



# CRIA UPDATE

COMMUNITY RESEARCH INITIATIVE ON AIDS

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## contents

- 4 *Life with Guidelines*
- 5 *Getting Started with Antiretrovirals*
- 7 *Seeing Double: A Tale of Dual Protease Inhibitors*
- 8 *Strategies for Salvage Therapy*
- 11 *New Drugs in Development*
- 13 *Nuke'em: A Look at Triple Nucleoside Regimens*
- 16 *CRIA Study Results*
- 19 *CRIA News*

## HIV Treatment Strategies

Thanks to ongoing research and people's real life experiences, our understanding of HIV and its treatment continually expands. More treatment options are now available to people living with HIV than ever before. Having more options can be overwhelming and confusing. So many drugs with so many names. So many things to keep track of – viral load, CD4 count, and results of resistance tests. But as the saying goes, knowledge is power. The treatment decisions we make today can affect our future options and,

ultimately, our health. Strategizing about treatment has become increasingly important.

This *CRIA Update* looks at some of the issues to consider when developing a personal treatment strategy – when to start therapy, what drugs to use, how best to use them and in what situations. There are no simple answers to these questions, but we hope that the information and insights offered by our writers will help people make more informed decisions and feel more comfortable with those decisions.

*J Daniel Stricker, Editor-in-Chief*

## To Start or Not to Start? Still Looking for Answers

BY JAMES LEARNED

The question of when it's best to begin antiretroviral therapy may be as controversial and frustrating as any of the many HIV treatment questions to which we have no clear answers. The US Department of Health and Human Services (DHHS) HIV treatment guidelines were revised in February, and the biggest change in the guidelines addresses this question.

Since their first appearance in 1997, the guidelines have been relatively aggressive in their recommendations about when people with no symptoms should consider starting treatment. They've recommended that treatment be considered once CD4 counts fall below 500 or viral load rise above 20,000 copies/mL by PCR, the most commonly used test. The newly revised guidelines lean more toward delaying therapy in people without symptoms – they now recommend considering therapy if CD4s fall below 350 or viral load

rises above 55,000. Many people living with HIV and their healthcare providers have been delaying treatment despite the guidelines' previous recommendations, but this is still a big change.

When combination therapy first went into widespread use in 1996, people increasingly needed help figuring out how to best use the drugs. The DHHS guidelines, often simply referred to as the federal treatment guidelines, were created to offer people a roadmap to help them navigate their way through their options. Developed by a group of researchers, physicians and community members, the guidelines can help in the process of determining if and when to start therapy, what drugs to start with, when to stop or switch, and how best to use available diagnostic tests. They reflect our current understanding of HIV progression and treatment and are periodically revised as ongoing re-

*(Cont. on page 3)*

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CRIA is an independent, non-profit, community-based AIDS research and treatment education organization dedicated to rapidly improving the length and quality of life for people living with HIV/AIDS. CRIA studies new treatments for HIV-related diseases through its clinical research and conducts a comprehensive treatment education program. Bulk copies of *CRIA Update* are available free to agencies that provide services to people living with HIV/AIDS. For more information, call Judy Codrington at 212-924-3934 ext. 119.

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### Study of 3 Different Drug Combinations in Drug-Naïve, HIV+ Individuals

CRIA is participating in 96-week study sponsored by Glaxo Wellcome. It will look at the effect of three different anti-HIV drug combinations on people infected with HIV. Some individuals with HIV experience changes in body shape as a result of fat redistribution. The primary purpose of this clinical trial is to study this effect. The study is for adults who are HIV-1+, have a CD4+ lymphocyte cell count greater than or equal to 50 cells/mm<sup>3</sup>, have a viral load greater than 1,000 copies/mL and less than 200,000 copies/mL, and have *NOT* received anti-HIV drugs in the past or have very limited use of certain anti-HIV drugs.

### Serostim® for HARS (Currently Enrolling)

CRIA has begun enrollment on this multicenter study that follows-up on a national level a previous pilot study that CRIA sponsored and conducted. This current 26-week, double-blind, randomized, placebo-controlled study looks at the effectiveness and safety of Serostim® (human growth hormone) when used to treat the abnormal fat distribution that occurs in patients treated with antiviral drugs for HIV infection. Patients with the condition know as HARS (HIV-related adipose redistribution syndrome) often have increased amounts of fat in the abdomen, the upper back, and (especially in women) in the breasts. If you are an adult who is HIV+, are on a stable anti-HIV drug regimen, and have problems with abnormal fat distribution, you may be eligible for the study.

### Vigilance II Genotyping Study (Currently Enrolling)

The purpose of this study is to determine if an HIV-1 RNA genotype report is effective and safe to use for choosing therapy for HIV infection. We will be gathering data regarding an experimental test called genotyping, in this case the TruGene® HIV-1 Assay, developed by Visible Genetics Inc. Genotyping may allow doctors to see which drugs may or may not work against HIV infection. It may tell you if HIV may be resistant to certain drugs. Resistance means that the drugs given to you for your HIV may not work as well as thought. Genotyping is still being studied as an aid in treating HIV infection.

You may be eligible for this study if: 1. you are an HIV-1 infected person with a viral load of greater than or equal to 1,000copies/mL 2. you and your doctor have determined that a change in your anti-HIV therapy is indicated; or if no prior therapy has been given for HIV-1, then you and your doctor agree that therapy needs to be started.

You will come in for one blood draw specifically for the study. This blood will be used for the genotyping test. Your personal doctor will get the results of the genotyping test within 7-10 business days and use these results to help choose a drug regimen that may be beneficial to you. We will gather data about your progress (up to one year) from later blood draws by your personal doctor that are part of your regular care. You will be paid \$15 after enrolling into the study to cover transportation, lost time from work, or meals. Your insurance company or a state health insurance agency will be billed for the blood tests. If you do not have insurance or state coverage and if you cannot pay for the tests, your study doctor will try to enroll you in a special patient assistance program.

FOR MORE INFORMATION ON ANY OF THESE STUDIES, PLEASE CALL DR. IRENE CERGNUL OR DR. DOUGLAS MENDEZ AT (212) 924-3934, OR VISIT OUR WEB SITE (WWW.CRIMARY.ORG).

### Editor's Notes

\* All material in *CRIA 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.

\* *CRIA Update* refers to all 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.

# To Start or Not To Start

CONTINUED FROM PAGE 1

search increases our understanding of HIV.

Clearly, current anti-HIV drugs can't rid the body of HIV. Even when viral load is undetectable, HIV is still reproducing at low levels. The realization that treatment with current drugs will probably be lifelong is the impetus behind the change in the guidelines. The change also reflects an appreciation of long-term drug side effects, the recognition that these drugs require an almost impossible level of adherence, and the likely development of drug-resistant virus while on lifelong therapy. If we had drugs that completely suppressed HIV, caused no short or long-term side effects, and were easy to take, everyone would start them soon after infection. But that's unfortunately not the case.

As much as we'd like a clear answer about when to start treatment, the debate continues. In the rush to get to the tables and charts, it can be easy to overlook the guidelines' thoughtful discussion of some of the benefits and risks of starting treatment later rather than earlier. Possible benefits of delaying treatment include better quality of life, no drug-related side effects, putting off the development of drug-resistant virus, and having more drug options later on, when you might need them more. On the other hand, the risks of delaying treatment include the possibility that your immune system might have suffered irreversible damage and it might be harder to achieve an undetectable viral load.

But starting treatment early requires a consideration of risks and benefits, too. The stronger your immune system is when you start, the easier it is to achieve and maintain an undetectable viral load – and drug resistance is less likely to develop when your viral load is undetectable. Earlier treatment might also delay or even prevent damage to the immune system. Conversely, possible risks of starting treatment early include a reduced quality of life due to short and long-term side effects, the develop-

ment of drug resistance if viral load doesn't stay undetectable, and limited treatment options in the future.

The information we have to help us answer the question of when to start comes from retrospective studies based on patients' medical records, rather than from prospective studies designed specifically to answer the question. Such a prospective trial is extremely difficult to design. It would have to run for years and enroll thousands of people. And a trial that started now would, at best, answer the question of when to start therapy in 2001, with the treatments available in 2001. By the time

*"the guidelines have limitations, and it's important that we recognize those limitations."*

the trial ended years from now, new, hopefully better drugs and strategies would be available and our understanding of HIV disease would be more complete.

At the 8<sup>th</sup> Conference on Retroviruses and Opportunistic Infections (CROI) in February, there were many reports on retrospective studies that looked at the relationship between disease progression and CD4 counts and/or viral load levels of people when they first started combination therapy. A retrospective study from Johns Hopkins University looked at what happened to 1,014 patients who began two- or three-drug combinations after July 1, 1999. There was a strong correlation between disease progression and starting therapy with CD4 counts below 200. The higher rate of disease progression in these patients may be at least

*"...therapeutic decisions require a mutual understanding between the patient and the health care provider regarding the benefits and risks of treatment."*

- Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents, February 5, 2001

## Community Forums

CRIA co-sponsors monthly educational forums on AIDS research and treatment issues. Upcoming forums:

Wednesday, May 2nd  
**Vaccine Therapy**

Wednesday, June 13th  
**HIV, Hepatitis & Liver Health**

Wednesday, July 11th  
**Ups and Downs:  
Party Drugs and HIV Meds**

The forums are held at 7PM in the Cronin Auditorium, 10th Floor of St. Vincent's Hospital at 11th Street and 7th Avenue, Manhattan. Forum summaries are available on CRIA's website: [www.criany.org](http://www.criany.org).

partly explained by observations made by the Johns Hopkins group (and other studies) that people are less likely to achieve undetectable viral load if they start treatment with a CD4 count below 200. Progression rates in people who started therapy with CD4 counts between 200 and 350 didn't differ substantially from those who started when their CD4s were above 350. Interestingly, pre-treatment viral load levels, independent of CD4 count, didn't predict clinical outcome. The study looked at pre-treatment viral loads less than or greater than 20,000, 100,000, and 200,000, and found no differences in disease progression between the groups.

A study from the Centers for Disease Control and Prevention (CDC) looked at more than 5,100 people who started two- or three-drug combinations in 1994 or later. The risk of death was significantly higher for people who started treatment when their CD4s were below 200 compared to those who started treatment when their CD4s were above 200. The study showed a trend for better clinical outcomes in people who started treatment with CD4 counts

between 200 and 350, but the difference wasn't statistically significant. And people who started  
*(Cont. on next page)*

## To Start CONT. FROM PAGE 3

treatment with CD4 counts above 350 showed no clear benefit.

These and other studies show pretty convincingly that people who begin therapy before their CD4s dip below 200 do better clinically. So is it best to consider treatment before you reach that point? Probably. But what's the cutoff? Somewhere between 200 and 350, perhaps. But even then, there are so many factors to consider. Is someone whose CD4 count has dropped from 700 to 300 in a year in the same situation as someone whose CD4s have remained steady at 300 for five years? Clearly not. This is where the individual flexibility called for within the text of the guidelines comes into play.

As people living with HIV and their healthcare providers make complicated treatment decisions – including the decision about when to start therapy – the federal guidelines can be enormously helpful. But the guidelines have limitations, and it's important that we recognize those limitations. They are *guidelines*, a tool. They include recommendations, suggestions, information and discussion. They are *not* a “one-size-fits-all” formula for treatment, nor are they intended to be.

The data we have on HIV disease progression are based on what seems to happen to groups of people – populations, not individuals. These data and the real-life experience of people living with HIV support the revision to the guidelines, that therapy be considered by people without symptoms when the CD4 count is below 350 (rather than 500 as previously recommended), or the viral load is above 55,000 (rather than 20,000). But if there's one thing we've learned over the last twenty years, it's that HIV disease varies widely from person to person. The percentages and probabilities don't necessarily apply to you, your very particular situation, and the many factors that contribute to who you are – a unique individual.

*James Learned is CRIA's Director of Treatment Education and Editor of CRIA Update*

## Life with Guidelines: *A Personal Perspective*

BY MARK MILANO

“Have you ever heard of AIDS?” Since it was March of 1982, I hadn't. But I was glad to have someone put a name to my chronic illness. I asked the intern in the emergency room what treatment he suggested, and he replied there was none. “Okay,” I said “I'll find something on my own.”

That was my first experience looking for a treatment recommendation for HIV, and I'm grateful for it now. It taught me never to take any “official word” as gospel, but to look for my own answers.

The first “official” recommendation for HIV treatment appeared in 1989 when the results of trial ACTG 109 were released. The pressure on anyone with fewer than 500 CD4 cells to start AZT became tremendous – pressure not only from my doctor, but also from every nurse who took my temperature. “So are you on AZT?” “No, I don't feel it's appropriate for me yet.” “I see – and where did you get your medical degree?” And pressure from fellow activists, who were starting AZT as soon as they dropped below 500. Even greater was the pressure I put on myself. Though I was stable at 300 CD4s, I felt I had to do something. So I tried AL-721, oral alpha interferon, Chinese herbs – even infusions of Compound Q at a guerilla clinic, an experiment that almost killed me.

I know now, from frozen blood, that my viral load at that time was 360 copies, so there was no need to be on antiretrovirals. But the experience taught me how powerful official treatment recommendations can be. Even though I was feeling fine, and my CD4 count was stable, I thought it was foolish to do nothing.

As time went on and my counts remained around 300, I began to feel that “magic numbers” like 500 weren't the an-

swer. The trend over time seemed more important. In 1992, I lobbied unsuccessfully for New York State to put something like this in their guidelines. When the results of the Concord study showed that starting treatment below 500 didn't extend life, that information was inserted into the state guidelines.

When triple-combination therapy appeared in 1995, everyone (including my ex-doctors) told me I had been smart to avoid AZT monotherapy, but that now it really was time. “Hit Hard, Hit Early” was the mantra of the day. I couldn't find any clinical data showing that starting treatment when your CD4s were above 200 extended life, so I promised myself that I would start only if my count dropped below 200. In early 1996 it did, and I prepared to start a three-drug combination. While I hesitated, my count went back up to 300. I decided once again to wait, which is where I am now – still waiting to start treatment.

Living with the rigid numbers of guidelines has been one of the hardest parts of having HIV. I felt vindicated when the new federal guidelines were released saying that waiting until CD4 counts drop below 350 is reasonable. And I tell myself that if mine drop below 200 or my viral load goes above 50,000 I'll start treatment. But to be honest, when it happens I tend to wait for the numbers to get better. Having waited almost 20 years, I have a somewhat higher psychological hurdle than most people, but I've always said I would start treatment when the time is right. I'll decide when the time is right using my own guidelines, not someone else's.

*Mark Milano is a longtime AIDS treatment activist and educator.*

# Getting Started with Antiretrovirals: Thoughts on Initial Therapy

BY ANNE MONROE

Triple combination therapy has been around for over five years now – we should all be getting the hang of it, right? Well, we certainly know a lot about treating HIV disease. But with more medications to choose from, more knowledge of the long-term side effects of therapy, and more sophisticated laboratory tests such as drug resistance profiling, things are getting trickier. The goals of therapy are straightforward – getting viral load as low as possible and keeping it there, boosting the immune system and keeping it strong, reducing illness and death, and improving quality of life. But the best way to achieve those goals is not always so clear.

One question in particular – “Which therapy should I start with?” – doesn’t have an answer. Recent research has addressed the question, but there isn’t one right way to begin treatment.

## What’s Out There

The first regimen is generally a protease inhibitor (PI)- or non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen. Another possibility is a triple nucleoside reverse transcriptase inhibitor (NRTI) regimen with Ziagen (abacavir) as its base. The PI-based and NNRTI-based regimens both include two NRTIs.

PIs work by stopping the action of the protease enzyme. The protease enzyme is a protein that is used during the assembly of new copies of the virus. Six protease inhibitors have been approved by the US Food and Drug Administration (FDA): Crixivan (indinavir), Fortovase (saquinavir soft gel, called Invirase in the old hard gel formulation), Viracept (nelfinavir), Agenerase (amprenavir), Norvir (ritonavir) and Kaletra (lopinavir, with a small dose of ritonavir to increase lopinavir blood levels).

NRTIs and NNRTIs also block enzyme action, in this case, the reverse transcriptase enzyme, which HIV uses to copy its genetic information. The FDA has approved six NRTIs: Retrovir (AZT), Zerit (d4T), Videx (ddI), Epivir (3TC), Hivid (ddC) and Ziagen (abacavir); and three NNRTIs: Sustiva (efavirenz), Viramune (nevirapine), and Rescriptor (delavirdine).

## Using the Guidelines

The federal treatment guidelines’ recommendations for initial therapy are based on what is known about the safety and effectiveness of different medications over time, as well as quality of life considerations such as number of pills, dosing convenience and side effects. The guidelines separate these medications into two categories: “Strongly Recommended” and “Recommended as Alternatives.” Within each category, they’re listed alphabetically by generic name, not in any order of preference.

The “strongly recommended” medications follow:

The alternatives to the drugs in Column A are:

Ziagen (abacavir)  
Agenerase (amprenavir)  
Rescriptor (delavirdine)  
Viracept + Fortovase  
(nelfinavir + saquinavir)  
Viramune (nevirapine)  
Norvir (ritonavir)  
Fortovase (saquinavir)

Alternatives to Column B pairs are:

Videx + Epivir  
(didanosine, ddI) + (lamivudine, 3TC)  
Retrovir + Hivid  
(zidovudine, AZT) + (ddC, zalcitabine)

## Comparing PIs

A quick glance at the guidelines reveals that most of the drugs in Column A are PIs. PIs have been around for over five years, and there is long-term evidence from clinical trials that they are effective in lowering viral load, boosting the immune system and preventing HIV-related illness and death. PIs are powerful drugs that can reduce the amount of HIV both in the blood and in other places in the body

*(Cont. on next page)*

Choose one from Column A and one pair from Column B

### Column A

Sustiva (efavirenz)  
Crixivan (indinavir)  
Viracept(nelfinavir)  
Norvir + Crixivan  
(ritonavir + indinavir)  
Kaletra (lopinavir/ritonavir)  
Norvir + Invirase or Fortovase  
(ritonavir + saquinavir)

### Column B

Zerit + Videx  
(stavudine, d4T) + (didanosine, ddI)  
Zerit + Epivir  
(stavudine, d4T) + (lamivudine, 3TC)  
Retrovir + Videx  
(zidovudine, AZT) + (didanosine, ddI)  
Retrovir + Epivir  
(zidovudine, AZT) + (lamivudine, 3TC)

# Getting Started

CONTINUED FROM PAGE 4

where HIV is found (like the lymph nodes). The Column A PIs have all been shown to be effective in initial therapy, so how do doctors and patients choose between them?

Some recent clinical trials have compared PIs to each other. Abbott Laboratories' M98-863 study compared a Viracept-based regimen with a Kaletra-based regimen for initial therapy. At Week 48 of the study, 67% of patients on Kaletra and 52% of patients on Viracept had an undetectable viral load (less than 50 copies), a statistically significant difference. The study showed no statistically significant difference in CD4 cell count increases between the two treatment groups. Interestingly, Kaletra is the only protease inhibitor that has been shown to be as effective in individuals with high baseline viral load measurements (viral load greater than 100,000 copies) as

those with lower measurements.

At the 8<sup>th</sup> Conference on Retroviruses and Opportunistic Infections, results were presented from an international study comparing two PI choices from Column A – Crixivan vs. Crixivan + Norvir. The researchers found the two regimens to be equally effective after a year of therapy. Crixivan + Norvir is more convenient than Crixivan because it is taken twice a day instead of three times a day. The convenience of the regimen alone makes it preferable for many people. [For more information on regimens containing two PIs, refer to Tim Horn's article on page 7.]

At last year's International AIDS Conference in Durban, a group of Spanish researchers compared the effectiveness of three protease inhibitors – Norvir, Fortovase and Crixivan. Patients who enrolled in the study

had taken therapy before, but had never taken a PI. The study showed the three treatments were equally effective for patients who stayed on therapy for a year. Of the patients who began treatment with Fortovase, 75% stayed on Fortovase for the entire year, while only 28% of patients who started with Norvir and 50% of patients who started with Crixivan completed the year on those treatments. Of the patients who stopped Fortovase, 95% stopped for treatment failure and 5% stopped for intolerance. Of the patients who stopped Norvir, 19% stopped for failure and 73% stopped for intolerance. The figures were 57% for failure and 38% for intolerance with Crixivan.

With so many powerful drugs to choose from, the safety and tolerability of a regimen, its effect on quality of life, and the impact of resistance on future treatment options all in-

*(Cont. on page 15)*

## FDA-Approved Antiretrovirals for the Treatment of HIV

The fifteen anti-HIV drugs that are now available all go by at least two names – a brand name (sort of like Coca-Cola®), and a generic name or names. Add to that pills like Combivir and Trizivir that combine medications, and it can be pretty confusing. The following medications are organized by class and listed by brand name first, followed by their generic names in parentheses.

### Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

*(also called nucleoside analogues or nukes)*

Ziagen (abacavir)  
Videx (didanosine, ddI)  
Epivir (lamivudine, 3TC)  
Zerit (stavudine, d4)  
Hivid (zalcitabine, ddC)  
Retrovir (zidovudine, AZT)

Combivir (AZT + 3TC combined in one pill)  
Trizivir (AZT, 3TC + Ziagen combined in one pill)

### Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

*(sometimes called non-nucleosides or non-nukes)*

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

### Protease Inhibitors (PIs)

Agenerase (amprenavir)  
Crixivan (indinavir)  
Kaletra (lopinavir/ritonavir)  
Viracept (nelfinavir)  
Norvir (ritonavir)  
Fortovase (saquinavir)

# Seeing Double: A Tale of Dual Protease Inhibitors

BY TIM HORN

It's hard to believe, but it has been more than five years since the protease inhibitors (PIs) made their therapeutic debut and forever changed our approach to managing HIV. Perhaps the most impressive aspect of this milestone is that researchers and healthcare providers are continuously finding new and improved ways to use this powerful class of anti-HIV drugs. For evidence of this, one doesn't need to look much further than the current trend of dual-protease inhibitor therapy—the combination of two PIs with two nucleoside analogues.

There's nothing really new about taking two PIs at the same time. Soon after the first PIs were approved—or, more precisely, after people began experiencing viral load rebounds while taking regimens containing only one PI—people figured out that doubling up on PIs seemed to be an effective way to maintain control over drug-resistant virus. What is new is the fact that more people who are just starting anti-HIV therapy are now using dual-PI regimens. Surely they're not doing this to double their pleasure or double their fun. Then what, exactly, is so fascinating about dual-PI therapy?

## Doubling Up

To appreciate the reasoning behind dual-PI therapy, it's important to understand the drawbacks of regimens that contain only one PI. All too often, PIs fail because of the difficulties many HIV-positive people have in maintaining adequate levels of these drugs in their blood. For example, indinavir (Crixivan) must be taken every eight hours with either no or minimal amounts of food to ensure proper drug levels. And there's very little room for slippage—no following the strict three-times-daily regimen or taking the medication while there's still fatty food in your stomach can cause Crixivan levels to fall below the minimum needed to suppress HIV. This can cause viral load levels to

fluctuate and, ultimately, the development of irreversible drug resistance.

There are also the side effects associated with “full-dose” PI therapy to consider. Standard ritonavir (Norvir) therapy, for example, requires that six pills be taken twice a day. Even for people with stomachs of steel and a high tolerance for toxicities, Norvir can be an extremely harsh drug to take. Diarrhea, nausea, vomiting, numbness or tingling around the mouth, and general discomfort are quite common when using a standard Norvir regimen. Yet it's an extremely powerful and useful PI op-

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*"Intensification is a relatively new concept in the struggle to deal with drug-resistant virus."*

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tion for HIV-positive people. So finding ways to use it safely and effectively has always remained a priority.

Given the drawbacks of individual PIs, it's hard to believe that taking two of these drugs at the same time can actually make things easier. After all, this would mean more pills, taken more times a day, greater dietary restrictions, and a risk of more side effects, right? Not necessarily.

The magic behind dual-PI regimens can be found in the effect that some protease inhibitors, especially Norvir, have on other PIs. All PIs are broken down (metabolized) in the body by the cytochrome P450 system of enzymes found in the liver, gut, and other tissues. More than any other PI, Norvir blocks these enzymes and, as a result, slows down the rate by which other drugs are metabolized and forced out of the body. In other words, Norvir dramatically increases the amount of many other drugs in the body and increases the length of time these drugs remain in the bloodstream.

## Dosing Benefits

Because it has such a profound impact on the P450 enzyme system, Norvir can spell trouble for people who combine this PI with other prescription and over-the-counter drugs. For example, people who take Norvir should either avoid or greatly reduce their dosage of certain sedatives, antihistamines, lipid-lowering drugs, and even Viagra. Yet behind these sinister details are a number of potential advantages. For example, when Norvir is combined with Crixivan, the amount of Crixivan in the blood is increased by approximately 480%! This allows people to take lower doses of both drugs (one or two Norvir capsules plus two Crixivan capsules) twice a day. In other words, the increased amount of Crixivan in the blood allows people to do away with the pesky mid-day dose. What's more, combining both drugs does away with dietary restrictions—even if Crixivan is taken with food, enough of it is available in the bloodstream to combat HIV.

Crixivan is hardly the only PI that has been paired with Norvir. In fact, Norvir has a long history with saquinavir (both the old hard-gel Invirase version and the newer soft-gel Fortovase version). When Norvir and Fortovase are combined, researchers have determined that the safest dose for both drugs is 400 mg taken twice a day. It might also be possible that combinations of Norvir/Fortovase and Norvir/Crixivan can be taken once a day—a few clinical trials are currently looking at this possibility.

And the list goes on. Norvir significantly increases the amount of amprenavir (Agenerase) in the blood. The same holds true for nelfinavir (Viracept). Combined with Norvir, the amount of Viracept in the blood is increased more than 15 times. It's also true that when Viracept is combined with Fortovase—without the addition of Norvir—the levels of both drugs are increased significantly. This al-

*(Cont. on page 12)*

# Strategies for Salvage Therapy

BY MATT SHARP

Enormous strides in HIV treatment have been made over the last several years. Fifteen approved anti-HIV drugs have saved thousands of lives and have helped many people return to mostly healthy, productive lives. Unfortunately, these drugs are not perfect. This is especially true for people who have used these drugs in the past and no longer respond to them. For these folks, new drugs – along with, perhaps, improved ways to reap benefits from older ones – are an absolute necessity.

People who have become fully or partially resistant to current drugs are searching for what is called *salvage therapy*. Like visitors to auto salvage yards where junked car parts are sold, people who need salvage therapy are seeking drugs in new classes, older drugs to recycle, and other treatment strategies that may slow HIV and make their bodies' immune systems run efficiently again.

What happens when someone becomes resistant to their anti-HIV drugs and runs out of options to keep viral load undetectable? Dr. Steven Deeks and his colleagues at the University of California San Francisco now have some data from a study to answer this question. Dr. Deeks found that, for HIV-positive people who are unable to keep their viral load undetectable (<500 copies/mL) because of drug resistance and limited treatment options, 41% would progress to AIDS within four years. The risk of progression to AIDS – which includes life-threatening opportunistic infections – was highest among people who were unable to keep their viral load at least somewhat lower than it had been before therapy was even started. In other words, keeping viral load at least partially suppressed is better than nothing at all.

## Waiting in the Wings – New Drugs

What are the latest drugs to be used in salvage regimens? In a closing lecture at February's 8<sup>th</sup> Conference on Retroviruses and Opportu-

nistic Infections (CROI), Dr. Roy Gulick from Cornell University Medical Center provided a detailed overview of the newest anti-HIV therapies, both approved and in the pipeline. Dr. Gulick admitted that one of the major challenges in HIV research is the development of salvage therapies for people with drug-resistant HIV. His discussion focused on new drugs in each class that may have different resistance patterns than the older drugs, along with new classes of drugs that hit different targets in HIV's replication process. Fortunately, each scenario offers options for salvage therapy.

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*"What we need are drugs that target different parts of the virus and act at different points in HIV's lifecycle."*

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Protease inhibitors currently in phase II studies include tipranavir, mozenavir, and BMS-232632. All of these drugs have varying degrees of activity against strains of HIV resistant to currently approved protease inhibitors. Additional studies are definitely needed to determine how effective they will be for patients starting therapy for the first time or in need of salvage options.

DAPD, a nucleoside guanine analogue, may be effective against Retrovir (AZT) and Efavir (3TC) resistant virus and is in early human testing. In a small study, patients who had used AZT or Efavir, added DAPD (500mg twice a day) to their current regimen. Within two weeks, viral loads decreased by two logs from baseline levels.

Tenofovir DF, a nucleotide analogue, is now available through an expanded access program (*see box on page 10*). The drug is active

against many AZT and Efavir resistant viruses and may be even more active against strains containing the Efavir-associated resistance mutation, M184V. Tenofovir DF, administered once a day, appears to be safer and more potent than its cousin adefovir, which was denied FDA approval last year because of its causing kidney damage.

Early results from a study involving approximately 550 people who had tried and failed other anti-HIV drugs in the past have been reported. In this study, volunteers who had been on an anti-HIV drug combination for at least eight weeks and were not able to push their viral load to undetectable levels added either tenofovir DF or a placebo (sugar pill) to "boost" their current regimen. After 6 months, 22% of patients who added tenofovir DF were able to reduce their viral load to undetectable levels (less than 50 copies/mL), compared to only 1% of patients who added the placebo. In other words, tenofovir DF was active against HIV, even in people who had failed other anti-HIV drugs in the past.

Capravirine, an investigational non-nucleoside reverse transcriptase inhibitor (NNRTI), has been shown to be effective against virus that is resistant to currently approved NNRTIs. Unfortunately, development is on hold due to a severe toxic problem seen in dogs. Another NNRTI, TMC-120, has been shown to be effective against the common NNRTI mutation, K103N. These drugs are in early development, and larger human studies need to be completed before we can know how effective they really might be.

## And New Classes

New classes of anti-HIV drugs are particularly important for people who need salvage therapy. We already have a number of drugs that target HIV's protease and reverse transcriptase genes. What we need are drugs that target different

parts of the virus and act at different points in HIV's lifecycle.

A veritable new field of research has opened up with the HIV entry inhibitor drugs. These compounds prevent entry, attachment, or fusion of HIV to the host cell. People are most familiar with the fusion inhibitor pentafuside (T-20) because it is furthest along in development. There is also a second-generation fusion inhibitor, T-1249, that doesn't seem to be cross-resistant to T-20 and appears to be 2 to 100 times more active.

Because pentafuside and T-1249 target proteins on HIV's outer shell, resistance will always be a problem. Luckily, researchers are developing drugs that target proteins on the outside of cells – cellular proteins that won't become resistant nearly as quickly as viral proteins. These new drugs target the CXCR4 and CCR5 co-receptors on CD4+ cells. While they are still in the early stages of development, there is already a lot of talk about using these drugs in combination since they may be synergistic, meaning that they work better together than separately. Although they offer great hope, most, although not all of these drugs, must be injected, a possible barrier for people who are uncomfortable with needles. As exciting as the new attachment inhibitor field is for people who need salvage therapy, caution is warranted since these drugs are all in early stages of development.

Other classes of HIV drugs being investigated are only worth mentioning until further human studies are done: DC-sign inhibitors, regulatory protein inhibitors, uncoating inhibitors, assembly inhibitors, capsid protein polymerization inhibitors, RNAase H inhibitors, and integrase inhibitors. Even zinc finger inhibitors, thought to be useless, are back in development. And there are adjunctive therapies such as hydroxyurea and mycophenolic acid, which may make some current antivirals such as Videx

(ddI), Zerit (d4T), tenofovir DF, and Ziagen (abacavir) even more effective.

### Everything But The Kitchen Sink

One salvage strategy studied by Canadian researcher Julio Montaner uses a mega-HAART approach, employing between five and nine

antiviral drugs in people who were heavily pre-treated with antivirals and at least partially resistant to most of them. Some consider mega-HAART a desperate approach due to the compounding toxicities of so many drugs. At the 3rd International Workshop on Salvage Therapy in HIV Infection last April, Montaner's data on  
*(Cont. on page 10)*

### What Role, Kaletra?

Kaletra (lopinavir), Abbott Laboratories' recently approved protease inhibitor (PI), has caused a great deal of confusion among researchers and healthcare providers. The reason for this is that nobody fully understands this drug's resistance profile. In one study presented at the 8<sup>th</sup> CROI, a team of researchers from Abbott examined 96 HIV samples collected from people on treatment for the first time who saw a rebound in their viral load while taking either Viracept (nelfinavir) or Kaletra with Zerit (d4T) and Epivir (3TC). Of the 65 samples collected from those who failed the Viracept regimen, 32% had mutations that were clearly associated with Viracept resistance. Of the 41 samples collected from patients who failed the Kaletra regimen, *none* contained mutations in the virus's protease gene (42% did contain mutations associated with Epivir resistance).

On the surface, the lack of Kaletra mutations might be considered to be a good thing. However, without information about its resistance profile, it is difficult to determine which protease inhibitor people can switch to if they start therapy with Kaletra and eventually fail the drug. Fortunately, another study presented at the 8<sup>th</sup> CROI helped shed

some light on this situation. Upon testing samples collected from people who had failed other protease inhibitors in the past, researchers at Abbott concluded that people who are no longer responding to Kaletra may benefit from switching to either Fortovase (saquinavir) or Agenerase (amprenavir). On the other hand, patients failing Kaletra were less likely to respond upon switching to Norvir (ritonavir) or Crixivan (indinavir).

What about patients who have failed other protease inhibitors in the past and need to switch to Kaletra? Of all the mutations that can arise during therapy with other protease inhibitors, 11 are associated with cross-resistance to Kaletra. As a rule of thumb, researchers have determined that HIV containing *six or fewer* of these 11 mutations will still likely respond to Kaletra. Strains of HIV containing *seven or more* of these 11 mutations are less likely to respond to Kaletra therapy. Many laboratories currently conducting drug-resistance testing are aware of this new information, so people hoping to use Kaletra as a salvage protease inhibitor can benefit from the information produced by these tests.

# Salvage Therapy

CONTINUED FROM PAGE 9

three separate groups showed that mega-HAART kept virus at undetectable levels (below 400 copies/mL) in up to 44% of patients who had been on their regimen for as long as 57 weeks. Not surprisingly, there was a very high dropout rate because of side effects. For people who don't have new HIV drugs to choose from, recycling older drugs in the form of mega-HAART remains a promising possibility, although the probable side effects limit that promise.

Besides complicated strategies using drugs for salvage therapy, a method of *not* using drugs is being studied – structured treatment interruptions (STIs), stopping and restarting antivirals. When a person stops treatment, the HIV that replicates most quickly and usually becomes dominant is “wild-type” virus – HIV without resistance mutations. The idea behind stopping, then restarting therapy is that the response to the restarted treatment may last longer because wild-type virus is more susceptible to antivirals.

At the 8<sup>th</sup> CROI, Steven Deeks presented the results of a small study in salvage patients who went on a treatment interruption for an average of 20 weeks. As expected, viral loads increased while off treatment. But CD4 cells decreased substantially, and three of the 22 participants developed opportunistic infections

while off therapy. Most – but not all – participants' CD4 counts went back up after restarting treatment. People who were able to introduce a NNRTI to their regimen after the treatment interruption did significantly better than those who didn't have a new class of drug to add.

STIs may have some role in the salvage setting and need to be studied further. *But* the risk of developing an opportunistic infection while off therapy and the possibility that restarting treatment may not increase CD4s to pre-STI levels make it clear that this strategy is particularly risky for salvage patients.

## Immune-Based Therapies

For years, patients have been hoping for better immune-based therapies. In the salvage setting, Interleukin-2 (IL-2) appears to be promising. ACTG 328 looked at people with CD4 counts between 50 and 350, some on HAART alone, others on HAART and IL-2. None of the study participants had taken a protease inhibitor before. After a year and a half of treatment, those using IL-2 had significantly higher CD4 cell counts compared to those not on IL-2. Although this wasn't a salvage study, it has implications for people who need salvage strategies.

There has been concern about using IL-2 in people whose HIV disease is further

progressed. It was thought that IL-2 would stimulate HIV by pumping out new CD4 cells for HIV to infect. But it appears that IL-2 can be used effectively to boost CD4 production without necessarily increasing virus levels. ACTG 328 is the largest prospective randomized study of IL-2 in advanced HIV patients to show significant increases in CD4 counts. It remains to be seen whether these CD4 cells are functional, rather than just carbon copies.

Other immune modulators such as GM-CSF (colony stimulating factor) are also being studied in patients with higher levels of virus and lower CD4 counts. As with IL-2, the concern has been about stimulating more “food” for the virus. But if antivirals can keep virus levels low, but not necessarily undetectable, research can go forward with immune modulators.

## In Closing

Finding new ways to treat people who have used up all their treatment options remains a major challenge. In order to discover new drugs and develop useful strategies, randomized, controlled, studies in the salvage population must be conducted. But such trials are difficult to design. And pharmaceutical companies usually want to study their newest drugs in people who have never taken antivirals before because the resulting data looks better. Finally, salvage studies focus on drug failure, something that, for complicated reasons, almost no one wants to look at too closely. It may take time before more studies are done, but this is time that many people with AIDS simply don't have.

*Matt Sharp has been living with AIDS for ten years. Now living in Chicago, he is an AIDS treatment activist with Survive AIDS (formerly ACT UP Golden Gate) and a member of the Coalition for Salvage Therapy, a group that advocates for treatments for people with AIDS in late stage.*

## Tenofovir Expanded Access

Tenofovir DF, Gilead Sciences' experimental nucleotide analogue, is now available through a small expanded access program.

To qualify, you must:

- Be at least 18 years old;
- Have a viral load greater than or equal to 10,000 copies and a CD4 count below 100  
or  
a CD4 count below 200 and an opportunistic infection within the past three months;
- Have had treatment failure with or intolerance to at least two protease inhibitors (PIs) or one PI and one NNRTI; and
- Be unable to put together a useful drug combination with available antivirals.

To register in the program, your doctor should call 800-445-3235.

The dose is 300mg taken once a day. Tenofovir DF is expected to be considered for FDA approval this summer. Hopefully, the program criteria will be expanded before then.

# New Drugs in Development

BY TIM HORN

## Everything old is new again!

Scanning the list of all the drugs currently in development, it's hard not to notice some very familiar names: AZT (Retrovir)... d4T (Zerit)... efavirenz (Sustiva)... nelfinavir (Viracept). While these four drugs are approved and being used by a large number of people, their manufacturers have taken them back to the lab for pharmaceutical facelifts. After all, it takes more than just a strong efficacy record for these drugs to remain popular treatment options. They must also be easy to take. So pharmaceutical companies are scurrying to find new ways to reduce the number of pills—and the number of times these pills need to be taken every day—in order to make these drugs more attractive to those of us who are always “in the market” for the next best thing.

The process by which older drugs are tweaked to make them more attractive is called “reformulation.” One of the first drugs to undergo reformulation was saquinavir, Hoffmann-LaRoche's protease inhibitor. Invirase, the first formulation of saquinavir approved, suffered from “poor bioavailability”—only a small percentage of the drug actually found its way into the bloodstream. This drawback considerably weakened saquinavir's activity against HIV and caused the development of drug resistant virus in many people who used it. In response, the manufacturer repackaged the drug into capsules made of soft gelatin (the original capsules were made of hard gelatin) to increase the amount of drug released in the gut. While treatment activists grumbled that reformulation work should have been completed before—not after—the drug was approved, the experience of saquinavir (now sold as Fortovase) proved that it's never too late to make important changes.

## They're Here!

Saquinavir is not the only example of approved anti-HIV drugs that have undergone

reformulation. In September 1997, Glaxo Wellcome (now GlaxoSmithKline) released Combivir, a single tablet containing both AZT (Retrovir) and 3TC (Epivir). More recently, GlaxoSmithKline received FDA approval for Trizivir, a three-drugs-in-one tablet containing Retrovir, Epivir, and abacavir (Ziagen). These combination tablets successfully reduce the number of pills that need to be taken on a daily basis.

Bristol-Myers Squibb's ddl (Videx) has also gone through its share of reformulations. First the size of the 100 mg chewable tablets was decreased and infused with a more tolerable mandarin orange flavor. This was followed by the development of the 200 mg Videx tablets and FDA approval to use the drug only once a day. Last year, the company received approval for enteric-coated Videx (VidexEC), a capsule that can be taken once a day without the need for chewing or dissolving in water. Although ddl takers must still be mindful of dietary restrictions—it still needs to be taken on an empty stomach—the capsules do away with that chalky orange taste first thing in the morning and can be taken at the same time as other anti-HIV meds.

Last but not least is delavirdine (Rescriptor), a non-nucleoside reverse transcriptase inhibitor marketed by Agouron Pharmaceuticals. Instead of four 100 mg tablets that need to be dissolved in water and taken three times a day, the manufacturer has developed a 200 mg tablet that can be instantly swallowed, also three times a day. A twice-daily dosing schedule for the new 200 mg tablets is currently being studied.

## They're Coming!

As for reformulations currently under way, the first worthy of mention is Aztec, an “extended release” version of AZT. This drug is being developed at glacial speed—the last time data supporting its use were presented was at the 11<sup>th</sup> International AIDS Conference in 1998! Still, Verex Laboratories, the manufac-

turer of the drug, contends that it will be an important option for people wanting to simplify their regimens. Aztec requires one pill to be taken once a day and, if combined with other once-daily drugs (e.g., Videx EC or Sustiva), will allow for a complete one-time daily regimen.

As with VidexEC, Bristol-Myers Squibb has been reformulating d4T (Zerit) for once-daily administration. ZeritEC is in clinical trials using a once-daily 100 mg dose and is being compared to the twice-daily 40 mg dose that is currently being used in clinical practice.

Another reformulation in the making involves nelfinavir (Viracept), Agouron Pharmaceuticals' protease inhibitor. Right now, the typical pill burden is five 250 mg Viracept tablets twice a day—that's a total of ten pills to meet the 1,250 mg daily requirement. The new 625 mg tablets being developed would reduce the pill count to two tablets twice a day.

As for the non-nucleoside reverse transcriptase inhibitors, Boehringer-Ingelheim is conducting studies of once-daily nevirapine (Viramune). If approved—the company will be checking in with the FDA later this year—people taking Viramune will only need to swallow two 200 mg tablets once a day instead of the current dosing schedule of one 200 mg tablet twice a day. Last but not least is efavirenz (Sustiva), a drug that already boasts once-daily usage. To make a good thing even better, DuPont Pharmaceuticals is hoping to combine the current three 200 mg capsules into a single 600 mg capsule.

While it's unlikely that these new formulations will increase the effectiveness of these drugs, it's safe to say that some new and improved formulations will make a world of difference in the way the drugs are viewed and, ultimately, taken on a daily basis. Less is sometimes definitely more. It looks as if we're finally going to get it.

lows both drugs (five Viracept tablets and six Fortovase capsules) to be taken twice a day. There are also dual-PI regimens to watch out for: combinations of Crixivan/Fortovase don't appear to be any more beneficial than each drug taken separately, and Agenerase, when combined with Fortovase, actually *reduces* the amounts of both drugs in the blood.

## More PI = More Power?

For people starting PI therapy, numerous studies have determined that one protease inhibitor is usually enough to reduce viral load and keep it undetectable for a prolonged period of time. It's still not clear if dual-PI therapy is any more (or less) effective than single-PI therapy in treatment-naïve patients. But the fact that low doses of Norvir can simplify a regimen may be reason enough to start therapy using two PIs. After all, a regimen that is easier to take is much more likely to be taken correctly.

For HIV-positive folks who have tried and failed regimens containing single PIs, using two PIs together is not so much about *simplification*—although this never hurts—as it is about *intensification* and improved effectiveness. Intensification is a relatively new concept in the struggle to deal with drug-resistant virus. When HIV begins to show signs of drug resistance, such as an increasing viral load while taking a regimen containing a single PI and two nucleoside analogues, the usual approach is to switch to another regimen. Unfortunately, switching from a regimen containing one PI to another regimen containing yet another single PI is rarely successful in returning viral load to undetectable levels or in keeping it there. The reason for this is cross-resistance—HIV mutations associated with resistance to one PI almost guarantees that all of the other currently available PIs will be of limited use.

What's now being studied in clinical trials—and practiced by many healthcare provid-

ers and patients—is the use of Norvir to intensify a failing regimen. When HIV mutations start accumulating during PI therapy, what's really changing is the sensitivity of the virus to the drugs being used. With each additional mutation in HIV's structure, the virus's sensitivity to the drug or combination of drugs dwindles further. The way to overcome HIV's decreasing sensitivity is to either use drugs with a different resistance profile or to increase—intensify—the amount of the drug to which HIV has become resistant.

*"It's still not clear if dual-PI therapy is any more (or less) effective than single-PI therapy in treatment-naïve patients."*

Picture it like this: drug resistance is like a brick wall. To keep viral load undetectable, you'll either need to go around the wall by finding new drugs or you can go over the wall by increasing the amount of drug in your bloodstream to keep HIV in check. The best way to do this—without doubling the dose (and the risk of side effects) of your current PI—is to add a P450-blocking PI to the mix.

There are two variations on this theme. The first is to simply add Norvir to a combination that shows early signs of resistance. For example, if you have experienced a low-level rebound in your viral load while taking a Crixivan-based regimen and a drug-resistance test shows that you only have a few mutations associated with Crixivan resistance, adding Norvir to “boost” the effectiveness of Crixivan might do the trick. In this case, a low dose of Norvir (usually two 100 mg capsules twice a day) is added to the Crixivan (reduced from two pills three times a day to two pills twice a

day), a minor change that has been shown to help people with low-level Crixivan resistance regain control over their viral load.

Another option is to switch from one PI to another PI in combination with Norvir. For example, switching from a Viracept-based regimen to a Crixivan/Norvir-based regimen not only introduces a new PI into the mix, but also uses Norvir to boost the activity of the second PI against whatever cross-resistance mutations are present. In fact, this is the concept behind Kaletra, Abbott's newest PI, which contains lopinavir and a low dose of Norvir. By itself, lopinavir is only moderately effective against strains of HIV resistant to other protease inhibitors. With the addition of Norvir, however, lopinavir is usually active against HIV harboring as many as six key PI-resistance mutation.

It's not at all clear when intensification is most likely to succeed. While some studies have demonstrated that HIV with only a few mutations is likely to respond nicely to Norvir intensification, it's difficult to say how effective it is against strains with several key PI mutations. And while it's true that Norvir can be used to radically increase the amount of other PIs in the blood—to the point that they will overcome highly-resistant virus—the risk of side effects must be considered.

## Downsides to Consider

Unfortunately, as with any anti-HIV treatment strategy that is potentially good, there is always a list of potentially negative problems waiting somewhere in the wings. With dual-PIs, one potential downside revolves around side effects. Some researchers argue that the risk of side effects is lower with dual-PI therapy because the doses of each PI used are usually lower than the standard doses. Alternatively, other researchers are concerned that toxicity may, in fact, be greater when two PIs are used. For example, taking two PIs might increase the

# Nuke'Em: A Look at Triple Nucleoside Regimens

BY ASIA RUSSELL

risk of liver damage, especially in HIV-positive patients who are coinfecting with either hepatitis B or hepatitis C. There is also the possibility that people taking two PIs may be at greater risk for the body-fat changes associated with lipodystrophy, along with increased lipid and/or glucose levels in the blood.

Another fear is that patients who fail a dual-PI regimen will develop a wider range of HIV drug-resistance mutations, more extensive cross resistance, and have fewer future PI options than those failing single-PI regimens. This may be less of a concern with some dual-PI regimens, such as Crixivan combined with low doses of Norvir. Both of these drugs share almost identical resistance mutations. But what about patients—particularly those who are new to anti-HIV drug therapy—who start treatment with Kaletra, a drug containing two protease inhibitors with somewhat unique resistance patterns? Oddly, *none* of the patients who experienced a viral load rebound while taking this drug in clinical trials so far produced any signs of drug-resistance mutations. So it's difficult to tell which PIs can be used after Kaletra has stopped working correctly. While some research suggests that Fortovase and Agenerase are possible options, nothing has been conclusively stated (see “What Role, Kaltra?” on page 9).

In the grand scheme of things, it's clear that new protease inhibitors are very much needed—drugs that are easier to take, associated with fewer side effects, and active against virus resistant to current options. Luckily, the pipeline has a few promising PIs in development. In the meantime, however, it's good to see that we've got some new tricks to teach these old dogs.

*Tim Horn is executive editor of The PRN Notebook, published by Physicians' Research Network in New York.*

People with HIV have a bit more clarity about when to start anti-HIV treatment, thanks to the recently revised federal treatment guidelines. But the question regarding which regimen to start with remains unanswered. One type of regimen in particular—a combination of three nucleoside analogues without either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI)—is one of today's options. However, there are still a number of questions about how useful this strategy is in the long run for someone who is just starting treatment.

Nucleoside analogues are the oldest class of antiretrovirals, comprising Retrovir (AZT), Videx (ddI), Hivid (ddC), Zerit (d4T), Epivir (3TC), and Ziagen (abacavir). The nucleoside analogues block HIV's reverse transcriptase enzyme, preventing HIV's genetic information from converting its RNA into DNA, and therefore stopping it from being able to replicate inside cells.

Given the cross-resistance that plagues the PIs and NNRTIs, as well as the risk of long-term toxicities associated with these drugs, some people who are naïve (new) to treatment are deciding against starting with PI- or NNRTI-containing combinations. But what is the likelihood of sparing both of these drug classes and still ending up with a powerful, effective, and safe drug combination?

## When is simpler better?

For years patients have been juggling complex regimens, choking down handfuls of pills, and living anxiously with the knowledge that missing as few as five to ten percent of doses—that's less than one dose a month—can lead to drug resistance and failure. As a result, healthcare providers and people living with HIV are constantly looking for regimens that are easier to take.

Trizivir combines three nucleoside analogues in one pill: AZT, Epivir, and Ziagen, all manufactured by the same company, GlaxoSmithKline. Trizivir appears an attractive option — one tablet, two times a day, with no food or water restrictions.

But is simpler always better? The federal guidelines give Ziagen-containing combinations — including Trizivir — “alternative” rather than the higher “strongly recommended” status. Ziagen is the only nucleoside analogue with any recommendation to be used in combination with two other nucleosides. There are several reasons for this distinction. One is Ziagen's potency—it's stronger compared to the other nucleoside analogues individually. Also, several clinical trials have shown the combination of Ziagen, AZT and Epivir to be as effective as PI-containing combinations for first line treatment.

CNA 3005, a GlaxoSmithKline study, compared the impact of Ziagen/AZT/Epivir versus Crixivan/AZT/Epivir on viral load and CD4 cell counts. This trial was randomized (people were assigned to either arm randomly) and double-blinded (neither the study participants nor the study nurses and doctors knew which combination the patients had been randomly assigned to) and enrolled 562 patients who had never taken anti-HIV drug therapy before.

By 48 weeks, both groups were as likely to have viral load suppression below 400 copies/mL (51% of participants on either combination). However, there was a difference among patients who entered the study with high viral loads. Approximately 35% of the study patients started the trial with viral loads above 100,000. These patients were more likely to keep their viral load undetect-

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# Nuke'Em

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able (less than 50 copies/mL) if they were in the Crixivan group than if they were in the Ziagen group (45% versus 31%).

CNA 3104, a trial of the same combinations, was open-label, meaning that both the participants and the study personnel knew which combination the participants were taking. The Ziagen group performed slightly better than the Crixivan group, but the difference wasn't statistically significant: 63% of patients on the Ziagen combination and 60% of patients on the Crixivan combination kept their viral loads below 50 copies/mL after 24 weeks of therapy. Adherence issues may have played a role in achieving such similar results. 74% of the people taking Ziagen reported taking all of their doses or missing only one dose of their twice a day regimen in the past week, compared to 45%

of the people taking Crixivan three times a day.

Strangely, the 37% of patients who entered this trial with viral loads above 100,000 performed no worse on the Ziagen combination than on the Crixivan combination (56% versus 43% were below 50 copies/mL by week 24). This preliminary finding has not been reproduced in other, more controlled settings and should be monitored as the study progresses.

## Risk versus Benefit

For Trizivir and other triple-nucleoside analogue combinations, the potential for increased mitochondrial toxicities warrants close attention. Mitochondria are the powerhouse of our bodies' cells. They serve the critical function of producing energy for a host of life-sustaining cellular activities. Nucleoside analogues can affect the DNA in mitochondria. This can harm the mitochondria and irreversibly damage the function of certain cells. Some researchers believe that nucleoside analogue damage to mitochondria is to blame for a number of side effects, including fatigue, muscle weakness and loss (myopathy), peripheral neuropathy, and fat loss in the face, legs, and arms (lipoatrophy).

Nucleoside analogue treatment can also sometimes result in life-threatening toxicities, such as severe lactic acidosis with hepatomegaly, or fatty liver. Cells that contain too many severely damaged mitochondria must resort to an abnormal type of energy production that doesn't rely on the mitochondria. Lactic acid is the chemical byproduct of this sort of abnormal energy production. The liver is responsible for ridding the body of lactic acid; when the liver becomes too overwhelmed with lactic acid, lactic acidosis with hepatomegaly can result. Scientists are intensifying research on this neglected topic. However, there is no clinical information yet about whether or not

triple nucleoside combinations intensify the risk for mitochondrial toxicities.

On a positive note, early results from one study indicate that triple-nucleoside analogue combinations may help remedy the cholesterol and triglyceride problems associated with protease inhibitors. The TRIZAL study (AZL 30002) randomly switched people whose viral loads were undetectable (<50 copies/mL) using a PI-based regimen to Trizivir, or continued them on their standard treatment. At 24 weeks, viral load rebounded to levels above 400 copies/mL in 17% of patients on the PI-based regimen and 20% of patients on Trizivir. Interestingly, triglycerides and total cholesterol levels improved significantly in the Trizivir group. Surprisingly, 10% of patients who were taking Trizivir reported hypersensitivity reaction, a dangerous allergic response to Ziagen that can be fatal. This unexpected finding is twice the typical 5% rate reported in other studies using regimens that contained Ziagen and warrants future study.

## The Bottom Line

Trizivir seems like an attractive, dramatically simplified HIV therapy. But there is a potential danger that Trizivir will be prescribed more often among populations inappropriately labeled "bad" at taking medication. Without rigorous attention to baseline viral load, prior nucleoside analogue exposure, thorough education regarding Ziagen hypersensitivity reaction, and other factors, Trizivir's already restricted potential for therapeutic effect may become even more limited.

*Asia Russell is a member of ACT UP Philadelphia and Health GAP Coalition, and coordinates an HIV treatment and activist training program for HIV positive ex-inmates at Project TEACH in Philadelphia.*

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# Getting Started

CONTINUED FROM PAGE 6

fluency decision-making in initial therapy. Both short- and long-term side effects must be carefully considered. Possible side effects of a PI-based regimen include fat redistribution, high cholesterol and/or triglycerides, and insulin resistance that may contribute to the development of diabetes. Others to watch for include kidney stones (with Crixivan), elevated liver enzymes, hepatitis (liver inflammation) and pancreatitis (inflammation of the pancreas). The short-term side effects of PIs are extensive and can significantly impact quality of life. The Column A PIs are all associated with gastrointestinal upset (nausea, vomiting, diarrhea, stomach pain, gas or a combination of those side effects). Rash is a possible side effect of Crixivan and Viracept, and patients on Norvir may experience oral tingling or numbness.

A final consideration in choosing a spe-

cific PI-based regimen is the role that drug resistance plays in the course of HIV treatment. For example, we know that the mutation that leads to Viracept resistance is at site D30N in HIV's genetic material. This resistance mutation is unique to Viracept, so it does not lead to resistance to other PIs. If the decision is made to begin treatment with a protease inhibitor, Viracept may be a good first choice because it may leave other PI treatment options available for later use.

While we generally think of resistance in a negative context since it can make treatment less effective, there is evidence that some drug-resistant strains of HIV are less "fit" than other strains. A virus that is less fit is not as good at making copies of itself or infecting other cells. In a study out of the University of California at San Francisco, researchers showed that some HIV that is resistant to PIs

is less fit than wild-type virus (virus with no resistance mutations). This may keep viral load low even when PI-resistant virus is present. We're just starting to learn how to use this information to make decisions about treatment. In the future, it may be possible to use resistance mutations to turn wild-type HIV into mutated virus that is unfit and cannot do its dirty work on the immune system. Currently, there is not enough information to determine if this is a reasonable possibility.

## Comparing PIs with NNRTIs

NNRTI-based regimens are generally considered to be more "patient-friendly" than PI-based regimens – NNRTIs have fewer side effects and easier dosing schedules than PIs. In addition to being easier to take, NNRTIs are powerful treatment options that lower viral load and increase CD4 cells. Sustiva is a first choice from Column A for initial therapy, while Viramune and Rescriptor are alternatives that may be considered (there isn't enough data to support the inclusion of either as a first choice). Sustiva was included as a first choice after data from study DMP-006 (first reported at the Geneva AIDS Conference in 1998) showed that it was at least equivalent to Crixivan in an open-label study, even in patients with high initial viral loads. Three years later, the data still support the recommendation.

In the study, 422 patients received Sustiva, and 80% of those patients achieved and maintained an undetectable viral load (below 50 copies) after two years of therapy. 415 patients received Crixivan, and 65% had an undetectable viral load after two years of therapy. The study team concluded that if current trends continue, the Sustiva regimen could be effective for over six years. Interestingly, patients with less than 200 CD4s when they started treatment were more likely to have vi-

*(Cont. on next page)*

## Who's on First? Sequencing NRTIs

Let's not ignore the nucleoside reverse transcriptase inhibitors (NRTIs) in Column B of the federal treatment guidelines. While the pairs listed have similar effectiveness, there are some interesting resistance questions that may influence the selection of NRTIs in initial therapy. Researchers have theorized that treatment with AZT or Zerit (d4T) might lead to decreased effectiveness of AZT, Zerit, or Ziagen (abacavir) in later regimens. These drugs, like other NRTIs, depend on phosphorylation (the addition of a group of molecules to the drug compound) to be activated inside cells. A study presented at the 8<sup>th</sup> CROI showed that more than a year of treatment with AZT or Zerit did not lead to a decrease in the phosphorylation of the drugs, nor did it lead to a decrease in phosphorylation of Ziagen. The researchers concluded that either AZT or Zerit can be used first without making the other one or Ziagen less effective.

But other researchers disagree. Data were presented at the 8<sup>th</sup> CROI from a GlaxoSmithKline study that compared two groups: patients treated first with a HAART regimen containing Zerit who switched to a regimen containing AZT, and patients treated first with a HAART regimen containing AZT who switched to a regimen containing Zerit. For consistency, most patients had never taken an NNRTI and switched to an NNRTI-based regimen at the time of their NRTI switch. More patients in the AZT to Zerit switch group had an undetectable viral load (less than 400 copies) at 16 weeks of therapy and a greater average reduction in viral load than patients in the Zerit to AZT switch group. The jury is still out on the implications of these studies, and no recommendations on sequencing these NRTIs have been made.

# Getting Started

CONTINUED FROM PREVIOUS PAGE

rologic failure – an increase in viral load to above the limit of detection – on Crixivan after three years of treatment than patients with more than 200 CD4s, but there was no difference in virologic failure rates based on initial CD4 count in patients taking Sustiva.

The Combine study, conducted in Spain and Argentina, compared a PI-based regimen containing Viracept with an NNRTI-based regimen containing Viramune. After 36 weeks, there was no statistically significant difference between the two groups in terms of the number of patients who achieved undetectable viral loads. Gains in CD4 cell counts were also similar for the two treatment groups.

Viramune has also been compared with a PI-based regimen containing Crixivan and a triple-NRTI (Epivir/Zerit/Videx) regimen in the international Atlantic study. After a year of treatment, about half (49%) of patients on the Viramune and Crixivan regimens had an undetectable viral load (less than 50 copies), and 40% patients on the triple-NRTI regimen were undetectable. The differences were not statistically significant using the strictest data analysis. Using a more lenient analysis (patients who dropped out were not included), patients on Crixivan did better than patients on Epivir, but no other significant differences were seen. It can be concluded from these studies that Viramune may be considered for initial therapy.

An NNRTI-based regimen spares PI side effects but comes with its own toxicities. One long-term side effect of NNRTIs is increased transaminase levels, which can indicate liver damage. Additionally, a long-term side effect specific to Viramune is severe hepatitis. In the short term, Sustiva can cause rash, drowsiness, insomnia, central nervous system side effects (confusion, inability to concentrate, dizziness, vivid dreams), gastrointestinal side effects (nausea, stomach pain), and fever, while

Viramune is associated with rash, stomach upset and headaches.

These drugs have simple dosing schedules with fewer pills than PIs. Sustiva is taken once daily in combination with NRTIs that are taken twice daily, and the Sustiva dose is three capsules. The Viramune dose is one tablet twice a day. To simplify things even further, researchers have been testing NNRTI-based regimens that are taken once daily.

A final consideration when comparing NNRTIs with PIs is that only one mutation in the genetic material of HIV causes NNRTI drug resistance, and once that mutation occurs, resistance to the entire class develops. With PIs, the development of resistance is a multi-step process, and resistance to one PI does not necessarily result in resistance to the entire class.

## Comparing NNRTIs

Patients who want to start treatment with an NNRTI may wonder how to choose between Sustiva and Viramune. Side effects will certainly factor into the decision – patients at risk for hepatitis may wish to avoid Viramune, and some patients choose to avoid Sustiva because of the central nervous system side effects described above.

There has not been a controlled study directly comparing Sustiva and Viramune, but information was collected from a group of over 1,900 European patients who were treated with either Viramune (1,202 patients) or Sustiva (730 patients) since July 1997. In total, 525 patients experienced virologic failure, and individuals taking Sustiva were more likely to stay undetectable than those taking Viramune. This data must be verified by a controlled trial.

## Final Thoughts

There is no single approach to treating HIV infection that works for everyone and no

## CRIA Study Results

The results of two CRIA studies were presented recently (see pages 17 & 18). Because of their potential practical applications, the study results were well received by both medical providers and people living with HIV.

### Topical aspirin for peripheral neuropathy.

Patients who are experiencing painful peripheral neuropathy should consult with their primary care providers. Most pharmacies can compound this preparation of aspirin dissolved in ether with a prescription. Some pharmacists are concerned about the safety of people storing an ether preparation because of its flammable nature. Because of the positive results of this study and the frequency of painful peripheral neuropathy, CRIA is looking at other topical aspirin preparations.

### SAM-e to treat severe depression in HIV positive patients

Most health food stores and many buyers' clubs carry various brands of SAM-e (S-adenosyl-L-methionine). No independent agency regulates these products, so the quality may vary from brand to brand and even from bottle to bottle within a brand. Some bottles labeled as SAM-e may not even contain any active substance. As with any complementary therapy, talk with your healthcare provider before taking SAM-e.

“best” first regimen. Complicated choices are par for the course in HIV infection. With new treatments on the way, these choices may get tougher – but a knowledgeable HIV care provider who stays on top of current research can provide guidance to help you make choices that work for you.

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Poster Presentation at the 8<sup>th</sup> Conference on Retroviruses and Opportunistic Infections, #601, February, 2001

**Topical Application of Aspirin/Diethyl Ether in Treatment of Painful Distal Sensory Polyneuropathy in HIV-Positive Individuals: A Randomized, Double-Blind, Crossover Placebo-controlled Study.**

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**INTRODUCTION**

With the increase in survival of people infected with HIV, many medical complications are occurring with increased frequency. Among these are the HIV-associated neuropathic disorders. Distal symmetric polyneuropathy (DSP) has been reported to be the most common neurological complication in patients with HIV. Patients commonly present with slowly progressive sensory loss and dysesthesias such as numbness, burning sensations, tingling and pain in the feet.

The Multicenter AIDS Cohort Study found that, between 1985 and 1992, DSP had the highest yearly increase in incidence among the neurologic complications of HIV infection, peaking at 2.81% in 1992. Treatment of DSP is problematic. Most treatments involve symptomatic pain control using nonopioid analgesics combined with a tricyclic antidepressant. Greater levels of pain require the use of opioids. Topical agents have also been used with varying degrees of success.

Topical nonsteroidal anti-inflammatory drugs have been used to treat local painful conditions of skin, joints and muscles. An advantage of a topical preparation is the ability to achieve high local concentrations of the agent with negligible systemic levels and, therefore, fewer adverse side effects or drug-drug interactions. Acetylsalicylic acid (aspirin), when applied topically, has been shown to have such a profile.

**OBJECTIVE**

The aim of this investigation was to elucidate whether a topically applied solution of acetylsalicylic acid in diethyl ether (ASA/DE) provided adequate pain relief for HIV-infected people with distal symmetric polyneuropathy.

**PATIENT ELIGIBILITY**

- HIV Infected
- Age > 18
- Presence of painful DSP as diagnosed by a comprehensive history and neuralgic examination
- Duration of symptoms for > 1 month
- Grade 5 or higher on Brief Pain Inventory (BPI) scale

**METHODS**

The study was a randomized, double-blind, crossover, placebo-controlled trial of a solution of acetylsalicylic acid dissolved in ether applied topically to the affected limbs of HIV infected patients with DSP. The primary outcome measure was the patients' description of pain as scored on the Brief Pain Index (BPI) using a 10 point scale.

43 HIV positive adults with DSP were randomized to one of two treatment arms. Patients in the first arm applied 7 ml. of a solution containing 375 mg. ASA/DE three times a day to their distal extremities for 2 weeks. After a three-day washout period they then applied ether alone three times a day for an additional two weeks. Patients randomized to the second treatment arm self administered the placebo t.i.d. for two weeks, no treatment for three days and then two weeks of t.i.d. ASA/DE (375 mg/dose). BPI was administered at the start of the study and then at the end of each week of treatment in each arm. All BPI questionnaires were administered, in person, by the same investigator (Dr. Cerngul).

**RESULTS**

Of the 43 patients enrolled, 31 completed the study. Demographics and clinical characteristics were as follows: males-55%, median age- 43, median length of HIV infection-10 years, average time affected with DSP-3 years. 90% of patients had an AIDS defining illness. The median CD4 cell count was 300 cells/ml. A median improvement in BPI of 30 % over baseline was present in the ASA/DE arm. The ASA/DE arm was also found to be 30% better than placebo. "Best" days on ASA/DE were 30 % better than baseline, and the "worse" days were 25% better on ASA/DE than at baseline. All results were statistically significant at p<0.001.

**CONCLUSIONS**

Our study showed that the topical administration of aspirin in diethyl ether applied three times a day produced statistically significant pain relief when used in HIV infected patients with distal symmetric polyneuropathy. No side effects were reported by any of the study participants. Of note is the fact that 8 out of the 12 patients who dropped out of the study did so after the pain relief they felt in the first two-week period of the study disappeared when they were switched to the other solution in the second period. These 8 patients were found at the close of the study to have received topical aspirin in the first two week period.

A solution of ASA/DE applied topically is a valuable alternative to other modalities of pain relief currently in use in the treatment of DSP in HIV infected individuals.

Poster Presentation at the 13<sup>th</sup> National HIV/AIDS Update Conference in San Francisco, #3002, March, 2001

**S-adenosylmethionine (SAM-e) in the Treatment of Depressive Disorders in HIV-Positive Individuals: Interim Results**

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**INTRODUCTION:**

Depressive mood disorder is the most common reason for mental health assessments and interventions in HIV-positive individuals. Great strides have been made in the pharmacological treatment of depression and increasingly primary care providers are becoming proficient in the chemical treatment of depression. However, it is a major challenge in clinical research to identify a more efficient antidepressant, faster in onset of activity, with fewer side effects and few drug-drug interactions, which is especially important in HIV patients who are on complex antiretroviral regimens.

**RATIONALE:**

SAM-e (S-adenosyl-L-methionine) is a naturally occurring molecule, present in almost every tissue and fluid in the human body. It has been extensively studied for over 25 years and is marketed in Europe as a prescription drug used in treatment of depression. The body uses this substance in a variety of biochemical reactions involving enzymatic transmethylation which is crucial to the proper functioning and structure of proteins, nucleic acids, lipids, hormones and neurotransmitters. In earlier placebo-controlled studies, treatment with SAM-e showed an increase in the metabolism of norepinephrine and serotonin (neurotransmitters implicated in the onset of depression). The likelihood of drug interactions (particularly important to HIV-patients on antiretroviral therapy) is significantly reduced because SAM-e is not metabolized by the liver, but rather used by the liver. Side effects reported in the literature prior to this study were mild and the SAM-e was well tolerated.

**METHODS:**

This was an open-label 8-week study that involved the enrollment of 20 HIV-positive patients with the diagnosis of Major Depressive Disorder (DSM-IV). Severity of depression was assessed by using the Hamilton Rating Scale for Depression (HAM-D) and Beck’s Depression Inventory (BDI). Both scales are standard tools in assessing the level of depressed mood with the higher the score, the greater the severity of depression.

After the initial assessment by a study psychiatrist and baseline blood work, enrollees were started on 200mg of SAM-e twice a day with a daily supplementation of 1,000mcg B12 and 800mcg of Folic Acid (vitamins that assist the activity of SAM-e). During the study the oral dose of SAM-e was adjusted gradually on an individual basis up to 800mg twice a day. The doses were adjusted according to the severity of symptoms and rate of improvement. Patients were seen by the study psychiatrists at weeks 1, 2, 4, 6, and 8. At each visit the BDI was completed by the patient, the HAM-D, Karnofsky score, and HIV-symptoms checklist were administered by a study psychiatrist.

**ELIGIBILITY CRITERIA;**

Inclusion Criteria:

1. HIV-positive serostatus
2. Major depression (DSM-IV)

Exclusion Criteria:

1. Unstable medical illness
2. Pregnancy, lactation or refusal of participants to employ an acceptable method of contraceptive
3. History of substance abuse in the prior month
4. Treatment with another psychotropic medication within 2 weeks prior to initiation of SAM-e treatment
5. Concurrent treatment with MAO-inhibitors
6. Active suicidal ideation and/or psychotic symptoms
7. Reversible medical pathology thought to be causing depression
8. History of mania or diagnosed bipolar disorder.

**RESULTS:**

This report includes the preliminary results from the first 15 patients that have completed the study to date. The blood results are not presented as they are still being evaluated.

<u>Total number of patients</u>	15
males	11
females	4
Mean age(range)	39 (24-56)
HIV positive	15
AIDS	14

The median dose of SAM-e given was 400 mg b.i.d.

Patients showed significant clinical improvement at weeks 4 and 8 of 74 % and 87% on BDI, and 78% and 87% on HAM-D. No side effects were reported at any time by any study participant.

	Baseline	Week 4	Week 8
BDI (0-63)	35	9	5
HAM-D(0-79)	27	6	3

**CONCLUSION:**

In our trial, SAM-e appears to significantly reduce depressive symptoms in HIV-positive individuals and to dramatically improve mood and quality of life with no sign of side effects. Continuation of this study as well as other longitudinal, randomized, double-blinded studies are justified to further assess the full spectrum of activity, elucidate the mechanism of action and the safety of SAM-e.

## **First Clinical Trials Directory Published**

CRIA recently published its first edition of *HIV/AIDS Clinical Trials: A Directory for New York State*. This resource is being supported by a contract from the New York State Department of Health AIDS Institute and is being distributed free of charge to local medical and non-medical care providers. It offers the most comprehensive, up-to-date listing available of enrolling HIV trials within New York, New Jersey, Connecticut, and Philadelphia.

CRIA's grant required a thorough assessment of the previous directory on enrolling HIV trials published by another agency before we even started to design our new publication. The statewide assessment included input from both consumers and care providers to learn how they would change the document to make it more useful. These findings are reflected in *HIV/AIDS Clinical Trials: A Directory for New York State*.

Completely updated editions of the directory will be available every six months. CRIA will eventually offer listings of enrolling trials online at [www.criany.org](http://www.criany.org), which we will update regularly.

CRIA thanks HIV InSite at the University of California, San Francisco for their assistance in identifying trial sites, data development, and collection of information. Visit them online at [hivinsite.ucsf.edu](http://hivinsite.ucsf.edu) for a listing of HIV clinical trials nationally.

## **New Education Brochure Published**

CRIA has created its third in a series of topic specific treatment education brochures for consumers nationwide, called *Clinical Trials Explained*.

Our new brochure was developed as part of the directory project described above. It is meant to complement the directory by providing consumers with an overview of the clinical trial process and information on the risks and

benefits of participating in HIV clinical trials. In fact, the single most significant finding from the statewide assessment was that most patients and non-medical care providers don't know enough about the clinical research process to make informed decisions about considering trial participation. CRIA's new brochure will help address this issue.

While the directory itself is only for New York residents, CRIA has printed enough additional copies of the new brochure to ensure that clients of AIDS service organizations outside of our area can also benefit from the information contained within it. CRIA has already begun to distribute free bulk copies of *Clinical Trials Explained* to non-profits nationwide. As with all of our publications, the new brochure can also be read online at [criany.org](http://criany.org).

## **Serostim® Study Initiated**

CRIA has begun its participation in a multi-site Serono Laboratories sponsored trial of Recombinant Human Growth Hormone (Serostim®) to treat lipodystrophy.

Back in 1998, CRIA conducted the first research of this agent to address the abnormal metabolic side effects afflicting PLWAs across the United States who are on antiretroviral therapies. Since then, our independent research in this area has become widely recognized as drawing attention to one of the few potentially beneficial treatments for lipodystrophy. As such, Serono Laboratories had decided to conduct more comprehensive research of Serostim needed for FDA approval of its use in correcting metabolic abnormalities in HIV patients. CRIA began enrolling patients in March.

This is a double blind, randomized triple arm trial where participants will either take the drug and placebo every other day, only the drug, or only the placebo daily over a 12-week period, followed by another 12-weeks on one of the alternative arms. Maximum dose will be

4mg of drug per day depending on an individual's height and weight, and six visits to CRIA's clinic will be required to perform sophisticated body measurement, blood tests, and glucose tolerance tests. All participants will have the opportunity to enroll in a maintenance phase of Serostim following the 24-week study period. For more information on this protocol, see the Clinical Trials In Process section of *CRIA Update*.

## **CRIA Mourns the Passing of Brian Schuman (1960 – 2001)**

After a long battle with AIDS and then ALS, CRIA volunteer and Community Advisory Board (CAB) member, Brian Schuman, died on February 22<sup>nd</sup>, 2001. Brian was an active supporter of CRIA's mission from very early on in our existence. He was among the first community members to not only contribute financially to CRIA's research program, but also to give of his time to help our staff develop and implement new programs. When he was well enough, he was at CRIA's clinic nearly every Tuesday. He also provided valuable contributions to agency policy-making discussions through his membership on our CAB.

Brian exemplified why CRIA has been and must continue to remain so dedicated to its research and education mission. His experience with HIV was extremely difficult, having to endure multiple hospitalizations for serious complications. Yet, he was always energized to fight hard for his life. When he finally was able to achieve some semblance of health stability through use of combination therapy, he was diagnosed with ALS. Throughout all of these challenging times, Brian remained firmly committed to helping others with dire medical circumstances by actively supporting CRIA's work. We will forever miss his humor and thoughtful guidance.

ACKNOWLEDGING OUR FRIENDS...

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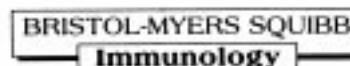
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