HIV Research - Directions After Durban

Highly active antiretroviral therapy (HAART) has been successful for many people, at least in the short-term, highlighting the immune system’s amazing ability to restore itself. HAART’s limitations are also clear, however, both in terms of long-term side effects and the seeming impossibility of making antiviral drugs accessible to the millions of people living with HIV worldwide. The 13th International Conference on AIDS in Durban, South Africa cast a long-overdue spotlight on the disparities between the availability of HIV treatment for people in developing countries compared to those in North America and Western Europe. It also brings into sharper focus the urgent need to research and develop strategies that boost the immune system’s ability to suppress HIV replication.

We’ve asked three regular CRIA Update contributors to discuss various aspects of immune reconstitution. Tim Horn provides an update on structured treatment interruptions, a follow-up to his report in our Spring 2000 issue. Anne Monroe looks at the recent data concerning when it’s safe to stop medications to prevent opportunistic infections. Richard Jefferys offers a detailed overview of T-cell function, particularly as it relates to HIV, and explains why further research into the complex processes of the immune system is so important for the development of more successful and accessible HIV treatment strategies.

Our regular feature, “Drugs in Development,” provides a look at the data on the most recently approved protease inhibitor and another in the pipeline. Finally, to start the issue off, our very own Dr. Jerome Ernst, CRIA’s medical director, shares his insights after attending the Durban conference.

J Daniel Stricker, Editor-in-Chief

Impressions from South Africa
A Personal Perspective

Even now, two months after the close of the 13th International AIDS Conference in South Africa, I still sense a certain feeling of bewilderment among my medical colleagues about all that happened. Being exposed to the harsh reality of life in South Africa brought a lot of us up short and, hopefully, lent a new perspective to our work.

Coming of age in what feels like the distant past, our feelings towards South Africa were pretty straightforward. Apartheid was in firm control, we all read Cry the Beloved Country, bought Miriam Makeba albums and supported the boycott. With the recent miraculous change in government and the ascent of Mandela, we all hoped that peaceful progress could happen.

Visiting South Africa, I was overwhelmed by many conflicting feelings. The countryside is gorgeous. The stark mountains of the Cape area, the beauty of Capetown and the lushness of the wine country clash jarringly with the black shantytowns, the palpable fear of crime in the cities, and the monstrous economic gulf that exists between blacks and whites. The statistics are mind numbing. This is a country with almost 50% unemployment. Whites are leaving in droves. Most of the land and most of the wealth is definitely not in the hands of most of the people. And an ever-increasing percentage of those are HIV infected.

(Cont. on page 9)
CRIA TRIALS IN PROGRESS

Study of 3 Different Drug Combinations in Drug-Naïve, HIV+ Individuals (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 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/mm3, have a viral load greater than 1,000 copies/mL and less than 200,000 copies/mL, and have NOT taken 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 (Enrollment Closed)

CRIA is conducting 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 aspirin in diethyl ether, another with an inactive placebo in diethyl ether. 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.

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

Enrollment is continuing 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.

Directly Observed Antiretroviral Therapy (DART)

CRIA is currently conducting the pilot study “Historical Prospective Study of Directly Observed Antiretroviral Therapy (DART)” with the CDC. Patient records from three types of settings providing antiretroviral therapy (AIDS residential health care facilities, day health centers, and ambulatory health clinics) are being compared to study the effect of DART on the clinical outcome of people living with AIDS. This research should generate data that will maximize the effectiveness of antiretroviral therapies and minimize the development of HIV resistance to these drugs.

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.
An Update on Structured Treatment Interruptions: Possibilities & Pitfalls

By Tim Horn

Ever since CRIA Update published its first review of the hope—and hype—surrounding structured treatment interruptions (STIs) six months ago, there has been a great demand among readers to remain up-to-date regarding this highly experimental treatment approach. This article discusses the results of studies reported since CRIA Update ran the original article in the Spring 2000 issue.

The list of possible reasons why someone on anti-HIV therapy might want to go on an STI continues to grow:

- **Side effects**: STIs might help control or reverse some of the long-term side effects caused by anti-HIV therapy. However, it is not yet known if side effects such as liver damage, peripheral neuropathy, or body-shape and metabolic changes improve during a drug holiday. If they do improve during an STI, it’s still not clear if or when these side effects will return.

- **Poor countries**: This is a relatively new concept discussed at the 13th International AIDS Conference this past summer in Durban, South Africa. Because of the high costs of therapy, a treatment strategy employing an “on again-off again” approach—called “pulsed” or “intermittent” therapy by researchers—has been proposed as a possibly feasible option for HIV-infected people living in the developing world (e.g., Africa, Asia, and Latin America).

- **Pregnant women**: Some HIV-positive women may become pregnant while they are receiving anti-HIV drug therapy. While combination therapy is needed to keep the woman’s viral load undetectable, it is still not known if anti-HIV drugs are completely safe for the developing baby. During the first three months, or first trimester, of pregnancy, it is known that some prescription and over-the-counter drugs can cause fetal damage. In turn, STIs may be an option for women during the first three months of pregnancy.

- **Treatment failure**: There is a growing number of HIV-infected people who have been on several anti-HIV treatment combinations and are unable to keep their viral loads undetectable. Temporarily stopping therapy might help their virus “switch” to a strain that is sensitive to the drugs, much like it was before therapy was started in the first place. This might allow a combination of drugs to be used effectively and, possibly, help decrease viral load to undetectable levels once combination therapy is started again.

- **Immune system boost**: Some studies suggest that carefully planned STIs may help boost the number of T-cells—called HIV-specific T-cells—needed by the immune system to help it control HIV. STIs to boost the immune system are still highly experimental. Researchers do not yet know if they work.

**Immune Restoration: New Data**

As mentioned above, STIs to boost HIV-specific T-cell activity hold a great deal of promise. One way to look for HIV-specific activity of the immune system is to see what happens to viral load during an STI. Researchers believe that, if HIV-specific T-cells are present, the rebound in viral load that occurs during the STI should be lower than the viral load seen before therapy was started in the first place. According to a study reported at the 4th International Workshop on HIV Drug Resistance and Treatment Strategies this past summer in Sitges, Spain, this appears to be the case.

In the study, ten HIV-infected patients who had an average pre-therapy viral load of more than 10,000 copies/mL received a four-drug anti-HIV drug combination consisting of indinavir (Crixivan), ritonavir (Norvir), d4T (Zerit), and 3TC (Epivir). Patients who had undetectable viral loads (less than 20 copies/mL) for at least 32 weeks were permitted to undergo a series of three STIs. After the last cycle, in which therapy was stopped indefinitely, half the patients had a virus level that was significantly lower than their pre-therapy viral load. What’s more, the low viral loads seen in these patients persisted for more than eight months before having to restart therapy again.

Early results from a second, still-ongoing study—reported at the 13th International AIDS Conference—are also intriguing. The study is being conducted in Spain and Switzerland and is the largest STI study currently ongoing anywhere in the world. Patients taking a protease inhibitor-based regimen with a viral load below 50 copies/mL and a CD4+ count above 300 cells/mm³ are undergoing a series of two-week STIs. Each STI is followed by an eight-week course of therapy. After 40 weeks of these cycles (four cycles in total), treatment is discontinued until viral load increases to levels above 5,000 copies/mL, regardless of how long this takes. Approximately 120 patients have already been enrolled in the study.

(Cont. on the next page)
If HIV-specific T-cells were becoming increasingly more active with each STI, viral load should peak at a lower level during each STI. However, this was not the case in this study. On average, each two-week STI resulted in a viral load increase of 1,000 copies/mL. But something interesting happened as well—after the first STI, 24% of the patients did not experience any rebound in viral load. After the fourth STI, 14% did not experience any rebound in viral load and an additional 28% are seeing their viral loads creep up at a very slow rate.

A few warning flags have been raised in this study as well. First, some patients have seen their viral loads increase at a rapid rate—sometimes to levels above 100,000 copies during the STIs. Second, more than 7% of patients were unable to bring their viral loads back down to undetectable levels upon re-starting therapy after an STI. Both of these findings underscore the potential risks of STIs and need to be studied much more carefully in the months to come.

The Potential of Pulsed Therapy

There was also an interesting report in Durban from Dr. Anthony Fauci’s lab at the National Institutes of Health (NIH). In this ongoing study, patients are receiving Crixivan, Norvir, Zerit, and Epivir using one of two highly unorthodox dosing schedules: seven days on therapy followed by seven days off therapy, or two days on therapy followed by five days off therapy. With almost ten weeks of “pulsed” therapy under their belts, most of the patients are doing extraordinarily well. All four of the patients who began the seven days on/seven days off schedule have an undetectable viral load (<500 copies/mL). Of the three patients who began the two days on/five days off dosing regimen, two had undetectable viral loads at the time data were presented by Dr. Fauci’s team.

Of course, there’s no telling what these results really mean. For starters, the number of patients enrolled in this study is very small. Second, the length of time these patients have been followed is incredibly short. However, these early results are promising and represent a radical departure from the current standard of care. More data from this study—and other “pulsed” therapy studies in development—are eagerly awaited.

STIs in Treatment Failure

As discussed at the beginning of this article, using STIs to help “switch” drug-resistant HIV to drug-sensitive “wild-type” virus is of major interest among researchers. Veronica Miller, PhD, a researcher in Frankfurt, has found that 26/39 (66%) patients resistant to as many as eight drugs saw their virus switch to wild-type virus during a 12-week STI. Upon restarting therapy, these patients experienced, on average, a 2.6 log reduction in their viral loads. Among the 13 patients who did not see a shift in their drug-resistant virus, the average viral load reduction upon restarting therapy was only 1.02 log. Also of interest was Dr. Miller’s finding that patients who switched from drug-resistant to wild-type virus were more likely to see an increase in viral load and decrease in T-cell counts during the STI.

Dr. Miller recently reported follow-up data involving patients who completed the 12-week STI and restarted therapy. Unfortunately, most patients—regardless of whether or not they experienced a drug-resistant-to-wild-type switch—saw their viral load rebound within three months of restarting therapy. According to Dr. Miller, there was no “statistically significant” difference between these two groups of patients. In other words, while there was a slower viral load rebound among patients who experienced a switch, this may have been due to chance.

What’s more, Dr. Miller has found that some patients who are failing therapy and initiate an STI actually experience rapid disease progression. In a recent study involving 165 multi-drug resistant patients with a history of low T-cells, those who initiated an STI were much more likely to experience a new AIDS-related illness than those who remained on a “failing” regimen. Thus, even though rebounding viral load indicates that a regimen is no longer doing all that it should, therapy is still offering some benefit.

Like the possible use of STIs to boost the immune system and, perhaps, to reduce side effects and make treatment more economically feasible, knowing how and when to use STIs in patients experiencing treatment failure remains uncertain. More research is definitely needed and, luckily, much research is currently underway.

Tim Horn is the executive editor of The PRN Notebook, published by Physicians’ Research Network in New York, and a member of CRIA’s Research Advisory Committee.
Second Time Around: T-cell Memory and HIV

By Richard Jefferys

The idea of enhancing the immune system's ability to cope with HIV has always been attractive. Various theoretical approaches have been proposed; some have been tried, but none have yet met with much success. Among the immune-based therapies studied to date are interleukin-2 (IL-2) and Jonas Salk's therapeutic vaccine Remune, both of which have now been in clinical trials for well over a decade. While frustrating, the slow pace of this research should not be surprising. Scientists' understanding of how the immune system fights viruses has been extraordinarily limited until very recently. Over the past few years, a quiet revolution has been occurring in immunology, the science of studying the immune system.

It has long been known that T-cells are a vital component of our defense against disease, but attempts to understand exactly what these cells do - and how they do it - have been limited by technical difficulties. Two breakthroughs have helped remedy this situation. Mice have proven a boon to immunologists, since the genetic factors that can influence a T-cell's structure and function can be tightly controlled in mice with a combination of genetic manipulation and careful breeding. Secondly, new lab tests are allowing a much more detailed assessment of T-cell function than was previously possible.

"...new lab tests are allowing a much more detailed assessment of T-cell function than was previously possible."

Getting Specific

A typical adult has a lot of T-cells running throughout their body (see table on page 10). A logical question is, how do they know which infection to fight? This feat is accomplished by another structure on the outside of the cell called a T-cell Receptor (TCR). The TCR acts as a sort of docking bay for pieces of infectious agents (any piece of infectious agent that can trigger an immune response is called an antigen). One way to think of it is to remember the children's game where you fit various shapes into their matching holes. Each TCR is like one of those holes, having a particular shape. Only an antigen that matches the shape of that TCR will fit snugly into it. And only that snugly fitting antigen will trigger the T-cell to respond.

The metaphor of the children's game only goes so far. If the game had as many shapes and holes as there are potential antigens and TCRs, it would be a recipe for tears and tantrums. A study published in the journal Science last October estimated the number of potential TCRs at around 250 million. This is the body's way of ensuring that its T-cells are ready for anything.

T-cell Production

Both the TCR and CD4 or CD8 marker are acquired by T-cells in an organ called the thymus, located just behind your breastbone. Each T-cell generates one out of the potential 250 million TCRs by an essentially random shuffling of the T-cell's genetic code, or DNA. Once acquired, the TCR does not change. The T-cell stays specific for one particular antigen for its entire life. The thymus churns out billions of T-cells during childhood, but production slows in adulthood. In a typical 20 year old, the thymus is thought to produce about 6 billion or so new T-cells each day. This slowly declines to around 1.8 billion by the time we get past 50 years of age. Both CD4 and CD8 T-cells get made, but CD4 T-cells tend to outnumber CD8s by a ratio of around 2:1.

Naïve T-cells

When a new T-cell leaves the thymus, equipped with a freshly generated TCR, it is called a naïve T-cell. Naïve means that it hasn't encountered or fought any infection. The job of the naïve T-cell is to patrol the body, looking out for antigens that are the right shape to fit the cell's TCR. Specialized cells called dendritic cells chop up bits of potentially infectious material and hold them out to naïve T-cells for inspection. This function is called antigen presentation.

Memory T-cells

The events set into motion when a patrolling naïve T-cell encounters an antigen that fits its TCR are key to understanding immunity. Using a variety of animal models, particularly mice infected with a virus called LCMV (Cont. on page 10)
<table>
<thead>
<tr>
<th>Condition</th>
<th>Preferred Medication</th>
<th>Alternate Medications</th>
<th>Primary Prophylaxis</th>
<th>Secondary Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCP</td>
<td>Bactrim (TMP-SMZ)</td>
<td>Dapsone; Dapsone + Daraprim (pyrimethamine) + Leucovorin; NebuPent (aerosolized pentamidine); Mepron (atovaquone)</td>
<td>Use if CD4 count is &lt;200 or CD4% is &lt;14% or if patient has a history of oral thrush. Discontinue when CD4 count is &gt;200 for 3-6 months</td>
<td>Risk of recurrence is low if CD4 count increases to above 200 (or CD4% increases to above 14%), but there is currently no recommendation to discontinue secondary prophylaxis.</td>
</tr>
<tr>
<td>MAC Infection</td>
<td>Biaxin (clarithromycin); Zithromax (azithromycin)</td>
<td>Mycobutin (rifabutin)</td>
<td>Use if CD4 count is &lt;50 Discontinue when CD4 count is &gt;100 for 3-6 months with sustained HIV suppression</td>
<td>Risk of recurrence is low if CD4 count increases to above 100, but there is currently no recommendation to discontinue secondary prophylaxis.</td>
</tr>
<tr>
<td>CMV Infection</td>
<td>Cytovene (oral ganciclovir)</td>
<td>Not applicable</td>
<td>May be used if CD4 count is &lt;50</td>
<td>Discontinue when CD4 count is &gt;150 for 3-6 months with sustained HIV suppression, only if non-sight-threatening lesions are present and the patient can undergo regular ophthalmic exams.</td>
</tr>
<tr>
<td>Toxoplasmic encephalitis</td>
<td>Bactrim</td>
<td>Dapsone+Daraprim; Mepron-/Daraprim</td>
<td>Start prophylaxis when CD4 count is &lt;100 Discontinue when CD4 count is &gt;100 for 3-6 months</td>
<td>After an incidence of toxoplasmonic encephalitis, lifelong secondary prophylaxis with Bactrim should be administered. There is no data to support discontinuing secondary prophylaxis.</td>
</tr>
<tr>
<td>Cryptococcosis</td>
<td>Diflucan (fluconazole); Sporanox (itraconazole)</td>
<td>Not applicable</td>
<td>May be used if CD4 count is &lt;50</td>
<td>After an incidence of cryptococcosis, lifelong secondary prophylaxis with Diflucan should be administered. Risk of recurrence is low if CD4 count increases to above 100, but there is currently no recommendation to discontinue secondary prophylaxis.</td>
</tr>
<tr>
<td>Histoplasmosis</td>
<td>Sporanox</td>
<td>Not applicable</td>
<td>Use if CD4 cell count is &lt;100 and patient lives in area with hyperendemic rate of histoplasmosis</td>
<td>After an incidence of histoplasmosis, lifelong secondary prophylaxis with Sporanox should be administered. Risk of recurrence may be low if CD4 count increases to above 100, but there is inadequate data to support discontinuing secondary prophylaxis.</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Nydrazid (isoniazid); Rifadin (rifampin) or Mycobutin + Pyrazinamide</td>
<td>Not applicable</td>
<td>An individual who has a positive TB skin test but no evidence of active TB should initiate prophylaxis lasting 9 months (Nydrazid) or 2 months (Rifadin/Pyrazinamide)</td>
<td>Lifelong secondary prophylaxis is not necessary once an individual completes treatment for active TB.</td>
</tr>
<tr>
<td>Bacterial respiratory infections</td>
<td>Bactrim</td>
<td>Biaxin, Zithromax</td>
<td>Do not use solely to prevent respiratory infections as resistant organisms may develop</td>
<td>Bactrim may be prescribed for individuals with frequent respiratory infections.</td>
</tr>
</tbody>
</table>

Long before HAART, the use of medications to prevent opportunistic infections (prophylaxis) was an important component of HIV care. And while there has been a decrease in the incidence of opportunistic infections since the introduction of HAART, paying attention to prophylaxis remains crucial. Recent reports show high rates of admissions for opportunistic infections among individuals not receiving HAART in the U.S., and OIs are a serious concern in parts of the world where HAART is not available at all or available to very few people. For people who have experienced immune reconstitution with HAART, however, prophylaxis against opportunistic infections is not always necessary.

With the goals of decreasing the number of pills a person needs to take and minimizing side effects while maintaining health, researchers have examined the effects of discontinuing prophylactic regimens. The first studies showed that it is safe to discontinue primary prophylaxis (preventive treatment for someone who has never had the infection) against infections such as MAC (mycobacterium avium complex) and PCP (pneumocystis carinii pneumonia) following immune reconstitution. The positive results of early studies led researchers to look at the safety of discontinuing secondary prophylaxis (preventive treatment for someone who has already had the infection).

Several studies presented at the 13th International AIDS Conference in Durban, South Africa, indicate that it is safe to discontinue secondary prophylaxis against PCP. Swiss researchers studied 41 people with a history of PCP who had an increase in CD4 count from an average of 23 to an average of 369. All study participants discontinued PCP prophylaxis, and after a median follow up of over 5 months, no cases of PCP were observed. The results of an Italian study were similar. 124 patients on secondary prophylaxis for PCP were enrolled, and half discontinued their prophylactic medications. No PCP events were observed in either group. One of the inclusion criteria for these studies was a CD4 count greater than 200 after being on HAART, but the average count of participants in both studies was above 300.

A third study, tracking over 70,000 people with HIV, identified 450 people with a history of PCP. Of the 450, about 175 never had an increase in CD4 count to above 200. Within that group, nine people discontinued their secondary PCP prophylaxis, a factor that was associated with a greater risk of PCP recurrence. PCP recurred in 18 patients overall, illustrating the importance of continuing prophylaxis in an immunocompromised state. Additional research is necessary to determine exactly when it is safe to discontinue secondary PCP prophylaxis. At present, the Centers for Disease Control and Prevention has not issued a formal recommendation.

Rates of CMV (cytomegalovirus) infection are very low, even in patients with advanced HIV disease. Primary prophylaxis against CMV infection is not generally recommended, since oral ganciclovir (Cytovene) is expensive and its efficacy as a prophylactic agent is controversial. Recognizing early signs of CMV infection, such as decreased visual clarity, is currently the best defense against CMV. An observational study from France examined the relation between CMV seroconversion and AIDS progression. 1700 subjects enrolled in the study, 290 of whom were CMV seronegative when they enrolled. 61 of the subjects seroconverted during follow-up. The 61 subjects who seroconverted had a median CD4 cell count of 102 at the time of an AIDS-defining illness, while the seronegative individuals had a median CD4 count of 26 at the time of an AIDS-defining illness. While the difference was not statistically significant, it illustrates a trend towards more rapid HIV disease progression in CMV-positive individuals. CMV is shed in semen, cervical secretions, and saliva. Safer sex decreases the risk of CMV exposure. Basic hygienic practices such as hand washing also decrease the transmission of CMV and other germs.

Studies from the 7th Conference on Retroviruses and Opportunistic Infections in February examined the effects of discontinuing prophylactic therapies for cryptococcosis, a fungal infection, and for MAC. A team from the University of California in San Francisco followed six patients with a history of cryptococcosis to examine the effect of discontinuing antifungal prophylaxis. The group had CD4 counts greater than 150 and had been asymptomatic for cryptococcosis for at least four months after a year of fluconazole (Diflucan) therapy. Patients who discontinued therapy in April and May of 1999 were still asymptomatic when the conference abstract was submitted, leading researchers to conclude that cryptococcal infection can be “cured” in some individuals after immune reconstitution.

The recommendation for primary MAC prophylaxis is to begin prophylaxis when...

"...while there has been a decrease in the incidence of opportunistic infections since the introduction of HAART, paying attention to prophylaxis remains crucial."

(Cont. on page 12)
New Drugs in Development

I hate the term “salvage therapy.” “Salvage” is raising a nuclear submarine from the icy depths of the Barents Sea. “Salvage” is picking through charred fuselage to look for Concorde flight recorders. “Salvage” is not, however, a term I’m particularly fond of when it comes to defining options for HIV-infected individuals in need of new therapies. We don’t need salvaging. We need new drugs.

Yet, options for HIV-infected folks who have tried and failed existing HAART regimens leave a lot to be desired. This is particularly true when it comes to the protease inhibitors (PIs). There are five PIs currently available, all of which are hobbled by similar resistance mutations. HIV-positive folks who fail one of these drugs often have a difficult time keeping their viral load undetectable upon switching to another PI, even when the new drug is combined with new nucleoside analogues or, perhaps, a second protease inhibitor.

New protease inhibitors are desperately needed for patients who have failed one or more of the current PI options. Here’s a look at one that was just approved by the Food and Drug Administration (FDA) and another that is furthest along in clinical trials:

**Lopinavir (Kaletra; ABT-378/r)**

In test tube studies, lopinavir—which was awarded the brand name Kaletra by Abbott Laboratories—is approximately 10 times more powerful than its predecessor, ritonavir (Norvir). When used with small amounts of ritonavir—hence, the little “r” in its name (ABT-378/r)—lopinavir’s blood levels remain high for a long period of time. One Kaletra capsule contains 133 mg of lopinavir and 33 mg of ritonavir. The recommended daily dose is three capsules taken twice a day with food.

In terms of its resistance profile, lopinavir was specifically developed to be active against HIV strains carrying mutations at position V82 of the protease gene. This is a major mutation associated with resistance to ritonavir (Norvir), indinavir (Crixivan), and possibly saquinavir (Fortovase). Thus, lopinavir has at least one foot in the door when dealing with strains of HIV resistant to any of these three drugs. Unfortunately, the activity of lopinavir weakens a bit when going up against viruses containing mutations at positions M46 and I84. The former mutation can result from Crixivan therapy, whereas the latter mutation is caused by all currently approved PIs.

The true test of lopinavir is its activity in clinical trials. Results of three studies have been reported to date: one involving folks who have never taken a PI before, a second that enrolled patients who had failed only one PI in the past, and a third study involving patients who had failed more than one PI before enrolling in the study. Data from the third study were presented at the 13th International AIDS Conference in Durban.

A total of 57 patients were enrolled in the trial. On average, each patient had tried—and failed—three protease inhibitors in the past. In looking at some blood samples collected at the start of the trial, it appeared that most patients were already resistant to lopinavir before even starting therapy. However, this turned out not to be the case.

All patients were treated with one of two doses of lopinavir: 400 mg (with 100 mg ritonavir) or 533 mg (with 133 mg ritonavir), both taken twice daily. Lopinavir was combined with efavirenz (Sustiva) and two nucleoside analogues.

After six months of therapy, approximately 80% of patients receiving the lower-dose lopinavir regimen and 96% receiving the higher-dose lopinavir regimen had undetectable viral loads (<400 copies/mL). Good news… but wait a minute! All patients who enrolled in this study had never taken an NNRTI before and, thus, would definitely respond well to Sustiva. Yet according to Dr. Joseph Eron of the University of North Carolina at Chapel Hill, who spoke recently with CRIA Update, there’s more to this than meets the eye. Most patients in the study were not only resistant to many of the PIs currently available, but were also resistant to most of the nucleoside analogues currently on the market. Without the addition of lopinavir, Sustiva would have been nothing more than monotherapy. And, as we know from previous clinical studies, NNRTI monotherapy results in rapid resistance. So lopinavir worked well for folks with an extensive prior treatment history, regardless of the added benefit of an NNRTI.

Sadly, the side effects of lopinavir are similar to those being seen with other PIs: nausea and headache are chief complaints, along with increased liver enzymes and increased lipid (fat) levels in the blood.

Lopinavir was approved by the FDA in mid-September and is now available.

**Tipranavir**

Like lopinavir, tipranavir has a great deal to offer folks at the end of their PI rope. Tipranavir represents a new class of protease inhibitors believed to have greater flexibility in binding with HIV protease enzymes resistant to current PIs. The compound was originally developed by Pharmacia & Upjohn and was recently sold to Boehringer Ingelheim, the manufacturers of nevirapine (Viramune).

Tipranavir is different from other PIs in a number of ways. All PIs now on pharmacy shelves inhibit the liver enzyme system known as P450. In other words, current PIs slow down the way in which the liver breaks down drugs in the bloodstream, allowing for the PIs to stay in the body for long periods of time. Tipranavir is different. This drug speeds up the liver enzyme system, requiring very high
doses of tipranavir three times a day to keep adequate blood levels.

Nobody wants to take a lot of pills multiple times a day, regardless of how “unique” a drug’s resistance profile is. To make the drug more user friendly, the people at Boehringer Ingelheim are working on a new formulation—called a self-emulsifying drug-delivery system (SEDDS)—to slow down the rate at which tipranavir is metabolized in the body. Like lopinavir, tipranavir will also need to be taken with low doses of ritonavir to block the P450 enzyme system. Using the SEDDS formulation, along with low doses of ritonavir, will permit much lower doses of tipranavir to be taken twice daily.

Unfortunately, not a whole lot of data have been produced by clinical trials involving patients resistant to current PIs. However, some interesting test tube study results have been reported over the past year. Dr. Brendan Larder, a researcher at Virco Laboratories, manufacturer of a phenotypic drug-resistance test, tested tipranavir against 107 different strains of HIV. Most of the strains studied were highly resistant to three or four of the PIs now available. According to Dr. Larder, only 3% of all the strains tested were highly resistant to tipranavir. Most strains—90%—remained sensitive to tipranavir.

Of course, what happens in test tube studies rarely proves the effectiveness within the human body. Unfortunately, studies involving HIV-positive folks with multiple-PI resistance are not expected to begin until mid-2001 and it’s unlikely that we’ll see an expanded access program or approval until 2002 or 2003.

Both lopinavir and tipranavir are testaments to the hope that exists in the drug-development pipeline. We need these drugs and we need them studied in combination with each other. “Salvage” is not an option. New drugs—studied together in people who need them most—are.

Personal Perspective

Being a guest in another country should temper one’s usual hypercritical New York attitude. After all, it’s a different culture, there are different demands and priorities, not everything from the West is the best, what makes you think you know it all? But then, printed in a South African daily newspaper was an exchange of letters, a debate between South Africa’s President Thabo Mbeki and a science correspondent. And President Mbeki was persisting in distorting scientific reality to mask his political failure as a leader of his people.

If you’ve read this far, you may be asking yourself, “what does this have to do with AIDS research?” Well, that depends. Many of us clinicians got into AIDS research because we suddenly had many patients dying of a new disease that didn’t even have a name. In order to help our patients we began, resumed or intensified familiar activities in politics, social activism, research and public health. Those of us working in the inner cities intensified our efforts to make good health care available to the medically uninsured. Issues of jobs, education, crime, drug abuse, inadequate resources, ignorance and racism were exposed and addressed. Good health care in AIDS also meant good research and the access to new drugs, new prevention methods and new clinical knowledge that comes with it.

Most of us clinicians got into AIDS research to find ways to help our patients. With time, this initial clarity often became blurred, diluted by other issues, both personal and professional. For me at least, South Africa restored that clarity and then some. The meeting has been widely criticized as having been somewhat light on science. Actually, that criticism has been made of every international AIDS meeting since the first one in Atlanta in 1985. The feeling that the “purity” of science is attacked by allowing all those “nonscientific community people” to attend the meetings is still present among a good number of so-called scientists. The issue that became abundantly clear in South Africa was that merely having the meeting in South Africa saved lives.

AIDS research has made incredible progress when measured against the usual timelines existent with other diseases. Current antiretroviral therapies, the product of AIDS research, are restoring health to many people infected with HIV. But not in Asia, Africa, parts of Europe, the Caribbean and South America. At least, not among the vast majority of the poor of those regions who are infected with HIV. Without radical change, as many as ten million South Africans will die in the next ten years.

Science has a responsibility to society. Society has given us the means (money) to do our work. We have repeatedly seen what happens when science operates in a vacuum. We as scientists have a responsibility to society to make sure that our work can affect the good that is its goal. Having discovered increasingly effective (somewhat) treatments for AIDS, we must take the next step and ensure that these treatments are available to all. Welcoming all those “nonscientific community people” to our meetings is one step. Their energy and commitment have done wonders in changing the course of the epidemic. Having our meetings in countries where the epidemic is most prevalent is another. The public attention brought to the failure of the government of South Africa to engage the issue of HIV in a responsible manner will save lives. The continuing exposure of the extent of the epidemic is galvanizing local prevention efforts. The exposure of the issues of drug company profits and wealthy countries’ greed will also bring about change.

True, there is little medical infrastructure in South Africa. But some of my best teachers in medical school were trained in South Africa. It is a dirty trick for the government there to use the current situation as an excuse for inaction. As an activist pleaded during a session at the conference: just begin to distribute the drugs, the infrastructure will follow. While we continue working on improving drugs, developing better treatment strategies, enhancing prevention efforts and working on vaccine development, we must also make sure that the results of our efforts, anxiously awaited by so many, are made widely available.

Jerome Ernst, MD is CRIA’s Medical Director
(lymphocytic choriomeningitis virus), scientists have now studied the process in great detail. Although there are varied responses to different viruses, some common themes - thought to be highly relevant to HIV infection - have emerged.

Dendritic cells pick up pieces of the virus to which the body has been exposed and transport them to the lymph nodes. Lymph nodes are immune system command centers, and naïve T-cells regularly pass through them on their way to and from the blood and other body tissues. When the dendritic cells arrive in the lymph nodes, they hold out pieces of the virus - or, to use the correct term, viral antigens - for passing T-cells to check out. This is the process of antigen presentation mentioned earlier. The dendritic cells will embrace any naïve T-cells with TCRs that dock snugly with the viral antigens (usually this means several hundred thousand naïve T-cells, because a virus gets chopped up into many different shaped antigens). This takes these T-cells off patrol and begins the process that will kick-start the antiviral immune response.

The T-cell/dendritic cell embrace lasts several days, during which time signals are exchanged that cause the T-cell to prepare for battle. Eventually, the T-cell becomes activated, which means that it begins making copies of itself or, to use the technical term, proliferate. One naïve T-cell can make twenty or more copies of itself, and this process generates a fleet of T-cells that all have the same TCRs. All of these T-cells are thus specifically targeting a particular viral antigen.

These activated, virus-specific T-cells leave the lymph nodes on a search-and-destroy mission. Their task is to find and eliminate any infected cells and limit the ability of the virus to reproduce. To perform this mission, activated T-cells also develop enhanced infection-fighting skills. They release chemicals called cytokines and chemokines that can communicate with other cells and, in some cases, directly block viral replication. CD8 killer T-cells release special chemicals such as perforin that cause virus-infected cells to die.

Within a week or two, T-cells have usually gained the upper hand. Viral replication is controlled, and most of these newly made, activated T-cells automatically die off. What has been long suspected, but only recently proven, is that some of the virus-specific T-cells survive. Out of the twenty or so duplicates made by each naïve T-cell that was activated by the virus, it seems that a few don’t die but live on as “memory” T-cells. These memory T-cells can be thought of as a SWAT team that the body retains to deal with the viral infection should it ever try and cause trouble again.

Recent studies have helped show how memory T-cells prevent infections from recurring. Remember the lingering embrace between the antigen-presenting dendritic cell and the naïve T-cell? A memory T-cell can be activated and go into battle after a much shorter period – the immune system equivalent of a hug, perhaps. Memory T-cells also seem to be able to copy themselves more rapidly, and release cytokines, chemokines and other infection-fighting chemicals almost instantly.

The reason that memory T-cells have these enhanced skills relates to the activity of genes within the cell. Genes are short stretches of DNA that contain code for making certain proteins. The proteins then perform specific functions in the body. Most of us know that we inherit genes from our parents for things like eye color. It’s often less appreciated that our genes are at work every second that we are alive. Every cell in our body (except for red blood cells) contains a complete copy of our DNA blueprint (called the genome) and all our genes are contained within it. However, cells only use the genes they need to function. A T-cell uses certain genes to make the proteins it needs to fight infection. A kidney cell will use different genes to perform the waste-eliminating functions of the kidney. One way to think of it is that each cell carries an entire library containing many volumes of instructions needed for making the body. But each cell only pulls off the shelves those volumes needed to carry out that cell’s specific functions.

When a naïve T-cell begins copying itself in response to an infection, genes that make infection-fighting proteins such as cytokines and chemokines are slowly switched on. Each new copy of the cell that is made seems to get better at making these proteins. The cells that survive as the memory T-cell swat team end up with these genes set in a sort of hair-trigger position - as soon as they reencounter the infection, the genes almost immediately start producing the relevant cytokines and chemokines.

Vaccines typically work by triggering this process. Because vaccine antigens are

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<th>Approximate Numbers of CD4 and CD8 T-cells in Adulthood</th>
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<td>Naïve</td>
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<td>CD4 T-cells</td>
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usually either fake copies or weakened versions of the real thing, naïve T-cells with matching TCRs get activated and leave a legacy of memory T-cells ready to rapidly respond if the real deal shows up. If this year’s flu vaccine is close enough to this season’s flu strain when it comes around, your flu-specific memory T-cells should be able to protect you by quickly eliminating the virus from your body.

**T-cell Teamwork: Helpers and Killers**

There is another important lesson that’s been learned from experiments with virus-infected animals. CD4 helper and CD8 killer T-cells rarely seem to work independently when dealing with viruses. Instead, they cooperate with each other to keep the virus under control. The process of naïve T-cell activation and the eventual generation of long-lived memory T-cells apply to both CD4 and CD8 T-cells whose TCRs match the viral antigens. The memory T-cell swat team incorporates both CD4 and CD8 T-cells specific for the same virus. Studies in mice suggest that when it comes to viruses, the CD8 members of the swat team outnumber their CD4 helpers by a ratio of about 50:1.

With so many more CD8 T-cells targeting a virus than CD4 T-cells, you might wonder if the helper cells are really needed at all. Several research teams have removed CD4 cells from mice and then exposed them to virus infections to see what happens. Naïve CD8 T-cells seem to get activated and leave a legacy of virus-specific memory CD8 cells in the normal way. As a result, CD8 T-cells alone can often deal with viruses that don’t stay in the body for long. But viruses that can persist in the body (chronic viral infections such as certain strains of LCMV in mice and hepatitis B & C, CMV, Epstein-Barr virus and HIV in humans) are not dealt with effectively in the absence of CD4 cells. With chronic infections, the virus-specific CD8 memory T-cells lose their ability to kill virus-infected cells if they don’t have some virus-specific CD4 companions to tell them to keep it up.

Based on recent study results, researchers think the virus-specific CD4 T-cells are needed to provide the CD8 T-cells with an ongoing “license to kill.” This licensing is done through a middleman, which turns out to be another job for the dendritic cell. The current thinking is that virus-specific CD4 T-cells persuade the dendritic cell to show a special molecule on its surface called CD40, along with the viral antigen. The CD4 T-cell then departs. When a CD8 killer T-cell that’s specific for that same viral antigen shows up, it gets a signal from the CD40 molecule, which allows it to go off and kill virus-infected cells. Without the signal delivered via CD40, the ability of the CD8 T-cell to produce perforin - its cell-destroying weapon – seems to be impaired.

While the first examples of this CD4/CD8 memory T-cell teamwork were from animal studies, there is now evidence that the same cooperation occurs in human viral infections. Researchers using new technologies to track T-cell responses have found that cytomegalovirus (CMV)-specific CD4 and CD8 memory T-cells are generated in response to this virus. Studies have also tried treating active CMV with infusions of CMV-specific T-cells. Tellingly, CMV-specific CD8 T-cells given alone do not work well. When people are infused with both CMV-specific CD4 and CD8 T-cells, the treatment is usually effective. One of the key differences between people who control hepatitis C infection vs. those who don’t (and may be at risk for liver damage as a result), is the strength of the hepatitis C-specific CD4 memory T-cell response.

**What About Antibodies?**

In addition to assisting CD8 killer T-cells, CD4 T-cells provide help to B-cells. B-cells, or B-lymphocytes, are factories for making antibodies. Antibodies are small proteins designed to lock on to infectious agents floating in the bloodstream, disarming them and marking them for elimination from the body. Viruses like HIV, which do most of their dirty work while inside cells (scientists refer to these nasties as “intracellular pathogens”), are notorious for evading antibodies. So far, scientists have struggled to find ways of generating antibodies that effectively block HIV - what they call “neutralizing antibodies.” HIV cloaks itself in an ever-mutating envelope that seems designed to shuck off the antibody attack. This has led to the highly productive focus on killer T-cells described in the main body of this article. Researchers haven’t given up on antibodies, however. Several novel antibody approaches have now shown some promise in animals and are moving slowly toward human testing.

**And HIV?**

Since the publication of an important study by immunologist Bruce Walker and colleagues in late 1997, the significance of the HIV-specific CD4 and CD8 response has been increasingly recognized. It has long been known that everyone with HIV has HIV-specific CD8 memory T-cells. In fact, people seem to accumulate more and more of these as disease progresses. But, now that the importance of T-cell teamwork has been revealed, what about the HIV-specific CD4 memory T-cell response?

Strong HIV-specific CD4 memory T-cell responses are almost exclusively found in one group of people: long-term non-progressors. These are the individuals who have maintained low or undetectable viral loads during long stretches of asymptomatic infection. Then, some years back, two researchers in what was then the fledgling field of HIV and AIDS, John Mellors and experimentally infected monkeys, observed that long-term non-progressors seemed to have a huge number of HIV-specific CD4 memory T-cells. It seemed that these lymphocytes kept the virus in check. Could it be that the helpful CD4 T-cells are the ones that really stop the virus? That’s the question that’s been asked, and some researchers have tried to find answers.

By the end of the year, it seems as if this critical part of the T-cell machinery to fight HIV is more important than ever. The big questions now pertain to why some people have these and others don’t. If the answers can be found, there may be new strategies to improve treatment and even prevent infection. For now, it seems that to kill a virus, you need a swat team.
loads and normal T-cell counts despite being HIV infected for 20 years or more in some cases. Additionally, these people have CD8 killer T-cells that are particularly enthusiastic when it comes to destroying HIV-infected cells.

In the majority of people with progressive HIV infection, HIV-specific CD4 memory T-cell responses are either weak or difficult to detect. Recent studies have found that HIV-specific CD4 memory T-cells are not absent, but apparently dysfunctional. One of the primary features of memory T-cells is their ability to copy themselves (proliferate) rapidly when they re-encounter their target. In people with progressive HIV infection, HIV-specific CD4 memory T-cells appear unable to proliferate when they reencounter the virus.

As was seen in animals lacking CD4 cells, this dysfunction of HIV-specific CD4 memory T-cells has a domino effect on the function of their CD8 killer compadres. In July’s *Journal of Experimental Medicine*, a team of researchers led by immunologist Sarah Rowland-Jones showed that, in progressive infection, HIV-specific CD8 memory T-cells lack the essential cell-killing substance perforin. It is important to note that Rowland Jones studied people infected with both HIV and the common viral infection CMV. This allowed the researchers to compare the cell-killing abilities of HIV-specific and CMV-specific CD8 memory T-cells from the same person. Unlike those targeting HIV antigens, the CMV-specific CD8 memory T-cells produced normal amounts of perforin and efficiently killed CMV-infected cells. The researchers suggest that the presence of CMV-specific CD4 memory T-cells, but the absence of functional HIV-specific CD4 memory T-cells, may explain these differences.

Because HIV - unlike almost all other viruses - can infect naïve CD4 T-cells as they become activated in response to viral antigens, scientists speculate that the normal process that should lead to the development of HIV-specific CD4 memory T-cells is thrown off. As a result, researchers are focusing on ways to trigger the development of HIV-specific CD4 memory T-cells without the interference of HIV replication. One strategy under study is a therapeutic vaccination given to people whose HIV is being controlled by HAART. While studies have shown that HIV-specific CD4 memory T-cell responses can be generated this way, it remains uncertain how big a response might be needed to control HIV once HAART is stopped. Clinical trials are ongoing. Another strategy is structured treatment interruptions, or STIs. (See page 3 for an update on this approach.)

Taken together, the mix of basic science and new clinical research described here is beginning to get even skeptical immunologists excited. Louis Picker, one of the first to study HIV-specific CD4 memory T-cell responses, has outlined at least four key questions that need to be addressed by future research:

- How many HIV-specific CD4 memory T-cells need to be generated?
- How many different HIV antigens might need to be targeted by these T-cells?
- What functions should these cells be able to perform? (For instance, is the ability to make particular cytokines and chemokines important? Is the ability of the cell to make copies of itself important?)
- How can these responses be maintained over time?

With scientists hotly pursuing answers to these questions, the idea of immune-based containment of HIV may finally be nearing the realm of reality.

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

**OI Prophylaxis**

CONT. FROM PAGE 7

CD4 count falls below 50 and to stop prophylaxis when CD4 count increases to above 100. This recommendation was supported by the results of ACTG 362, an AIDS Clinical Trials Group study in which about 650 patients with immune reconstitution received either azithromycin (Zithromax) or placebo for MAC prophylaxis. There was no statistically significant difference in MAC incidence between the two groups. Other serious bacterial infections, such as pneumonia, sinusitis, and sepsis may be prevented by azithromycin, however. The patients in the ACTG 362 trial are still being followed, and the impact of discontinuing azithromycin on the rate of serious bacterial infections will be examined.

Although opportunistic infections may seem forgotten, they are certainly not gone. Any decision to discontinue prophylaxis should be done in conjunction with vigilant monitoring of immune function, and prophylactic therapies should be restarted if or when immune status changes. This way, the serious illness associated with opportunistic infections can be delayed or completely avoided.

For references, contact CRIA’s Treatment Education Department or check our website at criany.org

Anne Monroe is research associate at Cornell’s Clinical Trials Unit in New York City and a writer on HIV/AIDS topics.
CRIA's Shaman SB-300 Diarrhea Study

By Douglas Mendez, MD, Steve Blum, and Mark Condon

In our continuing effort to improve the quality of life for people living with HIV, Community Research Initiative on AIDS this year conducted an open labeled pilot study to observe the health benefits and safety of SB-300 in people with HIV and chronic diarrhea.

Diarrhea is a frequent problem among patients infected with HIV. Over 50% and possibly up to 90% of all people with HIV will become afflicted with diarrhea at some point during their clinical course, requiring a physician visit or hospitalization for the syndrome. Diarrhea constitutes such a prevalent aspect of HIV that the Centers for Disease Control (CDC) has designated weight loss greater than 10% associated with more than 30 days of diarrhea in an HIV-positive individual as a criterion to the diagnosis of AIDS, even without an AIDS defining infection or malignancy.

SB-300 is a standardized herbal extract (dietary supplement) developed and sold by Shaman Botanicals. The company contributed the product for the study. It contains the compound SP-303 (proanthocyanidin oligomer) that has been isolated and purified from the bark of a South American Amazonian rainforest tree called Croton lechleri. The bark has a red latex that is taken orally by indigenous and mestizo peoples in numerous South American countries to treat diarrhea, dysentery, gastritis and stomach ulcers.

Although SP-303’s precise cellular mechanism of action is not well understood, the agent has been found to block the secretion of fluid and chloride into the intestine. Pharmacokinetic studies in humans have demonstrated that there is no significant absorption of SP-303 into the bloodstream. Its anti-diarrheal action occurs entirely within the intestine.

Seven HIV+ participants were followed in CRIA’s open labeled pilot study of SB-300, each of whom had had chronic diarrhea for two weeks prior to study enrollment. Chronic diarrhea was defined as three or more abnormal stools (i.e. soft or watery) per day. Diarrhea caused by an infection was ruled out in each case. Participants were required to discontinue any other anti-diarrheal agents 24 hours prior to enrollment. Each participant received SB-300 and was instructed to take two tablets (700 mg) every 6 hours for a two-week period. They were also asked to record in a diary the time and consistency of each stool for the duration of the study. Study visits were required at the end of each week.

The consistency of stools was broken into three categories for this study: watery (can be poured), soft (takes shape of container), and formed (retains shape).

The two weeks’ experience on SB-300 were averaged for each participant and compared to the average daily estimates for the 10 days prior to enrollment. In addition to the two-week averages, we also examined averages for an 11-day period (day 4-day 14) to determine whether there was an immediate response or if a few days’ treatment were necessary.

There appears to be a considerable decrease in the daily average number of stools, from 5.6 to 3.4, that is attributable to the treatment with SB-300. There is also a corresponding decrease in the average number of watery stools, accompanied by a decrease in the number of soft and an increase in the number of formed stools. The treatment appeared to be immediately effective since there were no significant differences between the two week and 11 day averages.

The participants reported no side effects from SB-300 and generally acknowledged that the drug was beneficial to them. Prior to treatment, participants were largely confined to their homes due to the urgency of their diarrhea. Once on the SB-300, they spoke of a greater freedom to conduct normal lives as a result of their reduced problem of diarrhea.

While CRIA’s pilot study into the efficacy and safety of SB-300 in the treatment of chronic diarrhea in HIV+ individuals shows some benefit, our results cannot be considered statistically significant given the small number of participants. To further research into this specific agent, CRIA has given its data to Dr. Johannes Koch at San Francisco General Hospital who is conducting a larger trial of SB-300. It is hoped that the results of our work and that of Dr. Koch will help improve the quality of life for the majority of PLWAs who will at some point develop chronic diarrhea.

The abstract of results from CRIA’s Shaman SB-300 Diarrhea Study can be found on the web at www.criany.org.
Optimizing HIV Treatment Success Through Education

Stricker, J Daniel; Pieribone, David; Scheuer, Jeff; Community Research Initiative on AIDS (CRIA), 230 West 38th Street, 17th FL, New York, USA www.criany.org

**Issue:** People living with HIV/AIDS (PLWAs) must be informed of the myriad complexities in HIV treatments to realize optimum success in utilizing them. Medical providers frequently do not have time to adequately explain these issues; consequently PLWAs are increasingly relying on non-medical staff at community based organizations (CBOs) for this information. CBO staff must be knowledgeable about HIV treatments to ensure that accurate information is conveyed to their clients.

**Visual Tools**
Easy to understand visual tools are used to enhance the learning process. Staff are given copies of the visual tools to help explain key concepts to their clients. The reverse side of each visual tool includes explanation of the image.

**Written Materials**
CRIA produces a variety of written materials to support the educational process. The “HIV Treatment Education Training Manual” provides CBO staff with both a comprehensive reference tool and training curricula which can be used for educational presentations to clients. A quarterly treatment newsletter, “CRIA Update” provides up-to-date information on HIV/AIDS treatments and research.

**Curriculum includes:**
- The Human Immune System
- Basics of HIV/AIDS
- Opportunistic Infections
- Combination Therapy
- Resistance & Cross-Resistance
- Treatment Adherence
- Managing Drug Side Effects
- Treatment Guidelines
- Doctor/Patient Relationship
- Understanding Lab Tests
- Clinical Trials
- Women’s Issues
- Substance Use & HIV
- Hepatitis C/HIV Co-infection
- Treatment Guidelines
- Doctor/Patient Relationship
- Understanding Lab Tests
- Clinical Trials
- Women’s Issues
- Substance Use & HIV
- Hepatitis C/HIV Co-infection

**Conclusion:** Staff at CBOs receive critical information about HIV disease and the related treatment options. They, in turn, are better able to convey this information to HIV+ individuals, to empower them to maximize their treatment and healthcare success, especially underserved populations.

Poster presentation at the 13th International AIDS Conference July, 2000, in Durban, South Africa.
CRIA is pleased to report on two poster presentations at the 13th International AIDS Conference held this past July in Durban, South Africa.

For the second consecutive time, planners of this major world meeting of HIV researchers and care providers have selected a novel component of CRIA’s HIV Treatment Education Program as noteworthy for discussion. This year, CRIA presented an outline of its new technical assistance initiative to teach other AIDS service organizations (ASOs) within a few selected regions of the United States, including New York, how to provide HIV treatment education themselves. CRIA’s program is unique in its comprehensive series of graduated workshops covering the full range of treatment issues which ASO staff will want to convey to their clients, in its use of several unique testing and role playing devises, and in its supplementary tools designed to help participants counsel people living with AIDS. These tools include a detailed 300+ page reference manual and a variety of color visual aids for use in explaining the basic concepts of HIV pathogenesis and treatments.

The second abstract was presented by CRIA Board Vice President, Donald Kotler, MD, on results of our pilot independent trial of Recombinant Human Growth Hormone (Serostim®) as a treatment for lipodystrophy. CRIA’s partner researchers at St. Luke’s Roosevelt Hospital Center provided information on what was among the first studies completed to address the metabolic complications which are now being seen in so many long-term survivors of HIV. Findings from this small preliminary trial showed Serostim to have rapid success at reversing abnormal fat redistribution. Unfortunately, the long-term efficacy of growth hormone at restoring and maintaining more normal metabolic function could not be determined by our pilot protocol. Several significantly larger prospective trials of Serostim are now being conducted across the United States as a result of CRIA’s groundbreaking work.

2000 Combined Federal Campaign Participation

For the third consecutive year, CRIA has been approved for membership in the Medical Research Agencies of America (MRAA). Participation in this federation of 32 nationally prominent medical research non-profits allows CRIA to solicit donations from federal employees across the United States through the Combined Federal Campaign (CFC). If you are a federal employee, including armed services personnel, and want to support CRIA’s clinical research agenda, look for our member number 1713 in the MRAA federation section of your CFC guide.

CRIA extends a warm welcome to Jecenia DeJesus who has recently joined our staff as a Treatment Educator. She replaces Eduardo Guzman who left the agency after three years of service to New York’s HIV/AIDS community.

Jecenia comes to us with the ability to immediately assume Eduardo’s important responsibilities. She has a long history of community activism and involvement in promoting healthcare opportunities for people infected with HIV. Most recently, she counseled clients of the Jamaica Y Transitional Housing Unit on a broad array of service and healthcare issues. Prior to that time Jecenia was Director of the Women’s Treatment Project at the People With AIDS Health Group. We expect that Jecenia will want to focus a large portion of her time at CRIA on helping women understand the critically important treatment issues as well as on assisting Latinos who require healthcare information entirely in Spanish.

CRIA would also like to welcome LaQuitia DeJesus as Treatment Education Assistant. She fills an extremely key position since CRIA’s HIV Treatment Education Program has grown to offer such a large array of services. Over 170 separate community-based organizations now call upon our educators to speak at their offices about the latest advances in HIV medicine. Hundreds of agencies across the United States regularly request bulk copies of our agency’s treatment education publications. We will rely on LaQuitia to ensure that our treatment educators can focus on providing counseling rather than on the many necessary administrative tasks which make these services possible.
ACKNOWLEDGING OUR FRIENDS...

GENEROUS CONTRIBUTORS

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- Stuart A. Sundlun

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- Barry Binkowitz, MD
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- Carl Parisi
- Fred & Betty Santangelo
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- Robert Deckert
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