throw NNRTIs into the spotlight and lead to Sustiva's FDA approval. In the trial, 450 people took either Sustiva or Crixivan, along with Retrovir (AZT) and Epivir (3TC). 80% of the trial participants had never taken antiretrovirals. After 11 months, 64% of those taking Sustiva had viral loads below 50, compared to 43% of those taking Crixivan. Some of this difference was probably due to the difficulty of taking Crixivan (every 8 hours on an empty stomach) compared to Sustiva's once-daily dosing. Still, this result flew in the face of conventional wisdom, which held that it was necessary to hit the virus at different points in its lifecycle. The combination of Sustiva, Retrovir, and Epivir targets the reverse transcriptase enzyme only – people were surprised to find that this was as effective as combinations that target both the reverse transcriptase and protease enzymes.

Other trials have supported Sustiva's effectiveness. In the FOCUS study that began in 2000, 161 people who had never used anti-HIV drugs took either Sustiva or a combination of the protease inhibitors (PIs) Fortovase (saquinavir) and Norvir (ritonavir), both taken once a day. Everyone also took two nucleosides. Once again, Sustiva outperformed the PIs. After 11 months, 71% of the participants on Sustiva had viral loads below 50, compared to 51% of those taking the PIs. Contributing to Sustiva's success in both of these studies was the fact that more people taking a protease inhibitor dropped out due to side effects.

A number of studies have shown that people can successfully switch from a protease inhibitor to Sustiva. DMP-049, a study of 346 people who had viral loads below 50 while taking a PI, found that 84% who switched to Sustiva kept that low viral load after 11 months, compared to 73% of those who stayed on their PI. A similar trial (DPC-049) found that 93% of those who switched to Sustiva were able to keep their viral loads below 50, compared to 85% of those who stayed on their PI.

Unfortunately, the news surrounding Sustiva hasn't always been terrific. Shortly after Sustiva was approved, DuPont announced that the price of their drug would be 60% higher than the other NNRTIs – closer to the more expensive PIs. This was the first

(continued on next page)

Sustiva *(continued from previous page)*

non-PI to do so and it led to a long series of loud protests by activists. DuPont never budged. Bristol-Myers Squibb later bought DuPont Pharma and has left the price relatively unchanged.

Side Effects: Sustiva is famous for its effects on the central nervous system, which can result in strange dreams that are experienced by many people. These are usually not nightmares but, rather, as the manufacturer describes them, “vivid dreams” (one person we know dreamt that he was a superhero saving the world every night). No one is sure why Sustiva causes these dreams and other central nervous system side effects. For most people, the dreams subside after a few weeks. For others, however, they can become a chronic problem, along with difficulty sleeping, drowsiness, and trouble concentrating.

The best strategy for lessening these side effects is usually to take Sustiva at bedtime, and on an empty stomach. Taking it with food can raise the amount of drug in the body by up to 51%, increasing the side effects. Combining Sustiva with recreational drugs, particularly marijuana, can also increase the psychological side effects.

About 2% of people taking Sustiva have more severe psychiatric problems, including severe depression, strange thoughts, or angry behavior. Some patients have thoughts of suicide and a few have actually committed suicide. People with a history of mental illness should be especially careful if they start Sustiva.

Rash is also a common side effect, affecting 26% of adults and up to 46% of children. Rashes usually go away in a few weeks, but are serious enough to cause 2% of adults and 9% of children to stop taking Sustiva. Other common side effects include tiredness, upset stomach, vomiting, and diarrhea.

There have been a handful of cases of swelling of the breasts (gynecomastia) reported in men taking Sustiva, but it is not yet known if this is due to Sustiva or something else.

Drug Interactions: Sustiva lowers the levels of the protease inhibitors Reyataz (atazanavir), Crixivan, Agenerase (amprenavir), Fortovase and Invirase, and Kaletra (lopinavir/ritonavir) in the body. Adding low-dose Norvir may help increase PI levels, but it may be best to avoid using these drugs together in a combination.

Some drugs may cause serious and life-threatening side effects when taken with Sustiva including drugs used to treat anxiety,

like Versed (midazolam) and triazolam (Halcion, Restoril, Dalmane and others), and the ergotamine drugs (used to treat migraines). These drugs should not be taken with Sustiva.

Sustiva lowers levels of Biaxin (clarithromycin) so these drugs should not be taken together. Sustiva can reduce levels of Mycobutin (rifabutin) by 50%, so the Mycobutin dose should be increased. Sustiva can also lower levels of methadone by up to 57%. If withdrawal symptoms occur, the methadone dose should be increased – the average increase needed in one study was 21%.

St. John's wort (hypericum) may reduce the levels of all NNRTIs and PIs, so it is best avoided.

When To Consider It: Sustiva's popularity as part of a first regimen is clear, due to its strength, dosing simplicity, and the fact that it lacks the metabolic side effects seen with most of the protease inhibitors. But recent studies have found Viramune to be equally effective (see page 22), so Viramune's significantly lower price and lack of nervous system side effects could help it challenge Sustiva as “king of the hill.”

People also choose to switch to Sustiva, usually for one of two reasons – to simplify their regimen with its once-daily dosing or to try to improve lipodystrophy. Unfortunately, most studies have found that simply substituting Sustiva for a protease inhibitor does not significantly improve body shape. For example, a study from Spain of 39 people found that while 76% reported body shape improvements, objective measurements (like body mass index) did not back this up. In addition, triglycerides increased from 169 to 201 (not good), but HDL cholesterol (the “good” cholesterol) also increased, from 36 to 50. Other studies have shown that a switch to Viramune has a better effect on cholesterol and triglyceride levels than a switch to Sustiva.

Good To Know:

- Even though less than 5% of Sustiva enters the CSF (cerebrospinal fluid – the fluid around the brain), it can still inhibit 95% of the HIV in the CSF.
- Sustiva can cause a false positive test for marijuana if the CEDIA DAU Multi-level TCH immunoassay is used. People taking Sustiva should ask for a gas chromatography test, which will provide accurate results.
- For children or people who have trouble swallowing pills, Sustiva capsules can be opened and the contents added to liquids or foods. The drug has a strong, unpleasant taste, so it may take a while to find a food or liquid that will disguise the drug's taste.

(continued on page 29)



PIs : Protease Inhibitors

The protease inhibitors, or PIs, work at a later stage in the HIV life cycle than the NRTIs and NNRTIs. Once HIV's genetic material has been changed from RNA to DNA and is integrated into the DNA in the cell's nucleus, the cell produces a long chain of genetic material (proteins and enzymes). HIV's *protease* enzyme acts like a pair of scissors, cutting the chain into smaller pieces which then come together to form new copies of the virus.

Protease inhibitors attach to the protease enzyme and keep it from cutting the long chain of proteins and enzymes into smaller pieces – they block the scissors. HIV is unable to package itself into new infectious virus. When a PI is combined with other antiretrovirals – usually two NRTIs – the rate of HIV

replication can be slowed down dramatically.

To varying degrees, PIs have been associated with certain long-term side effects, including increased blood sugar levels, insulin resistance, elevated cholesterol and triglyceride levels, osteonecrosis (death of bone tissue), and osteoporosis (a decrease in bone mineral density). Some of these conditions may increase a person's risk of heart disease, diabetes, and bone fractures. PIs have also been linked to various types of fat redistribution, which may be part of a larger syndrome involving changes in people's metabolism as a result of HIV disease, antiretrovirals used to treat HIV (not only the PIs), or both.

PIs have considerable drug interactions – between each other, with non-

nucleosides, and with many drugs used to treat other conditions. For example, each of the PIs interacts with the anti-tuberculosis drug rifampin, Viagra (sildenafil), St. John's wort, and a long list of other drugs. Be sure to talk to your healthcare provider about other medications you're taking, including over-the-counter treatments, herbs, and supplements.

Complete resistance to some of the PIs can develop as a result of just one mutation (change) in HIV's protease enzyme, such as the D30N mutation for Viracept (nelfinavir) or the I50V mutation for Agenerase (amprenavir). But with most of the PIs, it takes several mutations for complete resistance to develop. Partial or complete resistance to one PI can cause partial or complete cross-resistance to other PIs.

Invirase and Fortovase (saquinavir mesylate, SQV) are different versions of the same drug. Invirase caused a big splash in December 1995 when it became the first protease inhibitor approved by the FDA – the first in a whole new class of antiretrovirals. Unfortunately, Invirase isn't absorbed by the body as well as other anti-HIV drugs, so a more readily-absorbed formulation called Fortovase was eventually released in November 1997. The plan was to gradually pull Invirase from the market, but it has made a comeback of sorts in recent years. When used as the only protease inhibitor in a combination, either version required taking many pills a day, and neither had the punch to reduce viral load as well as other protease inhibitors. Because of these factors, most people take Invirase or Fortovase with low-dose Norvir (ritonavir). This “boosting,” as it's called, lowers the daily number of pills and increases the amount of saquinavir that's absorbed by the body.

Background: When Invirase was being developed, there were only a handful of nucleoside analogs on the market and a lot of questions about how best to use them. Many people were desperate for new options, especially drugs that worked at a different part of the HIV life cycle. At the time, some activists complained that this desperation led to cutting corners when it came to what we demanded to know about Invirase before its approval.

What *was* known was gathered not by comparing the drug to other approved drugs, but by observing the effect of adding

Invirase to existing drug combinations. (At the time, we were just learning that using two drugs together was better than using one alone.) The company developing Invirase, Hoffmann-La Roche, was very specific about which drugs it used to test with Invirase and mainly conducted studies with its own approved HIV medication Hivid (ddC). In ACTG 229, 302 people who had been on Retrovir (AZT) alone for at least four months took Retrovir plus Invirase, Retrovir plus Hivid, or Retrovir, Hivid, and Invirase together. After six months, 70% of the people on the triple-drug combination had an increase in their CD4 counts, although by one year, only 51% still had an increase compared to 33% in the Retrovir plus Invirase arm and 34% in the Retrovir plus Hivid arm. The triple-drug combination also seemed to reduce viral load more than the other two arms and didn't seem to increase the number of side effects. Eager to have the first approved protease inhibitor on the market, Roche made the case for the accelerated approval of Invirase. Some activists were concerned about the small size (only 302 patients!) of the study and appealed to the FDA not to approve the drug so quickly but, instead, to ask Roche to design a “large simple trial” that would enroll thousands of people and gather more information. Others were furious at the idea of community members delaying the approval of a drug that many were desperate for.

In response, Roche doubled the size of ACTG 229 with a new trial called NV14256B, in which people took Invirase, Hivid, or both together. Everyone in this study had previously been on

(continued on next page)

Invirase/Fortovase *(continued from previous page)*

Retrovir. Even as the weakest drugs in their respective classes, Hivid and Invirase used together had stronger results than either one used alone. A later study (SV14604) showed that using Invirase with Hivid and Retrovir reduced disease progression by up to 50% (compared to using Retrovir or Hivid alone) based on 17-month follow-up. Once four-month data from ACTG 229 were available, the FDA quickly approved the drug.

Unfortunately, Invirase had many drawbacks, some of which arguably could have been addressed prior to its speedy approval in 1995. For one, Roche went ahead with its clinical trials using a 600-mg dose three times a day, which was too low to have enough of an antiviral effect. Roche didn't conduct further dosing studies to see if a higher dose might be necessary, even though doses as high as 3,600-5,400 mg/day were found to be safe in HIV-negative individuals. A study done in 1995 showed that a 1,200-mg dose was more potent than and just as tolerable as the 600-mg dose. Regardless, the ACTG 229 and NV4256B studies were pushed ahead using what was known to be a dangerously low dose. There was a real concern that people taking this low dose could develop resistance to Invirase as well as other protease inhibitors to come. Also troubling was how little Invirase was absorbed by the body – only 4%. However, these concerns didn't deter Roche from establishing an average wholesale price of about \$7,000 per year for the drug, a price that set the precedent for other protease inhibitors to come.

Roche also angered community groups with its meager attempt at an early access program for Invirase. In 1995, almost 30,000 people got Epivir (3TC) through an expanded access program. But in that same year, people desperate for Invirase had a difficult if not impossible time trying to get it before FDA approval. Roche argued that their supply of the drug was limited and offered a lottery in July for only 2,200 people. A second lottery was held in November of that same year, even though many lucky winners from the first lottery had never received drug. Surprisingly, Invirase received FDA approval the next month, leaving many "winners" of both lotteries on their own. Roche's lotteries have been cited many times by activists whenever a drug company claims it doesn't have enough drug for an expanded access program. In November 1995, Roche claimed to have only enough drug for a small lottery. One month later, they had enough drug for every pharmacy in the country.

After its approval, important lessons were learned about how to use (or not use) Invirase. The FDA didn't originally recommend Invirase for advanced HIV disease, largely because it was only moderately effective at lowering viral load. This was because

drug levels were too low and the drug itself just wasn't that strong to begin with. The suboptimal dose had many activists and physicians concerned that people taking Invirase would develop resistance to future protease inhibitors. While it's uncertain whether or how many people *did* develop resistance by using this dose, it is known that HIV that develops resistance to Invirase or Fortovase can also be at least partially resistant to other protease inhibitors. As a result, many people did anything they could to increase the levels of Invirase in the body, including drinking grapefruit juice which was known to increase levels of the drug. Out of both necessity and a struggle to make saquinavir a desirable choice,

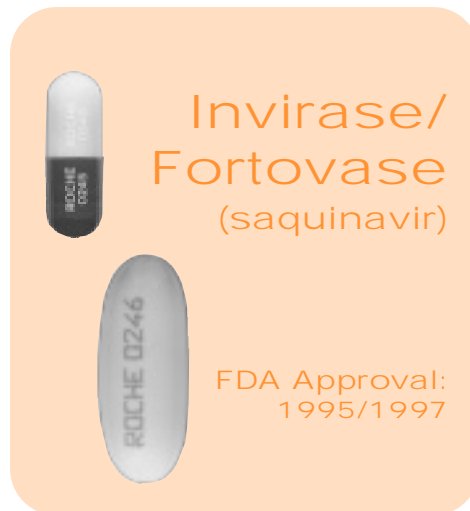
Roche developed a soft-gel formulation (Fortovase), which was approved in 1997. The dose was higher in this new formulation and was four times better absorbed by the body than Invirase. Also, 80% of people taking Fortovase saw a significant drop in their viral load, twice that of Invirase.

While Fortovase was indeed a new and improved version of its predecessor, several factors have kept it from becoming a treatment favorite. More people experience gastrointestinal problems on Fortovase and no one is thrilled about taking the daily dose of eighteen (!) huge pills. But don't count Invirase out – it has re-entered the scene in a potent twice-a-day combina-

tion with low-dose Norvir.

Side Effects: Overall, both formulations of saquinavir are well tolerated. The most common side effects are gastrointestinal (diarrhea, nausea, abdominal pain), which are more common with Fortovase. About 10-20% of people on Fortovase have diarrhea or nausea, and this rate is higher when it is taken with Norvir. Headaches are also relatively common. Saquinavir can also cause liver enzymes (ALT/AST) to increase, but this isn't necessarily a cause for concern or a signal to stop the drug; overall, saquinavir doesn't interfere with liver function as much as most other protease inhibitors do.

Drug Interactions: Invirase and Fortovase have several interactions with other antiretrovirals. Viracept (nelfinavir), Kaletra (lopinavir/ritonavir), and Rescriptor (delavirdine) can raise levels of either formulation of saquinavir in the body and may increase the risk of side effects, so it may be best to lower the dose of saquinavir. On the other hand, Viramune (nevirapine), Agenerase (amprenavir), and Sustiva (efavirenz) can *lower* levels of saquinavir in the body. These interactions, however, are dealt with differently – lower doses of Invirase or Fortovase together with a small dose of Norvir are recommended when using Viramune or Sustiva. There isn't enough information about whether the dose needs to be adjusted if you're on Agenerase, and no recommendations to change the dose exist.



Other drugs should be used with caution and, in some cases, avoided, when using either Invirase or Fortovase. Both formulations can cause large increases in levels of the lipid-lowering drugs Zocor (simvastatin) and lovastatin (Mevacor or Atocor); other drugs, like Pravachol (pravastatin) and Lescol (fluvastatin) are recommended. Lipitor (atorvastatin) should not be used with boosted Invirase because it can increase the amount of Invirase to dangerously high levels (450% higher). Nizoral (ketoconazole) can triple levels of either formulation and may need to be lowered in dose if gastrointestinal side effects result. Furthermore, Fortovase can increase levels of Viagra (sildenafil) by up to 210%, so caution should be used if the two are taken together.

Some natural products, specifically garlic supplements and St. John's wort (hypericum), can reduce levels of saquinavir to dangerously low levels and should be avoided. Drinking grapefruit juice while taking either formulation can raise drug levels in the body and increase the risk of side effects, so that morning glass of juice may not be the best idea.

In addition, the anti-tuberculosis medications rifampin and Mycobutin (rifabutin) can lower Invirase/Fortovase levels significantly.

When To Consider It: Because both formulations mean swallowing a large number of pills and, at full dose, lower viral load only moderately, neither Invirase nor Fortovase are popular HIV medications. Neither formulation has been a top seller since its approval. For someone choosing a first treatment combination, the Department of Health and Human Services treatment guidelines currently *require* boosting Invirase or *recommend* boosting Fortovase with Norvir as part of an alternative, rather than preferred, regimen. Most people do not use either formulation at full dose unless they have few other options. When boosting, the newly-approved 1,000-mg twice-a-day dose of Invirase may provide more punch, as more drug seems to get into the body than with Fortovase, but either can be used. Boosting of both formulations with Norvir has become relatively common and by reducing the number of pills may make the drug more bearable to those who have to take it.

Sustiva *(continued from page 26)*

Pregnancy: Sustiva is classified as an FDA pregnancy category C drug. Pregnant women should not take Sustiva. While there have been over 100 reported cases of infants born without birth defects after being exposed to Sustiva in the womb, there is one report of an infant born with severe birth defects after Sustiva exposure in the womb. It has also caused birth defects in monkeys. Because of these findings, no studies of Sustiva in pregnancy are planned. Women should have a pregnancy test before starting Sustiva, and the manufacturer recommends using a barrier method of contraception in addition to an oral or other hormonal contraceptive.

Good to Know:

- A new 500-mg Invirase tablet is being developed by Roche and may be available early in 2004. These new tablets will be smaller than the current Invirase and Fortovase capsules and will only require taking two pills twice a day (compared to five) when used with low-dose Norvir.

Pregnancy: Saquinavir is classified as an FDA pregnancy category B drug. Animal studies fail to demonstrate a risk to the mother and fetus, but well-controlled studies of pregnant women have not been conducted.

Dose: Both Fortovase and Invirase come in 200-mg capsules.

- The FDA-approved dose of the soft-gel Fortovase is 3,600 mg a day taken as six 200-mg capsules every 8 hours. Many healthcare providers also prescribe Fortovase using a twice-daily dosing schedule based on data from clinical trials, even though it isn't officially approved by the FDA. Twice-daily dosing calls for eight 200-mg capsules every 12 hours. Fortovase is better absorbed when taken with a large meal or within two hours after a large meal.
- Hard-gel Invirase is not recommended unless it's taken together with low-dose Norvir. Invirase can be taken with or without food when taken with Norvir.
- When used with low-dose Norvir, five 200-mg capsules of either formulation are taken twice a day.
- The 1,200-mg dose of Fortovase every 8 hours may not be sufficient for pregnant women. Instead, these women may choose to consider a higher dose of Invirase taken with a small dose of Norvir. One study found that this combination was well tolerated and maintained adequate levels of the drug in women.
- Neither formulation has been approved for use by children, but both appear to be effective in small studies.

FDA Approval: Invirase 1995; Fortovase 1997

Manufacturer: Hoffmann-La Roche

Patient Assistance Program: 800-282-7780

Dose: 600 mg once a day, usually taken as one 600-mg tablet, preferably on an empty stomach. Sustiva also comes in 50, 100, and 200-mg capsules. For children 3 years and older who weigh less than 88 pounds, the dosing is based on body weight. The recommended dose for children weighing 88 pounds or more is the same as that for adults – 600 mg once a day. Sustiva is available as a strawberry-flavored liquid through an expanded access program. Doctors can call 877-372-7097 to enroll patients.

FDA Approval: 1998

Manufacturer: Bristol-Myers Squibb

Patient Assistance Program: 800-474-2762

Norvir (ritonavir, RTV) is one of the strongest but least prescribed protease inhibitors on the market today. In several studies, Norvir has shown a strong reduction in viral load and an increase in CD4 cells, especially when taken with one or two other anti-HIV medications. After its approval in March 1996, the hope that Norvir would be the Superman of its class faded as people struggled with the foul taste, nausea, diarrhea, vomiting, and other intense side effects of the drug, as well as its many drug interactions. These days, Norvir is most often used at much lower doses to increase the levels of other anti-HIV medications in the body, resulting in simpler dosing of the “boosted” drug as well as effective suppression of HIV.

Background: Many people hoped that Norvir would be the protease inhibitor that Invirase (saquinavir) wasn't. Several studies that led to the drug's approval made the case for Norvir in what was then just the beginning of combination therapy. In study M94-247, 1,090 people who had been on treatment for at least nine months and had less than 100 CD4 cells took either Norvir or a placebo in addition to the nucleoside analogs they were already taking. After seven months, 13% of the people taking Norvir experienced disease progression or died compared to 27% of those taking the placebo. Norvir had reduced the risk of disease progression or death by half. These results were quite compelling, as Norvir was the first drug that seemed to extend survival.

In study M94-245, 356 people who had never been on antiretroviral treatment with CD4 cells above 200 and viral loads greater than 15,000 were assigned to take Retrovir (AZT), Norvir, or both together. After 16 weeks, people who took Norvir alone or with Retrovir did better than those who took Retrovir alone. On average, their viral loads dropped more than 90%, and those taking Norvir alone seemed to have the greatest reduction in viral load. On average, CD4 counts increased by 62 in people who took Norvir alone, compared to 35 in those who took Retrovir with Norvir, and 11 in those who took Retrovir alone. It was surprising that participants taking both drugs didn't do better than those who took Norvir alone. One reason may have been that people taking both drugs were far more likely to experience nausea and vomiting than those taking one drug.

In a smaller study done in France, 32 people who had never been on antiretrovirals before took Norvir for two weeks, and then added Retrovir and Hivid (ddC). At the beginning of the trial, participants had an average CD4 count of 170 and an average viral load of 50,000. After 72 weeks, 17 of the 32 trial participants had viral loads below 200 copies. The average CD4 increase was 160 cells. So it was no surprise when Norvir was approved faster than any anti-HIV medication before – just one day after the FDA's advisory panel recommended approval! Inspired by Roche's tiny early access program for Invirase, Abbott Laboratories, Norvir's manufacturer, provided very limited

access to people who needed their drug before FDA approval. Beginning in December 1995, a mere 1,480 people worldwide with CD4 counts of 50 or below received Norvir by lottery, leaving thousands with no access until the drug was approved. Once again, a manufacturer had "extremely limited supplies" of its drug. Yet when Norvir was approved two months later, there was no supply problem whatsoever. Access to the drug was again limited in September 1998, when manufacturing problems led to a worldwide shortage of the commonly used capsule form. People had to tolerate the bitter taste and aftertaste of the substitute liquid formulation for months.

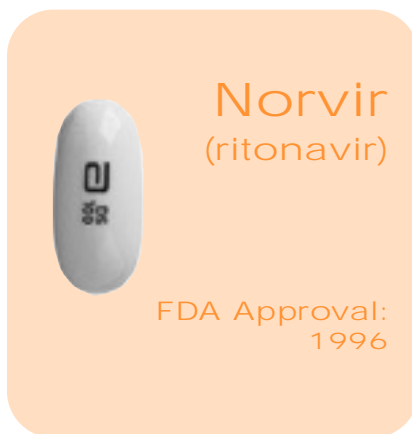
In recent years, Norvir has re-entered the scene in a modified role. All of the protease inhibitors (PIs) are broken down (metabolized) by the same family of enzymes in the liver. In order for the PIs to be metabolized by these liver enzymes, they must first either slow down or speed up the enzymes' activity. All of the currently approved PIs slow down the activity of these liver enzymes. Norvir is the most powerful of all of the PIs in this regard, even when low doses of the drug are used. In turn, Norvir can prevent other PIs from getting to the enzyme, causing levels of these other PIs to increase – to become “boosted” – in the bloodstream. This can make the other PIs more effective against HIV. It also means that lower doses – or less frequent doses – of these other PIs can

be taken. With Agenerase (amprenavir), for example, adding that small amount of Norvir increases the levels of Agenerase in the body up to ten times, reducing the number of Agenerase capsules required each day from sixteen to ten. For this reason, when Kaletra (lopinavir/ritonavir) was developed, it was packaged to already include a small dose of Norvir in the pill so that less lopinavir would be needed.

Boosting with Norvir is useful with many drugs and holds promise for once-a-day dosing options. Crixivan (indinavir), Viracept (nelfinavir), Agenerase, and Invirase are already being boosted, and other drugs, including the recently approved Reyataz (atazanavir), are being studied with low-dose Norvir in clinical trials. Agenerase has been approved for once-a-day dosing when boosted with Norvir, and several other PIs are in line for review.

Side Effects: Norvir's most common side effects are gastrointestinal – nausea, vomiting, diarrhea, and abdominal pain. Other side effects include taste perversion, tingling or numbness in the hands, feet and around the mouth, loss of appetite, and tiredness. People taking Norvir may also experience hepatitis (liver inflammation), or pancreatitis (inflammation of the pancreas). Women may be at greater risk for anemia (low red blood cells) because of excessive menstrual bleeding that's sometimes caused by Norvir. Women also seem to experience Norvir side effects more commonly than men, especially nausea and vomiting.

To lower the risk of side effects, some people who took full-dose Norvir early on started with a smaller dose (no lower than 300 mg)



and gradually increased it until reaching the full dose of 600 mg twice a day. Today, dose escalation is not as much of an issue, as people usually take smaller amounts of Norvir to boost another drug. Although Norvir can be taken with or without food, it may be easier on the stomach if it's taken with food. Some people say that taking it with yogurt can be particularly helpful in reducing some of the side effects.

Using Norvir to boost PIs can ease food restrictions and allow less frequent dosing, but it can also increase the risk of side effects. For example, there's no need to worry about Agenerase's food restrictions when boosting with Norvir, but the risk of a rash is greater than when taking Agenerase without Norvir. When boosting Fortovase, there is a higher risk of Fortovase's gastrointestinal side effects, which is why many people boost Invirase, the hard-gel version of saquinavir, instead. When used to boost Crixivan, Norvir eliminates Crixivan's food restriction, but the trade-off is that there may be a higher risk of kidney stones. Therefore, people taking boosted Crixivan should be particularly sure to drink lots of water.

Drug Interactions: Norvir has the longest list of drug interactions of any antiretroviral by far. This list includes some antihistamines, tranquilizers, sleeping pills, antiarrhythmics (used to regulate an erratic heartbeat), and ergot alkaloids (used to treat migraines). Combining Norvir with any of these drugs may cause serious or even life-threatening interactions. Norvir capsules and liquid contain small amounts of alcohol, which can cause severe reactions, even death, when taken with Antabuse (disulfiram). Because of Norvir's alcohol content, Flagyl (metronidazole) should also be avoided.

Other drugs that shouldn't be used with Norvir include Vascor (bepidil), Zocor (simvastatin), lovastatin (Mevacor or Atacor), Priftin (rifapentine), Mycobutin (rifabutin), and St. John's wort (hypericum). Viagra (sildenafil) levels can be twice as high when taken with Norvir, so starting with a lower dose of Viagra and increasing it every 48 hours, if necessary, can help reduce the risk of serious side effects. Norvir can increase or decrease levels of warfarin, a blood thinner, depending on which type of warfarin is used. A dose adjustment of warfarin may be necessary. Sporanox (itraconazole) and Flonase (fluticasone) may require lower doses when either is combined with Norvir and should be used with caution. Because the list of interactions is so long, it's best to check the package insert that comes with the drug and talk with your healthcare provider about the other medications you're taking.

Norvir can also raise levels of certain street drugs, such as Ecstasy (MDMA). At least one person died when taking the two together. Norvir may also lower methadone levels by 37%, so the methadone dose may need to be increased to compensate.

When To Consider It: The current Department of Health and Human Services (DHHS) treatment guidelines don't recommend full-dose Norvir as part of *any* combination. For someone just beginning treatment, the PI-based regimen most highly recommended by the guidelines includes Kaletra (which already has some Norvir in it). Some PI-based regimens recommended as alternatives

include PIs boosted with Norvir. The number of pills in these combinations is still anywhere from 8 to 16 a day, which is one reason why Norvir-boosted combinations haven't made first picks as starting regimens.

Norvir has significant cross-resistance with Crixivan, meaning that if someone has resistance to one drug, they will most likely be resistant to the other. Resistance to Norvir is also likely to eliminate Viracept as an option, although the reverse isn't necessarily true – resistance to Viracept doesn't seem to eliminate Norvir as an option. Cross-resistance with other protease inhibitors is also possible, but depends on the number and types of mutations acquired. However, if someone has become partially or even fully resistant to Norvir, it can still be useful as a boosting agent.

Good To Know:

- Taking Norvir with a light, low-fat meal may help the drug to be better absorbed in the body.
- Norvir levels may be up to 40% lower in people with moderate liver damage who take the drug. No dose adjustment is recommended, but response to treatment should be monitored particularly carefully in such cases.
- Many people don't like to use the liquid form of Norvir because of the bitter taste. Adults who have a difficult time swallowing pills sometimes use the liquid version and for young children it's the only choice. Some tips to help get the liquid version down include:
 - Drinking the liquid through a straw so that it goes straight down.
 - Mixing the liquid with chocolate milk or a nutritional supplement.
 - Coating your tongue with peanut butter.
 - Sucking a popsicle beforehand to numb the taste buds.

Pregnancy: Norvir is classified as an FDA pregnancy category B drug. Animal studies fail to demonstrate a risk to the mother and fetus, but some long-term animal studies have shown the development of liver tumors in rats as well as developmental problems in unborn rodents. This doesn't necessarily mean that the same would be true in humans. Well-controlled studies of pregnant women have not been conducted.

Dose: Norvir comes in two forms: soft gelatin capsules of 100 mg each and a liquid formulation (80 mg/mL). If taken alone, the standard dose is 1,200 mg a day, (600 mg taken twice a day) with or without food. If being used to boost another drug, the dose is usually 100 to 200 mg twice a day. Refrigeration used to be recommended for both the liquid and capsule forms, but that has changed. The capsules no longer need to be refrigerated if they'll be used within a month and are kept in a cool place (below 77°F). The recommended dose for children ages 2-14 is 400 mg twice a day.

FDA Approval: 1996

Manufacturer: Abbott Laboratories

Patient Assistance Program: 800-222-6885

Crixivan (indinavir sulfate, IDV) was approved by the FDA in March 1996, just two weeks after Norvir (ritonavir). Crixivan's ability to lower viral load to undetectable levels in most people who used it in a three-drug combination made it the "gold standard" of the day. As more drugs with less severe food restrictions and fewer doses per day have become available, Crixivan's popularity has waned. Originally, Crixivan needed to be taken every eight hours on an empty stomach. Combined with low doses of Norvir – an option that has become increasingly common – the number of daily Crixivan doses is reduced from three to two and the food restrictions are no longer necessary. Although no longer the "gold standard" it was in the late '90s, Crixivan remains a powerful part of many people's regimens.

Background: Several studies made the argument for Crixivan's original FDA approval. The first was ACTG 320, a trial that recruited 1,156 people with CD4 counts less than 200 who had been on Retrovir (AZT) for at least three months. Everyone in the study took Retrovir with Epivir (3TC), and half also took Crixivan. Although designed to follow people for one year, the study was stopped after only 38 weeks because people taking the three-drug combination were 50% less likely to progress to AIDS or die than those taking only the two NRTIs. A second study, Protocol 035, followed 97 people who took Crixivan alone, Retrovir plus Epivir, or all three drugs together. After one year, just as in ACTG 320, people taking Crixivan with the two other drugs did best. Those on the triple combination had an average increase of 215 CD4 cells compared to 160 in those taking only Crixivan and 20 in those on Retrovir and Epivir. A similar difference was seen in viral load – 86% of those on the triple combination had viral loads less than 500 copies compared to 56% of those on Crixivan alone and none of those on Retrovir and Epivir.

Further studies compared Retrovir to Crixivan and also found the protease inhibitor to be stronger. Protocol 028 was conducted in Brazil, where there would be a greater chance of including participants who hadn't already taken – and become resistant to – Retrovir. In this study, 224 people who had never been on anti-retroviral therapy took Retrovir, Crixivan, or both together. This study, too, was stopped early (after 58 weeks) because people taking Crixivan alone or with Retrovir were significantly less likely to experience disease progression, and were more likely to have viral loads less than 500 copies and greater CD4 count increases than those on Retrovir alone.

There was no question that when it was released, Crixivan was one of the strongest protease inhibitors out there and would be an appealing option to many. Because adding Crixivan to a drug combination lowered the amount of virus so much, the drug's manufacturer, Merck Laboratories, knew that there would be a high demand for this powerhouse of a drug. To entice people further, they set their average wholesale price for a year's worth of drug at \$5,500, significantly lower than Norvir's \$8,100 average wholesale price. Many

factors made Crixivan a desirable drug, even before its approval in 1996 – the only problem was getting it.

While expanded access programs are meant to provide access to people who really need a drug, Merck made no greater effort than either Roche or Abbott to make Crixivan accessible before it was approved. In August 1995, more than 11,000 people applied for the drug through a lottery system, but only 1,100 received Crixivan in the months prior to its approval. The thousands who were turned away – and many others – hoped that once the drug was approved, access would be easier. Unfortunately, it became even more complicated. Because Merck claimed not to have enough drug to distribute to pharmacies throughout the country, it made an exclusive agreement with Stadtlanders, a mail order pharmacy, to distribute the drug. Stadtlanders was able to set whatever price it chose, which was

especially difficult on people without any insurance. The price for them included a whopping 37% mark-up – over \$1,600 higher than the price the pharmacy charged insurance programs that were covering the drug. This mark-up had many activists in an uproar, and soon after protests, Stadtlanders offered individuals the same discount offered to insurance companies.

Once Crixivan became widely used, many people on the drug raised concerns about the long-term side effects that it might be causing – fat gain in the belly, what they called "Crix belly" or "protease paunch." According to some studies,

as many as 64% of people on any of the protease inhibitors – not just Crixivan – experience changes in body fat and/or blood fat levels (lipodystrophy), including the "Crix belly." Later on, this effect was seen in people who were not using protease inhibitors at all, and studies show that it may be related to the use of antiretrovirals in general, rather than one single drug or group of drugs. HIV itself may also contribute to body fat redistribution and changes in blood fats.

One of the challenges of taking Crixivan as it was originally prescribed was the strict every eight hours dosing schedule, made even more difficult by the empty stomach requirement. In 1998, Merck launched a 287-person study to see if Crixivan would be as effective if it were taken every twelve hours. The study was short-lived. After just six months, only 64% of those on the twice-a-day dose had undetectable levels of virus compared to 91% of those taking the drug three times a day. Unfortunately, twice-a-day dosing allowed drug levels in the body to drop too low, and some people in the trial developed resistance to Crixivan. People can now successfully use Crixivan twice a day by adding a small dose of Norvir.

The current Department of Health and Human Services (DHHS) treatment guidelines differ significantly from the original 1997 version, which gave Crixivan a higher recommendation as a starting regimen. Studies at the time showed that 80-90% of people starting treatment with a protease inhibitor achieved undetectable viral loads. This began a push to get everyone, including people with undetectable viral loads who were on other regi-



mens, to switch to Crixivan or other protease inhibitor-containing combinations. The current guidelines recognize that, while Crixivan is a strong drug, it may be saved for later use, and drugs with more convenient dosing may be better to start with.

Side Effects: Kidney stones, the main concern when using Crixivan, occur in 2-3% of people who take the drug. They're more common in women than in men. If someone on Crixivan experiences pain in their side or back, they should tell their healthcare provider. Left unchecked, kidney stones can lead to kidney damage, which can lead to kidney failure. Crixivan can also cause levels of bilirubin (a substance produced when red blood cells are broken down) to go up, but levels usually return to normal after a few months on the drug.

Other side effects include rash, dry skin, altered sense of taste, mild to moderate hair loss, ingrown toenails, nausea, headache, blurred vision, dizziness, and anemia. The anemia is important to watch for, as it can get dangerous very quickly. Symptoms may include tiredness, feeling lightheaded, and shortness of breath.

Drug Interactions: Crixivan interacts with many other HIV drugs. Drug levels *increase* when taken with some antiretrovirals, including Norvir, Viracept (nelfinavir), Kaletra (lopinavir/ritonavir), and Rescriptor (delavirdine). Others drugs, such as Sustiva (efavirenz) and Viramune (nevirapine), *decrease* levels of Crixivan. If any of these drugs are used with Crixivan, the Crixivan dose may need to be adjusted. Crixivan also seems to increase levels of Agenerase (amprenavir), but no change in dose of either drug is recommended.

Other drugs should be used with caution and, in some cases, avoided when using Crixivan. Nizoral (ketoconazole), for example, raises Crixivan levels by 68% and the dose of Crixivan may need to be lowered. The tuberculosis drug Mycobutin (rifabutin) doubles Crixivan levels and doses of both drugs may need to be adjusted. Rifampin has severe interactions with Crixivan and should be avoided. Crixivan can increase levels of the lipid-lowering drugs Zocor (simvastatin), lovastatin (Mevacor or Atacor), and Lipitor (atorvastatin), and they should be avoided if possible. Ergot alkaloids (used for migraines) should also be avoided. Viagra (sildenafil) levels can triple when taken with Crixivan, so starting with a lower dose of Viagra and increasing it every 48 hours, if necessary, can help reduce the risk of serious side effects.

Strong interactions have also been seen with both grapefruit juice and St. John's wort (hypericum). Grapefruit juice and St. John's wort lower levels of Crixivan by 26% and 57% respectively when taken with Crixivan and should be avoided.

When To Consider It: The 2003 DHHS treatment guidelines recommend Crixivan as a component of two protease inhibitor-containing alternative regimens for people choosing their first combination. Both the regular, three-times-a-day dose and the twice-a-day dose boosted with Norvir are included. "Boosting" – taking the drug with low-dose Norvir – allows people to take Crixivan twice a day. This seems to be as effective at reducing viral load as when the drug is taken three times a day without

Norvir – one study showed the two dosing strategies to work equally well for over two years. The twice-a-day dosing is much easier, but can increase side effects, including nausea, vomiting, dry mouth, rash, kidney stones, and elevations in cholesterol and triglyceride levels.

If your virus becomes resistant to Crixivan, it may also be resistant to other protease inhibitors (cross-resistant). The strongest cross-resistance is seen with Norvir. If Norvir no longer works, then Crixivan is unlikely to work, and vice versa, even if the other drug has never been used before. Similar cross-resistance can also occur with Viracept, Agenerase, and Kaletra.

Good To Know:

- HIV reproduces in many parts of the body, including the brain. Crixivan is the only protease inhibitor that we know reaches the brain and can help lower levels of HIV there.
- Crixivan and the buffered versions of Videx (ddI) need to be taken at least one hour apart and both on an empty stomach.
- The dosage of Crixivan should be lowered in people with serious liver damage (cirrhosis).

Pregnancy: Crixivan is classified as an FDA pregnancy category C drug. Its safety in human pregnancy hasn't been determined. Animal studies looking at dangerous effects to the newborn have been negative, but some studies did show the growth of extra ribs in rodents. Crixivan shouldn't be used during pregnancy unless the potential benefit outweighs the potential risk to the mother and fetus.

Dose: Crixivan comes in 100, 200, 333, and 400-mg capsules. The standard dosage is 800 mg (usually two 400-mg capsules) every 8 hours on an empty stomach, one hour before or two hours after you eat. Boosting Crixivan with Norvir allows for twice-a-day dosing (usually two 400-mg Crixivan capsules with either one or two 100-mg Norvir capsules), but the side effects are often greater with the twice-a-day dosing. Crixivan is not approved for pediatric use.

Although Crixivan was originally approved to be taken on an empty stomach, guidelines were developed by the HIV/AIDS Dietetic Practice Group of The American Dietetic Association and approved by the FDA in August 1997 that listed certain foods that could be eaten with Crixivan without affecting the drug's absorption. An ideal snack, for example, would be low-fat and might include dry toast with jelly or cornflakes with skim milk.

It's important to drink at least eight glasses of water a day while taking Crixivan to reduce the risk of kidney stones. Taking the capsules with other beverages such as skim milk, most juices, coffee or tea should be fine, but be careful not to drink grapefruit juice while on Crixivan since it significantly lowers levels of drug in the body. 1%, 2% or whole milk should be avoided.

FDA Approval: 1996

Manufacturer: Merck & Co.

Patient Assistance Program: 800-850-3430

Viracept (nelfinavir mesylate, NFV) has enjoyed wide use since its FDA approval in March 1997. By 1999, it was the most frequently prescribed protease inhibitor (PI) on the U.S. market and today is second only to Kaletra (lopinavir/ritonavir). Viracept's original approval was for use in both adults and children, which was a first. For other antiretrovirals, pediatric approval – if it happens at all – usually occurs years after approval for use in adults.

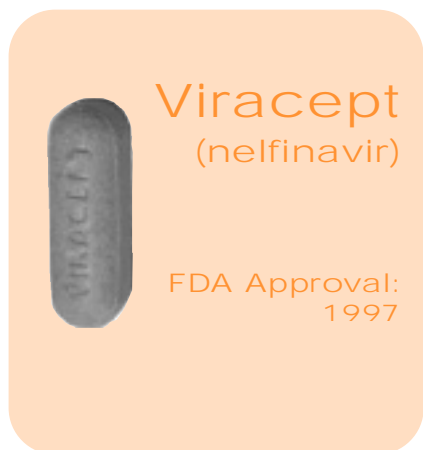
One plus for Viracept is that if it's used as your first PI and your HIV develops resistance to it, most other PIs are still likely to work. Another plus is that, although Viracept was originally approved to be taken three times a day, it was later shown to be equally effective when taken twice a day at a slightly different dose. For people with HIV who also have chronic hepatitis B or C, Viracept is a useful option because it's easier on the liver than the other PIs. There are some important trade-offs when considering Viracept, though. It doesn't have the strength of many other anti-HIV drugs when it comes to reducing viral load, and it causes diarrhea more often than any other commonly-used antiretroviral. Many people who take Viracept experience this infamous side effect, so it's important to figure out ways to manage the diarrhea when considering this drug.

Background: From the time Viracept was first studied in clinical trials through its FDA approval, there were many questions about which dose to use. In developing the drug, Agouron Pharmaceuticals had looked at 500, 750, and 1,000-mg doses in trials such as AG 503. While the 1,000-mg dose reduced viral load more than the two lower doses, it also caused kidney stones more often. So Agouron ditched the 1,000-mg dose and used the 500 and 750-mg doses in later clinical trials. In the studies submitted to the FDA for the drug's approval, the two lower doses worked equally well.

In AG 511, 297 people who had never been on anti-HIV medications were divided into three groups. They took Viracept at a dose of either 500 mg or 750 mg three times a day with Retrovir (AZT) and Efavir (3TC) or just Retrovir and Efavir. After 48 weeks, people on either dose of Viracept did much better than those on just Retrovir and Efavir – 57% on 750 mg and 38% on 500 mg had viral loads less than 400 copies. Only 4% on just Retrovir and Efavir had viral loads that low. Another trial, AG 506, enrolled 308 people who had been on antiretroviral therapy but had never taken a PI or Zerit (d4T). The trial participants took Zerit alone or with one of the same two doses of Viracept. After six months, people taking either Viracept dose had a 90% drop in viral load, while those on Zerit had only a 75% drop. People on Viracept also had greater rises in CD4 cells (100 cells compared to 40 in the Zerit arm). Overall, both doses of Viracept provided a benefit when used with at least one nucleoside analog, but it was hard to tell which dose worked best. Furthermore, people on

either dose were just as likely to experience diarrhea. Agouron petitioned the FDA to approve the lower, 500-mg dose three times a day, arguing that it might save people from long-term side effects.

Some activists and doctors were concerned that this dose was too low and would allow resistance to develop. The FDA took a closer look at the AG 511 study data and found that people who entered the study with viral loads over 100,000 and took the 750-mg dose did better than those who took the 500-mg dose. 81% of those on the higher dose had undetectable viral levels after 48 weeks, compared to 65% of those on the lower dose. With no significant difference in the incidence of diarrhea between the two doses, the FDA approved the 750-mg dose.



Side Effects: Viracept's most common side effect is diarrhea, which can be debilitating. As many as 20% of people who took Viracept in clinical trials had diarrhea. Based on anecdotal and community clinic reports, an even higher percentage have diarrhea outside of the trial setting. For most people, the diarrhea is mild to moderate, but it can be hard to control and significantly interfere with quality of life. Other side effects include nausea, vomiting, weakness, gas, and rash.

Drug Interactions: Viracept can affect and be affected by other anti-HIV medications. When combined with Viracept, levels of Agenerase (amprenavir) and Invirase/Fortovase (saquinavir) can *increase*, while levels of Kaletra and Rescriptor (delavirdine) can *decrease*. Viracept levels can increase when it's taken with Norvir (ritonavir), Crixivan (indinavir), Kaletra, Rescriptor, or Sustiva (efavirenz). These interactions don't affect the way that Viracept and the other anti-HIV medications are used, and no dose adjustments are recommended.

Viracept interacts with a number of other medications. Drugs to avoid while on Viracept include Zocor (simvastatin), lovastatin (Mevacor or Atacor), rifampin, triazolam (Halcion, Restoril, Dalmane, and others), Versed (midazolam), and ergot derivatives (used for migraines). Some of these interactions can lead to serious events such as irregular heartbeats (cardiac arrhythmia) and can even be fatal.

Some drugs might require dose adjustments when taken with Viracept, while others might require the Viracept dose to be adjusted. For example, Viracept can lower the amount of methadone in the body by up to 47%, and a higher dose of methadone may be necessary to avoid symptoms of opiate withdrawal. Viracept can lower levels of the oral contraceptives norethindrone and ethinyl estradiol, so an alternative or additional method of birth control may be necessary. Blood levels of Viagra (sildenafil) can be eleven times higher when taken with

Viracept. Starting with a lower dose of Viagra and increasing it every 48 hours, if necessary, can help reduce the risk of serious side effects. The tuberculosis drug Mycobutin (rifabutin) requires that doses of both drugs be adjusted when the two are taken together.

When To Consider It: Viracept is undoubtedly the weakest protease inhibitor on the market. It has been removed from the preferred list of recommended starting regimens and is now listed by both the U.S. Department of Health and Human Services and the British HIV Association treatment guidelines as part of an alternative regimen for adults who are beginning treatment with a protease inhibitor.

In the EuroSIDA study, 9,800 people from twenty-six European countries recruited between 1994 and 2001 were followed to see when they started and/or stopped their drug regimens. When data from 1,500 people in the study were analyzed, those on Viracept or Invirase were much less likely to have viral loads below 500 copies and were more likely to later see their viral loads bounce back up than people taking other PIs. Compared to Crixivan and Norvir, Viracept was no match.

Because Viracept is considered to be the weakest PI, it has been used (some would say unfairly) as the control arm in many studies testing new drugs. In ACTG 364, for example, 189 people who had been on treatment took Viracept, Sustiva, or both with two NRTIs. In comparing how well Viracept stood up to Sustiva, the answer was not well at all. After 48 weeks, 60% of those on Sustiva had viral loads below 500 copies, compared to only 35% of those on Viracept. The COMBINE study compared Viracept to Viramune, both taken with Combivir (Retrovir plus Efavirenz), in 142 people who hadn't been on antiretrovirals before. Again, Viracept was clearly the weaker drug, at least at first. After six months, only 33% of people on Viracept had viral loads below 200 compared to 58% of those on Viramune – a statistically significant difference. But after 48 weeks, both drugs worked almost as well: 62% versus 75%, respectively. Although there was still a difference, it was no longer statistically significant. Study M98-863 compared Viracept to Kaletra (along with two NRTIs) in 653 people who hadn't been on antiretrovirals before. Those who took Kaletra were significantly more likely to have lower viral loads after 60 weeks. With such generally inferior results, Viracept probably wouldn't be used as often as it is if it weren't for its unique resistance profile.

Many people who use Viracept as a first PI still have all of their PI options intact, even if the drug stops working because their HIV develops resistance to Viracept. The reverse, however, is not true. If someone takes other PIs, develops resistance, and later wants to switch to Viracept, Viracept doesn't usually work. For example, people whose HIV has developed resistance to Invirase, Norvir, or Crixivan have also been found to be resistant to Viracept. So if you decide to start treatment with a PI, Viracept might be a good choice since it leaves other PI options open even if you develop resistance.

Managing Diarrhea: Combining several of the following tips and strategies have helped many people manage diarrhea, including Viracept-related diarrhea:

Over-the-counter remedies:

- Imodium A-D, Kaopectate, Maalox Anti-Diarrheal, and other products that contain loperamide
- Metamucil
- SB-Normal Stool Formula

Medications that require a prescription:

- Lomotil (diphenoxylate)
- Ultrase (a pancreatic enzyme)
- Tincture of opium

Dietary options:

- BRATT diet – **B**ananas, **R**ice (white), **A**pple juice or sauce, **T**oast, and **T**ea (herbal)
- Foods high in starch (white rice, white bread, oatmeal, tofu)
- Juices with less acid, such as apple, pear, and peach
- 10-13 glasses of water per day
- Sports drinks like Gatorade that replenish electrolytes

Avoid:

- Coffee, tea, and other caffeinated beverages like soda
- Chocolate
- Alcohol
- Fried and fatty foods
- Spicy foods
- Foods high in insoluble fiber (raw vegetables, potato peels, beans, brown rice)
- Cookies, cakes, donuts, etc.
- Dairy products, although those with less lactose are okay (yogurt, buttermilk, aged cheeses)

Nutritional supplements and vitamins:

- Calcium or calcium carbonate supplements
- Probiotic tablets (acidophilus, lactobacillus)
- Glutamine
- Zinc

Pregnancy: Viracept is classified as an FDA pregnancy category B drug. A review of over 700 births in which the fetus had been exposed to Viracept *in utero* found no increased risk of birth defects. According to the Antiretroviral Pregnancy Registry, when Viracept has been used during the first trimester, the prevalence of birth defects was 2.9%, compared to an overall prevalence of 3.1% in the U.S. population. In other words, using Viracept during the first three months of pregnancy – the time when a fetus is most susceptible to birth defects caused by toxic chemicals and medications – doesn't seem to have any serious negative effects.

Dose: Viracept is currently available as 250-mg tablets. The FDA approved a 625-mg tablet in April 2003, but it won't be available in pharmacies until sometime early in 2004 due to manufacturing problems. Once the 625-mg tablets are available, twice-daily dosing will require fewer pills and be much simpler.

(continued on page 37)

Agenerase (amprenavir) and Lexiva (fosamprenavir calcium) are different versions of the same drug. Agenerase was the fifth protease inhibitor to hit the market when the FDA approved it in April 1999. Agenerase's lackluster performance in clinical trials and its high pill count have made it one of the least-prescribed protease inhibitors. In fact, its official Web site contains little text other than the statement that one trial "found Agenerase to be significantly less effective than indinavir [Crixivan]." When even the manufacturer warns you about its drug, you know there's a problem. Lexiva, which received FDA approval in October 2003, lowers the pill count dramatically and has performed better in clinical trials than Agenerase.

Background: Like Invirase (hard-gel saquinavir), Agenerase was a drug waiting for a second life. It was approved in spite of poor showings in clinical trials. In PROAB3001, for example, a study of Agenerase with Efavirenz (3TC) and Zidovudine (AZT) in 232 people who had never taken antiretrovirals, only 41% of people had viral loads below 400 after 11 months. And in PROAB3006, a study of 504 people who *had* taken NRTIs but no protease inhibitors, only 30% of people who took Agenerase with two NRTIs had viral loads below 400 after 11 months compared to 49% of people who took Crixivan with two NRTIs.

In addition to these poor results, Agenerase capsules are so big that they're sometimes called "horse pills" and the required dose is 16 of them a day! Because of these problems, the manufacturer (GlaxoSmithKline) developed Lexiva, a pro-drug of amprenavir called fosamprenavir. A pro-drug is a compound that changes into the actual drug once it's in the body, sometimes delivering more of the actual drug. Lexiva requires significantly fewer pills than Agenerase, whether it is taken with Norvir or not.

In the SOLO study, 660 people who had never taken antiretrovirals took either Lexiva with low-dose Norvir once a day or Viracept (nelfinavir) twice a day, each with two NRTIs. After 11 months, 58% of those taking Lexiva had viral loads below 50 compared to 55% of those taking Viracept. Also, half of the people on Viracept had developed mutations associated with resistance to protease inhibitors compared to none of those on Lexiva. Similar results were seen when Lexiva was taken twice a day without Norvir – in the NEAT study, 57% of those taking Lexiva had viral loads below 50 compared to 42% of those taking Viracept after 11 months.

For people who have taken protease inhibitors, Lexiva is only approved for twice-a-day dosing. This is because of the CONTEXT study, in which 315 people who had already taken one or two protease inhibitors took either Kaletra (lopinavir/ritonavir) or Lexiva once or twice a day with low-dose Norvir. Everyone also took two NRTIs. After 11 months, 50% of people taking Kaletra had viral

loads below 50, compared to only 37% of those taking Lexiva once a day. However, 46% of those taking Lexiva *twice* a day had viral loads below 50, so the FDA only approved twice-a-day dosing for "experienced" patients and warns that this study was not large enough to prove that Lexiva was as effective as Kaletra.

Side Effects: The most common side effects of both Agenerase and Lexiva are nausea, vomiting, diarrhea, and rash. Users of Agenerase also have reported a tingling feeling around the mouth, and a change in taste sensation. Depression and mood problems have also been reported.

In two studies (PROAB3001 and PROAB3006), 22% of people who took Agenerase developed a rash. It was usually mild or moderate and lasted an average of ten days, but 3% of people had to stop the drug because of the rash. Nausea was also a common side effect – one of the trials (PROAB3001) reported that 74% of people taking Agenerase with Zidovudine and Efavirenz experienced nausea, compared to 50% of those taking only Combivir (Zidovudine and Efavirenz). About 1% of people taking Agenerase in clinical trials had a severe or life-threatening rash, including cases of Stevens-Johnson syndrome (a severe allergic reaction).

In clinical trials, Lexiva caused fewer gastrointestinal side effects than Agenerase – only 5-9% of people reported nausea or diarrhea. This is probably because Agenerase capsules contain small amounts

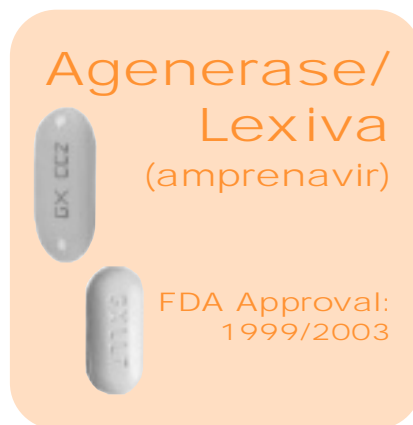
of propylene glycol (used in deodorants, cosmetics, fat-free ice cream, and other products), while Lexiva doesn't. Rash occurred in only 2-7% of people taking Lexiva in clinical trials – a much lower rate than has been seen with Agenerase.

Drug Interactions: Both Agenerase and Lexiva interact with many other drugs, so anyone taking either drug should be sure that their healthcare provider knows everything they're taking, including over-the-counter drugs and herbal medicines. Check the package insert for a complete list of known drug interactions. The following is a partial list:

Neither Agenerase nor Lexiva should be taken with triazolam (Halcion, Restoril, Dalmane, and others), ergot medicines (used for migraines), Versed (midazolam), or Orap (pimozide). Other drugs that require careful monitoring or dose adjustment include Mycobutin (rifabutin) and Viagra (sildenafil).

Agenerase contains a lot of vitamin E, so avoid taking vitamin E supplements while on Agenerase. Too much vitamin E can lead to blood thinning and worsen already existing blood clotting problems or high blood pressure.

Videx (ddI) and antacids should be taken at least an hour before or after taking Agenerase. Rescriptor (delavirdine), rifampin, the oral contraceptives norethindrone and ethinyl estradiol, and St. John's



wort (hypericum) may lower blood levels of Agenerase or Lexiva and shouldn't be taken with either drug. Sustiva (efavirenz) lowers levels of Agenerase, so the two drugs shouldn't be combined unless Agenerase is boosted with Norvir. If Lexiva is taken with Norvir once a day in a regimen that includes Sustiva, the Norvir dose should be increased from 200 mg to 300 mg.

Anyone using the liquid formulation of Agenerase shouldn't take Antabuse (disulfiram) or Flagyl (metronidazole). Alcohol should also be avoided if the liquid formulation is used.

Since Lexiva is often taken with Norvir, even more drug interactions can be expected. Be sure to check out the drug interactions associated with Norvir before combining it with either Agenerase or Lexiva. Serious interactions could occur between Agenerase or Lexiva and amiodarone (Cordarone, Pacerone), systemic lidocaine, tricyclic antidepressants, and quinidine. Careful monitoring is required if any of these are taken with Agenerase or Lexiva.

When To Consider It: The Department of Health and Human Services treatment guidelines do not recommend Agenerase as part of a preferred first regimen. It's included as part of an alternative regimen, but only when combined with low-dose Norvir to reduce the number of pills. There's no recommendation regarding Lexiva since the guidelines haven't been updated since its approval.

One of the mutations (changes) found in HIV that's resistant to Agenerase (I50V) does not seem to cause cross-resistance to other protease inhibitors, but other mutations (I84V, M46I) do. ACTG 373, a study of people who had previously taken Agenerase, found that 59% of the participants had viral loads below 500 after 11 months on Crixivan, Viramune (nevirapine), and two NRTIs. So it's possible to switch to another protease inhibitor after taking Agenerase – at least it was for many people in this study.

Other than the CONTEXT study, there have been few trials of Lexiva or Agenerase in people who have taken other protease inhibitors. CNA 2007, a study of Agenerase, Sustiva, and Ziagen (abacavir) in people resistant to at least one protease inhibitor, had poor results – only 26% of people had viral loads below 400 after four months. But that was probably due to the interaction between Agenerase and Sustiva, which lowers Agenerase levels. As mentioned above, the CONTEXT study had better results with Lexiva, but it was too small to prove whether Lexiva is as effective as Kaletra in people with resistance to other protease inhibitors.

Pregnancy: Agenerase and Lexiva are FDA pregnancy category C drugs. The Antiretroviral Pregnancy Registry only contains information on 24 infants exposed to Agenerase in the womb. One child was born with a birth defect, but since there's only data on 24 infants, it's impossible to know whether this was a result of Agenerase exposure or something else. Agenerase should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus. The liquid form of Agenerase should not be used during pregnancy because it contains propylene glycol, which could be toxic to the fetus. There's no information yet on the use of Lexiva during pregnancy.

Dose:

- **Lexiva** comes in 700-mg tablets. For people who have never taken antiretrovirals, the dose is 1,400 mg twice a day (two tablets twice a day). If taken with Norvir, the dose is either 700 mg Lexiva with 100 mg Norvir twice a day, or 1,400 mg Lexiva with 200 mg Norvir once a day. For people who have taken protease inhibitors, the only approved dose is 700 mg Lexiva with 100 mg Norvir twice a day. Lexiva can be taken with or without food. It is not yet approved for pediatric use.
- **Agenerase** comes in 150-mg capsules. The dose is 1,200 mg twice a day without Norvir or 600 mg twice a day with 100 mg of Norvir. It can also be taken once a day at a dose of 1,200 mg with 200 mg of Norvir. Agenerase can be taken with or without food, but not with a high fat meal, as this will lower blood levels of the drug.

Agenerase is also available as a liquid (15 mg/mL), but children under age 4 should not use it due to the risk of side effects from the propylene glycol it contains. The liquid should only be used if the Agenerase capsules or Lexiva tablets can't be swallowed.

The pediatric dose is based on weight. For children 4 to 12 years old (and adolescents 13 to 16 years old who weigh less than 110 pounds), the dose is 20 mg/kg twice a day or 15 mg/kg three times a day, up to a maximum of 2,400 mg a day.

FDA Approval: Agenerase 1999; Lexiva 2003

Manufacturer: GlaxoSmithKline

Patient Assistance Program: 866-728-4368

Viracept *(continued from page 35)*

The total twice-a-day dose is 2,500 mg (five 250-mg tablets twice a day or two 625-mg tablets twice a day). The total three-times-a-day dose is 2,250 mg (three 250-mg tablets three times a day).

Viracept is also available as a powder (50 mg/gram). It comes in fruit flavors and can be mixed with water, milk, or pudding to make an oral solution, which can help soften its bitter taste. This can be a useful option for adults who have trouble swallowing pills and for children. The pediatric dose (ages 2-13) is based on weight: 20-30 mg/kg (9-14 mg/pound) three times a day. Adolescents age 14 and older take the adult dose.

Viracept should be taken with food. Meals that are high in calories (500-1,000) and include 15-20% fat increase blood levels of Viracept and may make the drug more effective without causing more diarrhea.

FDA Approval: 1997

Manufacturer: Agouron Pharmaceuticals (a subsidiary of Pfizer)

Patient Assistance Program: 888-777-6637

Kaletra (lopinavir/ritonavir, LPV) is one of the strongest and most prescribed protease inhibitors on the U.S. market today. Its approval by the FDA in September 2000 marked the first time that a protease inhibitor (PI) was designed and approved as a boosted drug – the capsules contain the active drug, lopinavir, along with a small amount of Norvir (ritonavir). Kaletra was approved at the same time for use in adults and children. Resistance to Kaletra doesn't develop as quickly as it does with other PIs (at least those not boosted with low-dose Norvir), and many people whose HIV is resistant to other PIs benefit from Kaletra. Its ability to lower viral load dramatically and keep virus levels low for as long as several years *and* its relatively favorable resistance profile make Kaletra a valuable option for people just starting treatment as well as for those whose HIV no longer responds to other PIs.

Background: Kaletra has enjoyed wide use since its release in 2000. Its appeal, however, is largely the work of an already approved PI, Norvir. Early studies had shown that, by itself, lopinavir was a relatively weak drug, particularly against HIV with resistance to other PIs. At the same time that Abbott Laboratories was developing what would come to be called Kaletra, research was finding that adding low doses of Norvir to other PIs could help those drugs overcome existing resistance. The same was true when low-dose Norvir was added to lopinavir. So Abbott, which also manufactures Norvir, decided to test and market both drugs together in one pill – a smart move. Kaletra proved itself by lowering viral loads in people starting antiretrovirals as well as those who had already been on at least one PI. Kaletra's convenient co-formulation and benefits for people with PI cross-resistance set a new precedent. Many other PIs continue to be tested for possible use with low-dose Norvir, led by Kaletra's example.

Study M98-863 compared Kaletra to Viracept in 653 people who had never been on treatment. Trial participants also took two NRTIs. After 60 weeks, 64% of those on Kaletra had viral loads below 50 compared to 53% on Viracept. Study M97-720 also showed Kaletra to be effective in people who had never been on antiretrovirals. This 100-person study compared three doses of Kaletra taken with two NRTIs. After 48 weeks, it became clear that one dose (400 mg lopinavir/100 mg ritonavir) worked better than the others, and everyone in the study was switched to that dose. By 96 weeks, 78 people had viral loads below 50. And after four years on their Kaletra combination, 70 people *still* had viral loads below 50 copies. These impressive results show that a Kaletra regimen can maintain undetectable viral loads for up to four years.

Several studies have also demonstrated Kaletra to be effective for

people who have taken PIs before. Study M98-957 enrolled 56 people who had been on at least two other PIs and had viral loads over 1,000 copies. Most of the participants had resistance to multiple PIs. They took one of two doses of Kaletra twice a day (533/133 or 400/100) together with Sustiva (efavirenz) and two NRTIs. After six months, more people on the higher dose had viral loads below 50 (82% compared to 69%), which prompted the study investigators to switch everyone in the trial to the 533/133 mg dose for the remainder of the study. After 48 weeks, 56% had viral loads below 50 copies. Among those, 52% had more than five PI-associated mutations (changes in HIV's genetic structure), indicating that the drug had a great deal to offer people who had tried and failed other PIs in the past. Clinical trials are now looking at various high doses of Kaletra in people who have high-level resistance to other PIs.



In study M97-765, 70 people who weren't responding to treatment and whose virus was resistant to at least one PI, switched their PI to one of two doses of Kaletra – the approved dose or a higher one that included twice as much Norvir. Everyone in the study also took Virmune (nevirapine) and two NRTIs. After 72 weeks, the response in both groups was equivalent: overall, 57% had viral loads below 50 copies. And after 96 weeks, 49% had viral loads below 50 copies. These results showed Kaletra to be effective in people who had previously used other PIs. This study also suggests that adding more Norvir to Kaletra doesn't necessarily offer any additional benefit, although this

strategy is still being investigated.

Side Effects: Kaletra's most common side effect is diarrhea. In Study M98-863, almost as many people on Kaletra had diarrhea as those on Viracept (16% vs. 17%), although the diarrhea for people on Kaletra was much milder after the first three weeks. Other possible side effects of Kaletra include nausea, shortness of breath, abdominal pain, weakness, swelling in the legs, headache, and vomiting. People taking Kaletra may also experience increases in liver enzymes, and less than 1% of people develop pancreatitis (inflammation of the pancreas).

Drug Interactions: Kaletra interacts with other medications, including other antiretrovirals. Its most significant interactions are with the NNRTIs Sustiva and Virmune. Kaletra levels can decrease by 40% and 55% respectively when taken with these drugs – increasing the Kaletra dose is usually recommended. On the other hand, Kaletra can *increase* levels of Crixivan and Invirase/Fortovase, which may require dose adjustments. Kaletra can also increase levels of Agenerase (amprenavir), which usually requires decreasing the Agenerase dose, and possibly increasing the Kaletra dose as well.

Because Kaletra contains Norvir, the list of other interactions is long and includes some antihistamines, tranquilizers, sleeping pills, antiarrhythmics (used to regulate an erratic heartbeat), and ergot alkaloids (used to treat migraines). Combining Kaletra with any of these drugs may cause serious or even life-threatening reactions. Other drugs that shouldn't be used with Kaletra include Zocor (simvastatin), lovastatin (Mevacor or Atacor), and St. John's wort (hypericum). Levels of Lipitor (atorvastatin), Nizoral (ketoconazole), and certain anticonvulsants are also affected by Kaletra and should be used with caution. (Refer to Norvir's many drug interactions on page 31.)

Using other drugs with Kaletra may require some dose tweaking. Kaletra levels can decrease by 75% when taken with the anti-tuberculosis drug rifampin, so it may be necessary to take additional Norvir or increase the Kaletra dose. On the other hand, levels of Biaxin (clarithromycin) and Mycobutin (rifabutin) can increase by 77% and 300% respectively when combined with Kaletra and may need to have their doses lowered.

Levels of the oral contraceptive ethinyl estradiol can decrease by 42% when taken with Kaletra, so an alternative or additional method of protection is recommended. Levels of Viagra (sildenafil) can be eleven times higher when taken with Kaletra, so starting with a lower dose of Viagra and increasing it every 48 hours, if necessary, can help reduce the risk of serious side effects.

Kaletra may also lower methadone levels by as much as 53%, so the methadone dose may need to be increased to avoid symptoms of opiate withdrawal.

When To Consider It: For people who start treatment with a protease inhibitor, both the U.S. Department of Health and Human Services and the British HIV Association treatment guidelines recommend Kaletra as part of a preferred regimen. These two sets of guidelines differ significantly from one another in many ways but, because the data from study M98-863 is so compelling, both agree that if you're going to start treatment with a PI regimen, Kaletra is generally the one to use. Kaletra can also be beneficial as part of a later treatment regimen for people who have been on other antiretrovirals, including other PIs.

Few people taking Kaletra so far have developed resistance to it. None of the participants on Kaletra in study M98-863 developed resistance to it, while 48% of those on Viracept developed resistance to that PI. Similarly, people in three other trials with viral loads over 1,000 copies while on Kaletra developed no resistance to the drug but, rather, to the NRTIs they were taking. People who took Kaletra in M98-863 also developed no cross-resistance to other PIs, while 48% of those on Viracept did.

What is particularly beneficial about Kaletra's resistance profile is that several mutations are necessary for the virus to become resistant to the drug. One study indicates that between seven and ten mutations are necessary, while another study indicates that as few as four mutations are necessary.

Cross-resistance is also possible but hasn't been seen in great numbers so far. Among the PIs likely to affect how well Kaletra works are Crixivan, Norvir, and Agenerase – having resistance to any of these may preclude or decrease the effectiveness of Kaletra. More information is needed about the cross-resistance profile of Kaletra and which PIs are likely to be effective if the virus becomes resistant to this drug.

Good To Know:

- Because Kaletra is a co-formulation of two drugs in one capsule, people sometimes take Kaletra with just one other drug, thinking that they're on a three-drug combination. But Kaletra counts as only one drug – the small amount of ritonavir in Kaletra doesn't work to slow down HIV replication. Kaletra contains only enough ritonavir to boost lopinavir levels, turning a relatively weak drug into a strong one, and is intended to be taken with at least two other antiretrovirals.
- Once-a-day dosing of Kaletra is now being studied in clinical trials.

Pregnancy: Kaletra is classified as an FDA pregnancy category C drug. Long-term animal studies show a delay and/or defect in the formation of bones in the skeletal system in rats whose mothers were given high doses. This doesn't necessarily mean that the same would be true in humans. Kaletra has not been studied in pregnant women. Kaletra should be used during pregnancy only when the potential benefit outweighs the potential risk to the mother and fetus.

Dose: Kaletra comes in two forms: capsules and liquid. Each capsule contains 133 mg of lopinavir (the main drug in Kaletra) and 33 mg of ritonavir. The total daily dose is 800/200 mg, taken as three capsules twice a day. The liquid formulation is 80 mg/mL lopinavir with 20 mg/mL ritonavir, and the standard dose is 5 mL twice a day. Both the capsule and liquid forms should be taken with food.

Most adults don't like the liquid because of the bitter taste, but for children it's the only option. The liquid formulation is recommended for children ages 6 months to 12 years, and the dose is based on weight. For those weighing less than 15 kg (33 pounds), the twice-daily dose is 12 mg (lopinavir)/3 mg (ritonavir), and for those weighing between 15 and 40 kg (33-88 pounds), the twice-daily dose is 10/2.5 mg. Adolescents weighing more than 88 pounds should take the adult dose.

FDA Approval: 2000

Manufacturer: Abbott Laboratories

Patient Assistance Program: 800-222-6885

Reyataz (atazanavir sulfate, ATV) was approved by the FDA in June 2003 as the first protease inhibitor (PI) to be taken once a day. For people who are just starting treatment, studies showed that Reyataz lowers viral load almost as well as Sustiva (efavirenz), a strong non-nucleoside, and almost as well as (although not better than) Viracept (nelfinavir), a relatively weak PI. These studies also showed that Reyataz may be the only PI that doesn't raise lipid levels (cholesterol, triglycerides). In one study, it actually *improved* lipids. Levels of bilirubin (a product of red blood cell breakdown) can increase in many people taking Reyataz. The drug has a favorable resistance profile in that its most common mutation doesn't cause cross-resistance to other PIs. Other mutations, however, can cause cross-resistance.

Background: Three critical studies led to the FDA's approval of Reyataz. One was a non-inferiority study. Using this increasingly popular trial design, study AI424-034 compared Reyataz to Sustiva, both taken with two NRTIs, in 810 people who had never been on antiretrovirals before. Unlike other comparative studies, this one was designed to show that Reyataz wasn't worse than Sustiva, even if it wasn't better. After 48 weeks, the two groups did just about as well, with no statistically significant difference – 32% of people on Reyataz had viral loads below 50 compared to 37% of those on Sustiva. But the results were somewhat unsettling. While they did show that Reyataz wasn't inferior to Sustiva, the question was – why did the people taking Sustiva in this trial do so poorly? In study DMP 266-006, for example, 64% of people on Sustiva and two NRTIs had viral loads below 50 at 48 weeks – almost twice the rate seen in study AI424-034. Bristol-Myers Squibb (BMS), the manufacturer of both Sustiva and Reyataz, attributes Sustiva's (and Reyataz's) relatively poor performance to a problem with new procedures and vials used in the study.

A second study, AI424-008, compared two different doses of Reyataz to Viracept in 467 people who had never taken antiretrovirals before. Trial participants also took two NRTIs. After 48 weeks, there were no statistically significant differences between the three groups – approximately 35% of people on either dose of Reyataz and 38% of those on Viracept had viral loads below 50. Again, Reyataz did about as well as the drug it was being compared to. Together with those of AI424-034, these results show that Reyataz can lower viral loads to below 50 copies in about a third of people who are just starting treatment, a modest response at best.

Lastly, study AI424-043 provided important, although incomplete, information about how Reyataz works in people who have used other PIs in the past. In this study, 300 people whose HIV wasn't responding to another PI switched to either Reyataz or

Kaletra, in addition to two NRTIs. After six months, 34% of people taking Reyataz had viral loads below 50 compared to 50% of those on Kaletra. When the results of these three studies were presented to the FDA, the agency was convinced that Reyataz was comparable enough to Sustiva and Viracept to grant the drug approval for use in a first treatment regimen. But the FDA didn't have compelling information about how Reyataz should be used in people who had already taken, and failed, other protease inhibitors. Data that weren't presented in time for the drug's approval showed that boosting Reyataz with a small amount of Norvir (ritonavir) raised levels of Reyataz sufficiently to lower viral load in people who had previously failed multiple PIs. In fact, boosted Reyataz (300 mg Reyataz plus 100 mg Norvir once a day) performed as well as Kaletra. Because the FDA was unable to review this information (it was presented late), there are no current recommendations for the use of boosted Reyataz for people with multi-drug resistant virus.



Concerns about Reyataz's side effects, cross-resistance, dosing, and other issues made some activists ask if there was enough information for full approval in June 2003. They wanted more studies to evaluate the short and long-term risks and how best to use this drug. In May 2003, a group of activists sent a consensus letter to the FDA asking for postponement of full approval until more studies were completed. Despite these efforts, Reyataz was granted full approval weeks after receipt of the letter.

Side Effects: Reyataz's most common side effect is an increase in bilirubin, a substance produced when red blood cells are broken down. High levels of bilirubin can cause jaundice (yellowing of the skin and the whites of the eyes) – the higher the bilirubin level, the more likely jaundice will appear. If the drug is stopped, bilirubin levels return to normal and the yellow color goes away. High bilirubin levels can also be a symptom of liver damage, so this unusual side effect raises concern about whether taking Reyataz could harm the liver. But so far, using Reyataz doesn't seem to have caused any liver damage. Among the studies done to date, about 40% of people taking Reyataz at the boosted dose and 47% of those taking the standard dose had bilirubin levels more than two and a half times above normal and 15% experienced jaundice. People starting Reyataz should closely monitor bilirubin levels and liver health. Reyataz should be used with caution in people with pre-existing liver problems such as hepatitis B or C, although no differences in bilirubin levels have been seen in people who are co-infected.

Unlike other PIs, Reyataz hasn't caused increases in blood fats (cholesterol, triglycerides) in clinical trials. In AI424-007 and 008, no elevations in lipids were seen after 48 weeks on Reyataz. Similar results have been seen in other studies of this drug. Furthermore, people taking Viracept for 48 weeks in study

AI424-034 who switched to Reyataz had, on average, a 76% drop in total cholesterol, a 41% drop in LDL (bad) cholesterol, and a 50% drop in triglycerides 48 weeks after switching. These levels began to drop as early as four weeks after switching and were maintained for up to 108 weeks after switching. Unfortunately, despite these positive findings, some people on Reyataz have experienced increased fat in the upper back, neck, trunk, and breasts, as well as increases in blood glucose levels. More information from follow-up studies is needed to determine if Reyataz is a possible cause of these body-shape changes.

Other potential side effects include nausea, diarrhea, headaches, rash, and abdominal pain.

Drug Interactions: Reyataz interacts with other medications, including other antiretrovirals. Videx (ddI), Sustiva, and Viread (tenofovir) can each lower the amount of Reyataz in the blood. Videx's food restrictions are also quite different than those for Reyataz. Therefore, BMS recommends that Reyataz be boosted with low-dose Norvir when taken with Sustiva or Viread and that it be taken a few hours before or after Videx. Crixivan (indinavir), another PI, can also cause high levels of bilirubin and shouldn't be taken with Reyataz.

The list of other interactions includes rifampin, the antineoplastic Camptosar (irinotecan), Vascor (bepridil), the benzodiazepines Versed (midazolam) and triazolam (Halcion, Restoril, Dalmane, and others), ergot alkaloids (used to treat migraines), Zocor (simvastatin), lovastatin (Mevacor or Atacor), and St. John's wort (hypericum). Combining Reyataz with any of these drugs may cause serious or even life-threatening reactions.

Reyataz can also increase blood levels of antiarrhythmics (used to regulate an erratic heartbeat), the blood thinner warfarin, tricyclic antidepressants, Mycobutin (rifabutin), certain calcium channel blockers, Lipitor (atorvastatin), certain immunosuppressants, Viagra (sildenafil), the oral contraceptives ethinyl estradiol and norethindrone, and Biaxin (clarithromycin). Dose adjustments may be necessary to reduce the risk of side effects. Reyataz levels can *decrease* when taken with certain antacids and H₂ receptor antagonists, so spacing your dose of Reyataz and these medications as far apart as possible is recommended.

When To Consider It: The most recent Department of Health and Human Services treatment guidelines don't discuss Reyataz in any detail or include it in any preferred or alternative regimens. That doesn't mean that the drug couldn't be useful in a first or later combination – it's just that it was approved shortly before the revised guidelines were released. In fact, Reyataz may join Kaletra as a particularly versatile PI, valuable for people just starting treatment and for those whose virus is no longer responding to certain PIs. According to a member of the panel that drafts and approves the guidelines, Reyataz will probably be listed as an alternative protease inhibitor in future versions of the guidelines.

For people beginning treatment with a PI, Reyataz is appealing

because of its once-a-day dosing, the fact that it doesn't seem to raise lipid levels, and its unique resistance profile. However, many healthcare providers are prescribing Reyataz in combination with low-dose Norvir in order to boost Reyataz levels in the body, making it even more powerful against HIV and prolonging the effect of therapy. While there is some concern that low-dose Norvir might "cancel out" Reyataz's minimal effect on lipid levels, data from clinical trials and anecdotal reports suggest that this isn't a big problem.

If your virus becomes resistant to Reyataz, you're still likely to respond to other PIs. In fact, some data suggest that HIV that becomes resistant to Reyataz may be even more sensitive to other PIs used down the line. And for people whose virus is already resistant to other PIs, early data suggest that Reyataz should still work. In one study of HIV isolated from 551 people, Reyataz worked against virus that was resistant to Viracept. What's more, the primary mutation that results in partial resistance to Reyataz (the I50L mutation) is believed to make the virus even more sensitive to other PIs, most notably Agenerase (amprenavir). However, cross-resistance is still possible, even if it's less common than with most other PIs. Several people who had been on antiretrovirals before and took Reyataz together with Invirase/Fortovase (saquinavir) developed cross-resistance to almost all of the PIs – with the exception of Agenerase.

Good To Know:

- The original brand name chosen for atazanavir was Zrivada. The new name, Reyataz, may have been chosen because Zrivada didn't fly with focus group participants or because "Taz" was already being used as a nickname for the drug while it was in development.

Pregnancy: Reyataz is classified as an FDA pregnancy category B drug. Animal studies fail to demonstrate a risk to the fetus, but well-controlled studies of pregnant women haven't been conducted. Reyataz should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Dose: Reyataz comes in 100, 150, and 200-mg capsules. The once-a-day standard dose is 400 mg, usually taken as two 200-mg capsules. Reyataz should be taken with a light meal or snack – meals of around 350 calories help make Reyataz more available in the body. When used with Norvir, the dose is two 150-mg Reyataz capsules plus one 100-mg Norvir capsule once a day.

Reyataz is not approved for pediatric use. Due to the risk of increased bilirubin, Reyataz should not be given to children under the age of 3 months.

FDA Approval: 2003

Manufacturer: Bristol-Myers Squibb

Patient Assistance Program: 877-758-7877

Entry Inhibitors

Entry inhibitors work at HIV's first point of contact with a human cell. This occurs at an earlier stage in the HIV lifecycle than the other antiretrovirals. To successfully infect a cell, HIV needs to attach to and enter the cell through a series of steps. Proteins on the surface membrane of HIV (gp120 and gp41) interact with receptors on the surface of the cell (the CD4 receptor and a chemokine receptor, either CCR5 or CXCR4). Once this happens, a process called fusion occurs – the membranes of the virus and the

cell fuse together, allowing HIV's genetic material to enter the cell.

An entry inhibitor interferes with one of the steps in this process. It targets either one of the proteins on the surface of HIV or one of the receptors on the surface of the CD4 cell. So far, only one drug in this class, a fusion inhibitor called Fuzeon (enfuvirtide), has been approved, but several others are in development. Fuzeon blocks HIV's gp41 protein. With its gp41 occupied by the drug, HIV is

unable to fuse with the CD4 cell and send its genetic material inside. Entry inhibitors in development interfere either with HIV's gp120 or gp41, or with one of the receptors on the CD4 cell, including CCR5 and CXCR4.

One of the biggest challenges with this class of drugs is that stomach acids break them down, so they can't be taken in an oral form. Like Fuzeon, many (but not all) entry inhibitors will need to be taken as an injection or by intravenous infusion.

Fuzeon (enfuvirtide, T-20) ushered in a new class of anti-HIV drugs (fusion inhibitors) when it received FDA approval in March 2003. For people whose HIV had become resistant to many drugs from the other classes, it offered new hope of bringing viral loads down below detection, but it came with two major obstacles. Since the stomach destroys the drug, it can't be taken as a pill, but has to be injected twice a day under the skin. And it has a retail price of over \$25,000 a year – nearly three times that of any other anti-HIV drug.

Background: Fuzeon was originally developed by Trimeris (hence the “T” in T-20), a small company that conducted the first studies of the drug. In 1999, Trimeris partnered with the much larger (and better-financed) Hoffmann-La Roche to further develop and manufacture the drug.

As the first drug in a new class, Fuzeon entered the scene with the same kind of splash that accompanied Retrovir (AZT), the first antiretroviral, and Invirase (saquinavir), the first protease inhibitor. But as in those cases, the anticipation seems to have exceeded the actual event and, once again, the drug came with a price that set a new precedent.

Clinical trials have found that Fuzeon works for some people who have tried and failed other anti-HIV drugs, but usually only if it can be combined with older drugs that the virus is still sensitive to. In the TORO studies (T-20 vs. **Optimized Regimen Only**), nearly 1,000 people who had used an average of 12 antiretrovirals and were resistant to drugs from all three classes chose an “optimized” regimen of approved drugs. The regimens were individualized based on resistance testing and each person's treatment history. Two-thirds of the trial participants then added Fuzeon to their optimized regimen and the rest used only their optimized regimen. After 11 months, 18% of people taking Fuzeon had viral loads below 50 compared to 8% of those who weren't taking Fuzeon.

People taking Fuzeon had an average increase of 91 in their CD4 counts compared to a rise of 45 for those on the optimized regimen alone. While adding Fuzeon worked more than twice as well as taking the optimized regimen alone, the fact remains that 82% of people on Fuzeon didn't achieve viral loads below 50 (the gold standard in treatment today, and the drop that is usually needed to keep viral loads low over time).

These modest results did not seem to dampen enthusiasm over Fuzeon's approval. And they did not prevent Roche from charging a price even higher than the most pessimistic forecasts. Roche says that the drug's manufacturing process requires the high price, and it is true that Fuzeon is the most difficult antiretroviral to make, with over 100 steps required for each batch. But many activists said that did not justify Fuzeon's price, and their protests helped AIDS Drug Assistance Programs (ADAPs) across the country negotiate significant price reductions.

According to the TORO studies, Fuzeon works best in people who have: taken less than ten antiretrovirals; a viral load below 100,000; a CD4 count above 100; and two other anti-HIV drugs that still work against their virus. 80% of people who had all these characteristics were able to get their viral loads below 50 with Fuzeon. But if you don't meet these criteria, your chances are worse. For example, people who had only one antiretroviral available saw viral load drops of just 0.2 logs (37%) after six months on Fuzeon, a result that is so minimal that it could be due to normal fluctuations. Those who had three or four drugs available saw viral load drops of 2.3 logs (99.5%) – an impressive change. So people whose virus is resistant to all of the approved drugs will most likely not benefit by adding Fuzeon to a failing regimen. Many people have waited to start Fuzeon until they could get access to newer drugs like tipranavir (an experimental protease inhibitor) through clinical trials, so that they could start both drugs together.

The biggest challenges Fuzeon users face are the twice-daily injections and problematic injection site reactions. Roche has published detailed information about how to prepare and inject Fuzeon, and anyone starting it needs to take great care to learn how to use the drug properly. The drug comes as a powder that must be mixed with sterile water – it can take up to 45 minutes to properly dissolve (usually about 15), and must not be shaken. Once mixed, it should be used right away (two doses can be made at once if the second is refrigerated). Similarly, the injections must be given correctly to minimize skin reactions and ensure that the drug is delivered properly. People starting Fuzeon must be carefully trained by their healthcare providers to make sure they know how to mix and inject the drug properly.

Fuzeon's difficult injections may have had an effect on its popularity. As of October 2003, Roche had received only 5,700 requests for Fuzeon – less than expected. Other people have had difficulty getting their insurance or ADAP to pay for the drug. People considering Fuzeon should be aware of the barriers to its use and prepare for them before starting.

Side Effects: Almost everyone who takes Fuzeon gets injection site reactions (ISRs), which can include itching, swelling, redness, pain or tenderness, hardened skin, and bumps. The reactions are usually mild to moderate, but can be severe in a few people. The best way to minimize them is to follow the preparation and injection instructions carefully. There are also detailed suggestions at the drug's website (www.fuzeon.com).

Fuzeon has caused a serious allergic reaction in less than 1% of people in clinical trials – anyone who has trouble breathing, fever with vomiting and a skin rash, blood in the urine, or swelling of the feet while taking the drug should call their healthcare provider immediately.

In clinical trials, people taking Fuzeon got bacterial pneumonia more often than people who weren't taking Fuzeon, especially those who had lower CD4 counts, higher viral loads, used injection drugs, smoked, or had lung disease in the past. It's not known how, or even whether, Fuzeon contributed to this, only that people taking Fuzeon in trials were more likely to get bacterial pneumonia.

Other side effects seen in people using Fuzeon include pain and numbness in the feet or legs, loss of sleep, depression, decreased appetite, weakness or loss of strength, muscle pain, constipation, and pancreas problems.

Drug Interactions: Fuzeon does not seem to interact with other antiretrovirals, and there are no other drug interactions listed in the package insert.

When To Consider It: Fuzeon is approved for use only in people whose HIV has become resistant to available antiretrovirals. Because of the drug's difficult dosing and high cost, it's best used only by people who need the drug to put together an effective treatment regimen. Since Fuzeon is the first drug in its class

and works at a completely different point in HIV's lifecycle, no cross-resistance with drugs from the other classes has been seen. But trials have shown that Fuzeon doesn't work if a person has no other antiretrovirals available – at least one, or better yet, two other drugs are needed to keep viral loads below detection.

Early studies have shown that people whose virus has become resistant to Fuzeon can benefit by switching to T-1249, a fusion inhibitor that's in clinical trials. This is especially true for people with resistance who have taken Fuzeon for less than 11 months.



Fuzeon Tips:

- Fuzeon should be injected every 12 hours. Delaying a dose by more than an hour increases the risk of developing resistance to the drug.
- Some users have experienced syringe failures – Fuzeon leaking out from the “hub” (the point where the needle meets the syringe). If this happens, contact Roche at 877-438-9366 and report the problem. If you weren't able to take your full dose, they'll usually recommend that you mix another dose and will add extra drug to your next shipment to make up for the lost dose.
- A study looking at techniques that may minimize ISRs is starting. The methods being studied are gentle massage, heat from a warm moist cloth, hydrocortisone cream, self-injection, and having a partner inject the drug. We won't know which techniques work best until the study is finished, but people have reported some success with each of them.
- Other tricks people have tried to reduce ISRs include:
 - using an electric hand massager after the injection;
 - showering before injections to soften the skin;
 - avoiding shots in the butt if you have to sit for long periods;
 - wearing loose clothing to avoid irritating injection sites;
 - squeezing the skin like a bow tie and injecting into the sides, to lessen the pain and to make sure that you're not injecting into muscle.
- Find the injection sites that work best for you. For most people, the skin on the abdomen is best since it is often the loosest skin on the body. But one user finds injections in the upper thigh to work best – he feels that walking massages the site and leads to faster healing.

(continued on next page)

Fuzeon *(continued from previous page)*

- The angle and depth of the needle may have an effect on the ISR – find the technique that works best for you.
- Roche recommends inserting the needle 3/4 of the way in, but users with little body fat have found that this may place the needle in the muscle rather than under the skin, leading to worse ISRs. Avoid injecting Fuzeon into muscle tissue – ask your healthcare provider for advice about changing your injection technique if needed.
- Fuzeon comes with safety syringes (the needle retracts after use), which have caused problems for some users. You can use other syringes if you need to, but ask your healthcare provider first.
- Some users have reported that mixing Fuzeon is easier and faster in a warmer room, so that the drug is at room temperature.
- As with all medications delivered by injection, Fuzeon may be a challenge for some people with a history of injection drug use. Some people balked at the thought of participating in the Fuzeon trials because they couldn't imagine using syringe needles regularly without triggering their disease of addiction. For other people who have used injection drugs, it may not be an issue.

Pregnancy: Fuzeon is classified as an FDA pregnancy category B drug. Studies in rats and rabbits have not found any harm to the fetus. Fuzeon has not been studied in pregnant women, so it should be used during pregnancy only if absolutely necessary.

Dose: 90 mg (1 mL) twice daily, as a subcutaneous (under the skin) injection in the upper arm, thigh, or abdomen. Each injection should be given at a different site than the one before and only where there is no injection site reaction from an earlier dose. Fuzeon should not be injected into moles, scar tissue, bruises, or the navel.

The pediatric dose (ages 6 to 16 years old) is based on weight: 2 mg/kg twice a day up to a maximum of 90 mg twice a day. There's no recommendation for its use in children younger than 6 years old, since it hasn't been studied in them. The label includes a chart to find the correct dose based on weight.

FDA Approval: 2003

Manufacturer: Hoffmann-La Roche

Patient Assistance Program: 866-487-8591

Fuzeon Medical Questions: 877-4FUZEON (438-9366)

Glossary of Terms

Accelerated Approval: The process by which the FDA rapidly approves experimental treatments for serious or life-threatening conditions.

ACTG (AIDS Clinical Trials Group): A clinical trials network of medical centers, sponsored by the National Institute of Allergy and Infectious Disease, which conducts trials of treatments for AIDS/HIV and opportunistic infections.

Antiretroviral Pregnancy Registry: A voluntary databank established by the FDA to collect and evaluate the results of exposures to antiretrovirals during pregnancy in mothers and their children.

Arm: A group of participants in a clinical trial who receive the same treatment. Participants in a controlled trial are assigned to either a "treatment arm" (people who get the drug being tested) or the

"control arm" (people who get the standard treatment or a placebo).

Blinded: A method for assigning treatment regimens in a clinical trial that keeps trial participants from knowing which treatment regimen they are taking.

Combination Therapy: Using at least two drugs at the same time to treat a disease. With current HIV treatment, combination therapy usually refers to the use of at least three drugs (see HAART).

Compassionate Use: A phrase used to describe programs that provide experimental drugs on an individual basis to seriously ill people with few or no treatment options. Often, case-by-case approval must be obtained from the FDA.

Controlled Trial: A clinical study in which two (or more) kinds of care or treatment are compared. Those in the

"control" group are regarded as the standard of care to which the second kind of care or treatment is compared.

Cross-Resistance: The phenomenon by which HIV (and other disease-causing organisms) that develops resistance to one drug also becomes resistant to other drugs. For example, HIV that develops resistance to one of the non-nucleoside reverse transcriptase inhibitors will also likely have resistance to other drugs in the same class.

Disease Progression: The way that a disease develops, including the specific events involved, bodily tissues or systems affected, mechanisms of damage, and the course of disease over time. HIV disease progression is usually described in terms of CD4 counts, viral load, and new or recurring opportunistic infections.

DHHS HIV Treatment Guidelines: A guidance document for the medical man-

agement of HIV disease created and periodically updated by a panel of HIV specialists, physicians, people with HIV, and community activists under the auspices of the U.S. Department of Health and Human Services (DHHS). The most recent revision to the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* was published in July 2003. There are similar HIV guidelines that focus on pediatrics, mother-to-child transmission, and other subjects.

DNA (deoxyribonucleic acid): A double-stranded molecule that carries genetic information and that makes up the chromosomes in a cell's nucleus.

Double-Blind: A method for assigning treatment regimens in a clinical trial which keeps both trial participants and members of the research staff from knowing which participants are on which assigned treatments.

Drug Interaction: The effect that can occur when two or more drugs are used together. These include changes of absorption in the digestive tract, changes in rate of the drugs' breakdown in the liver, new or increased side effects, and changes in the drugs' activity.

DSMB (Data and Safety Monitoring Board): An independent panel of clinical research experts that reviews the results of clinical trials while they are underway. The DSMB can change or close a trial if the early results call for that.

Efficacy: The effectiveness or ability of a drug to control or cure an illness. The efficacy of an anti-HIV drug usually refers to the drug's ability to lower viral load.

Expanded Access: A program that distributes experimental drugs to people who are unable to participate in clinical trials and have few or no other treatment options.

FDA (Food and Drug Administration): The agency of the U.S. Department of Health and Human Services that regulates the testing of experimental drugs

and approves new drugs and medical products based on evidence of their safety and efficacy. The FDA also regulates the safety of foods, cosmetics, and other products.

First-Line Treatment: The best starting therapy for someone who has never received therapy before. Because of the potential for the development of cross-resistance by HIV and other microbes, the choice of first-line medication(s) may affect the efficacy of later medications.

HAART (Highly Active Antiretroviral Therapy): Anti-HIV treatment that uses a combination of drugs (usually three or more) to reduce viral load to undetectable levels.

in vitro: Latin phrase for "in glass" that refers to lab experiments conducted in cell cultures grown in an artificial environment, for example in a test tube or culture plate.

in vivo: Latin phrase for "in life" that refers to studies done in humans or animals.

Lactic Acidosis: A buildup of lactic acid in the body. Lactic acid is a byproduct of the breakdown of carbohydrates. Our bodies usually clear excess lactic acid. Lactic acidosis is a rare side effect of the nucleoside analogs. Nucleoside analogs can damage the mitochondria (the power plants of cells), making them unable to clear excess lactic acid from the blood. Severe lactic acidosis can be life-threatening.

Lipids: Fats stored in the body and used for energy. Lipids include cholesterol, fatty acids, and triglycerides.

Lipoatrophy: The loss of fat stored under the skin, especially in the limbs and cheeks.

Lipodystrophy: Changes in body composition. Symptoms include fat loss in the limbs or face, excess fat in the abdomen, breasts, and upper back, increased triglycerides and cholesterol, insulin resistance, and glucose intolerance, possibly leading to a higher risk of heart disease and diabetes. There is no clear definition of

lipodystrophy, and there is no one cause, although it is at least partly associated with the use of antiretroviral drugs.

Mitochondria: Structures in human cells that turn nutrients into energy for the cells. Essentially, they are the cells' "power plants."

Mitochondrial Toxicity: Damage to the mitochondria caused by factors such as heredity, aging, infections, or certain anti-HIV medications, particularly nucleoside analogs. Mitochondrial toxicity may be responsible for side effects such as muscle weakness and muscle loss, peripheral neuropathy, pancreatitis, low platelets, low levels of other blood cells, and lactic acidosis.

Monotherapy: Treatment consisting of only one drug.

Myopathy: a general term referring to any disease of muscles. Inflammation of muscle tissue, resulting in muscle weakness is a rare side effect of long-term use of Retrovir (AZT), which is also part of Combivir and Trizivir. Myopathy can also be caused by HIV disease itself.

PACTG (Pediatric AIDS Clinical Trials Group): A clinical trials network that studies treatments for infants and children with HIV and for the interruption of mother-to-child HIV transmission. The PACTG is a joint effort of the National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute for Child Health and Human Development (NICHD).

Patient Assistance Program: Programs run by drug companies to provide free medications to people who have no insurance, inadequate insurance, or financial difficulties. Most programs have strict requirements, such as income no more than 300% above the federal poverty level.

Phase I Trial: The first stage in testing a new drug in humans. The studies are usually done to gather preliminary information on the chemical action and safety of the drug using healthy volunteers. Usually done without a comparison group.

(continued on next page)

Phase II Trial: The second stage in testing a new drug in humans. Performed in patients with the disease or condition being studied. The main purpose is to evaluate the activity of a drug, and to possibly provide information on how well the drug works.

Phase III Trial: The third and usually final stage in testing a new drug in humans. Used to collect information about the safety of a drug and how well it works. Once this phase is complete, the drug manufacturers may request permission from the Food and Drug Administration to market the drug.

Phase IV Trial: A large trial designed to evaluate the long-term safety and effectiveness of a drug that has been approved by the Food and Drug Administration.

Placebo: An inactive agent given as a substitute for an active agent for the purpose of comparison in a clinical trial. A placebo usually looks like the experimental treatment being studied. If a placebo is used in trials of HIV combination therapy, people taking the placebo usually get approved drugs also.

Placebo-controlled: A trial in which the effectiveness of an experimental drug is compared to that of a placebo.

Pregnancy Category: The Food and Drug Administration rates drugs in terms of their safety during pregnancy from A (safest) to X (least safe – do not use). Most medications have not been studied in pregnant women to see if they cause damage to the fetus.

- **Category A** – Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote.
- **Category B** – Either animal studies have not shown a fetal risk but there are no controlled studies in pregnant women, or animal studies have shown an adverse effect that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).
- **Category C** – Either animal studies

have shown adverse effects on the fetus and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

- **Category D** – There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (for example, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
- **Category X** – Studies in animals or human beings have demonstrated fetal abnormalities, or there is evidence of fetal risk based on human experience or both. The risk of the use of the drug in pregnant women clearly outweighs any possible benefit.

The antiretrovirals are all classified as either category B or category C drugs.

Resistance: The ability of a virus (or other germ) to become less sensitive to a drug, usually by genetic mutation. In HIV, the viral enzymes and proteins mutate, or change, so that an antiretroviral drug cannot attach to them. (See cross-resistance).

RNA (ribonucleic acid): A single-stranded molecule composed of nucleotides. It is similar in basic structure to half of the double-stranded DNA. In healthy cells, RNA is used to copy portions of the cell's DNA in order to produce other cell components. HIV's RNA stores the viral genes that are later converted to DNA.

Side Effect: The action or effect of a drug beyond what it is supposed to do. The term usually refers to negative effects, such as headache, nausea, or liver damage. Side effects can be expected or unexpected, desired or undesired. Experimental drugs are studied for both short- and long-term side effects. (Side effects are also referred to as adverse events.)

Statistically Significant: The probability (usually less than 5 percent) that a finding or result of a clinical trial is caused by something other than just chance.

Treatment IND (Investigational New Drug): A program that allows a drug developer to give physicians an experimental drug for people who have no other treatment options, once the drug has shown signs that it works and is safe.

Unblinded: The decision to stop the blinded or double-blinded process in a clinical trial and reveal the treatment assignment of an individual trial participant or group of participants.

Viral Load: The amount of HIV RNA per milliliter of blood. An undetectable viral load means that the number of copies of HIV RNA is less than the test is able to measure, usually less than 50 or 400 copies (depending on which test is used).

Some of these definitions are adapted from *CPCRA Glossary of Medical, Statistical, and Clinical Trials Terminology* by Carlton Hogan, University of Minnesota.



**is looking for new
COMMUNITY
ADVISORY BOARD
members.**

ACRIA's Community Advisory Board (CAB) fosters partnership between the education staff and the local community impacted by HIV/AIDS. Involving community members in the development of our education programs ensures that community values and cultural differences are respected in ACRIA's educational work.

Community Advisory Board members meet every other month, review program materials and help us identify education needs.

For more information about the CAB or if you are interested in volunteering at ACRIA, please call Mark Milano at (212) 924-3934, ext. 123.

New Technical Assistance Program for NYC

Thanks to a new Ryan White Title I funded contract from the New York City Department of Health and Mental Hygiene, ACRIA will soon be providing HIV treatment education technical assistance to community-based organizations (CBOs) in New York City. This contract allows ACRIA to offer multi-day trainings and ongoing, individual follow-up support to staff of local CBOs. The goal of the program is to help service providers develop the skills and knowledge to provide accurate, practical HIV treatment information to their clients in ways that are culturally appropriate. We plan to include 50 CBO staff members in the program annually, helping them to integrate HIV treatment issues into the provision of social services at their organizations. The new program is modeled on ACRIA's established National HIV Treatment Education Technical Assistance Program. Our national initiative, which provides training and follow-up support to organizations and individuals in regions outside of New York State, is funded entirely by private sources. We expect the technical assistance services in New York City to begin in early 2004.

ACRIA Hosts National Technical Assistance Program Participants

Over the past few months, ACRIA had the pleasure of bringing five participants in our National HIV Treatment Education Technical Assistance Program to work with us in New York City. Following a

competitive application process, two program participants from Baltimore, Maryland and three from Wisconsin – two from Madison and one from Milwaukee – joined us for a week of intensive work with ACRIA staff. Our guests worked on research projects, updated educational materials, participated in program development meetings and literature reviews, and accompanied ACRIA treatment educators to agencies throughout the city to observe and participate in client workshops and staff trainings. Our guests provide HIV treatment education to varying degrees in very different settings, from case management to street outreach, but one thing that they all have in common is a commitment to offer useful, accurate information to their communities. We invite program participants to work with us so that they can receive hands-on technical assistance as they're in the process of expanding or developing treatment education programs at their own organizations. According to our guests from Maryland and Wisconsin, the time spent at ACRIA was extremely valuable. Their visits were equally valuable to us, and we appreciate having been able to collaborate with such thoughtful, community-focused individuals.

ACRIA Presents Study Findings on HIV in People Over 50

ACRIA has completed its first studies focusing on the emerging healthcare needs of people living with HIV/AIDS (PLWAs) as they age. In the past year, ACRIA has developed one of the largest

databases of PLWAs who are 50 years and older. Two studies were conducted in 2003, findings from which were recently presented at several major city, state and national conferences.

Data from our study of care provider arrangements for PLWAs were presented at the New York State Society of Aging meeting in Albany and the HIV Health and Human Services Council of New York City, both in October, as well as at the November meeting of the American Gerontological Society in San Diego. While the presentations covered numerous points, a central finding described the likely heavy reliance that PLWAs will have on the healthcare system as they age. This is because we found that PLWAs are more apt to live alone than the general public and to have relatively few informal care giving relationships, such as those provided by a spouse or children. The implications of this research are significant for the public health system. ACRIA's future studies will be designed to identify which co-morbidity factors are more likely to impact on the health of older PLWAs, in part to help better plan for the specific needs of this aging cohort.

A detailed description of ACRIA's findings from our initial research into the over 50 PLWA cohort can be read online at www.acria.org. Data on this topic will also be presented by our researchers at the New York Association for HIV Over 50 meeting in December.

Thanks to donations from thousands of individuals and our corporate sponsors, ACRIA's publications are provided entirely free of charge to people living with HIV and AIDS and to nonprofit organizations across the United States. Please help to ensure that this newsletter can continue as a free educational resource for those who are fighting AIDS by making a gift in support of ACRIA's mission.

Donate online at acria.org or by mail to 230 W. 38th St., 17th floor, New York, NY 10018

generous contributions

The following persons, corporations and organizations made major donations between June 16, 2003 and October 17, 2003 to support ACRIA's research and education efforts:

Agouron Pharmaceuticals, Inc.	Marci Klein and
Altria Group, Inc.	Scott Murphy
Banana Republic	Robert A. Landau
Bristol-Myers Squibb Company	Lehmann Maupin Gallery
Champagne Taittinger	Jeffery Locker
Deutsche Bank	Joshua Mack and
Americas Foundation	Ron Warren
The Diller-Von Furstenberg	Open Society Institute
Family Foundation	Cynthia and Ron Rose
Brandon Fradd	The Louis & Rachel
Vincent Gagliostro	Rudin Foundation
The David Geffen Foundation	St. Francis Wines
Jane B. Holzer	David Yurman
In Style Magazine	Bradley Zipper
J.P. Morgan Chase Foundation	

Thoughtful donations were made in memory of the following individuals:

L Cliff Adams	Bennie W. Kreuger Jr.
Timothy Ancona	Tim Layton
Eric Bean	Mason Martens
Tom Beatcher	Jeffrey L. Mitchell
Barry Binkowitz, MD	Ned Morgan
Bill Black	Robert Rose
Charles Brown	Robert Schorzer
Michael Callen	Anne Sullivan
Stephen Cattano	Joseph John Tamburo
David Ecklund	Paul Trombley
Michael Koenigsberg	Leslie Wasson

Contributions in support of ACRIA's vital research initiatives were made in honor of the following individuals:

Luke Cohen	Rick A. Schwreter
Kathy Finley and Doug Landy	Mr. and Mrs. Ulysses Sherman
Daisy Graciano	J Daniel Stricker

AIDS COMMUNITY RESEARCH INITIATIVE OF AMERICA



230 West 38th Street, 17th Floor
New York, N.Y. 10018
T 212 924-3934 F 212 924-3936
www.acria.org

Change Service Requested

NON-PROFIT ORG.
U.S. POSTAGE PAID
New York, NY
Permit No. 4732

*ACRIA Update is sponsored in part by
unrestricted educational grants from:*

