



# CRIA UPDATE

COMMUNITY RESEARCH INITIATIVE ON AIDS

VOL. 9 NO. 2

## HIV Research 2000: Unanswered Questions

The Spring issue of *CRIA Update* focuses on some of the hot topics in HIV research that were covered at the 7th Conference on Retroviruses and Opportunistic Infections which took place in San Francisco this past February.

The purpose of our agency's newsletter is to educate and inform. We are certainly not adverse to controversial topics when they provoke wider discussion. For some of our readers this issue of important health care topics will be controversial. In fact, only after much heated discussion could our editorial staff reach consensus on this issue.

The fact is that new discoveries in many fields of medical research often raise more questions than they answer and lead to varied interpretations of the information. Often, things that at first glance seem to be clear turn out to be far more complicated. HIV is no exception. For example, as the lifesaving promise of antiretroviral therapy begins to take a backseat to some disturbing metabolic side effects, drug holidays, once regarded as a taboo topic, have become the subject of much interest.

We start the issue with a discussion of this most controversial topic: structured treatment interruptions, or drug holidays, by regular contributor Tim Horn. Next, Anne Monroe provides an update on the utility of resistance testing in making treatment decisions. CRIA's own James Learned presents a comprehensive look at the emerging metabolic complications associated with HIV disease and antiretroviral treatment. Last but not least, Richard Jeffreys covers an exciting new area of research on the human thymus and its role in HIV disease.

In response to readers' requests, this issue contains the first installation of a regular new section entitled "New Drugs in Development." This section will focus on drugs in clinical development, review their performance so far, and what we might expect from them in the future. As usual, we hope you will find this issue interesting and informative, remembering that sound health care decisions are always made in consultation with your medical provider.

*J Daniel Stricker, Editor-in-Chief*

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## Hoping for a Holiday: Structured Treatment Interruptions

BY TIM HORN

Not too long ago, the idea of stopping anti-HIV therapy was a laughable notion. After all, possible eradication of the virus was at stake. But the hope of curing HIV using highly active antiretroviral therapy (HAART) has faded. Still, experts continued to warn against stopping therapy, including short-term drug holidays. There was a threat that nasty drug-resistant strains of the virus would emerge, along with the possibility that immune function would quickly decline and send patients' health spiraling downwards.

Preliminary results of several small studies reported at the recent 7th Conference on Retroviruses and Opportunistic Infections (CROI) suggest that not only may drug holidays be feasible and safe, but they may also be good for the immune system. While proving these suggestions will require a fair amount of additional research (none of the recent reports offer any guarantees) a dose of springtime optimism is certainly in the air.

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SPRING 2000

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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 Meredith Snow at 212-924-3934 ext. 121.

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**Fat Accumulation in the Belly (FAB) Study**

Fat build-up in the abdomen may be a complication of protease inhibitor use. CRIA is conducting a pilot study on the effect of Recombinant Human Growth Hormone (Serostim®) in the treatment of truncal obesity associated with HIV infection. The protocol was designed to examine the safety and efficacy of daily human growth hormone injections over a 24-week period. An extension phase is now being conducted for patients who have completed 24 weeks of therapy to determine longer-term effects. This study is closed to enrollment.

**Metabolic Effects of Protease Inhibitors**

CRIA is conducting a study in cooperation with Dr. Ann Danoff, Chief of Endocrinology at Bronx-Lebanon Hospital, to examine whether there is an association between short-term antiretroviral therapy (ARV) and glucose intolerance, hyperlipidemia, or body habitus changes. The trial will study HIV negative persons who have sustained needle stick injuries, before and at the conclusion of a course of ARV prophylactic therapy. This study will provide the opportunity to examine the impact of PI therapy independent of HIV infection.

**SAM-e for Depression in HIV+ Individuals (Currently Enrolling)**

Enrollment has begun at CRIA for an 8-week open-label study of the efficacy and safety of using S-adenosylmethionine (SAM-e) to treat depression in HIV+ individuals. SAM-e is a naturally occurring compound that is sold as a food supplement in this country. HIV-infected adults with diagnosed clinical depression may be eligible for this study. There will be a total of 7 study visits.

**SB-300 for Diarrhea (Currently Enrolling)**

CRIA is currently enrolling a 2-week pilot study of the dietary supplement SB-300 in the treatment of chronic diarrhea in HIV+ individuals. SB-300 is a standardized herbal extract that contains a compound that has been isolated and purified from trees of the Amazonian rainforest. HIV-infected adults who have had chronic diarrhea (three or more stools a day) for at least two weeks may be eligible for this study. There will be a total of 3 study visits. Study participants will be provided with a \$3 MetroCard at each visit.

**Study of 3 Different Drug Combinations in Drug-Naïve, HIV+ Women (Currently Enrolling)**

CRIA is participating in a 96-week study sponsored by Glaxo Wellcome. It will look at the effect of three different anti-HIV drug combinations on women infected with HIV. Some women 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 adult women who are HIV+, 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. Participants will be reimbursed \$15 plus a \$3 MetroCard per visit after enrollment.

**Topical Aspirin for Peripheral Neuropathy (Currently Enrolling)**

CRIA is now enrolling a 5-week double-blinded study looking at the efficacy of topical aspirin to treat painful sensory peripheral neuropathies in people with HIV. Over the course of the trial, participants will be given two separate bottles of solution: one with topical aspirin, another with placebo. The order in which these bottles will be provided is randomized. The solution will be applied on the skin over the painful area 3 times a day. HIV-infected adults with painful sensory neuropathy that has been present for at least a month are eligible. There will be a total of 5 study visits. Study participants will be reimbursed \$15 plus a \$3.00 MetroCard at each visit after enrollment.

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.CRIANY.ORG](http://WWW.CRIANY.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.

# Drug Holidays

CONTINUED FROM PAGE 1

## Backgrounder

Let's face it. HAART is not all that its cracked up to be. For people who started therapy "early", that is, while their viral loads were low and CD4+ cell counts were high, popping pills every day in the face of side effects has been a herculean task. At the same time, there are also patients who desperately needed therapy to bring their high viral loads down and CD4+ cell counts out of the red. Now that many of these folks have been saved, that is, have seen their viral load stay undetectable and their CD4+ cell counts linger at healthy levels, a fundamental question remains: "Why do I need to stay on this stuff?"

It's not at all clear what comes next. There are a number of different possibilities, all of which will drive research over the next few years. Researchers might prove that all patients, once they've started therapy, should remain on it. Another avenue to explore is the possibility of treating HIV like many other chronic diseases, initiating therapy when the immune system shows signs of damage or when a patient experiences symptoms of HIV disease, then stopping therapy when their health improves. And let's not forget new treatments, including novel anti-HIV drugs and immune-based therapies, that may prove to be the magic bullet everyone is waiting for.

In essence, figuring out how to treat HIV remains in a constant state of uncertainty. Structured treatment interruptions, more commonly referred to as "drug holidays", represent the first experimental approach to break with the current HAART model. While drug holidays are by no means ready for the "real world" of HIV care (in other words, they are not yet considered to be safe or effective enough for patients to try them at home) they are definitely the research trend to watch in the coming months.

## Structured Treatment Interruptions

While it would be nice to think that patients "sick of it all" were the driving force behind structured treatment interruption (STI)

research, the scientific rationale can actually be traced back to a phenomenon seen in a single patient living in Germany. A few years ago, Dr. Franco Lori, a researcher with labs in Pavia, Italy and Georgetown, reported on the highly irregular circumstances of an unnamed patient who, after a series of interruptions in his drug therapy, appeared to have cleared HIV from his body.

The "Berlin Patient," as he has come to be known by the world, was participating in a clinical trial for recently infected patients. He entered the study approximately two months after an unsafe sexual experience which, as he feared, resulted in HIV infection. Once enrolled, he started a triple-drug regimen involving indinavir (Crixivan), ddI (Videx), and hydroxyurea (Hydrea), but went off of his drugs after two weeks due to a bacterial infection. He

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*"...the present message remains clear: do not try a drug holiday at home, at least not without the cooperation and direct supervision of a health-care provider."*

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stopped his medication for three days, and predictably, saw his viral load increase. After restarting therapy, his viral load became undetectable. Four months later, he developed hepatitis A, causing his liver enzymes to increase dramatically, requiring that he go off therapy again. But this time, his viral load did not rebound; it stayed undetectable. While he opted to start therapy yet again after his hepatitis got better, he changed his mind and has been off therapy ever since and continues to enjoy an undetectable viral load.

Has he been cured? Dr. Lori says no. He still has a traceable amount of HIV in his lymph nodes. Instead, it appears as if the immune

## FORUM UPDATE

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

Wednesday, May 17  
**Opportunistic Infections & Cancers in HIV/AIDS**

Wednesday, June 14  
**Starting/Stopping & Switching Antiretroviral Therapies**

Wednesday, July 19  
**Diet & Exercise and HIV/AIDS**

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)

system of this very lucky patient has been able to keep his HIV in check, much like other viral infections that are never totally eradicated from the body (e.g., varicella, the virus responsible for chickenpox).

While no one is sure why this happened, Dr. Lori and his colleagues have offered an intriguing hypothesis. HAART is designed to drastically reduce the amount of virus in the body. While this is definitely a good thing with respect to protecting the immune system from additional damage, it may prevent the immune system from doing what it should be doing in terms of fighting HIV. Perhaps with so little virus in the blood and the lymph nodes, the immune system "forgets" that HIV is there. In turn, it calls off cells programmed to search and destroy the virus. If HAART is stopped, the virus comes back with a vengeance. If HAART is not restarted, the amount of virus will grow considerably, often to levels that overwhelm the immune system.

The key, Dr. Lori argues, is to keep the amount of virus at a controllable level, just enough to keep the immune system active, but not enough to dominate it. This may have been

*(Cont. on page 10)*

# The Skinny on Body Fat & Metabolic Changes

BY JAMES LEARNED

The 7<sup>th</sup> Conference on Retroviruses and Opportunistic Infections (CROI) included close to sixty reports and a symposium devoted to looking at the changes in metabolism and body composition that people on long-term antiretroviral therapy have been experiencing in recent years. These changes—increased triglycerides, increased cholesterol, insulin resistance, glucose intolerance, fat accumulation in the abdomen, breasts and upper back, fat loss in the face, buttocks and limbs (lipoatrophy) — had previously been lumped together under the term *lipodystrophy*. Osteoporosis and cardiovascular disease have recently been added to the list.

It is becoming increasingly clear that no single factor can explain such varied and confounding conditions. Protease inhibitors were initially thought to be the culprits because many of these conditions first appeared (or were paid attention to) in 1996, when the protease inhibitors came into use — thus the terms “Crix belly” and “protease paunch.” But 1996 was also the beginning of widespread use of long-term combination therapy. Protease inhibitors clearly play a major role, but mounting evidence shows that nucleoside analogs and HIV itself contribute to at least some of these conditions as well.

Many people are working hard to develop a common definition of this syndrome or, more likely, syndromes. Without a systematic definition in use, researchers and physicians employ various measurements to report data. Depending on the methods of measurement, studies of people on protease inhibitors, for example, have reported lipodystrophy prevalence rates ranging from 2% to 83%. These discrepancies are partly due to the lack of a common terminology, and they make it difficult to understand the causes and clinical implications of the conditions. They also make figuring out the risk/benefit ratio of long-term antiviral treatment a far more complicated process for everyone.

## Who's at Risk for What?

A number of studies at the conference reported on the prevalence of lipodystrophy syndrome in large groups of people. The CPCRA (Community Programs for Clinical Research on AIDS) evaluated 1,370 trial participants for fat accumulation or loss, diabetes and coronary artery disease. Almost 25% of the participants were antiviral-naïve, 14% were women, 34% African American and 12% Latino. Overall, the incidence of diabetes and coronary artery disease was almost identical in both the antiviral-naïve and antiviral-experienced groups, although certain factors significantly increased the risks. Diabetes rates were significantly higher in non-whites, older people, and those with higher CD4 and viral load, while older age was associated significantly with a greater risk of coronary artery disease, as might be expected. Overall, fat accumulation or loss appeared more frequently in older people, whites, and those who were antiviral-experienced (5.4% vs. none in antiviral-naïve). This comparatively low rate suggests that African Americans and Hispanics may be at lower risk for changes in body composition than whites. There was a clear correlation between length of time on treatment and an increased risk of body shape changes, regardless of protease inhibitor use: 14.3% for a subgroup with more than eight years of treatment compared to 2.7% for people with less than two years of treatment.

A study from Australia looked at body fat changes in 1,350 people surveyed between November 1998 and June 1999. Fat accumulation and/or loss was reported in 51% of all participants. Within this group, most of whom had extensive antiviral experience, body fat changes occurred in 81% who were protease inhibitor-experienced, 33% who were protease inhibitor-naïve, and 5% who were completely antiviral-naïve. As in many other studies, there was a clear correlation between length of treatment, particularly with a protease inhibitor, and

the degree of fat redistribution; the longer you've been on treatment, the more likely you are to develop fat redistribution.

In real life, we know that women often experience different patterns of fat redistribution than men, but most studies have so many more male participants that it has been difficult to sift through the data by sex. An update of the SALSA study (Self-ascertained Lipodystro-

## Protease Inhibitors & Osteoporosis

*Two reports at CROI highlighted a possible connection between the use of protease inhibitors and osteoporosis. An Australian group looked at 74 men who had been on protease inhibitor-containing combinations for various lengths of time and were experiencing symptoms of lipodystrophy. 28% had evidence of osteopenia (moderately low bone mineral density), and almost 10% had evidence of osteoporosis (severely low bone mineral density). Although there was a correlation between these conditions and lower weight and lean muscle mass, there was no correlation with the duration of antiviral therapy, baseline CD4, or baseline viral load.*

*The other report, from Washington University School of Medicine in St. Louis, looked at the rates of osteopenia and osteoporosis in 64 men on a protease inhibitor-containing combination compared to 36 HIV positive individuals not on a protease and 22 HIV negative individuals. 50% of those on a protease had osteopenia, and 21% had osteoporosis, clearly significant numbers. In this study, there was no association with weight or muscle mass. So far, there is no understanding of the relationship between these conditions, which can lead to bone fractures, and either HIV itself or protease inhibitor use.*

phy Syndrome Assessment) described metabolic and body shape changes in 395 HIV positive participants (324 men, 71 women). Almost all are on antiviral treatment and most have taken protease-containing regimens (81% of the men and 63% of the women). Fat accumulation occurred in 84% of the men compared to 97% of the women, fat loss occurred in 77% of the men compared to 61% of the women, and a mix of accumulation and loss occurred in 65% of the men compared to 58% of the women. Significantly higher levels of triglycerides and cholesterol were reported in the men than the women, while elevated glucose levels didn't significantly differ by sex. These data seem to verify the experiences of many people on HAART – women often have less fat loss and more fat accumulation than men do.

Longer duration of HIV infection also often correlates with higher rates of fat redistribution, but a report from Spain put a dent in that assumption. The abstract described a surprisingly high incidence of lipodystrophy in seventeen people who began therapy (d4T/3TC/indinavir) during or within 90 days of primary infection. Five of the seventeen switched from indinavir (Crixivan) to nelfinavir (Viracept) or nevirapine (Viramune) due to virologic failure or kidney stones. Within six months to two years of starting therapy, 35% of these individuals (four men, two women) developed lipodystrophy, defined as fat loss in the face, buttocks or limbs and/or fat gain in the abdomen, neck or chest. Incidence of lipodystrophy increased the longer people were on treatment. The overall incidence of elevated triglycerides and cholesterol was also high, 53% and 33% respectively.

### **Mitochondrial Damage**

Some of the long-term side effects that people experience are certainly due to mitochondrial damage caused by nucleoside analogs, although it's unclear how much this damage contributes to fat accumulation or loss. Mitochondria, found inside all human cells, use oxygen, fat and sugar to produce energy for the cells. A single human cell can have thousands of mitochondria, depending on how much energy is required for the cell to function properly. Mitochondria use the enzyme *polymerase gamma* to reproduce. The nucleoside analogs (AZT, ddI, ddC, d4T, 3TC, abacavir) inhibit *reverse transcriptase*, an enzyme that HIV uses to work its RNA into human DNA. They can also inhibit *polymerase gamma*. The result is the production of fewer mitochondria and a greater likelihood of mutations in the mitochondria that are produced.

*"Depending on the methods of measurement, studies of people on protease inhibitors have reported lipodystrophy prevalence rates ranging from 2% to 83%."*

Mitochondrial damage caused by nucleoside analogs has been recognized since the introduction of AZT in 1987. Some of the resulting symptoms may have been under-diagnosed in the past, but as people have been on these drugs for longer periods of time, increasing attention is being paid to their role in metabolic and morphologic changes. The degree to which each of the nucleosides contributes to mitochondrial damage is unclear. d4T (Zerit) often gets the lion's share of the blame, but combining two or more nucleosides may inhibit *polymerase gamma* in such a way as to exponentially increase the risk. Mitochondrial damage may be responsible for many of the common side effects of the nucleoside analogs: myopathy (inflammation of muscle tissue), peripheral neuropathy (nerve damage in the feet and hands), pancreatitis, and low levels of red

blood cells (anemia), neutrophils (neutropenia), or platelets (thrombocytopenia).

### **Lactic Acidosis**

Two particularly serious conditions can also result from mitochondrial damage – lactic acidosis and hepatic steatosis, or fatty liver. All of us are familiar with the aching muscles that often follow a physical workout. That soreness is caused by a buildup of lactate. Our bodies usually clear excess lactate, but mitochondrial damage can create very high levels of lactate in the blood, sometimes leading to lactic acidosis, a rare but potentially fatal condition. Symptoms of lactic acidosis are difficult to discern. They can include shortness of breath, abdominal pain, nausea, vomiting, fatigue and weight loss, subtle symptoms that can easily be ignored or mistaken for something else. If you experience these symptoms while on nucleoside analogs, see your doctor right away.

There are no simple blood tests to check lactate levels. However, serum bicarbonate levels are measured as part of routine blood work, and low levels are a sign that some kind of excess acid production is occurring. If you're taking a nucleoside and your serum bicarbonate levels are low, lactic acidosis should be suspected. Although riboflavin and coenzyme Q10 are sometimes used to treat lactic acidosis, there is no evidence yet to support the value of either. Usually, the only recourse is to stop nucleoside analog therapy or, if appropriate, reduce the dose.

At CROI, a poster from the Netherlands described four cases of fatal lactic acidosis. The four people had been on nucleoside-containing combinations (all with d4T) for six to twenty months, and all had previously experienced at least one nucleoside-related side effect. They entered the hospital with gastrointestinal and respiratory problems and died within three weeks.

(Cont. on page 12)

# Resistance Testing: What's New

By ANNE MONROE

When it comes to HIV resistance testing, there are still many unanswered questions. Should resistance testing be performed before initiating antiretroviral therapy? How useful is resistance testing when determining a salvage regimen? Are there new methods of resistance testing in development? Data presented at the recent 7th Conference on Retroviruses and Opportunistic Infections (CROI) addressed these issues, but there is more work to be done before conclusions can be drawn.

Let's review. What is drug resistance, and how is it measured with resistance testing? Antiretroviral drugs work by inhibiting HIV's ability to replicate and infect new cells. Drug resistance results from small changes, called mutations, in HIV's genetic material. These mutations occur frequently in HIV replication, as the virus reproduces at an exceptionally fast rate (1 to 10 billion new copies per day) too quickly to copy its genetic material very accurately. Multiple mutations lead to changes in the genes that code for enzymes, the proteins that regulate HIV production, including the reverse transcriptase enzyme and the protease enzyme. Antiretroviral medications work by blocking the action of these enzymes, but multiple mutations result in strains of HIV which are not affected by the presence of antiretroviral drugs, allowing HIV to replicate, usually resulting in an increase in viral load.

Two resistance tests are currently available, both with advantages and disadvantages. Genotypic testing identifies specific mutations in the genetic structure of HIV. Since specific mutations are usually associated with one or more antiviral drugs, the test can help determine which antiviral drugs may not be effective. Advantages of genotypic testing are that it is readily available, relatively rapid, and easy to perform. A disadvantage of genotypic testing is that it is expensive (about \$300 - 500 per test), and is not currently covered by Medicaid or ADAP programs in New York State. In addition,

genotypic testing does not identify mutations in minority species of the virus, species that can multiply rapidly and become dominant. Finally, the test can only be performed on individuals with a viral load greater than 1,000 copies/mL.

Phenotypic testing measures the con-

centration of a drug required to inhibit HIV replication in a test tube by an amount such as 50% or 95%. The defined amount is called IC (inhibitory concentration) 50 or IC95. Interestingly, this is the method used by researchers to determine whether a drug might be effective against HIV before starting a human clinical trial. Unlike genotypic tests, phenotypic resistance testing generally does not require a high viral load. Disadvantages of phenotypic testing are that it is extremely labor intensive and can take several weeks to perform. Phenotypic testing is very expensive, generally \$800 and up per test (again, not covered by NYS Medicaid or ADAP).

PRODUCT	TYPE OF TEST	COMPANY	TIME TO RESULTS	COST	VIRAL LOAD REQUIRED
Pheno Sense	Pheno	ViroLogic, Inc.	2 weeks	\$700 to \$900	>500 copies
Anti-virogram	Pheno	Virco	4-6 weeks	\$880	>1000 copies
True Gene	Geno	Visible Genetics	3-4 weeks	\$400 to \$500	>1000 copies

centration of a drug required to inhibit HIV replication in a test tube by an amount such as 50% or 95%. The defined amount is called IC (inhibitory concentration) 50 or IC95. Interestingly, this is the method used by researchers to determine whether a drug might be effective against HIV before starting a human clinical trial. Unlike genotypic tests, phenotypic resistance testing generally does not require a high viral load. Disadvantages of phenotypic testing are that it is extremely labor intensive and can take several weeks to perform. Phenotypic testing is very expensive, generally \$800 and up per test (again, not covered by NYS Medicaid or ADAP).

So what's the latest news on resistance testing and its benefits in clinical care? Prior to CROI, at the 3<sup>rd</sup> International Workshop on HIV Drug Resistance and Treatment Strategies held in June 1999, Clevenbergh and colleagues presented 12-month follow-up data from the Viradapt study, in which over 100 patients who were failing a protease inhibitor combination regimen started a salvage treatment regimen. The new regimen was assigned based on either treatment history or on resistance mutations as determined by genotypic testing. After six

months of treatment, about 32% of patients in the genotypic group had a viral load less than 200 copies, as compared to 14% of the patients in the treatment history group. The members of the treatment history group were offered genotypic testing, and almost 70% elected to have the testing performed. After 12 months, about 26% of these patients had a viral load less than 200 copies. Of the group who started the study with genotypic-guided therapy, about 28% still had a viral load less than 200.

On the whole, news from CROI supported the Viradapt data. A study by Melnick and colleagues examined the usefulness of phenotypic testing in determining effective salvage regimens for individuals failing a protease inhibitor combination regimen. In this short (16-week) study, 115 subjects were assigned to a salvage regimen based on phenotypic test results or treatment history. The subjects were heavily treatment experienced, but all were naïve to NNRTIs (Sustiva®, Viramune®, and Rescriptor®). The results showed that individuals in the phenotypic test group had a greater viral load decrease after four weeks of treatment, but did not sustain a decrease after 16 weeks of treatment. At the time of the study (1997-98), there were fewer drugs available on the market, limiting treatment options.

A study of phenotypic testing by Cohen and colleagues performed in a similar patient population showed more favorable results.

*(Cont. on page 11)*

# Star TREC: Revealing the Role of the Thymus

BY RICHARD JEFFREYS

Several studies presented at the 7<sup>th</sup> Conference on Retroviruses and Opportunistic Infections (CROI) looked at the role of the thymus in HIV. The thymus is a small organ located just behind the breastbone that acts as a finishing school for newly made T-cells. Over the past year or two, new technologies have allowed researchers to demolish what a veteran activist has called “the hoariest dogma of human immunology.” The dogma in question was a presumption among researchers that the thymus stopped producing new T-cells once a person reached adulthood. In fact, although the production of new T-cells slows down dramatically as we get older, freshly minted T-cells can be found even in people over 90 years of age.

## Thymus Function

Before reviewing the Retrovirus studies, it’s helpful to back up and look at the function of the thymus and how it contributes to the health of the immune system. T-cells are known to be vital to proper immune function, but the subtler distinctions between different types of T-cells and their various functions has only recently become clearer. T-cells belong to different families that can be identified using markers that are present on the cell’s surface. The CD4 marker generally defines helper T-cells, which act as conductors of the complex immune system orchestra. T-cells with the CD8 marker work alongside CD4’s, and the CD8 family includes cytotoxic T-lymphocytes or CTLs. CTLs have the vital job of killing cells in the body that are infected with viruses or other infectious agents.

T-cells start life in the bone marrow, as cells called progenitors. If the destiny of the progenitor cell is to become a T-cell, it leaves the bone marrow and heads to the thymus. It is here that progenitors become fully fledged T-cells, acquiring the CD4 or CD8 surface marker that helps govern their function. T-cells also develop another vital surface structure in the thymus: the T-cell receptor (TCR for short). The

T-cell receptor acts as a docking bay for materials, like pieces of an infectious agent, that will trigger the T-cell to respond. Any piece of foreign material that can trigger an immune response is called an antigen (in the scientific jargon).

T-cell receptors are generated in the thymus by an essentially random shuffling of the T-cell’s genetic code. T-cells with many different shaped receptors are made in this way, to ensure that any potential infection can be responded to by at least some T-cells. Due to the random nature of this process, many T-cells will come up with receptors that match your own body tissues. If these T-cells left the thymus they could trigger an immune response against the body, a problem called autoimmunity. The final job of the thymus is to eliminate these potentially dangerous “self-reactive” T-cells. A surprising 95% of new T-cells are eliminated for this very reason. The remaining 5%, equipped with T-cell receptors that will only dock with foreign materials, leave the

thymus to go on patrol around the body.

These new T-cells are called “naïve” because they have not yet met an infection that matches their receptor. Scientists now have a way of tracking these newly made, naïve T-cells. This technology involves tracking T-cells that have only recently left the thymus, or “recent thymic emigrants” (RTEs). These T-cells can be tracked because the generation of the T-cell receptor leaves some redundant genetic code (DNA) in the cell that scientists can now pick up on tests. These waste sections of DNA are called T-cell Receptor Excision Circles or TREC for short. If the naïve T-cell meets and responds to an infectious agent, the cell divides and the TREC degrades and disappears. This makes the TREC marker very specific for naïve T-cells that have recently left the thymus.

## TREC & the Thymus at Retrovirus

As you may have guessed, it’s tracking TREC that has allowed scientists to spot newly made

*(Cont. on page 14)*

## Memories are made of this...

A naïve T-cell has the potential to respond to a piece of infectious agent or antigen that matches its T-cell receptor. If the naïve T-cell never meets a matching antigen, it is likely to eventually die to make room for the new naïve cells that are being made by the thymus. Some naïve T-cells, of course, will meet a matching antigen and respond. The response involves proliferation, which means the T-cell copies itself rapidly by dividing. This generates a new fleet of T-cells, all matching the same antigen. Within a few days, most of these new T-cells will automatically die and the infection is usually brought under control. A few copies of the T-cell, however, will survive as memory T-cells. Memory T-cells can be thought of as a specialized SWAT team that have the job of responding rapidly to the infection should it try and cause trouble again.

Many infections only cause symptoms when you’re first exposed to them, even though the actual infectious agent stays in your body the rest of your life. Herpes zoster, the virus that causes chickenpox, is a good example. Opportunistic infections like PCP (pneumocystis carinii pneumonia), toxoplasmosis and CMV (cytomegalovirus) are also examples. These infections are controlled in the body by the specialized SWAT teams of memory T-cells that developed when the infection first showed up.

Unfortunately, most people don’t control HIV infection this way. From the earliest weeks of infection, it’s clear that there is a lack of functional memory T-cells fighting HIV. This may explain why new naïve T-cells continue to respond to HIV antigens throughout the course of HIV infection.

# New Drugs in Development

BY TIM HORN

Despite the fact that 14 anti-HIV drugs are approved for use in the U.S., there is a clear-cut need for new compounds that are potent, have unique resistance patterns, and minimal side effects. While some of these drugs look very much like those currently available, pharmaceutical companies and researchers have a number of tricks up their sleeves. Here's a look at a handful of drugs making their way down the drug-development pipeline with some predictions as to how they might be used if approved.

## Nucleoside/Nucleotide Analogues

While not really a new drug, **Trizivir** is a nifty three-drugs-in-one formulation being developed by Glaxo Wellcome. A single Trizivir pill contains the following drugs: Retrovir® (AZT), Efavir® (3TC), and Ziagen® (abacavir). It is not expected that Trizivir will be any more or less effective than these three drugs used together in their current formulations. For patients only taking AZT and 3TC, a combination tablet called Combivir will still be available. Also, any of these three drugs will still be available individually for use in combination with other anti-HIV drugs.

A new nucleoside analogue in development by Triangle Pharmaceuticals is **Coviracil** (emtricitabine), formerly known as FTC. The drug is currently being studied at a dose of 200 mg, taken once a day. While the chemical structure of Coviracil looks very much like that of Efavir® (3TC), test tube studies have shown Coviracil to be four- to ten-times more powerful against HIV than its predecessor. Unfortunately, Coviracil may not be very effective for people who have already taken Efavir®. This is because one of the key changes, or mutations, in HIV's genetic structure that occurs as a result of Efavir® therapy—the dreaded

M184V mutation—also causes resistance to Coviracil.

Gilead Sciences, still recovering from the FDA's rejection of its flagship drug Adefovir, is putting its efforts into the development of **Tenofovir**, its second nucleotide analogue contender. Tenofovir is active against several different viruses, including some that affect monkeys. This has permitted researchers to study the effect of the drug more extensively in animals, which has helped researchers understand what the drug might do in humans. For example, when Tenofovir was provided to monkeys immediately after becoming infected with SIV—the primate equivalent to HIV—the drug prevented the virus from establishing permanent infection. In turn, researchers will soon be looking at the role of Tenofovir as a potential post exposure prophylaxis pill against HIV transmission in humans.

As for Tenofovir's potential as an anti-HIV therapy, people who are resistant to either Efavir® or Coviracil might find Tenofovir to be even more active against their HIV than people who are not resistant to these drugs. This is because of the M184V mutation in HIV's genetic structure, which usually arises during therapy with Efavir® or Coviracil, appears to enhance the way in which Tenofovir binds to the virus.

A few studies of Tenofovir have found that the drug effectively reduces viral load by approximately 50% to more than 90%. In combination with other anti-HIV drugs, it is expected that Tenofovir will decrease viral loads even further.

## Non-Nucleoside Reverse Transcriptase Inhibitors

Furthest along in the non-nucleoside analogue—the “non-nucs”—development pipeline is **Coactinon** (emivirine). The drug is

being developed by Triangle Pharmaceuticals and was formerly known as MKC-442. Like the currently approved non-nucs, Coactinon will likely work well for HIV-positive folks who have never taken anti-HIV drugs in the past, when used in combination with other anti-HIV drugs. As for folks who have tried and failed other non-nucs in the past, it's not clear how effective Coactinon will be. All of the currently marketed non-nucs are highly cross-resistant to each other and, unfortunately, test tube data suggest that Coactinon might not be effective against strains of HIV that are already resistant to any of these approved drugs. Results from clinical trials are needed to reach any conclusion as to how this drug can be used.

From Agouron Pharmaceuticals, the makers of the protease inhibitor Viracept® (nelfinavir), comes **capravirine** (AG-1549). It's not clear what dose will be used, nor has it been determined how safe or effective it is. Test tube data suggest that capravirine will be at least partly effective against strains of the virus resistant to currently approved non-nucs. HIV only needs to develop a single key mutation (K103N) to become highly resistant to any of these older drugs. With capravirine, HIV must develop two or three key mutations in order to become highly resistant to the drug. More information about the effects of capravirine in clinical trials is expected soon.

From the depths of the South American rainforest comes a third non-nucleoside analogue: **calanolide A**. The drug is derived from an exotic plant (*Callophylum*) and is being developed by Sarawak MediChem Pharmaceuticals. While the exact dose of the drug has yet to be determined, it will likely need to be taken twice a day. Of particular interest to researchers is the way calanolide A works. Most non-



# New Drugs in Development

nucs dramatically reduce viral load soon after the first dose is taken. calanolide A seems to have a delayed effect. According to one recent study, calanolide A didn't show any effect against HIV for the first two weeks of therapy. With respect to its potential use for patients already resistant to other non-nucs, test tube data suggest that calanolide A might be effective against some strains of the virus that are at least partly resistant to any of these drugs.

## Protease Inhibitors

Abbott Laboratories' **Aluviran** (lopinavir), formerly known as ABT-378, is scheduled to be the next protease inhibitor to reach the FDA for its stamp of approval. The drug is currently being studied at a dose of 400 mg, taken twice-daily, and is combined with low doses of Norvir® (ritonavir) to boost the amount of Aluviran in the blood. In test tube studies, Aluviran did not appear to be very effective against strains of HIV resistant to currently available protease inhibitors. However, in humans, the amount of Aluviran in the blood is high when combined with ritonavir. This might make the drug effective for people who have tried and failed at least one protease inhibitor in the past.

Early results are available from one study that switched patients currently failing a standard anti-HIV drug combination (one approved protease inhibitor and two nucleoside analogues) to a combination of Aluviran, Viramune® (nevirapine), and at least one new nucleoside analogue. Patients in this study had viral loads between 10,000 and 100,000 copies/mL upon switching from their first protease inhibitor-based regimen to the Aluviran-based regimen. After one year, approximately

76% of the patients who switched to Aluviran in combination with nevirapine and at least one new nucleoside analogue had undetectable viral loads (<50 copies/mL).

In terms of side effects, the most common seen thus far include diarrhea, nausea, and muscular weakness (asthenia).

**Tipranavir**, a protease inhibitor originally developed by Pharmacia & Upjohn and now being produced by Roxane/Boehringer-Ingelheim, is one of the more exciting compounds in the pipeline. In early studies, a dose of 1,500 mg three-times-daily was used. In order to reduce the amount and number of pills needed to be taken, researchers are experimenting with tipranavir in combination with low doses of Norvir® (ritonavir), which will increase the amount of tipranavir in the blood.

No information is yet available from clinical trials evaluating the effect of tipranavir on viral load and T-cell counts in HIV-infected people who have taken other protease inhibitors in the past. Test tube study data, presented in the Fall of 1999, suggest that tipranavir will be effective for patients who have tried and failed at least one protease inhibitor-based combination in the past. As for folks who have never taken a protease inhibitor in the past, tipranavir, when combined with two nucleoside analogues, reduced viral load in the blood by more than 90% after two weeks of therapy.

## Fusion Inhibitors

**Pentafuside** (T-20) is a drug that has gained a lot of attention over the past year. It is being developed by Trimeris Pharmaceuticals and Hoffmann-LaRoche Pharmaceuticals and is now entering the final and most crucial testing phase.

Simply put, pentafuside binds to a protein on HIV's surface called gp41. Once it does this, HIV cannot successfully bind with the surface of CD4+ cells, thus preventing the virus from infecting healthy cells. Hence, pentafuside works differently than any of the currently available anti-HIV drugs.

A dose for pentafuside has not yet been determined. Because of its fragile structure (it is a peptide), T-20 cannot be taken by mouth. It is currently being developed in an injectable form and will require twice-daily shots.

It is expected that pentafuside, when combined with other anti-HIV drugs, will have strong activity against HIV in people who have never taken anti-HIV medications in the past. According to early results from one study, pentafuside taken alone reduced viral load from anywhere between 30% to more than 90% in patients who had not taken any other anti-HIV drugs in the past.

Pentafuside also holds promise for HIV-positive patients who have taken numerous anti-HIV drugs in the past. As discussed above, pentafuside targets HIV differently than currently available drugs. This means that most people living with the virus, regardless of their treatment history, will likely benefit from using pentafuside. According to one early study, the use of pentafuside alone reduced viral loads to undetectable levels (<400 copies) in approximately 60% of heavily pre-treated patients. Results from studies combining pentafuside with other experimental and approved therapies are expected soon.

what happened during the brief breaks, the structured treatment interruptions, in the Berlin Patient's therapy. During the first three-day STI, it's possible that just the right amount of virus was released and then controlled to spark the immune system. Then, upon stopping therapy the second time, the immune system was ready and waiting, able to control HIV on its own.

## Fast-Forward: New Data

Unfortunately, the Berlin Patient is still a unique case. No other patient who has taken an STI, whether in a clinical trial or more discreetly with a doctor, has come close to achieving this level of success. But, in light of some new data presented at CROI in early February, STIs may still offer some benefits.

Dr. Lori presented one study that received a considerable amount of attention, this time involving a cohort of nine patients taking hydroxyurea in combination with ddI, a relatively weak regimen in comparison to the triple-drug therapies used by most people. For the sake of seeing what would happen upon stopping therapy, these patients were compared to a group of eight patients being treated with a protease inhibitor-based regimen (HAART) who also elected to do an STI.

Seven of the eight patients receiving HAART had undetectable viral loads while on therapy. Within six weeks after the STI, five of these patients saw their viral load increase to levels above 100,000 copies/mL. Among patients receiving only hydroxyurea and ddI, only one of whom had an undetectable viral load while on therapy, none saw their viral load increase to levels greater than 10,000 copies/mL during the six-week period off treatment.

In discussing these results, Dr. Lori suggested that hydroxyurea and ddI succeeded in keeping patients' viral loads low, but not undetectable. This allowed for small amounts of the virus to circulate in the blood and in the lymph nodes, keeping the immune system stimulated and ready to kick in once therapy was stopped. This might also explain why the HAART-treated patients saw a dra-

matic increase in viral load, along with a decrease in their CD4+ cell counts, after stopping therapy; keeping levels of the virus low allowed for the immune system to be caught off guard once therapy was halted.

In another study, Dr. Lydia Ruiz and her colleagues in Spain randomized 25 patients—all of whom had undetectable viral loads for more than two years while on HAART—either to continue on therapy or to undergo an STI. Therapy was interrupted for 30 days or until patients saw their viral loads increase to levels greater than 3,000 copies/mL, whichever came first. After 30 days off therapy, treatment was resumed for an additional 90 days followed by a second STI.

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*"...STIs are by no means failproof and may in fact be dangerous in some cases."*

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After the first STI, viral load failed to rebound in two of the patients during the 30-day drug holiday. Upon restarting therapy, all patients who took a drug holiday did so without any problems—their viral load went undetectable again and it did not appear that any had developed drug resistance while off therapy. Thus, while more data are needed to see what happens to the patients' viral loads and CD4+ cell counts during and after the second STI, these early results suggest that STIs may be safe. That is, there does not appear to be any immediate danger associated with STIs in patients who have undetectable viral loads upon stopping therapy, at least in these 25 Spanish patients.

Also of interest was a late-breaking report from an international team comprised of researchers in New York, Switzerland, and Spain. According to their report, ten HIV-infected patients treated with HAART for 52 weeks, all of whom had undetectable viral loads for at least 32 weeks, underwent three STIs (one month each) separated by six months of the same triple-drug therapy.

While therapy was stopped three times during this study, upon restarting therapy, all patients were able to drive their viral loads to undetectable levels each time. This helps to confirm Dr. Ruiz' finding that STIs may at least be safe for patients with undetectable viral loads while on therapy. But the news doesn't stop there. An interesting thing occurred in four of the nine patients during the second STI. While their viral loads increased significantly within a few weeks, the amount of virus in their blood samples began to drop all by themselves. What's more, CD4+ and CD8+ cells collected from these patients during the second STI had taken on important HIV-specific characteristics that are not usually present in people who are either on HAART or have yet to start treatment.

Data from a study conducted at Massachusetts General Hospital in Boston have also added to the current level of optimism. Enrolled in this study were seven newly infected patients who were treated with HAART and willing to undergo two STIs lasting two months each. After the first STI, all seven patients saw major increases in their viral loads. But during the second STI, their viral loads failed to go any higher than 5,000 copies/mL. According to the presenters of these results, it seemed as if HAART followed by STIs during the earliest days of HIV infection could help preserve necessary components of the immune system needed to control the virus. Because these immune responses aren't usually seen in most HIV-infected patients, these results are of major interest.

## The Message To Go

Now that the foundation has been laid—we have preliminary data suggesting that STIs might be safe for people who have been on HAART and have undetectable viral loads—it's time to do some heavy-duty research. It will be important to determine if STIs are safe for people who have been on anti-HIV therapy and have a detectable viral load upon deciding to temporarily stop treatment. As for the potential benefits of STIs, a number of questions remain:

- 1) Do STIs help patients recover from side effects, such as lipodystrophy?

- 2) Will STIs help boost the immune system's response to HIV for prolonged periods of time? Will these immune responses help slow HIV's destructive activity in the body?
- 3) Can STIs be used in combination with immune-based therapies to help boost the immune system responses to HIV even more and help patients live longer healthier lives without anti-HIV drugs?

It's not entirely clear if the data presented at CROI will convince anyone of anything. The results are preliminary and have yet to be duplicated by large clinical trials. Results of these studies are eagerly awaited. And while the race is on to address the uncertainties of STIs, the

present message remains clear: do not try a drug holiday at home, at least not without the cooperation and direct supervision of a health-care provider.

According to one case report presented at CROI, an STI can go terribly wrong. The report came from researchers at the University of Alabama in Birmingham and involved a patient who secretly stopped therapy due to financial reasons on the same day he received a vaccination against the flu. Even though the patient had an undetectable viral load and a CD4+ count of almost 750 cells/mm<sup>3</sup>, his viral load shot up to more than 1 million copies/mL and his CD4+ count dropped to 164 cells/mm<sup>3</sup>

within three weeks. What's more, the patient required hospitalization due to flu-like symptoms. While the reason for this lightening-fast progression of HIV disease has not been fully evaluated, it's likely that the flu vaccine had a lot to do with it (vaccines have been shown to have a strong effect on viral load in patients not taking anti-HIV therapy). Still, this case report warns that STIs are by no means fail proof and, may in fact be dangerous in some cases.

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## Resistance testing

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Again, the researchers compared regimens based on phenotypic test results or on treatment history in subjects failing their first protease combination regimen. Almost 300 subjects enrolled, about 40% of whom were resistant to more than two drugs when they started the study. Preliminary 16-week data showed 62% and 33% of subjects in phenotypic testing and treatment arms, respectively, with a viral load below 400 copies.

We've examined some of the data from individuals failing treatment regimens, but what about individuals who have never taken antiretroviral treatment? In an interesting study out of Montreal, Canada, Routy and colleagues studied resistance mutations in patients with early HIV infection. Both genotypic and phenotypic testing were performed on samples from 87 recently infected patients. Mutations in both the non-nucleoside reverse transcriptase and protease gene were found in 5% of patients, mutations in the nucleoside reverse transcriptase and protease were found in 7% of patients, and mutations in all three were found in 2% of patients. Two patients in the study were determined to be resistant to all available drugs except ddI and d4T because of their

multiple mutations. These findings may indicate that resistance testing is necessary to determine the most effective initial treatment regimen.

### GENOTYPIC TESTING

#### Advantages

- **The entire viral gene is mapped.**
- **It is a cheaper way to predict susceptibility to treatment in newly infected individuals.**

#### Disadvantages

- **Unable to detect mutations in some virus species. These species can multiply rapidly and become dominant.**
- **It is not a direct measure of resistance, so results may be difficult to interpret.**

### PHENOTYPIC TESTING

#### Advantages

- **The results are easy to interpret, as the test is a direct measure of resistance.**

#### Disadvantages

- **The test is extremely labor intensive, and therefore very expensive (\$800 and up per test).**

Note: For both genotypic and phenotypic testing, it is recommended that patients continue on current antiretroviral regimens until the time of testing.

Qari and colleagues reported on a new approach to phenotypic analysis that is potentially less labor intensive and less expensive. This approach directly measures the activity of the reverse transcriptase enzyme to detect resistance to reverse transcriptase inhibitors (including 3TC, nevirapine, ddI, ddC, d4T, and AZT). The results from this new method were consistent with results obtained from standard testing. A less expensive approach to resistance testing that will make it an option for more people living with HIV certainly merits further study.

While we still don't have clear answers to all of the questions about resistance testing, researchers are gaining information that may ultimately move resistance testing from the realm of clinical trials to a component of standard care for HIV. The potential utility of resistance testing in HIV management must be balanced against its expense, and only further study can lead us to definitive answers.

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A team from Johns Hopkins University looked at lactate levels in 509 individuals who had been on combinations that included two nucleosides and a protease inhibitor for varying lengths of time. Although these data are only suggestive, people on combinations that included d4T/3TC had significantly higher lactate level than those on AZT/3TC, d4T/ddI or AZT/ddI. The potential for these people to develop lactic acidosis is unclear.

Another poster discussed abnormally high lactate levels in twenty patients on nucleoside analog-containing regimens (again, all included d4T) at the University of California Medical Center in San Diego from July 1998 to September 1999. The problems were identified early enough that no deaths resulted, and all twenty had normal lactate levels within 7 to 176 days of stopping antiviral therapy. Three of the twenty resumed antiviral therapy (without d4T), and still had normal lactate levels three months later.

A disturbing poster described the history of a child who developed extreme mitochondrial damage. At three months of age, he started AZT/ddI/nelfinavir, which resulted in a good clinical response – undetectable viral load and rising CD4s. A year and a half later, however, he had unusual patches on his brain, elevated lactate levels, liver damage, severe atrophy of muscle and nerve fibers, and an astounding 79% depletion of mitochondrial DNA compared to HIV negative children his age. He was taken off antiviral therapy for three weeks, during which time his viral load rebounded. Then he was started on a combination of ritonavir/nelfinavir/efavirenz (Norvir®/Viracept®/Sustiva®) and his condition has improved. This is the first reported case of a child experiencing such severe mitochondrial damage, seemingly as a direct result of nucleoside analogs.

Early last year, investigators in France reported on two HIV negative one-year-olds who died of neurologic disease associated

with mitochondrial damage and whose mothers had taken AZT/3TC during pregnancy. As more attention is directed at the potential for nucleoside analogs to cause damage to the mitochondria, an effort is underway in the United States to look at HIV negative children born to positive women who took nucleosides (primarily AZT) during pregnancy. Using databases from the National Institutes of Health and the Center for Disease Control, this effort has so far focused on 227 HIV negative children who have died for any reason. Mitochondrial damage has not been found in any of these cases. The next step is to look for possible mitochondrial damage in the thousands of children who are alive.

## Nucleosides and Fat Redistribution

Fat tissue cells also contain mitochondria. If nucleosides affect these mitochondria, lipid levels could rise in the blood and excess fat could build up in other body tissues, contributing to abnormal fat distribution. A poster from a French team looked at fat redistribution in 83 people from the ALBI trial, all of whom had been on dual nucleoside regimens for two and a half years. Half of the group had added either a protease or non-nucleoside to their regimen. Although 35% of the entire group had at least one symptom of lipodystrophy at 30 months, the lipodystrophy rate was 37% for the 42 who had remained on only two nucleosides the whole time. Of the dual nucleoside arms (d4T/ddI, AZT/3TC or d4T/ddI followed by AZT/3TC), the d4T/ddI arm showed significantly higher rates of fat redistribution.

Another French team looked at fat redistribution in 149 protease-naïve study participants taking combinations of two, three or four nucleosides, with an average time on antiviral therapy of almost four years. Lipodystrophy was diagnosed in close to 40% of the participants – 29% with fat loss, 39% with fat accumulation, and 32% with a mix of both. There was no significant difference in triglyceride, cholesterol or glucose levels between those with fat redistribution and those without. Of particular inter-

est, lipodystrophy was more frequent in people taking d4T than those taking AZT.

Other studies also implicated d4T as having a particular role in causing both metabolic and body shape changes. One of many reports on switching or stopping therapy as a means of improving these abnormalities showed that stopping d4T significantly normalized triglyceride and lactate levels as well as resulting in major or partial improvement in fat loss. These data are particularly important because of unresolved questions about whether or not fat redistribution is reversible.

## Switch Studies

Most of the “switch” studies involved replacing a protease inhibitor with a non-nucleoside (NNRTI), in most cases, Sustiva®. Sustiva® is known to raise lipid levels in some people. The good news in most of the switch studies is that viral loads generally remained stable upon switching. The results concerning metabolic and body shape abnormalities are inconclusive, showing very little change in fat redistribution in most cases, even a year after switching. A Spanish study, for example, reported that switching 31 people with lipodystrophy from d4T/3TC/Crixivan to d4T/ddI/Viramune® resulted in significant improvements in cholesterol and triglyceride levels, but no significant improvement in body shape after nine months.

A French study reported on 32 people, all of whom had been on two nucleosides plus a protease inhibitor. Half of them stayed on their original regimen; the other half substituted abacavir (Ziagen®) for their protease inhibitor. Three months after switching, the protease group continued to experience elevated triglycerides, glucose intolerance and clinical signs of lipodystrophy. Triglyceride levels and glucose metabolism had improved for participants in the three-nuke arm, but there was only minor improvement in body shape abnormalities. In another study, there were significant improve-

ments in cholesterol, triglycerides and insulin sensitivity six months after 106 people substituted their protease with Ziagen®. In a subset, three out of nine people who had lipodystrophy before switching to abacavir reported body shape improvement. The nine who stayed on their protease reported further fat redistribution.

### **HAART and Heart Disease**

There were several reports concerning the possibility that people on protease inhibitors may be at increased risk for cardiovascular disease. A study from the University of Wisconsin found that blood vessel function (endothelial function) was impaired in 21 people on protease inhibitors compared to seven who weren't on a protease inhibitor. Using ultrasound technology, the study measured the width of the participants' brachial arteries, the main artery in the upper arm. Endothelial dysfunction can put you at higher risk for coronary artery disease. Some studies found no similar correlation, while others reported a correlation between coronary heart disease and HIV, but not necessarily protease use. Most of these studies, however, looked at very few people over a relatively short period of time.

A retrospective study compared hypertension in 42 people with lipodystrophy to 42 HIV positive people without lipodystrophy and 13 people who were HIV negative. High blood pressure rates were significantly greater in the group with lipodystrophy; yet blood pressure was also higher in the HIV positive participants *without* lipodystrophy compared to the HIV negative group.

Two studies looked into large existing databases to get an idea of the prevalence of coronary heart disease. The records of 4,526 HIV positive people who received care through Northern California Kaiser Permanente between January 1996 and June 1999 were looked at. Rates of hospitalization for coronary heart disease in people on protease inhibitors were

compared to those of people with HIV not on a protease. There was no difference between the two groups. Another poster pooled data from various clinical trials that included protease inhibitor-containing and nucleoside-only arms. Rates of myocardial infarction (cell death in the heart wall) within the arms were compared to each other and to rates from large non-HIV databases. There was no evidence of increases in myocardial infarctions, although the mean follow-up was only one year.

Elevated lipids, often found in people on protease inhibitors, may increase the risk of cardiovascular disease. Therefore, it's difficult to know what to make of the short-term, somewhat contradictory results reported at

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*"Mitochondrial damage may be responsible for many of the common side effects of the nucleoside analogs..."*

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the conference. A large, international study through EuroSIDA will look at the incidence of cardiovascular events (heart attacks, strokes, myocardial infarctions) in more than 30,000 people with HIV over a period of two years. These data will be enormously helpful in clarifying both prevalence and risk factors. Until they're available, however, monitoring lipid levels and blood pressure remain our best clinical tools.

### **Sonow what?**

An overview like this can only touch briefly on some of the recent data concerning the changes in metabolism and body composition that people on HAART are experiencing. Progress is being made toward a better understanding of the causes, clinical implications and potential management of these long-term side effects. But even with so much data on the

subject presented at the retrovirus conference, a clear understanding seems far in the future. As it becomes increasingly evident that researchers, physicians and people with HIV need to be talking the same language to accurately describe these conditions, it becomes equally evident that the development of useful treatment strategies is more complicated than ever.

Risk factors for changes in metabolism and body composition appear to be as varied as the individuals who develop them. In addition to protease inhibitors, nucleoside analogs, and at least one non-nucleoside (Sustiva®), factors that contribute to at least some elements of the syndrome include older age, longer period of HIV infection, longer period of time on treatment, and lower CD4 count and percentage before treatment. Sex, race and genetic predisposition also appear to play a role, although perhaps these are more indicative of the type of changes that might occur.

At the conclusion of the symposium at CROI, Dr. William Powderly of Washington University School of Medicine in St. Louis offered a cautionary overview of how little we understand about the causes, treatment, and clinical implications of these metabolic and body shape changes. Without denying the remarkable success of antiretroviral treatment, he urged the need to reassess the current goals of treatment as outlined in the federal treatment guidelines, including the questions of when to start treatment and which drugs to start with. As Powderly pointed out, the goal of therapy is to let your patient "live long and prosper." When you factor in the possible long-term side effects of treatment, figuring out how to best achieve this goal is difficult. Powderly concluded his summary with a fact that may be obvious but is sometimes downplayed: "The success of current therapy has a price."

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naïve T-cells in people over 90 years old. While most naïve T-cells are indeed produced during childhood, it's now clear that there is a slower, steady production of new naïve T-cells throughout adulthood which declines only slowly with age. At CROI, the first ever study looking at the link between production of new naïve T-cells and HIV disease progression was presented. The study was conducted by David Ho's team at the Aaron Diamond Center in New York City, and shortly after the conference it appeared in the medical journal *The Lancet*.

Ho's group found that the number of new naïve cells, as measured using TREC, declines as disease progresses. In fact, this decline of TREC was very strongly linked to disease progression, leading the study authors to suggest that TREC measurements may complement T-cell counts and viral load when monitoring HIV infection. The decline in TREC in HIV infection was much more rapid than the age-related decline seen in healthy individuals.

Other studies at CROI looked for explanations for the loss of naïve T-cells in HIV infection. Frank Miedema's team at the University of Amsterdam looked for evidence of thymus dysfunction, but found none. What Miedema did find was higher than normal levels of naïve T-cell division. In other words, new naïve T-cells seemed to be responding to an infectious agent of some sort. Unsurprisingly, Miedema revealed in a separate study that the agent responsible is likely to be HIV.

A second conference presentation by David Ho's group provided further evidence that this loss of naïve T-cells is important in HIV progression. Ho compared two species of monkey infected by their equivalent to HIV, SIV (simian immunodeficiency virus). One species, sooty mangabeys, does not experience disease from SIV infection. The other species, macaques, develops immune deficiencies similar to AIDS. Ho found that naïve T-cell division and TREC levels were normal in the sooty mangabeys, but abnormal in the macaques. Ho concluded, "nor-

mal T-cell turnover in SIV-infected mangabeys provides an explanation for the long-term maintenance of a functional immune system in these hosts."

Studies of HAART in both adults and children provided some good news. Viral load suppression was associated with increased TREC levels in adults after 48 weeks of treatment in a combined American/Canadian Study. A Texan study of children on HAART found that those who maintained undetectable viral loads also showed increased TREC levels.

An intriguing study from France looked at the role of naïve T-cell production in people with a "discordant response" to HAART treatment. In these individuals, CD4 counts had risen significantly despite a disappointing drop or rapid rebound in viral load. When compared to similar individuals with more modest CD4 increases, the "discordant" responses were associated with higher TREC levels (increased survival of newly made naïve T-cells).

A complementary study from Michael Lederman's team at Case Western Reserve looked at the other type of "discordant response" to HAART: good viral load reduction but poor CD4 cell increases. Lederman found that the failure of the thymus to generate new naïve T-cells may explain these responses.

It is clear from these studies that the production of new naïve T-cells by the thymus is important for maintaining health. The studies also suggest that increasing thymic production of new naïve T-cells might be useful therapeutically. It is currently unclear whether it's possible for the thymus to "speed up" production. So far, studies in mice have found it almost impossible to manipulate the thymus in this way. A study at CROI optimistically posited that a cytokine called interleukin-7 (IL-7) might increase thymic output of new naïve T-cells. The cytokine (one of the chemical messengers of the immune system) seemed to have this effect in genetically altered mice, although it also caused increased levels of HIV replication.

A late-breaking CROI presentation from Mike McCune and fellow researchers at the Gladstone Institute in San Francisco looked at IL-7 levels in HIV-infected humans. McCune found that IL-7 levels increased as disease progressed and T-cell counts declined. The research team concluded that the body may in fact be trying to boost T-cell production by increasing IL-7 levels as much as possible. Further investigations of the role of IL-7 are planned.

CROI included 20 studies looking at the role of the thymus, demonstrating that this is a growing field. The apparently critical role of the thymus in both disease progression and immune reconstitution will only increase the focus on this formerly under-appreciated organ. Stay tuned.

*Richard Jeffreys oversees the Access Project, a national database of AIDS drug assistance programs at the AIDS Treatment Data Network.*

## Visit CRIA on the Internet

Our web address is:

**[www.criany.org](http://www.criany.org)**

**CRIA Update**, summaries of CRIA's monthly Community Forums held at St. Vincent's Hospital, detailed information about CRIA's treatment education services and a list of currently enrolling clinical trials are all available on our Web page.

**Check it out!**

## **CRIA Begins Study to Address Depression in People Living with HIV and AIDS**

For a number of obvious reasons, people who are infected with HIV experience higher rates of clinical depressions than the general population. CRIA has occasionally conducted or sponsored studies to address this problem, and our latest independent trial will examine a possible treatment option for depression in PLWAs.

Our new pilot study is a cooperative effort with Dr. Richard Brown at Columbia University Medical Center, Dr. David Goldenberg at Cornell Medical Center and Dr. Kristine Jones of Memorial Sloan Kettering Cancer Center of S-adenosyl-methionine (SAM-e). This agent has been used widely in Europe to treat depression but has only just recently begun to receive serious consideration for this purpose in the United States. SAM-e is a naturally occurring compound in humans which may help to regulate a number of vital bodily functions, including those which affect a person's mood. Researchers have long known that persons who have clinical depression frequently have abnormally low levels of SAM-e in their system and it is hoped that our trial will confirm the drug's ability to rapidly enhance the psychological well being of our patients. Participants in this trial will be taking SAM-e twice daily over an eight-week period, and they will be completing a test to evaluate psychometrics six times. Patients will also have blood draws to measure SAM-e and homocysteine levels as well as viral load and CD4 counts.

This study is particularly important since so many of PLWAs are already on many toxic drugs and may be reluctant to use widely pre-

scribed antidepressants. SAM-e also does not have nearly the same number or severity of side effects as other drugs to treat depression. CRIA thanks the Pharmavite Corporation for contributing the product for this trial.

## **CRIA Awarded Contract to Produce Clinical Trials Directory**

CRIA is pleased to announce our recent award in March of a contract by the New York State Department of Health AIDS Institute to produce a hardcopy and online directory of HIV/AIDS clinical trials within New York and the Tri-State region. CRIA's charge is not only to ensure that this information reaches care providers in all regions of the state who can refer patients to proposed treatments which offer the greatest potential for advancing HIV medicine, but also to conduct an extensive assessment component. CRIA will be placing particular emphasis on examining how useful the directory is at reaching underserved populations and helping ethnic minorities and women to learn about the potential advantages of participating in clinical research. CRIA's assessment program will include many different constituencies involved in the clinical research process, from scientists, to care providers, to PLWAs themselves.

Although the hardcopy directory will be produced twice a year, CRIA plans to continually update the online version so that providers have the most current information to use when advising their patients. Look for updates on the progress of this new program in future editions of *CRIA Update*.

## **CRIA Completes City Funded Hepatitis C/HIV Co-infection Treatment Education Contract**

At the end of February, CRIA completed its work on a special three-month Ryan White Title I supported initiative to educate underserved people living with AIDS (PLWAs) in New York City on the many issues surrounding Hepatitis C (HCV)/HIV co-infection. CRIA was selected as the sole provider of this important new citywide initiative due to our unique experience speaking about the complex healthcare issues pertaining to co-infection. And, CRIA is pleased to report that we far surpassed the city's expectations for numbers of persons reached by this program. In fact, CRIA was able to serve nearly 45% more than the 1,180 persons we had hoped to reach within the contract period.

Unfortunately, CRIA's work on educating PLWAs about HCV/HIV co-infection has been so successful that many agencies we work with continue to request the specialized workshops for their clients, even though we no longer have the necessary funding to operate this program. We are attempting to at least meet a portion of the overwhelming demand for continuing HCV/HIV education by fundraising in the private sector. We are optimistic that at least some of these proposals will be successful. Also, James Learned, CRIA's recently hired expert on HCV/HIV co-infection issues has agreed to stay on with us full time. Nevertheless, we are hopeful that the New York City Department of Health will eventually recognize the continuing need for treatment education on HCV/HIV co-infection issues, and fund CRIA's work in this area in the near future to avoid a permanent end to these services.

ACKNOWLEDGING OUR FRIENDS...

# GENEREOUS CONTRIBUTORS

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