



UPDATE

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AIDS COMMUNITY RESEARCH INITIATIVE OF AMERICA

Reaching Further: ACRIA

On January 1, 2002, the Community Research Initiative on AIDS (CRIA) officially became the AIDS Community Research Initiative of America (ACRIA). We made this move to reflect the agency's current activities as a national HIV/AIDS clinical research and treatment education organization.

CRIA was founded on December 12, 1991. Now that our 10th anniversary is behind us, we have a sufficiently broad perspective to consider how the agency has changed over the past decade to meet a continually shifting HIV epidemic in the United States. Tremendous advances in HIV care have been realized since 1991, some of which have resulted from the trials we've conducted at our clinic and in partnership with other researchers. We've modified our research agenda substantially to include the types of studies that are necessary to improve healthcare in the era of highly active anti-retroviral therapy (HAART).

We've also seen the populations impacted by this disease shift dramatically since our early years of operation. In 1991, AIDS was characterized as a disease primarily affecting gay white men. Today, the epidemic is most deeply affecting women and people of color, many of whom experience rapid deterioration from AIDS related illness for complex reasons, including poverty, insufficient access to care and treatment, and other cultural and socio-economic barriers. ACRIA is deeply committed to providing education about important healthcare issues to all populations, offering information to

help people advocate for themselves and realize the full benefits of HIV treatment and care. Since the creation of our Treatment Education Program in 1997, this agency has become one of the largest providers of consumer-focused HIV health information in the United States. In fact, ACRIA's activities in both clinical research and treatment education are now largely national in scope – whereas we were primarily NYC-oriented in our early years.

So, in anticipation of our 10th anniversary, the agency's Board of Directors decided to make an important symbolic change by adopting a new name that reflects our growth and development. ACRIA will be fundamentally the same entity as CRIA was, with the same awareness that, to be effective, we must adapt to the changing needs and priorities of people living with HIV and AIDS (PLWAs) across the United States.

CRIA Update represented our first foray into the treatment education arena, followed by many other services designed to provide more direct education and counseling to HIV positive individuals. Now, this newsletter again allows us an opportunity to let the national PLWA community understand how we plan to move forward to better support people's needs. *CRIA Update* has become *ACRIA Update*. Although it has a new look, the basic format and focus of the newsletter remain the same – to offer clear, practical discussions of HIV treatment issues that are important to a broad audience. Best wishes for a healthy and happy new year.

J Daniel Stricker, Editor in Chief

Harnessing the Immune System

This issue of *ACRIA Update* focuses on the immune system and immune-based therapies. AIDS research has provided us with better understandings of both HIV itself and the immune system. Previous issues of our newsletter have often focused on the virus – discussions of antivirals, side effects and drug resistance. But for HIV treatment to advance further, the immune system side of the equation requires equal attention. This issue offers overviews of how the immune system works and

the concept of immune restoration. We've also asked some of our colleagues to look at specific therapies and strategies that might give the immune system the kick in the butt it needs to help slow down HIV disease progression and improve immune function. HAART has dramatically improved the lives of many PLWAs, but the limitations of antiviral therapy highlight the need to engage the immune system in the fight against HIV.

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ACRIA 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. ACRIA studies new treatments for HIV-related diseases through its clinical research and conducts a comprehensive treatment education program. Bulk copies of *ACRIA Update* are available free to agencies that provide services to people living with HIV/AIDS. For more information, call Judy Codrington at 212-924-3934 ext. 121.

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Atazanavir vs. Viracept in Protease Inhibitor Naive Individuals

This research study will compare the safety and effectiveness of atazanavir (BMS-232632) to Viracept (nelfinavir) in people who have seen their viral load rise while taking HIV drugs that did not include a protease inhibitor. Atazanavir is an experimental new protease inhibitor developed by Bristol-Myers Squibb Company.

Participants will be randomly assigned (like flipping a coin) to take either: 1. atazanavir (active drug) and placebo (inactive) nelfinavir, or 2. placebo (inactive) atazanavir and nelfinavir (active drug). Everyone in the study will also take two nucleoside reverse transcriptase inhibitors (NRTIs).

If you are an adult with HIV, have a CD4 count of 50 or more, a viral load of 1,000 or more, and have been taking anti-HIV medications but have NOT taken any protease inhibitors (or have had very limited use of them), you may be eligible for the study.

The study will last approximately 52 weeks, during which time participants will have to make 12 scheduled visits to ACRIA. All blood tests, study visits, and study drugs will be provided at no charge to the participants. Reimbursement: Once you have been enrolled in the study, you will be reimbursed \$18 per visit to cover lost time from work, transportation costs and/or meals.

Vigilance II Genotyping Study

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

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

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

**For more information on these studies, please call
Dr. Douglas Mendez at (212) 924-3934, ext. 126
or visit our Web site: www.acria.org**

Editor's Notes

- All material in *ACRIA Update* is presented for educational and informational purposes only, and is not intended as medical advice. All decisions regarding one's personal treatment and therapy choices should be made in consultation with a physician.
- *ACRIA Update* refers to 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.

Immune-Based Therapies for HIV: A History by Richard Jefferys

The discovery of HIV in the mid-eighties led to an intensive search for therapies that might inhibit the virus's life cycle, a search that eventually produced the sixteen antiretroviral drugs that are on the market today. Finding treatments that might work by improving the function of the immune system – immune-based therapies (or IBTs) – has proven a more daunting task, mainly because the mechanisms by which HIV impairs immunity are still not fully understood. Without that understanding, IBTs have largely been shots in the dark, with some aiming to improve overall immune function (and thus prevent or delay opportunistic infections), and others attempting to specifically improve the immune response to HIV. Over the years, many approaches have been proposed and studied, sometimes to great fanfare, but all have so far failed to demonstrate any measurable health benefit. As yet, there are no IBTs approved for the treatment of HIV infection or AIDS.

Cytokines

Among the first IBTs to be studied were cytokines, the chemical messengers of the immune system. Interleukin-2 (IL-2) is the only such treatment to have progressed to the final stages of clinical trials (see article on p. 5). Many others have been investigated as possible therapies for HIV. Gamma interferon is produced by immune system cells in response to infection, and activates elements of both innate and acquired immunity. A commercial form (Actimmune) is approved for the treatment of chronic granulomatous disease, an illness characterized by increased susceptibility to bacterial and fungal infections. A pilot study conducted at Boston's Dana Farber Cancer Institute in the late eighties reported very limited improvements in people with AIDS and Kaposi's sarcoma (KS), but subsequent trials conducted by the AIDS Clinical Trials Group (ACTG) failed to show significant benefit. The toxicities reported in these studies have become the signature of many cytokine therapies: fever, chills, headaches and muscle aches.

When test tube studies suggested that the combination of gamma interferon and another cytokine, TNF-alpha, might inhibit HIV replication, a trial was quickly put together by researchers at San Francisco General Hospital. TNF-alpha is a cytokine released by macrophages and T-cells that is involved in promoting fever and inflammation. The small pilot study of eleven people, published in late 1989, reported inconsistent changes in CD4 cell counts, and the approach was not pursued further. It later became appreciated that TNF-alpha levels are in fact abnormally high in HIV infection, eliminating the rationale for trying this cytokine as an IBT.

Two other members of the interferon cytokine family have been studied in HIV. Beta interferon is naturally made by cells called fibroblasts in response to viral infection, and a synthetic version made it as far as phase II studies for the treatment of KS in the

late 1980s. The results, presented in the *Annals of Internal Medicine* in 1990 by Steven Miles and colleagues from the UCLA (University of California at Los Angeles) AIDS Center, showed evidence of disease regression or stabilization in about half of the 39 study participants. Follow-up studies of beta interferon in combination with AZT were less successful, and this IBT seems now to have quietly dropped off the map. Two commercial versions (Betaseron and Avonex) are approved for the treatment of multiple sclerosis.

Alpha interferon is a cytokine that can be defined both as an IBT and as an antiviral. Of all the interferons, alpha is the most extensively studied. Normally produced by virus-infected white blood cells, this cytokine can both directly block viral replication and shift the balance of the immune response toward a more Th1 (virus-infected cell killing) profile (see article on p. 12). Early trials conducted at the National Institutes of Health (NIH) showed that alpha interferon could reduce KS lesions in people with relatively healthy CD4 cell counts. As a result, alpha interferon was approved in 1988 for the treatment of KS in people with over 200 CD4 cells. The side effects, however, quickly became notorious. Similar to many other cytokines, alpha interferon causes flu-like symptoms that can be accompanied by bone marrow suppression and even mental disturbances such as severe depression. Despite years of study both as a single therapy and combined with antiretroviral drugs, alpha interferon has yet to prove successful as an HIV treatment. Instead, this cytokine has found use as a therapy for some cancers and chronic hepatitis B and C infections.

“...the next few years saw the entire therapeutic vaccine effort unravel in a firestorm of controversy...”

Interleukins are another family of cytokines, the above-mentioned IL-2 being the most famous. But other family members with possible therapeutic potential have been identified and evaluated in clinical trials, including IL-3, IL-4, IL-10, and IL-12. IL-3 can promote the production of multiple cell types (including red cells, granulocytes, macrophages and lymphocytes) by the bone marrow. A Harvard study in people with HIV (published in 1995) showed that IL-3 enhanced white blood cell, neutrophil and eosinophil counts without increasing viral activity. However, other bone marrow stimulants have produced more consistent results (see G-CSF and GM-CSF, below) and IL-3 has not been commercially developed.

IL-4 appears to stimulate B-cells and antibody production but may also influence CD8 T-cell responses and inhibit production of TNF-alpha. A UCLA study of IL-4 as a possible KS treatment, reported in the *Annals of Oncology* in 1997, proved unsuccessful, although a few participants experienced temporary declines in HIV viral load. The major activity of the cytokine IL-10 is to suppress antiviral T-cell responses, gamma interferon production and antigen presentation. Conversely, IL-10 can also stimulate

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B-cell responses. A small pilot study at the NIH suggested IL-10 might reduce HIV replication, but a larger trial conducted by Canadian researchers (published in the journal *AIDS* two years ago) was unable to confirm these findings, and interest in the approach has waned.

At one time, there was considerable enthusiasm about the prospects for IL-12 as an IBT. This cytokine is known to promote the development of antiviral Th1-type CD4 cell responses and enhance the activity of natural killer cells. Test tube studies have found that IL-12 can sometimes improve defective CD4 cell responses to HIV and other antigens. Research plans were dealt a severe blow in 1995 when a phase II study of IL-12 for kidney cancer was halted due to severe toxicity. One participant died and ten others were hospitalized. Oddly, the IL-12 had appeared safe in a phase I trial, and a change in dosing and schedule of administration appears to have accounted for the sudden change in side effect profile. Eventually, the green light was given by the Food and Drug Administration (FDA) for a phase I dose-escalation study in HIV infection. The results, published in 2000 by Marc Jacobson from the University of California at San Francisco (UCSF), turned out to be inconclusive. No changes in viral load or CD4 cell counts were observed, and severe toxicities emerged at the highest doses. Some increases in gamma interferon and CD8 T-cell levels were seen, and the researchers are continuing to explore the role of low IL-12 doses in modifying the immune response.

G-CSF (granulocyte colony stimulating factor) is a cytokine that stimulates production of white blood cells called granulocytes. The synthetic form is approved for the treatment of AZT-induced neutropenia (low neutrophils) in people with HIV. However, G-CSF does not appear to influence HIV directly and is thus not considered an IBT. A related cytokine, GM-CSF (granulocyte-macrophage colony stimulating factor), appears to have broader activity, and there have been several trials aimed at assessing its potential as an IBT. A recent phase III study investigated GM-CSF combined with antiretrovirals in people with less than 100 CD4 cells. No overall difference in the number of opportunistic infections was seen in those that received GM-CSF compared to placebo, but CD4 cell counts were slightly improved. People that entered the study with undetectable viral load were also more likely to stay undetectable if they received GM-CSF. Despite these hints of some positive effect, the manufacturer of GM-CSF (Immunex, which markets the drug under the trade name Leukine) has not sought FDA approval for the treatment of HIV infection.

Therapeutic Vaccines

The idea of enhancing the natural immune response to HIV through vaccination arose soon after the virus was discovered. At that time, the long asymptomatic period between HIV infection and the development of AIDS was thought to be a time of viral inactivity or “latency.” Researchers theorized that immunizing with parts of HIV (HIV antigens) might extend the time before disease progression occurred. One of these researchers was legendary polio pioneer Jonas Salk, who emerged from semi-retirement in order to develop a candidate vaccine. Salk’s approach involved an almost entire HIV virus, chemically killed and given with a vaccine-booster called an adjuvant. Strategies pursued by other researchers included subunit vaccines, which included only a por-

tion of HIV (such as the gp120 and gp160 proteins from the virus’s outer covering or envelope), and vector-based vaccines which used weakened viruses such as vaccinia (the smallpox virus) and canarypox (a bird virus) to deliver HIV proteins into the body.

Early studies of these vaccines provided some evidence that new immune responses against HIV could be triggered, but only in individuals with relatively high CD4 cell counts. A phase I trial of Salk’s vaccine was begun in 1987 by UCLA researcher Alexandra Levine and found improvements in delayed-type hypersensitivity (DTH) responses to HIV antigens in 12 of 25 individuals studied. It was also claimed by Salk that these “responders” experienced fewer opportunistic infections during follow-up. But this interpretation was complicated by the association between developing DTH and having higher CD4 cells – the individuals who responded to the vaccine may have been at lower risk for disease progression simply due to their healthier CD4 cell counts. A similarly positive spin was put on early results from studies of a gp160 protein vaccine (made by a company called MicroGenesys), in this case by army researcher Robert Redfield. At the 1990 International AIDS Conference in Amsterdam, Redfield presented data suggesting CD4 cell counts in vaccine recipients were preserved compared to a progressive decline in study participants assigned to placebo.

While these hints of promise raised hopes, the next few years saw the entire therapeutic vaccine effort unravel in a firestorm of controversy. Redfield’s data were challenged by other researchers, including independent statistics experts who analyzed his results but found they did not support the claims made in Amsterdam. As if this were not troubling enough, MicroGenesys somehow managed to secure a specific \$20 million congressional appropriation for an army phase III trial of their now-suspect gp160 product, to be led by Redfield. The AIDS community erupted and eventually managed to ensure that the money was diverted to the army’s overall AIDS research effort.

Meanwhile, Salk’s vaccine was heading for trouble of its own. Results from a phase II/III trial involving 103 participants were slated to be presented at the 1993 International AIDS Conference in Berlin, provoking immense hype and hoopla in the media. Rather than present the data during a conference session, Salk’s company – The Immune Response Corporation – foolishly decided to hold a press event instead. Conference participants without press credentials were left loitering in the corridors, while Levine presented to an audience of journalists and Wall Street analysts. The results of the trial, once known, only compounded the bad blood created by Salk’s apparent grandstanding. After a year of follow-up, there were no significant differences in CD4 cell counts between the vaccine and placebo groups. Some improvements in DTH responses were reported, and using a precursor to the viral load test, Levine claimed a slower increase in HIV DNA (as opposed to the RNA measured by current tests) levels in vaccine recipients compared to those receiving placebo. The general audience reaction, however, was disappointment tainted with anger.

Although surrounded by less controversy, the other therapeutic vaccine candidates all met similar fates. The use of vaccinia as a vaccine vector was abruptly halted when an individual with
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IL-2: Promiscuous Cytokine or Steady Date?

by Tracy Swan

Interleukin-2 (IL-2) is the immune-based therapy that has been most extensively studied in HIV. Many people continue to be intrigued by its potential, yet questions about IL-2 remain unanswered, including the most basic one – is it an effective HIV therapy? IL-2 has also been called an immune booster, an immune modulator and T-cell growth factor. A man-made form of IL-2 was first developed in the early 1980s as a treatment for certain cancers. Although IL-2 has been studied in people with HIV since the 1980s, it hasn't been approved as a treatment for HIV disease.

IL-2 is a cytokine, or chemical messenger, released by activated CD4 cells. When a CD4 cell recognizes a pathogen – an infectious agent such as a virus or bacteria – the cell becomes switched on, or activated. Activated CD4 cells send signals to other vital members of the immune system's team. These signals coordinate the body's defense against diseases. At the same time, in order to maintain the immune system's battle, activated CD4 cells begin rapidly copying themselves in a process called proliferation. IL-2 sets off the proliferative response of CD4 cells.

IL-2 also spurs production and full development of many other infection-fighting cells. These include CD8 cytotoxic lymphocytes (CTLs), also known as "killer" T-cells, which seek and destroy infected cells; B cells, which make antibody against pathogens; dendritic cells and macrophages, which process and deliver pathogens to the immune system; and natural killer cells, which can block and kill pathogens. IL-2 research in HIV has focused on its ability to raise CD4 cell counts. The potential benefits or drawbacks of IL-2's effects on these other immune system cells have received less attention.

In HIV disease, the immune system remains "switched on" until it can no longer respond effectively to pathogens. IL-2 treatment causes an increased stimulation of the immune system. We still need to learn whether this stimulation also increases the stress on the immune system.

What Have We Learned So Far?

HIV enters CD4 cells and uses them to make more HIV. HIV disease attacks the immune system by entering, damaging and destroying CD4 cells. As a result, the immune system gradually loses the ability to recognize and respond to pathogens. This is partially because a person has less CD4 cells, and partially because some of their CD4 cells don't function properly.

IL-2's ability to increase CD4 cell counts created a new avenue of research – looking at IL-2 as an immune-based therapy for HIV disease. Although IL-2 was

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found to increase the number of CD4 cells in people with HIV, studies conducted before HAART (highly active antiretroviral therapy) became available showed that IL-2 also increased the amount of HIV in people's blood. It appeared that the CD4 cells a person gained after using IL-2 either could not fight HIV or became additional targets for HIV to infect before they had a chance to recognize and respond to HIV. Prior to HAART, there was no way to effectively control HIV, so having more CD4 cells also meant having more HIV.

HAART can lower and control the amount of HIV in a person's bloodstream and provide the immune system with a chance to recover from HIV's attack. HAART alone doesn't completely fix a person's immune system of course, but HAART has made it possible to reexamine the potential benefits of IL-2. It may

be an important way to help the immune system maintain enough CD4 cells to fight HIV and opportunistic infections. However, we still need to learn whether these new CD4 cells are effective at recognizing and responding to pathogens.

Synthetic IL-2, also called aldesleukin with the brand name Proleukin, is given as an intravenous infusion (injected into the vein) or by subcutaneous injection (injected under the skin). No one is certain yet of IL-2's best dose or dosing schedule. Although the body naturally secretes IL-2, the amounts given to people as a therapeutic immune booster are much larger and can cause many side effects – debilitating flu-like symptoms, confusion, depression, and severe toxicities such as damage to the heart, liver and kidneys. Studies have used a very wide dosing range and different scheduling strategies to lessen side effects. Both subcutaneous dosing and lower doses of IL-2 seem to reduce side effects for many people. Information from ongoing and recently completed studies will help identify the lowest possible effective dose.

Meanwhile, if you're considering IL-2 as part of a treatment strategy, prepare yourself by learning as much as possible about what side effects to expect. Many people report that taking ibuprofen and an antihistamine before starting a dosing cycle reduces the side effects. Having a good relationship with your medical provider is particularly important, and talking to people who have used IL-2 can be an excellent source of information.

IL-2 Research: Different Strategies

Several ongoing studies are looking at new and different ways to use IL-2:

- As a “prop” to increase CD4 cell counts before beginning an STI, structured or strategic treatment interruption of HAART;
- Adding IL-2 to HAART in combination with a therapeutic vaccine (ALVAC) to boost HIV-specific immune responses;

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- Using HAART and IL-2 in early HIV infection, to keep the immune system from being damaged by HIV;
- Examining the effects of IL-2 with HAART in HIV+ children; and
- New formulations, including an aerosolized version, that eliminate the need for injections.

Recent Clinical Trial Results

Four recent studies have compared HAART alone to HAART plus IL-2 in people with low HIV viral loads but different CD4 counts. People in ANRS 082, also called ILSTIM, had less than 200 CD4 cells, those in ACTG 328 had between 50 and 350 CD4 cells, those in CPCRA 059 had more than 300 CD4 cells, and those in ANRS 079 had between 200 and 500 CD4 cells. Each study gave IL-2 in five-day cycles, with several weeks between cycles.

Although each study was designed differently, all four showed that people who use IL-2 with HAART gain more CD4 cells than those who use HAART alone. In CPCRA 059, for example, the average increase in CD4 cell count in the IL-2 group was 276 compared to 22 in the HAART alone group. Importantly, these studies showed no increase in HIV viral load.

The increase in CD4 counts after IL-2 differed according to what the count was before starting therapy. Overall, the higher a person's CD4 cell count when they started IL-2, the greater the increase after therapy. For example, in ANRS 079, the study of people with 200-500 CD4 cells, the average CD4 cell increase in the IL-2 group was 865. In ANRS 082, the study of people with less than 200 CD4 cells, the average increase in the IL-2 group was 65.

ACTG 328 had an intravenous (IV) IL-2 group and a subcutaneous (SQ) group. The IV IL-2 group had a larger average increase in CD4 cells (309) than the SQ group (240). However, SQ IL-2 dosing was used in the other three studies, and those results suggest that using SQ IL-2 still produces significant gains in CD4 cells. Using lower doses of SQ IL-2 and less frequent dosing cycles may increase CD4 cell counts and lessen the sometimes severe side effects associated with high-dose IV IL-2.

Open and Enrolling IL-2 Studies

Two long-term studies, SILCAAT and ESPRIT, which compare HAART alone to HAART plus IL-2 are currently open and enrolling. Unlike many short-term studies in the past, these two studies are designed to measure clinical endpoints – progression to an opportunistic infection or death – in addition to CD4s and viral load. Studies using clinical endpoints are the only way to truly judge whether the increases in CD4 counts seen with IL-2 treatment translate into a longer, healthier life. SILCAAT and ESPRIT will last for five years, so it will be a long time before we have the results from these and other IL-2 studies. Hopefully, when they have been completed, the most important questions about the role of IL-2 as a treatment for HIV disease will be answered.

Some Key Questions

While it's exciting to see that adding IL-2 to HAART can increase a person's CD4 cell count, we're still left with many questions, including how long these increases will last after a person stops taking IL-2. It is also unclear how well these CD4 cells will work. More CD4 cells don't necessarily mean better immune responses. In ANRS 082, the study of people with CD4s under 200, no difference in immune response after treatment was found between the groups. However, ANRS 079 (people with CD4s between 200 and 500) found that the IL-2 group had better immune responses than the HAART-alone group. Immune responses were tested by measuring the degree of the immune system's response to such common organisms as tetanus and candida.

Some of the people in these studies had never taken a protease inhibitor until they entered their study, while others had been on HAART, including a protease inhibitor, for six months before enrolling. What about those people who are very treatment-experienced? Or those who have no treatment options left and are looking for "rescue" therapies? These people need new treatments the most – we need studies designed to learn if they will benefit from IL-2.

Other important questions about IL-2 remain unanswered:

- Could the immune system activity produced by IL-2 treatment actually harm people with HIV?
- What is the best way to use IL-2 – combined with HAART, during treatment interruption, or with a therapeutic vaccine?
- What dose of IL-2 will be most effective and cause the least side effects?
- Who is most likely to benefit from IL-2 therapy based on age, gender, race, ethnicity, and other factors?
- When is the best time to use IL-2?

Adherence to HAART and dealing with the side effects and toxicities it produces can be difficult enough. How many people living with HIV will be able to add IL-2 while enjoying and managing their lives, including holding down a job, taking care of children, partners, other family members and friends? Will the benefit of IL-2 be worthwhile in the long run when compared to the side effects, toxicities and adjustments in quality of life?

Ultimately, we are left with the most important question – will people with HIV stay healthier longer and live longer as a result of using IL-2?

Tracy Swan has been doing various HIV-related work since 1990 and is excited to be joining ACRIA as a treatment educator.

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Wondering Aloud: Theories of One (Quasi) LTNP

by Mark Milano

Speculation abounds as to what makes a long-term non-progressor (LTNP), as do definitions of exactly what a LTNP is. Some have looked at the maintenance of HIV-specific CD4 cells, others at cytokines like IL-10 (see page 10), and still others hope to create LTNPs by using therapeutic vaccines (see page 9). In my own case, I've wondered for years if I may have stumbled on a way to slow disease progression by the use of a simple, cheap and non-intuitive treatment.

I trace my infection back to 1981 or earlier, based on frozen blood from 1984 and a CD4 count below 500 in March of 1982. Though I'm still healthy twenty years later and have never taken antiretrovirals, I don't really fit into the category of LTNPs, who have normal CD4 counts around 1,000. My CD4 count has hovered around 300 for years, and my only clear-cut symptom of HIV disease has been occasional thrush (though I do struggle to maintain my pre-HIV body-weight).

My personal theory has to do with a fortunate hospitalization in 1985. After months of flu-like symptoms and a drop in weight of thirty pounds, I was hospitalized due to extremely high calcium levels. I was finally diagnosed with sarcoidosis, an autoimmune disorder not associated with AIDS in which the immune system attacks one's own tissues. Prednisone, a corticoid steroid, cleared up my symptoms immediately. A year later I stopped the prednisone, but I eventually went back on it when my symptoms returned. The trick was moving to alternate-day dosing, which eliminated all side effects but still controlled the sarcoid.

I thought my body was controlling HIV on its own, but I was surprised to learn years later that there was some evidence the prednisone might actually be the cause of my good health. HIV chronically stimulates the immune system, causing the over-production of a number of immune system components such as immunoglobulins, tumor necrosis factor and alpha-interferon. It also increases activation of T-cells, which leads to greater HIV replication. Using immunosuppressants to dampen some of this over-stimulation has been proposed, and some small studies have shown benefits for prednisone in people with HIV, but the data is far too sketchy to suggest using this approach in clinical practice.

The National Institutes of Health (NIH) began a study in 1999 to specifically look at the benefits of prednisone in people with HIV. Unfortunately, they took the "more is bet-

ter" approach, using 40 mg a day – far too high to take on a long-term basis (I'm currently on 15 mg every other day). When pre-clinical indications of bone loss were found, the study was stopped. Since the NIH rarely re-visits failed hypotheses, we'll most likely never find the answer as to whether a drug like prednisone could be beneficial if started early in disease.

Now, my lack of progression could be due to the sarcoid itself – the theory being that the sarcoidosis is creating excess CD4 cells and HIV is killing them off, leading to a steady state. But since my sarcoid is so well-controlled by the prednisone, I don't think that's the case. One could also say that I'm just a very slow progressor, but whenever I stop the prednisone I feel far less healthy, and HIV-related symptoms like sinusitis and rash start appearing.

It bothers me that I may have chanced on an effective way to slow HIV disease, but that no one else will benefit. If low-dose prednisone actually works to slow progression, it would be the answer for people who don't have advanced HIV disease, particularly for those in developing nations who can't afford combination therapy which costs over \$10,000 a year. Prednisone is one of the cheapest drugs in the world, and a regimen of one pill every other day is feasible in even the most resource-poor settings.

Of course, the very fact that prednisone is cheap and off-patent makes it extremely difficult to find funding for the controlled studies needed to prove its benefit. And the necessary trial would be considered unethical by many, since it would need to randomize people to either prednisone or placebo, with no other antiretrovirals to mask disease progression. But with the new U.S. recommendations that treatment can be delayed until CD4 counts drop below 350, and with the British recommending people wait until 200, a trial could be designed for those with higher CD4 counts.

So here I sit, wondering if it is the prednisone that's keeping me healthy, wondering if there will ever be a way to prove it, wondering what would have happened to me if I hadn't started the drug sixteen years ago, and wondering if we aren't missing entirely different ways to control HIV disease, since almost all research focuses on antiretrovirals and not on treatments that support the immune system.

Mark Milano is a treatment educator at ACRIA and a long-time AIDS activist.

A History (continued from page 4)

AIDS developed disseminated vaccinia infection and died. Candidates using gp120, p24 and p17 components of HIV all showed some ability to trigger new immune responses in people with high CD4 cell counts, but these responses were not associated with any clear health benefit.

These failures and controversies cast a pall over therapeutic vaccine research for many years afterward. Only with the advent of HAART has the idea of boosting HIV-specific immune responses once again found favor. Even Salk's vaccine (now known as Remune) experienced something of a revival in 1998, when Fred Valentine of New York University showed it could induce new HIV-specific lymphoproliferative responses (see "Measuring Memory T-cell Responses" on p. 15) in people on HAART. This vaccine has been haunted by its history, however, and trials were recently halted when the latest financial backer – Pfizer – decided it no longer wanted to support Remune's development. The hardiest survivor has been the canarypox vector produced by Aventis-Pasteur, which is currently in therapeutic trials at the ACTG.

Immune Suppressants

At the opposite end of the spectrum from stimulating immune responses, researchers have also studied drugs that might suppress the immune system in people with HIV. The rationale is based on HIV's preference for replicating in activated, dividing CD4 cells. Certain drugs can inhibit T-cell activation and thus may be able to reduce HIV viral load by indirect means. Among the drugs that have been studied are cyclosporine (CsA), prednisone, cyclophosphamide and methotrexate. These drugs are normally used to reduce potentially harmful immune activation, which occurs in autoimmune disease (when the immune system attacks body tissue) and during transplant rejection (when the immune system attacks transplanted tissue).

CsA was first tried in 1985, when French researchers reported temporary CD4 cell count increases in six people with AIDS treated in a week-long pilot study. A group of Canadian researchers followed up on this lead, treating eight people with CsA for about two months. Results were less encouraging, and significant toxicities including pain, fatigue, loss of appetite, weight loss and progression of KS were reported. A larger study by the original French group then gave CsA to 27 asymptomatic people with HIV for about a year, and claimed to show stabilization of CD4 cell counts. However, seven participants withdrew from the study due to declining T-cell levels, and most of the remaining individuals eventually had to stop taking CsA due to severe side effects. Although these initial results were inconclusive, studies of low-dose CsA are continuing even today. ACTG 334 is evaluating the drug in people with CD4 cell counts above 500, while Swiss researchers led by Guiseppe Pantaleo are combining CsA with HAART for the treatment of acute (very recent) HIV infection.

The immune suppressant prednisone has also received attention as a possible IBT. In 1992, the same French research team that studied CsA tried prednisone in 44 people with CD4 cell counts above 200. The dose was 0.5 mg/kg of body weight for six months, followed by 0.3 mg/kg for the remainder of the year-long trial. The result was an

average CD4 cell count increase of 119 cells, but the lack of a control group caused the data to be greeted with caution. A subsequent NIH study using a higher dose was stopped before results could be analyzed and, as Mark Milano reports in this issue, interest in prednisone has faded despite lingering questions about its potential.

Two other immune suppressants, methotrexate and cyclophosphamide, underwent trials as HIV treatments in the mid-nineties. Unfortunately, neither approach produced results that were deemed worthy of publication in the scientific literature.

Thymus-Derived Therapies

Several thymus-derived substances were the subject of IBT trials from the late eighties to the mid-nineties. These included thymomodulin, thymosin alpha-1, THF (thymic humoral factor), TP-5 (thymopentin), thym-uvocal, and thymostimulin. Some were "natural" thymic extracts (taken from calves, for example), while others were made synthetically. Despite early hints that some of these products might improve CD4 cell counts, research in this area has not persisted into the HAART era. The largest trial of any of these approaches was a 352-person, placebo-controlled study of TP-5 combined with AZT. The results (eventually published in 1995) showed no clear benefit from TP-5 treatment and, like so many IBTs before them, thymus-derived therapies subsequently disappeared from the scene.

Cell-Transfer Therapies

A number of research groups have explored the potential for manipulating T-cells in the laboratory and then re-infusing them into people with HIV. The leading approach involves expanding HIV-specific CD8 T-cells in the lab and then administering them as an IBT. At least three separate studies have been completed and published since 1997. The results were fairly consistent, with some short-term reductions in HIV replication noted without obvious toxicity. One study, by Stan Riddell and Phil Greenberg from the University of Washington in Seattle, found that the infused CD8 T-cells localized at sites of HIV replication in the lymph nodes but appeared unable to sustain a prolonged antiviral effect. Advances in the understanding of immunology have now led to an appreciation that HIV-specific CD4 T-cells are required to maintain the activity of HIV-specific CD8 T-cells, perhaps explaining the limited success of these early experiments. Studies are now underway using infusions of both T-cell types, a method that has already shown success in the treatment of active CMV (cytomegalovirus) infection.

Variations on the cell transfer theme have also undergone evaluation. In one Australian trial, CD4 cells taken from individuals with early HIV infection were frozen, preserved and then re-infused later in the course of disease. Results from a 12-person pilot trial were published in 1998, demonstrating CD4 cell count increases in seven participants. Other studies have tried transferring cells between HIV- and HIV+ twins, genetically modifying transfused cells to render them resistant to HIV, or expanding the most functional-seeming T-cells from the lymph nodes of people with HIV and then re-infusing them into the same individual. Results from all of these differing approaches have been mixed, and the overall expense and impracticality of cell transfer therapies make their use-

Therapeutic Immunization: A Vaccine By Any Other Name

by Jeff Gustavson

As the smoke of hope dissipates for eradication of HIV from the human body and the limitations of antiretroviral medications become all too apparent, efforts are being renewed to examine a role for immune-based interventions to help control HIV infection and potentially reduce ongoing exposure to antiretroviral medications. One way of intervening is to take vaccines that were originally designed to prevent infection and give them to people who are already infected with HIV. Strictly speaking, this is called a therapeutic immunization.

Although other methods of stimulating the immune system are also being considered, therapeutic immunization is likely to be less expensive and more easily tolerated than other immune boosting therapies. Despite healthy skepticism of how useful they'll be, many researchers as well as HIV positive persons are enthusiastic about their promise.

Robert Redfield, M.D., Director of Clinical Research at the Institute of Human Virology in Baltimore, points out that models of therapeutic immunization in other diseases have already proven benefit. "The rabbit herpes model in the

seventies, rabies, and a post exposure mechanism for immunization against smallpox in humans all have shown efficacy in moderating the course of disease."

Dr. Redfield continues. "If you look carefully at the Hepatitis B vaccine study, published in the *New England Journal of Medicine*, several of the persons enrolled

"Could immunization allow for the use of less drugs or... more time off treatment?"

tested positive for surface antigen, indicating that they were incubating Hepatitis B; yet, after administration of the vaccine, none got intercurrent infection. There are also examples in leishmaniasis in humans as well as animal anthrax data. Do I think this will work for HIV? I would have to say yes. The only questions are what are the right anti-

gens and how best to deliver them."

This sentiment is echoed by Pat Bucy, M.D., Ph. D., an immunologist and Professor of Pathology & Medicine from the University of Alabama at Birmingham. "Will a therapeutic immunization work? I think the answer is yes – but how big an effect it will have and what fraction of the population of HIV-infected individuals will have a significant benefit from this approach needs to be worked out in clinical trials."

Jim Kahn, M.D., an Associate Professor of Medicine at University of California San Francisco Medical Center and provider of HIV care at San Francisco General Hospital, is equally optimistic. "Could a therapeutic vaccine make it a more tolerable situation for our patients? Yes, I believe an immunization could help restimulate the immune system to recognize constitutively expressive cells [cells that are making HIV proteins and are flagging themselves for destruction]."

Dr. Kahn continues. "We've spent a lot of time on some candidate vaccines and
(continued on page 11)

fulness questionable, particularly now that HAART is available.

Antibody-Based IBTs

HIV has proven particularly capable of avoiding antibody responses, rendering it resistant to traditional antibody-based vaccine approaches. Similar problems have confronted antibody-based therapeutics. Passive immunotherapy utilized antibodies taken from individuals with early, asymptomatic HIV infection as a treatment for individuals for later stage disease and AIDS. Heavily promoted by Dr. Abraham Karpas from Oxford in the United Kingdom, passive immunotherapy was tried in several trials from the late eighties onwards. Results indicated that there might be some benefit in terms of reduced incidence of opportunistic infections, but a group of French researchers reported that disease could progress rapidly once the antibody infusions were stopped. Oddly, many of the studies also noted an apparent stabilization of CD4 cell counts in the individuals *donating* the antibodies, suggesting that they may also have experienced some benefit. This observation has never been followed up on. The practical difficulties in preparing and standardizing passive immunotherapy treatment, along with the arrival of HAART, have limited its potential for further development.

Another antibody-based treatment is actually approved for the prevention of bacterial infections in children with HIV. This

preparation is called intravenous immune globulin (IVIG, trade name Gamimune) and contains a purified, concentrated mixture of antibodies. A trial in 394 children with HIV (under 13 years old) found that IVIG reduced the incidence of serious bacterial infections by 41%, leading the FDA to approve the drug for this indication in December 1993. Results from a small study in 18 adults with less than 100 CD4 cells, presented in 1997, suggested that IVIG might also reduce the rate of infections in older individuals, but the drug has never been approved for this use.

Hormonal & Herbal IBTs

The definition of an IBT can be blurry, and many different experimental therapies, including some considered "alternative," might fall into this category. DHEA is a synthetic version of a natural testosterone-related hormone that has been proposed to improve the health of the immune system. Spurred by the observation that DHEA levels progressively decline over the course of infection, dose-escalating supplementation trials were initiated in people with HIV in the late eighties. Doses up to 2,250mg daily appeared safe, but no effect on CD4 cell count was noted. Later studies produced similarly inconclusive results, lessening interest in DHEA as an IBT (although it is still a popular supplement). A company called Hollis Eden is continuing to study a DHEA-derivative (HE2000) as a possible therapy, based on its theoretical ability to improve the functionality of impaired T-cell responses.

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The Role of IL-10 in Long-Term Non-Progressors

by Sean R Hosein

After becoming HIV-positive, most people usually remain physically well for years. During this time, despite outward appearances, HIV is constantly attacking the immune system. As the damage from HIV builds up, levels of important immune cells called CD4 cells gradually decline. Eventually the body is unable to repair the damaged immune system, leading to an AIDS diagnosis. This decline in the immune system is called disease progression.

It is noteworthy that a small proportion of people have a very different response to HIV – one that is found in only about 1% of HIV positive people. Researchers have found that this minority has relatively high and stable CD4 cells, low amounts of HIV in the blood, and no symptoms of HIV-related disease for prolonged periods. These people are not taking anti-HIV therapy and are called long-term non-progressors (LTNPs).

There may be several reasons that some people with HIV become LTNPs. Some are simply lucky to be born with immune cells that are difficult for HIV to enter and infect. Others may be infected with a relatively weak form of HIV. Yet research is accumulating that suggests that a vigorous immune response against HIV may play a role in helping to keep LTNPs healthy. If this immune response could be understood, perhaps better therapies against HIV could be developed.

A possible culprit

Researchers in North America and Western Europe have been studying the way the immune systems of LTNPs and other people with HIV respond to the virus. Several teams have begun to focus on a chemical signal – or cytokine – produced by the immune system called interleukin-10 (IL-10).

In one series of experiments, researchers in Toronto have been assessing the level of IL-10 producing cells in different groups of people. As reported in the *Journal of Infectious Diseases* in November, they found that the levels were greatest in HIV positive people whose CD4 cell counts were declining and/or whose viral loads were relatively high. The group with the second greatest amount of IL-10 producing cells was people who were newly HIV positive, and LTNPs made up the group with the lowest levels. Indeed their levels were almost as low as those of HIV negative people.

As always seems to be the case with HIV, different research supports different theories. Older studies have suggested that IL-10 injections could reduce the ability of HIV to replicate, both in vitro (in the test tube), and in people. In fact, daily IL-10 injections have been studied in clinical trials, the theory being that IL-10 may inhibit viral replication by controlling other cytokines and enhancing “killer” T-cells. Unfortunately, these studies showed no benefit for people with HIV/AIDS.

Why should IL-10 levels matter?

The immune system uses IL-10 to help suppress inflammation and prevent immune responses from getting out of control. In other words, once invading bacteria, fungi, parasites or viruses have been suppressed, the immune system uses IL-10 to shut down responses that are no longer needed and that could be harmful. But too much IL-10 is not a good thing. In infections such as tuberculosis and toxoplasmosis, over-production of IL-10 appears to allow these infections to persist. Interestingly, proteins produced by HIV cause the immune system to respond by producing IL-10. It seems, therefore, that in some people with HIV, the balance between fighting an infection and suppressing immune responses against that infection is lost in favor of weakening the immune response.

What can be done?

Use of highly active antiretroviral therapy (HAART) is able to reduce the level of IL-10 producing cells in some but not all people with HIV/AIDS. To go beyond this, perhaps a different approach is needed. In November, the *Journal of Experimental Medicine* reported on research conducted at the National Institutes of Health. Mice with a severe and persistent parasitic infection were given antibodies that blocked the effect of IL-10. The researchers found that blocking IL-10's effect helped the animals overcome their infection.

By extension, it's possible that this form of anti-cytokine therapy could have an impact in people with HIV/AIDS. But this idea needs to be tested in monkeys with simian immunodeficiency virus for at least two reasons: first, to explore its potential efficacy; and second, to highlight any toxicities that might occur if it's tested in people. It may be possible that regular doses of anti-IL-10 could help shift the immune system to a state resembling that of long-term non-progressors.

Sean R Hosein is the Science & Medicine Editor at the Canadian AIDS Treatment Information Exchange (CATIE).

Therapeutic Immunizations (continued from page 9)

have learned several important lessons. Not only have antibody-based vaccines proved insufficiently protective, they have not been of benefit therapeutically. I think now is the time to concentrate on the cellular side of the immune system." Dr. Kahn is currently enrolling low-risk HIV negative people into a phase I safety trial of Merck's so-called "naked DNA" vaccine, and plans are in the works to evaluate this in HIV positive people.

Dr. Bucy elaborates on the potential for therapeutic immunizations. "What we are currently missing is an understanding of what it is that controls viral replication off therapy." A "setpoint" – a relatively flat viral load over time – has been shown to occur in most people in the absence of therapy. A sort of natural equilibrium happens.

According to Dr. Bucy, "there is no commonly accepted model as to what drives this setpoint that is achieved relatively early in infection – although widely variable between persons – yet is sustained until the CD4 count drops below 200 in end stage disease. At that time, the whole immune system begins to decompensate [fail to provide protection against common bugs like PCP], and viral load begins to rise." The setpoint phenomenon has been demonstrated in invaluable historical natural history studies of untreated persons.

"So the question remains, why did the viral burden stay at such a relatively low level? What is the mechanism? To me, there are two theoretical choices – the target cell limitation theory and the theory of immune control." The target cell limitation theory was popularized in a 1996 article with, according to Dr. Bucy, little supportive data.

This theory says that the viral "ceiling" is maintained due to the finite number of target cells that HIV has available to infect. Since activated CD4 cells are those most susceptible to infection, their number would be limited at any given time. Dr. Bucy feels that this is difficult to believe considering the enormous variation in viral load during the flat "setpoint" period among different individuals with the same CD4 count. He says, "I find this conceptually hard to swallow."

This theory doesn't pay much attention to other cells of the immune system that are

vulnerable to infection by HIV, such as macrophages. Perhaps more tellingly, it fails to fully account for the rapid increase and rise in viral burden late in infection when there is less fuel (CD4 cells) for the fire. It could be argued that the immune system is in a general state of chaos at this point, and the entire population of dwindling CD4 cells is indiscriminately activated. Nevertheless, studies of general immune suppressing agents have yet to show a true antiviral effect.

Therefore, we are left with the theory of immune control to account for the stabilization of viral load through a relatively long period of chronic infection. Dr. Bucy draws the analogy of a lawn being mowed regularly by the immune system. The grass continues to grow, but is kept in check by the immune system. This implies that if such control could be enhanced – the grass mowed to a lower height – people could perhaps go longer without the destabilizing side effects of antiretroviral chemotherapy and prolong the period of symptom-free infection.

Since antiretroviral therapy slows down viral replication – offering T-cells protective cover from infection by HIV – a vaccine could kick-start CD4 cells that are specific for HIV antigens and the CD8 "killer" T-cells, also known as cytotoxic lymphocytes (CTLs), would be primed as well.

Dr. Redfield explains. "We are left with defining the clinical goals of therapeutic immunization. In the late eighties and early nineties, our goal was mid-level and early – to modify the rate of progression. Now that we are in the era of maximal suppression, we have different goals such as the durability of suppression." In other words, could an immunization delay time to the development of drug resistance? Could immunization allow for the use of less drugs or, alternatively, time off treatment with less immune destruction?

Such worthwhile goals would seem to argue for some urgency in testing a wide variety of vaccines among the HIV infected population. One could especially imagine their utility in the developing world, with an estimated 90% of the world's 40 million infections. As Dr. Bucy points out, there is a huge number of candidate vaccines all at the same or similar stage of development. Dr. Redfield

also feels the pipeline is healthy with candidate vaccines. "Merck, GlaxoSmith-Kline and Aventis are all actively pursuing testing their vaccines therapeutically." Dr. Redfield sees the commitment of the powerhouse pharmaceutical houses as "much more positive than the early days of minimally financed biotech companies."

Nevertheless, the path to FDA approval of a candidate vaccine for treatment is a little less clear since Pfizer recently abandoned its Remune trials. Upwards of \$100 million had already been spent on Remune, the "Salk" HIV vaccine; yet, as published by Jim Kahn from UCSF and Steve Lagakos from Harvard in the *Journal of the American Medical Association*, it had failed to show clinical benefit.

Dr. Bucy laments the current pace. "Slow is costly. For every year that things are not done, hundreds of thousands of lives are lost in the balance. In the scheme of things at this stage of the HIV pandemic, I think the lost opportunity cost has to be factored into decisions about testing such agents in humans."

Unfortunately, studies are often designed that are burdensome to the participant who is relatively healthy – high CD4 counts and maximally suppressed virus. Dr. Bucy says, "Potential trial participants have to balance possible benefit, still theoretical, with issues of time spent coming to the clinic. I can't say I blame them, but as a consequence progress is not being made".

Likely, the buzz behind some of the newer agents will make enrollment much more robust. Two new approaches are Merck's "naked DNA" vaccine and the Tat toxoid vaccine. Merck's vaccine, being tested as both a preventive and therapeutic vaccine, consists of genes extracted from HIV; the hope is that it may be better able to counteract the random changes in different HIV strains. The Tat toxoid vaccine, licensed from Aventis by the Institute of Human Virology in Baltimore, is a slightly modified version of HIV's Tat protein and has been shown to produce anti-Tat antibodies in early studies. The community as a whole could only benefit if its members enroll in these trials.

Jeff Gustavson is an HIV and HCV positive activist who lives and swims in San Francisco.

The Immune System: Behind the Scenes

by Richard Jefferys

The human immune system is a dazzlingly complicated mix of many different cells, tissues and chemical factors that work together to try to maintain health. The immune system has evolved over billions of years to accomplish a multitude of tasks, including responding to infections but also tolerating substances – like pollen and food ingredients – that pose no danger to the body. The system, as we know, is not perfect. Allergies represent a potentially dangerous overreaction to things that are ordinarily harmless, while weak or ineffective responses to harmful infections can lead to disease. The mounting of an immune response can be thought of as a major production, involving a vast cast of characters and a rough script to guide communications between them. The production often progresses seamlessly, but at other times, missed cues and forgotten lines may spell disaster.

Curtain Up

The immune system can be broken down into various divisions that help make the complexity understandable. *Innate* immunity is the first line of defense, encompassing a variety of cells and substances (including neutrophils, basophils, natural killer cells, macrophages and complement) that respond to infections in a non-specific way due to an ability to recognize certain common features of bacteria or other infectious agents. Due to their role as barriers to the outside world, the skin and the linings of the respiratory, intestinal, urinary and reproductive tracts are key sites of innate immune activity. Many smaller creatures (non-vertebrates like insects and worms) rely on innate immunity alone to protect them from disease.

Acquired (or *adaptive*) immunity is a more advanced add-on (major players are dendritic cells, macrophages, T-cells, B-cells and antibodies) that allows recognition of specific infectious agents and, most importantly, allows the immune system to “remember” a prior infection and prevent it from occurring again. Some cells, such as macrophages, fall into both innate and acquired categories

because they can act as links between the two systems.

The important capacity for retaining “memory” of infections resides in T-cells and B-cells. Your body maintains two vast pools (of several billion cells apiece) of T-cells and B-cells. One pool is made up of naïve or rookie cells that have not yet responded to any infection but are on the look out for any new infectious invaders. The second pool is made up of memory or experienced cells that developed in response to a previous infection and are ready in case that same infection shows up again.

Immunity’s Stage

Immune system cells can travel with relative freedom around the body, but certain locations are vital to immune activity. The bone marrow is the source of all immune system cells, but T-cells must also travel through a specialized organ called the thymus, located just behind the breastbone, before they enter the circulation. The lymphatic system is an immunological highway around the body that is separate from the blood and used only by immune system cells. Critical command centers along the way are called the secondary lymphoid organs. These include the spleen, an organ located in the abdominal region, lymph nodes, such as those under the ears, under the arms, and in the groin, and mucosal lymphoid tissue, such as areas in the gut known as Peyer’s Patches. Much of the communication between the players of the acquired immune system takes place in these secondary lymphoid organs.

Immunity’s Script *Cytokines and Chemokines*

Immune system cells can send messages by releasing substances known as cytokines and chemokines. Many of these substances have been identified and grouped into categories including interleukins, interferons and alpha- and beta-chemokines. The ability of a cell to respond to a particular cytokine or chemokine depends on whether a matching “receptor” or docking bay is dis-

played on the cell’s surface. For example, interleukin-2 (IL-2) is a well-known cytokine that can send a message to T-cells telling them to copy themselves (see article on p. 5). In order to receive this message, the T-cell must be displaying its interleukin-2 receptor (IL-2R), which binds to the IL-2 and delivers the cytokine’s message to the genetic machinery inside the cell.

Chemokines can attract cells that display appropriate receptors to specific locations within the body, acting as a type of guidance system. An ongoing immune response to an infection can be thought of as a very noisy time, with many different cytokine and chemokine messages being sent and “heard” by many different immune system cells. How well an infection is controlled can be influenced by the levels of particular cytokines or chemokines. Our understanding of this system of cellular communication has led researchers to test some of these substances as therapies (see article on p. 3).

Immunity’s Actors

Granulocytes

Granulocytes are a family of white blood cells involved in innate immunity. They’re produced in large numbers by the bone marrow but live only 2-3 days. The majority are neutrophils, whose job is to engulf and eat up dangerous bacteria in a process called phagocytosis. Low levels of neutrophils (called neutropenia) can lead to increased susceptibility to bacterial infection. Eosinophils represent a smaller proportion of granulocytes. They are also capable of phagocytosis, but their main job is releasing substances that damage parasitic infections such as worms. Eosinophils can also participate in allergic reactions, where their overabundance is called eosinophilia. Basophils and mast cells make up the remainder of the granulocyte population. These two very similar populations of cells can release substances that make it easier for cells and fluids to pass through the walls of blood vessels. This process can improve access to the site of an immune response, but can also lead to fluid build-

up (edema) and swelling, as can occur during allergic reactions.

Mononuclear Phagocytes

This grouping of cells plays a role in both the innate and acquired immune systems. They are capable of engulfing and digesting harmful organisms (phagocytosis). These cells have various names, depending on where they reside in the body and the specific functions they perform. They all start out in the bone marrow as monocytes – literally, “single cells” – but undergo a maturation process as they migrate to specific tissues. Macrophages are a type of grown-up monocyte that can scavenge for infectious invaders, surrounding and then digesting them. Under certain conditions, macrophages can also display fragments of infectious organisms (called antigens) on their surface where they can be seen by passing T-cells. This function is called antigen presentation. If T-cells recognize the antigen, the acquired immune system may be called into action.

Dendritic Cells

Dendritic cells (DCs) specialize in antigen presentation. These cells are the most effective kick-starters of the acquired immune response and are often called “professional” antigen-presenting cells for this reason. The skin and mucosal linings in the gut, vagina, mouth and nose, for example, are packed with DCs. Their role is to act as lookouts at the body’s exposed surfaces, where infectious organisms are likely to enter. DCs absorb infectious organisms, digest them into small fragments and then present these fragments as antigens on the DC surface. This process is accompanied by a migration of the DC to the secondary lymphoid organs, where passing T-cells are better able to take a look at the antigen being presented.

In an inhaled viral infection like influenza, for example, thousands of DCs will pick up virus as it enters the body through the nasal or oral passages. These DCs will process the flu virus into fragments, travel to the lymph nodes and display the flu fragments as antigens to patrolling T-cells. DCs and other antigen-presenting cells also interact with responding T-cells in other ways. Signals are exchanged through “co-stimulatory” molecules on

the DC and T-cell surfaces, and these signals can boost or limit the immune response. Cytokines released by DCs may enhance the survival of certain T-cells over others. Recent studies have revealed that DCs can play a critical role as middlemen, passing messages between CD4 and CD8 T-cells.

Natural Killer Cells

Natural killer (NK) cells are lymphocytes with the ability to destroy a limited range of virus-infected or cancerous cells. They can also be triggered to kill cells coated with antibodies. NK cells are part of the innate immune system and do not remember past infections.

“...an immune response can be... a major production that progresses seamlessly, but missed cues and forgotten lines may spell disaster.”

Complement

The complement system comprises a group of more than 30 different proteins that play a role in the immune response. These proteins normally circulate around the body in an inactive or “precursor” form. During an infection, complement proteins are broken down into active fragments that can perform a variety of functions, including: signaling to immune system cells (e.g. recruiting them to particular sites in the body), enhancing phagocytosis, direct killing of some pathogens, and amplifying T-cell responses.

T-Cells

One part or “arm” of the acquired immune system is referred to as cellular and comprises the T-lymphocytes, or T-cells. There are different families of T-cells that perform specific functions, and these T-cells are identified by markers on the cell’s surface. Most familiar are the CD4

“helper” T-cells, which typically act as both coordinators (hence the name helper) and participants during immune responses. Important partners are the CD8 T-cells, which include cytotoxic T-lymphocytes (CTLs), also known as “killer” T-cells. The major role of CTLs is to eliminate cells in the body that are harboring infectious agents. The majority (>80%) of the body’s T-cells are either CD4 or CD8, with the ratio normally around two to one in favor of CD4 T-cells. Most of the remaining T-cells belong to a small subset called gamma-delta T-cells whose precise function is not yet well understood.

T-cells “recognize” specific antigens from the flu to HIV using a docking bay structure on their surface called a T-cell receptor (TCR). Antigens that dock snugly with the TCR can trigger the T-cell to mount an immune response. Any given infection is usually recognized by several thousand T-cells. The first encounter with a new infectious agent must be dealt with by naïve or rookie T-cells. During this initial encounter, the naïve T-cells copy themselves and acquire the ability to perform key infection-fighting functions such as cell-killing and cytokine production. After the infection is controlled or eliminated, some of these highly skilled T-cells are retained as memory cells. Each infection you’re exposed to (like measles and chickenpox) triggers the development of a team of memory T-cells whose job is to prevent the disease from recurring.

New technologies are allowing memory T-cell teams to be broken down even further. It’s now known that each team is made up of T-cells with a variety of skills and functions. These include CD4 T-cells that make the cytokine interferon-gamma, which seem to work alongside CD8 T-cells and help them maintain their ability to kill infected cells in the body. These CD4 T-cells are called type 1 or Th1 helper cells. Other CD4 T-cells produce different cytokines such as IL-4 and work alongside B-cells, assisting in the production of antibodies. These are called type 2 or Th2 helper cells. Some CD4 T-cells make the cytokine IL-10 and seem to play a role in dampening down the immune response.

(continued on page 18)

Immune Restoration: Repairing the Damage

by Richard Jefferys

The ability of Highly Active AntiRetroviral Therapy (HAART) to suppress HIV replication, increase CD4 cell counts in the blood, and prevent or delay opportunistic infections is now well documented. Individual responses can vary, toxicities remain a problem and the best time to start HAART continues to be debated, but the overall trend of restored immunity and prevention of illness has come as a welcome surprise. Many researchers feared that the damage to the immune system caused by HIV would be irreversible, but HAART studies have contradicted this assumption. These studies paint a picture of immune restoration occurring in multiple phases – some fast and others slow and variable – ultimately leading to near-normal immune system function in many individuals. Research into immune restoration also provides a new opportunity to understand the mechanisms by which HIV damages the immune system, a necessary step for designing therapies that might speed immune recovery or help people whose immunity remains impaired despite HAART.

Assessing the Damage

HIV infection progressively impairs the immune system in several important ways. The pool of naïve T-cells (both CD4 and CD8) needed to mount responses to new infections slowly declines, making it harder for people with advanced disease to respond to vaccinations or new infectious challenges. At the same time, the teams of memory CD4 cells specific for common infections – such as pneumocystis carinii pneumonia (PCP), toxoplasmosis, thrush, mycobacterium avium complex (MAC), and cytomegalovirus (CMV) – are reduced in number. Eventually, the ability of these memory cells to police their respective pathogens is lost, leading to the illnesses known as opportunistic infections (OIs).

One marker for this process is the CD4 cell count. This routine test gives you the number of CD4 cells in a milliliter of blood. Declining counts are linked to an increasing threat of illness – especially when specific thresholds are crossed. Studies have found that a drop below 200 CD4 cells is the most significant risk factor for the development of OIs.

Along with the fall in numbers, there are profound changes in CD4 cell function, first revealed in the late 1980's by immunologist Gene Shearer and colleagues at the National Institutes of Health. Shearer demonstrated what can best be described as a spreading dysfunction among CD4 cells over the course of HIV infection. First to be impacted are memory CD4 cell responses to specific common antigens (pieces of infectious agent, from infections like influenza virus), which decline to below-normal levels early on. But eventually the CD4 cell population as a whole is affected. Due to the central coordinating role played by CD4 cells, this loss of function is almost inevitably accompanied by defects in B-cell and CD8 cell responses.

“This slow gain of naïve T-cells can continue for... years, until normal or near-normal levels are attained.”

The pace of immune system impairment is known to be linked to the level of HIV replication (the viral load) and the degree of abnormal immune activation. One of the great mysteries of HIV infection is that it both suppresses immune function and also hyper-activates some immune system cells. The late Janis Giorgi from the University of California at Los Angeles pioneered this area of research, showing that certain markers of T-cell activation (particularly surface molecules called HLA-DR and CD38) actually increase as HIV infection progresses.

HAART & CD4 Cell Numbers

One of the first detailed investigations of HAART's effect on the immune system was published by Parisian immunologist Brigitte Autran and colleagues in 1997. Autran described a two-phase process of immune reconstitution that many other researchers have since confirmed. The

first phase involves a rapid rise in CD4 cell counts of 100 and more during the first two months of therapy as HIV viral load is reduced. Autran showed that these are almost all memory CD4 cells (which can be distinguished from naïve cells by specific markers on their surface). Autran's theory – subsequently confirmed in a detailed analysis conducted by Pat Bucy from the University of Alabama – was that this initial gain reflected redistribution of memory CD4 cells that had been trapped in the lymphoid organs. The speed and extent of this early CD4 cell recovery is linked to the rate of CD4 cell loss during the year before HAART is started – the more rapid the loss, the more rapid the recovery. Factors such as age or how quickly viral load drops do not seem to have much influence on the first phase of immune restoration. Autran also noted that the improvement in absolute CD4 cell counts is accompanied by an increase in the CD4 percentage and normalization of the CD4:CD8 ratio, because the number and percent of memory CD8 cells drops as CD4 cell numbers rise.

The second phase of immune restoration described by Autran comprised a much slower but steady increase in naïve T-cells (both CD4 and CD8) that became detectable about four months after HAART was initiated. This increase continued during a year of follow-up. Longer-term studies have since shown that this slow gain of naïve T-cells can continue for a period of years, until normal or near-normal levels are attained. The source of these naïve T-cells has since been shown to be the thymus, an organ that was once thought to be inactive in adulthood. A young English researcher based in Texas, Danny Douek, overturned this assumption using a test that can identify naïve T-cells that have recently left the thymus. The test looks for TREC (T-cell Receptor Excision Circles), which are small pieces of DNA present almost exclusively in newly-made naïve T-cells.

In a search for factors that influence naïve T-cell increases, immunologist Mike Lederman from Case Western University in Cleveland, Ohio discovered that the pace of naïve T-cell recovery correlated

with age, with younger people gaining naïve cells fastest. In children, the effect is most dramatic – the rate of naïve T-cell recovery is 10-40 times faster than that of adults. This finding is consistent with Douek's recent TREC research showing that the thymus is most active in childhood, but then decreases production of naïve T-cells to a steady (but gradually slowing) daily output that continues into old age.

Memory CD4 Cell Function

Brigitte Autran also looked for evidence of improved memory CD4 cell function in people taking HAART. Memory responses to CMV and tuberculosis (TB) antigens were measured using lymphoproliferation tests (see sidebar). Before therapy, when the average CD4 cell count was 176, study participants showed no response to either antigen. Within three months of starting HAART, significant responses to both TB and CMV became detectable. Since this initial study in 1997, many other reports have confirmed improvements in antigen-specific T-cell responses, some using newer testing technologies. Additional antigens that have been studied include influenza, candida (the fungus that causes thrush) and tetanus. The one exception to this rule appears to be HIV. Responses to HIV antigens can sometimes be detected before starting HAART, but do not improve after beginning therapy. In fact, the reduction in HIV levels caused by HAART seems to cause a decline in HIV-specific T-cells.

Improvements in immune function after HAART can also be assessed more indirectly. Large, widely-publicized cohort studies involving thousands of people have demonstrated that HAART dramatically reduces the occurrence of OIs. Evidence that is even more persuasive comes from studies in which preventive treatments (prophylaxis) for OIs were successfully stopped if HAART boosted CD4 cell counts above certain thresholds. Even treatments for active OIs can sometimes be discontinued without recurrence of disease, a situation unimaginable just a few years ago. *

Naïve CD4 Cell Function

Although HIV does not appear to directly impair the function of naïve CD4 cells, the decline in overall numbers that

Measuring Memory T-cell Responses

These are some of the tests used to measure memory T-cell responses. While the presence of memory T-cells specific for a particular infection (e.g. CMV) is often associated with protection from illness, this is not always the case. Researchers are still working to understand which tests can provide the most accurate measure of protection against a given disease.

Delayed-Type Hypersensitivity (DTH): A test that introduces the antigen into a patch of skin on the arm. Swelling typically reflects the presence of a memory response to that particular antigen (as is seen with the TB skin test). DTH has been used for decades but is not very sensitive or easy to standardize – measuring the swelling only provides a very rough gauge of the strength of the memory response.

Lymphoproliferative Response (LPR, proliferative response): A laboratory test that measures the ability of memory T-cells (almost always CD4 cells) to copy themselves (proliferate) when exposed to a given antigen. Newly-made cells are counted using a specially-labeled DNA ingredient called thymidine which is incorporated into the new cells during the copying process. The test takes six days to produce a read-out and can be difficult to analyze. Results are usually given as a "stimulation index," which subtracts background proliferation (the number of cells that copied themselves without being stimulated with any antigen).

ELISpot (Enzyme-Linked ImmunoSpot): A lab test that measures the ability of memory T-cells (CD4, CD8, or both) to make cytokines when exposed to a given antigen. T-cells are first exposed to antigen, then 6-24 hours later antibodies that bind to a specific cytokine (most often interferon-gamma, but others such as IL-2 or IL-10 can also be tested for) are introduced. The cells are chemically treated so that any antibodies bound to cytokine-producing cells are stained blue and can be counted. They're called "spot-forming cells" or SFC for short. As with background proliferation, background cytokine production can be a problem and must be subtracted to get an idea of how many T-cells were specifically responding to the antigen.

Intracellular Cytokine Staining (ICS): Another lab test that measures the ability of memory T-cells (CD4, CD8 or both) to make cytokines when exposed to a given antigen. Unlike ELISpot, this test employs a substance that traps the cytokine within the T-cell. This allows the precise type of T-cell that is making a given cytokine to be more easily identified.

occurs during infection is associated with a poor response to vaccinations. This led Mike Lederman's research team to investigate whether HAART-related recovery of naïve CD4 cells improved people's ability to respond to new immunizations. Lederman found that three-quarters of HAART-treated participants developed antibodies to the hepatitis A vaccine, and

that the magnitude of these responses was indeed linked to increases in the number of naïve CD4 cells. Similarly, Dutch researchers have shown that HAART is associated with a greatly improved response to influenza vaccines in adults. Extending these findings to children, a recent study from the University of
(continued next page)

* The new United States Public Health Service (USPHS) guidelines on preventing OIs, updated in November, include specific criteria for stopping prophylaxis for PCP, MAC and toxoplasmosis. The USPHS guidelines also describe circumstances under which treatment for active MAC, toxoplasmosis, cryptococcal meningitis and CMV might safely be stopped. The guidelines are available on the Internet at <http://www.hivatis.org/guidelines/other/OIs/OIGNov27.pdf>.

Immune Restoration Disease

In some uncommon cases, an increase in CD4 cell count from very low levels (less than 100) can be associated with unusual flare-ups of infections. This phenomenon has been called “immune restoration disease” and appears to relate to the development of new immune responses against the particular pathogen (reported examples include mycobacterium avium complex [MAC], CMV, hepatitis B & C, tuberculosis and herpes zoster). A detailed report on immune restoration diseases by Australian doctor Martyn French is on the internet - a link is contained in the web version of this article at: www.acria.org.

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Washington in Seattle found that HIV-infected children on HAART experienced significantly better responses to the MMR (measles-mumps-rubella) vaccine than children who were untreated.

Calming Immune Activation

The improvements in immune function associated with HAART appear to occur in parallel with a decline in abnormal immune activation. Brigitte Autran’s study measured levels of the T-cell activation markers HLA-DR and CD38 and found they fell steadily, reaching normal or near-normal levels after a year of treatment. The researchers also discovered a strong correlation between these markers and HIV viral load levels. Subsequent research has confirmed these findings, with Israeli scientist Zvi Bentwich going so far as to suggest that changes in markers of immune activation are better at predicting immune restoration than viral load.

Persistent Defects, Paradoxical Responses

Both the effects of HIV infection and responses to HAART treatment vary from individual to individual. The overall trends seen in studies of immune restoration are not experienced by everyone, and cases of increased CD4 cell counts but

persistent defects in responses to certain antigens have been reported. For example, Krishna Komanduri from the Gladstone Institute in San Francisco used the intracellular cytokine staining test to look for memory CD4 cell responses to CMV and found they were generally restored after HAART. But recent work by Komanduri has also shown that, despite CD4 cell count increases to over 400, a very few individuals may show persistent defects in CMV-specific responses and develop CMV disease as a result. Fred Valentine from New York University has reported a similar case of persistent defects in PCP-specific CD4 cell responses despite a high CD4 count. This was also associated with the development of disease. Although rare, such cases suggest that individualized monitoring of antigen-specific responses might eventually help provide better guidance for OI prophylaxis than CD4 cell counts alone. So far, most T-cell function tests are only available in research settings.

Studies have also documented so-called “paradoxical” effects of HAART. Around 10% of people taking HAART experience ongoing CD4 cell count increases despite only temporary reductions in viral load. A number of theories have been put forward

to explain this phenomenon, such as drug-resistant HIV potentially being less harmful to T-cells and/or the thymus. Another possibility is that a brief reduction in viral load can be sufficient to cause a major redistribution of T-cells from the lymphoid organs. Some researchers have found that this type of paradoxical response is associated with a decrease in immune activation markers that persists after viral load has risen. At the other extreme, perhaps 5% of people on HAART experience sustained reductions in viral load but only minor increases in CD4 cells. Recent studies utilizing the TREC test have found that this problem may relate to a lack of production of naïve T-cells by the thymus.

The Road Ahead

It’s now clear that suppression of HIV replication can allow a phoenix-like reconstitution of the immune system in many people. Researchers are not resting on their laurels, however, but working on new strategies that may help correct remaining defects and aid people who do not experience an ideal response to HAART. Individualized monitoring of antigen-specific memory CD4 cell responses may already be on the horizon. Speeding up the process of naïve T-cell recovery is another highly desirable goal, although it’s currently unclear if the activity of the thymus can be increased by any therapy. Interleukin-2 is being studied for its potential to increase overall CD4 cell numbers by stimulating existing cells to copy themselves. The ultimate aim of many immunologists is to find ways of creating vigorous, functional HIV-specific memory CD4 cell responses, since HAART alone cannot accomplish this task. ■

A History *(continued from page 9)*

Various Chinese herbal compounds have also been described as immune boosters, but have never been thoroughly studied. In many cases, these compounds contain immune stimulants known as polysaccharides which might theoretically promote HIV replication (by causing immune activation) rather than help block it. The herb echinacea is one such example, since it appears to increase levels of the inflammation-associated cytokine TNF-alpha. While most doctors feel that short-term use of herbs like echinacea (e.g. to treat a cold) is unlikely to

be harmful, these types of broad immune stimulants are no longer being pursued as IBTs for HIV infection.

Will There Ever Be An IBT for HIV?

Despite this litany of failure and uncertainty, the success of HAART has refocused attention on IBTs as the “final frontier” for HIV research. As Tracy Swan reports, IL-2 is in its final phase of testing and might conceivably be approved within the next few years. New cytokines and chemokines are constantly being discovered and investigated for their potential as IBTs, including IL-15, IL-16 and IL-18. Several major

pharmaceutical companies have recently announced active therapeutic vaccine programs for HIV, including Merck and GlaxoSmithKline (see Jeff Gustavson’s article on p. 9). Unlike historical efforts, the latest IBT research is being informed by rapidly accumulating breakthroughs in the scientific understanding of the human immune system. Many researchers are confident the era of shots in the dark is over, and it’s only a matter of time before an IBT finally hits the target.

Richard Jefferys is Basic Science Project Director with Treatment Action Group.

Whatever Happened To Structured Treatment Interruptions?

by Matt Sharp

It seems like only yesterday that newsletters and web sites were filled to the brim with research reports about structured treatment interruptions (STIs). These reports on “drug holidays,” once full of hope and zeal, now appear scattered and rather lackluster – a possible indication that STIs are a trend of the past, a high-minded theory that failed to pan out in clinical trials.

Fortunately, this isn't the case. STIs, with their potential to boost the immune response to HIV, are still being examined in clinical trials, although fewer studies are now being conducted. The reason for this is simple – we now have a better sense of which HIV-positive people are most likely to benefit from STIs, along with those who are least likely to benefit. This understanding has led to a more concentrated effort to make sense of these risky treatment options.

STIs in Acute Infection

The potential for STIs during acute HIV infection cannot be overstated in light of legitimate concerns regarding long-term use of antiviral therapies, including toxicities and the possibility of developing drug resistance – all before treatment is actually needed for the sake of health and survival. Acute infection is loosely defined as the days and weeks that immediately follow HIV's entry into the body. Although studies of STIs in chronic infection show less favorable results, research involving acute infection should continue given recent successes, most notably in a handful of patients receiving care at Massachusetts General Hospital (MGH) in Boston.

Past work at MGH, under the direction of Drs. Bruce Walker and Eric Rosenberg, has shown optimistic results and has led the field in the study of STIs in primary infection. The determination that STIs would work better in acute infection was borne out in early studies looking at HIV-specific cytotoxic lymphocyte (CTL) responses in long-term non-progressors (LTNPs) – the small percentage of HIV-positive people who live for many years

with low viral loads and high CD4 cell counts without the assistance of drug therapy – compared to chronically infected people who see their viral loads increase and their CD4 cell counts decrease in the absence of therapy. In LTNPs, CTL responses are maintained long after HIV infection is established. Conversely, in chronically infected individuals, the CTL response dwindles shortly after infection is established. Protecting these CTL responses, Drs. Walker and Rosenberg argue, is the key to keeping viral load low and CD4 cells high, perhaps indefinitely, without the need for long-term treatment – a highly desirable scenario.

“...do chronically infected people have a chance at auto-immunization?”

The theory behind STIs is to stop treatment at a stage when the CTLs are still in place doing their job. Then, with further interruptions, an auto-immunization may occur with stimulation of the CTLs along with periods of therapy to help keep virus at extremely low levels, hopefully for good. And each time the interruptions occur, the viral load hopefully will become lower for longer periods of time.

The latest information comes from a study by Walker's team looking at 14 people who were HIV antibody-negative but had high HIV viral loads. In other words, HIV was reproducing rapidly in their bodies, but they hadn't yet developed HIV antibodies. All of the participants began treatment prior to, or at the time of, HIV seroconversion and had been on triple-drug therapy for at least eight months before their first STI. The plan was to restart treatment if their viral load exceeded 5,000 copies for three consecutive weeks or if viral load exceeded

50,000 copies at any one time.

During the first 17 days of the first treatment interruption, all participants had increased virus levels, but four people soon saw their levels fall below 5,000 copies. All four have remained off therapy, two of them for two years with viral loads staying below 500. The MGH team noted in a conversation with *ACRIA Update* that, compared to the first STI, the majority of participants experienced a much slower rebound in viral load during the second STI that would require them to restart therapy. Seven of the fourteen patients have maintained virologic control off therapy following one, two or three STIs. None of the participants who had to restart treatment has had any trouble reducing their viral loads to undetectable levels after any of the interruptions. Although this study is certainly small, it showed that STIs were effective in 50% of the participants – impressive results in an elegant study that shows promise for auto-immunization.

STIs in Chronic Infection

Is there a chance that chronically infected people – defined as anybody who has been living with HIV for longer than six months and/or has HIV antibodies detectable in his or her bloodstream – have a chance at auto-immunization? Unfortunately, the results from small studies in the past have been all over the map in terms of showing the effectiveness of STIs in this population. Remember, HIV-specific CD4 cells are typically destroyed by HIV soon after infection is established. There aren't many of these cells left to protect if therapy isn't started immediately. Still, some researchers believe that STIs can “draw out” those HIV-specific CD4 cells that do remain and, consequently, make them work effectively.

Unfortunately, the largest STI study to date has shown disappointing results in the chronically infected. The Swiss-Spanish Intermittent Treatment Trial (SSITT) now has one year data on 133 patients. These data show that STI may

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not be a useful strategy for auto-immunization, at least at this stage of infection. Participants in the trial were a relatively healthy bunch to begin with. Before starting antiretroviral therapy, the average viral load was just over 31,000 and the average CD4 count was 388. Participants had been taking HAART for an average of 26 months before their first STI and had undetectable viral loads for approximately 21 of those months. The average CD4 cell count before stopping therapy was 740.

All of the participants completed four STI cycles of eight weeks on treatment, followed by two weeks off. After 40 weeks, treatment would be stopped through week 52, at which time it would be determined how many patients had viral loads below 5,000 copies and, as a result, be able to delay going back on treatment.

The relative viral load rebounds seen during each of the four interruptions were not statistically significant, although higher viral loads were seen to decrease with each successive STI. If virus levels did not go to undetectable within nine weeks of reinitiating therapy following an inter-

ruption, participants were removed from the study. Ten were removed after the first interruption, nine after the second, five after the third, and six after the fourth.

Of the 99 participants who had completed all four interruptions as of February 2001, 21 were responders, maintaining viral loads below 5,000 copies. However, five of those responders had viral loads below 5,000 copies before beginning therapy in the first place. So if you subtract those five from the 21 responders, you get an unimpressive 17% overall favorable response. Participants, both responders and non-responders, lost an average of 150 CD4 cells throughout the trial – not a good thing! These data basically show the failure of STIs in chronically infected individuals. A bit of good news, though: only one participant showed evidence of mutations that would translate into drug resistance as a result of the STI strategy.

The SSITT study showed that people with low viral loads before starting HAART were more likely to respond to the STI strategy. Whether they may have maintained low viral loads without STIs – or

even without treatment – is impossible to tell. More STI studies in chronic infection – perhaps with immune modulators such as IL-2 or a therapeutic vaccine – might provide better results. The SSITT study may also help show that STIs could be useful as a simplification strategy by limiting the amount of time on drugs. If virus levels can be maintained using an intermittent strategy – continuing interruptions for an undetermined time – some of the toxicities associated with antiviral therapy might be prevented or delayed. And the exorbitant cost of therapy could be dramatically lowered.

Researchers stress that STIs in acute and chronic populations are not ready for prime time and should only be used in clinical trial settings. As a treatment strategy, STIs continue to have potential, particularly in acute infection, but they also carry considerable risk. The STI story is far from over.

Matt Sharp has been living with AIDS for ten years. Now living in Chicago, he is an AIDS treatment activist with Survive AIDS (formerly ACT UP Golden Gate) and the Coalition for Salvage Therapy.

The Immune System

(continued from page 13)

Both CD4 and CD8 T-cells can make chemokines with odd names like MIP-1 alpha, MIP-1 beta and RANTES that can inhibit the replication of some infectious organisms, including HIV. CD8 T-cells are able to kill infected cells by making specialized cell-destroying substances called granzymes and perforin. This complexity among each team of memory T-cells is, without doubt, confusing. It becomes important because the balance between different functions can determine how well an infection is controlled. Some immune-based therapies are designed to change the balance between responses – boosting the number of Th1 vs. Th2 CD4 T-cells, for example.

B-cells & Antibodies

The other arm of the acquired immune

system is referred to as humoral and involves B-lymphocytes or B-cells. The main role of B-cells is to act as factories for the manufacture of antibodies. Antibodies are small protein fragments that can bind to foreign material (such as parts of infectious agents) and interrupt their life cycle and/or mark them for elimination from the body.

Like T-cells, B-cells have a receptor (a BCR) that allows recognition of antigens. They undergo a similar transition from naïve to memory during the first encounter with an infection. In this case, the enhanced talent of memory B-cells is that they make antibodies that are more effective. Antibodies fall into different subclasses: IgM antibodies are made early in an immune response, but memory B-cells switch to making IgG antibodies that bind to their target more efficiently. Some B-cells, mainly those in the

mucosal areas, make antibodies of a class called IgA. Most of the time, antibody production by B-cells requires signals from CD4 T-cells specific for the same antigen. Tests can look for the presence of antibodies to specific infections, allowing doctors to know which common infections people have been exposed to in the past.

The Finale

The interaction between the players of the immune system and infections ultimately determines our health. Scientists are gaining a better understanding of what goes on behind the scenes during the production of an immune response, but many mysteries remain. Further progress in this field of research – immunology – promises to inform the design of new and improved immune-based therapies for HIV and other hard-to-treat diseases. ■

ACRIA begins study of new protease inhibitor

ACRIA recently began enrolling a Phase III trial of a new protease inhibitor in development by Bristol-Myers Squibb Virology called atazanavir. This study is looking at which of two protease inhibitors – atazanavir or FDA-approved Viracept (nelfinavir) – shows superior outcomes in patients whose current anti-retroviral regimens are failing them. Although study participants can be on HIV medications when they enroll, this trial is only open to individuals who have had very limited prior use of a protease inhibitor. Bristol-Myers Squibb Virology is currently conducting two other studies of atazanavir to address treatment failure, which allow patients to have used protease inhibitors in the past. For more information on these alternative trials, please call 1-888-847-6794.

ACRIA welcomes new staff members

Carlos Santiago has joined ACRIA as our newest HIV Treatment Educator. Mr. Santiago will be working on all of our HIV Treatment Education Program services for people living with HIV and AIDS (PLWAs) in New York City, with special emphasis on working with Spanish speaking clients. He comes to us with significant experience assisting underserved populations in gaining stability and improved quality of life. Immediately prior to joining ACRIA, Mr. Santiago was a case manager at the Exodus Transitional Community where he helped ex-offenders access a full array of services. He received his initial training on HIV treatment issues through a New York State Department of Health sponsored program. He is rounding out his knowledge of HIV treatment issues at ACRIA and is already proving to be an important asset to our programs and to the local PLWA community.

Virginia Turner has also recently joined ACRIA as a consultant to oversee our new Research Policy Advisory Committee (ResPAC) project. Dr. Turner has worked on many public health initiatives and holds a Masters in Public Health from Harvard and a Doctorate in Public Health from Johns Hopkins. She has devoted 18 years to trachoma research, control and elimination programs. With others, she created the “SAFE Strategy” (Surgery, Antibiotics, Clean Faces, and Environmental Improvement), designed to reduce disease transmission and eliminate trachoma as a cause of blindness. Trachoma, the world’s major cause of preventable blindness, is responsible for blindness in six million people worldwide. At ACRIA, Dr. Turner will complete ResPAC’s initial phase – a complete list of HIV/AIDS research currently being undertaken in New York State, meetings with researchers to review current research, identify research gaps and complete a set of research recommendations. The second phase of ResPAC will build a strategic plan for HIV research based on these recommendations and full community involvement.

New publications introduced

The Fall 2001 edition of ACRIA’s *HIV/AIDS Clinical Trials: A Directory for New York State* is available free of charge to medical and non-medical care providers in New York State. With 151 trials listed, this publication includes the most comprehensive roster of currently enrolling HIV clinical trials in the tri-state region. All trial listings have been written for the broadest audience possible, including people with no medical background. Again, our hope is that this publication not only informs PLWAs about the risks and benefits of participating in HIV studies, but also offers a clear explanation of trials that can be accessed. ACRIA will also list enrolling trials on our web site. Go to www.acria.org to conduct an online search of HIV studies in the New York

area after January 1, 2002. Call ACRIA at (212) 924-3934 x 123 for information on those organizations in New York State that have printed copies of the directory.

ACRIA has also introduced a Spanish language version of our existing brochure, *Managing Drug Side Effects*. This is our second topic-specific treatment publication to be translated into Spanish. Bulk copies of the new brochure, *Control de los Efectos Secundarios*, and *Entendiendo Sus Resultados del Laboratorio* (Understanding Your Lab Results) are available free of charge to community based organizations (CBOs) serving Latino populations throughout the United States. If you are a CBO wanting publications in either English or Spanish, place your order by calling ACRIA’s Treatment Education Department at (212) 924-3934 x 121 or fax us at (212) 924-3936 with contact and mailing information.

Special thanks to:

HIV InSite

at the University of California, San Francisco for their assistance in identifying trial sites and gathering data for ACRIA’s HIV/AIDS clinical trials directory.

Visit their website at:

hivinsite.ucsf.edu

for extensive information on HIV/AIDS clinical trials and treatment.

generous contributions

Thoughtful donations in memory of the following remind us of what is at stake in the fight against AIDS:

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

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