HIV AND THE IMMUNE SYSTEM

As the hope of halting HIV replication has become a reality in the short term for at least some persons living with HIV infection, focus has turned to whether the immune system can in fact be reconstituted after HIV has done its damage. HIV vaccine research has also been a hot topic this year, with the U.S. government's efforts to revive what has been a disappointing venture to date. To address these timely topics, this issue of CRIA Update is devoted to HIV and the immune system.

The human immune response to invasion by pathogens, such as bacteria or viruses, is an extremely elegant and complicated process which is not fully understood even by immunologists. In order to understand issues like immune reconstitution (see page 3) and vaccination (see page 6), a basic understanding of immune function is helpful. To bring everyone up to speed, Rich Lynn -- with the artistic help of Brian Schuman -- has skillfully distilled the key elements of the immune response in an overview of the immune system which follows.

BASICS OF THE IMMUNE SYSTEM

By Rich Lynn, PhD

The body's immune system is a complex network of cells and proteins that fight off infections and other foreign invaders. Some components of the immune system circulate through the body in the blood. Others are in the mucosa -- the cells lining the respiratory, genital, and digestive tracts, where infectious agents often first attack. Still other components of the immune system form the protective "lymphatic system," which has its own set of vessels. The fluid known as "lymph" flows through those vessels, and is filtered in the meshlike lymph nodes, which also provide a place for the different components of the immune system to interact. The main activities of the immune system are carried out by small white blood cells called lymphocytes. The two main types of lymphocytes are B cells (which mature in the bone marrow) and T cells (which mature in the thymus, an organ located in the upper chest).

Fighting off an infection involves three main steps -- (1) initial detection of and response to an invader; (2) amplification of that response; and (3) the eventual defeat of the infectious agent. The details of the steps vary, depending on the type of invader.

Cellular Invaders

For example, if the attack is by a cellular agent, such as the bacteria that cause pneumonia, the primary response comes from antibodies. Antibodies are Y-shaped molecules made by the body's B cells that have binding sites at the tips of the Y. Each binding site recognizes a unique structure (an "epitope") on the surface of a foreign agent (an "antigen") (see figure 1).

(Cont. on p. 4)
Adefovir Dipivoxil for Antiretroviral Naive Patients

CRIA is participating in a new 48 week study of Gilead Sciences’ nucleotide analog drug adefovir dipivoxil (formerly called bis-POM PMEA). Adefovir is a new type of drug that is active against HIV as well as some other viruses such as CMV, hepatitis B virus, and herpes viruses. The study is of HIV+ persons with more than 100 T-cells and HIV viral load of greater than 5,000 who have not taken other anti-HIV drugs in the past. Participants will be assigned to one of five treatments, all of which include the protease inhibitor indinavir (Crixivan™). Participants will be reimbursed $15 per scheduled visit after enrollment.

Adefovir Dipivoxil for Protease Inhibitor Naive Patients

CRIA is also participating in a 48 week study of adefovir dipivoxil for HIV+ persons who have taken nucleoside analog drugs (e.g., AZT, 3TC, ddI, dd4T, ddC) for at least four weeks. Participants will be switched to one of three possible combinations, all of which include adefovir dipivoxil and one or two protease inhibitors. To be eligible, participants must have more than 100 T-cells and a viral load greater than 500. Participants will be reimbursed $15 per scheduled visit after enrollment.

DMP 266

DMP 266 is Dupont Merck’s new non-nucleoside reverse transcriptase inhibitor (NNRTI) that appears to be quite active against HIV in early clinical studies when used in combination with other drugs. CRIA is participating in a study of DMP 266 for people with more than 50 T-cells and HIV viral loads greater than 10,000 who have not taken a protease inhibitor drug, 3TC, nevirapine, or delavirdine. Participants will be assigned to one of three combinations: AZT + 3TC + indinavir (Crixivan™), AZT + 3TC + DMP 266, or indinavir + DMP 266. The study will last 60 weeks and participants will be reimbursed $15 per scheduled study visit after enrollment.

Oxandrolone for Wasting

Oxandrolone is BTG’s anabolic steroid hormone similar to testosterone which has shown promise as a treatment for AIDS-related wasting in small, preliminary studies and, unlike testosterone, can be taken as a pill. CRIA is participating in two multicenter studies of oxandrolone for AIDS-related wasting, one for men and one for women. In these studies, different doses of oxandrolone will be compared with inactive pills (placebo) for 12 weeks, followed by a 24 week period during which all patients will receive oxandrolone. Participants must be HIV+ with unintentional weight loss of 10-20% of their usual body weight. Participants will be reimbursed $10 per scheduled study visit after enrollment.

141W94 protease inhibitor

CRIA is participating in a 48 week study that compares Glaxo Wellcome’s investigational drug 141W94 to indinavir (Crixivan™). To be eligible, participants must have taken nucleoside drugs (e.g., AZT, 3TC, ddI, ddC, ddT) for the past 12 weeks, have detectable viral load (greater than 400), and never have taken a protease inhibitor drug. Participants, in conjunction with their doctors, are encouraged to change at least one of their nucleoside drugs at the time of starting the study. Participants will be reimbursed $15 per scheduled study visit after enrollment.

SMART/EST Women’s Project

CRIA is participating in a multicenter study to test a 10 week stress management program to teach women how to cope more effectively with their illness and everyday problems. Two approaches — individual and group relaxation training — are being compared. Women 18 years of age and older with a diagnosis of AIDS may be eligible. Participants will be reimbursed $25 per visit after enrollment (up to $75). Free child care and refreshments will be provided. For more information, call Debra Munger at (212) 924-3934.

In addition to the above trials, CRIA is also enrolling participants in a Varicella-Zoster Virus study, a Testosterone and MET-Rx study, and DMP 266 expanded access.

For more information on any of these studies, please call Dr. Avinash Desai or Dr. Douglas Mendez at (212) 924-3934.
CAN HAART LEAD TO IMMUNE RECONSTITUTION?

by Craig Sterritt

Highly active antiretroviral therapy (HAART), usually defined as combination therapy with three or more drugs, can reduce viral loads to undetectable levels and can prevent the development of new opportunistic infections (OIs) and cancers. HAART, and the immune-based therapy interleukin-2 (IL-2), can lead to significantly increased T-cell counts. But can HAART (and/or IL-2) help the immune system to recover from damage caused by years of HIV infection? Can a damaged immune system regain the completeness and agility of an immune system that never tangled with HIV?

T-cells and Immune Function

The hallmarks of HIV disease are the progressive loss of T-cells and the susceptibility of people with AIDS to opportunistic diseases. Both the earliest and most advanced understandings of AIDS view these characteristics as cause and effect: people develop AIDS as a result of not having enough T-cells. Up until very recently, it was generally believed that restoration of normal T-cell counts—by antiretroviral and/or immune-based therapy—would restore immunocompetence. But now that substantial T-cell increases can actually be achieved, researchers are questioning the belief that a T-cell is a T-cell is a T-cell, and are asking whether quantity (T-cell counts) can blindly be used as a surrogate for quality (immunocompetence).

Some people who have significant T-cell increases on HAART experience what appears to be partial immune reconstitution. Not only do T-cells go up, but over time their entire immune systems begin to normalize, becoming more like those of uninfected persons. Most importantly, many people on HAART have been able to clear OIs, and the number of OIs occurring among people with HIV appears to be decreasing dramatically.

Conversely, however, some people who experience significant T-cell increases on HAART and on the cytokine therapy interleukin-2 (IL-2) have developed OIs in spite of having T-cell counts that normally preclude such infections. It is for this reason that continuing prophylaxis (OI prevention) is recommended when an individual's T-cell counts increase on HAART. And it is for this reason that T-cell counts alone may not be a reliable marker of immune status after treatment-related T-cell increases occur.

In order to understand how the same T-cell count might mean different things to different people, we will need to consider new ways in which the immune system is being examined by researchers—particularly in the context of HAART.

The Immune Response to HIV

In untreated HIV infection—even when T-cell counts are high—the immune response is usually characterized by a high degree of activation—or hyperactivation. Immune hyperactivation is evidence of the ongoing, dynamic interaction between the immune system and HIV. During this interaction, HIV continually replicates and destroys T-cells. The immune system responds by continually supplying new T-cells and attempting to fight HIV. This hyperactivity drives HIV replication by providing HIV with a constant supply of activated T-cells which it can infect and replicate in. Immune hyperactivation also results in defects in how the immune system responds to HIV and to other pathogens (such as those that cause OIs). But what types of immune function are affected? And how do these defects occur?

Function and Phenotype

Researchers have been investigating the "functional depletion" of T-cells for years. Evidence in the late 1980s indicated that even while T-cell counts are relatively high, T-cells may not be functioning as well as they could. In the test tube, they don't divide and multiply very well, and are less potent against certain types of pathogens than are cells from HIV-negative people. These findings were initially chalked up to insufficient production of immune regulators called cytokines: most notably, IL-2 and interferon (IFN)-gamma. It was clear, however, that defects in

( cont. on p.8)
There are millions of different T-helper cells circulating through the blood and the lymph. Each T-helper cell contains two important receptors: one to recognize the cells of the immune system and the other for particular protein signatures of the invading organism. If a T-helper cell meets a cell displaying the particular signature that its receptor is programmed to recognize, it becomes "activated," reproduces, and amplifies the immune response. It manufactures signal molecules called "cytokines," which stimulate appropriate components of the immune system such as the B cells specific to the invader. As the body fights off the infection, the number of activated T-helper cells decreases, and the immune system calms down.

Getting back to the end result of all of this activity, how do antibodies defend the body against invaders? Although the mere binding of the antibody to the antigen can neutralize the invader, other steps follow. Once a cellular invader becomes coated with antibodies, scavenger cells called macrophages and neutrophils recognize these encrusted cells and ingest them. (See Figure 3). The invader is then chewed up with special digestive enzymes.

**Viral Invaders**

When a virus -- rather than a cellular invader --
attacks the body, the immune response has a different emphasis. Unlike cellular invaders, viruses multiply within human cells, and antibodies cannot penetrate these cells. Thus, the body focuses the immune system attack on destroying its own cells infected by viruses. Otherwise, if allowed to survive, these virally-infected cells would continue to serve as viruses factories spawning out more viruses. Various cells of the immune system have the ability to recognize and destroy virally infected cells. Some of the key ones include “natural killer cells” and “cytotoxic T cells” (also called CTs for cytotoxic lymphocytes). Just as T-helper cells recognize specific protein signatures, cytotoxic T cells recognize specific protein signatures on the surface of infected cells and destroy them (see Figure 4). T-helper cells are also crucial in defeating a viral attack as they produce cytokines which stimulate the cytotoxic T cells and natural killer cells.

Other Components of the Immune Response
The body augments the immune response in a number of ways. There are at least 14 types of proteins known as “interferons,” which respond to infection by setting off a cascade of cellular events. For example, viruses induce the body's cells to produce alpha interferon, which can interfere with the synthesis of viral proteins in the cells, thus preventing further viral reproduction. Gamma interferon stimulates macrophages, helping them destroy foreign invaders that they have ingested but not yet killed.

Once the immune system successfully combats an infection, it responds more effectively the next time the body encounters that infectious agent. This “memory” phenomenon is the key to vaccines. Many vaccines consist of dead or weakened viruses or bacteria that still induce appropriate T cells and B cells so the body is primed for the next attack.

This brief summary is just a general introduction to the immune system. More detailed overviews, or in-depth articles on various components of the immune system, may be found in magazines such as Scientific American.

Rich Lynn is a member of the Treatment Action Group (TAG) and CRIA's Scientific Advisory Committee.

2E. The B cell is transformed into a cell that acts like an antibody factory, releasing antibodies directed against the original antigen.

2D. The T-helper cell recognizes the B cell and the signature strand on its surface. It produces cytokines that “wake up” the resting B cell.

Illustrations by Brian Schuman.
A vaccine is a substance used to teach the body’s immune system how to defend itself against a disease-causing organism or virus. A vaccine can be in many forms, such as a weakened (attenuated) form of the microorganism (as is the case with measles vaccine); a killed form of the organism (such as typhoid vaccine); a protein section of the organism (such as hepatitis B vaccine); or a more complex design. An effective HIV vaccine, given before exposure to HIV, could help the body completely rid itself of the virus (sterilizing immunity), or help the body control HIV enough to prevent AIDS and transmission to others.

The development of a preventive HIV vaccine is believed to be possible based on the successful protection of chimpanzees and monkeys by similar vaccines, some evidence that the human immune system can prevent or delay HIV infection and disease, and the immune responses seen in humans given current experimental HIV vaccines. An ideal preventive HIV vaccine would protect people against all subtypes of HIV and against all routes of possible transmission. An ideal HIV vaccine would also prevent transmission to others, be inexpensive, easy to transport and to administer to people, and would require few booster shots.

There are five generally agreed-upon challenges which scientists face in developing a preventive HIV vaccine: 1) understanding how HIV infects and causes disease in people, and developing an animal model that mirrors this process; 2) discovering why HIV is able to survive and replicate in HIV-positive individuals despite a strong immune response; 3) determining which parts of the immune system might be useful in protecting against HIV infection, by studying animals with vaccine-induced protection, or in adults and newborns who may have been exposed to but not chronically infected by HIV; 4) understanding how to cause the immune system to respond effectively against HIV; and 5) developing a vaccine that can make the immune system protect the body over a long time, work against diverse and changing viruses, and block all routes of transmission.

NIH funding for vaccine research has recently increased, but the pharmaceutical

<table>
<thead>
<tr>
<th>Type of Vaccine</th>
<th>Whole Killed</th>
<th>Live Attenuated</th>
<th>Recombinant/Subunit</th>
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<tr>
<td><strong>Mechanism of Action (How it works)</strong></td>
<td>Consists of whole HIV viruses which have been inactivated in the test tube. Unlike some other types of vaccines, which present a limited number of parts of HIV to the immune system, here a large number of different antigens are presented.</td>
<td>Consists of weakened (attenuated) live virus that is able to infect cells and replicate within the body, but is unable to cause disease. The vaccine antigens are presented to the immune system in a fashion that most closely resembles natural infection with HIV and can elicit strong, persistent antibody and cellular immune responses. The immune system is then potentially prepared to protect against future infection by pathogenic (disease-causing) strains.</td>
<td>Consists of synthetic single proteins of HIV, including structural envelope glycoproteins (e.g., gp120, gp160) and other proteins (e.g., p55, p24). The proteins are taken up by immune cells and digested into smaller pieces which are displayed on the cell surfaces to generate antibody and cellular immune responses.</td>
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<tr>
<td><strong>Stage of Development</strong></td>
<td>No private sector company is developing these vaccines for preventive trials despite data demonstrating that HIV can be safely inactivated and despite the success of whole-killed vaccines in feline retroviral diseases.</td>
<td>Because of safety concerns, no private sector company is developing this approach for testing in humans, despite success of naturally attenuated equine infectious anemia virus vaccine (EIAV—a horse retrovirus) in China and data in a handful of humans naturally infected with an apparently attenuated strain of HIV.</td>
<td>They are being tested in Phase II trials in combination with a canarypox vector vaccine in the United States, and are likely to be evaluated in Phase II and III trials in Thailand.</td>
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<td><strong>Comments</strong></td>
<td>Whole-killed vaccines are based on some of the oldest vaccine technologies. Whole-killed vaccines are used for such diseases as polio, influenza, mumps, and typhoid fever.</td>
<td>Studies of live attenuated Simian Immunodeficiency Virus (SIV) in macaques have shown unparalleled protection against wild-type SIV. However, further research is needed to determine what level of attenuation is needed so that live attenuated HIV is non-pathogenic yet still able to infect and elicit protective immune responses. Live attenuated vaccines are used for such diseases as measles, rubella, and polio.</td>
<td>The recombinant subunit approach was first used against hepatitis B virus, where viral envelope produced in yeast cells proved very effective in clinical trials.</td>
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companies able to develop vaccines have largely stayed out of HIV vaccine development due to the expected time frame and cost of development, the uncertain size of a profitable market, concerns about liability, and greater potential profits in other endeavors. Many different types of candidate vaccines have been developed for HIV, but only three have entered into Phase II clinical trials, and none has ever been tested for efficacy. The status of the major types of candidate vaccines is summarized in the table below:

**Sam Avrett is the Associate Scientific Director of the International AIDS Vaccine Initiative and the co-founder of the AIDS Vaccine Advocacy Coalition.**

<table>
<thead>
<tr>
<th>Peptide</th>
<th>Live Vector</th>
<th>DNA</th>
<th>Virus-like Particles</th>
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<tr>
<td>Consists of small portions (peptides) of synthetic HIV proteins. These peptides are taken up by immune cells and displayed on their surfaces where they in turn generate antibody and cellular immune responses.</td>
<td>Consists of harmless viruses (e.g., vaccinia, canarypox, adenovirus) or bacteria (e.g., BCG, attenuated salmonella) into which HIV genetic material has been inserted. The HIV proteins are manufactured in the body by the vector as it replicates and the resultant epitopes can elicit HIV-specific immune responses.</td>
<td>Consists of pieces of HIV DNA which are taken up by the body's cells and used to produce HIV proteins. These proteins induce an immune response that theoretically could protect against infection with HIV.</td>
<td>Consists of incomplete viruses produced by cells that are infected with parts of HIV DNA. Studies have shown that these incomplete viral particles can contain antibody and CTL epitopes, yet are safe and not infectious.</td>
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Several peptide vaccine candidates have been evaluated in Phase I clinical trials, where some were shown to induce cytotoxic lymphocyte (CTL) responses, but were not highly immunogenic in general.

Vaccinia vectors for HIV have been tested in animal models for more than ten years. Current efforts are focused on attenuated strains of vaccinia that will not cause disease in immunocompromised people yet will be able to infect, replicate, and be broadly immunogenic. Three generations of canarypox vector vaccine have been tested in clinical trials by Pasteur-Merieux-Connaught with substantial support from the National Institutes of Health and the French government. A recombinant canarypox virus vector is now being tested in the United States in a Phase II clinical trial in combination with a recombinant gp120 product.

All of these DNA vaccines are based on clade B virus, the strain of HIV that is predominant in Western Europe and North America.

Two HIV DNA vaccines are now in Phase I clinical trials in the United States. Other DNA vaccines are in development.

Two private sector companies have engaged in efforts to develop this type of product for clinical trials.

Further work is being done to engineer virus-like particles from primary isolates from different clades, and test these in animal models for immunogenicity and protection.
Our current understanding of HIV as a persistently replicating, T-cell-killing virus helps us to understand the preferential depletion of certain types of T-cells. Early in the course of HIV infection, the immune system has, more or less, a full team of players—i.e. T-cells of all phenotypes— that it can send out against HIV (warning: sports metaphor!). Evolution, the intelligent yet cocky head coach of the immune system, opts for an all-out first offensive plays (this is normally the way to deal with viruses) and uses the best players early in the game— all of which are carried out on stretchers. Because HIV these most desirable phenotypes replaced as well? When new T-cells are needed in a hurry, as they are during HIV infection, mature (adult) T-cells present in the blood and tissues of the body divide and multiply. This is called peripheral expansion, because T-cells in the blood and tissue (peripheral T-cells) grow in number (expand). Immune hyperactivation during HIV infection is thought to be evidence of the incessant expansion of peripheral T-cells. By this mechanism, T-cells that are already on the scene are rapidly ‘cloned’ in the immune system’s efforts to maintain a sufficient supply of T-cells.

But as we have seen, certain phenotypes of T-cells are preferentially eliminated from the periphery in the course of HIV infection, and are therefore increasingly less available for peripheral expansion. And because peripheral expansion is exponential (1-2, 2-4, 4-8, etc.), continual expansion of other phenotypes serves to ‘crowd out’ or reduce the proportional representation of preferentially depleted phenotypes. This crowding-out of desirable T-cells by suboptimal ones explains how immune function can decline in the presence of stable or slowly decreasing T-cell counts.

T-cell Replenishment during HAART
The good news is that when the rampant depletion of T-cell phenotypes is stopped— as happens during HAART—this crowding-out process also stops. Subsequently, peripheral expansion of all T-cell phenotypes continues along egalitarian lines, and every phenotype present is expanded— fairly and equally— according to their proportionate representation at the time when HAART is initiated. This has been referred to as the first phase of T-cell recovery following HAART (see table 1). Following this, the immune system mellow out because it no longer needs to intensely struggle to combat HIV and restore T-cells (phase 2). As

preferentially infects and destroys activated T-cells (i.e. those that are in attack mode), those T-cells that are working— against HIV or against other pathogens (germs and cancers)— become preferentially depleted. Phenotypically, these T-cells have been defined as good promoters and directors of immune responses to HIV and to pathogens not previously encountered by the immune system.

T-cell Replenishment in Untreated HIV Infection
If new T-cells are being constantly supplied, as current research suggests, why aren’t...
a result, the immune system attempts to recu-
perate by reverting to its normal ‘rested and 
ready’ state (phase 3).

This returns us to our first question: Can the immune system reconstitute itself after all 
of this has happened? For some people, partial reconstitution seems to be possible. In phenoty-
pic studies of people who started HAART, 
T-cell counts went up in the first phase of T-cell recovery, but phenotypic proportions stayed the same. In phase 2, approximately two weeks after HAART was started, markers of immune hyperactivation began to diminish, suggesting a de-escalation of anti-HIV im-
mune activity and the beginning of a trend towards normalization. Phase 3, which began 
about 4-6 months post-HAART, was charac-
terized by continued immune normalization 
that included phenotypic readjustment in about 
50% of patients. In some patients, phase 2 and 
3 changes were also associated with evidence of improved immune function.

The T-cell Repertoire

Although these findings indicate that some types of T-cells can be restored when viral 
replication is suppressed, there is evidence that T-cells that specifically target certain patho-
gens—CMV for example—can be permanently 
eliminated in the course of HIV infection. This 
type of T-cell deletion is not representative of 
a phenotypic defect, and does not manifest in 
decrease in general immune function. Rather, 
such T-cell deletions are defined as perturba-
tions or ‘holes’ in the T-cell repertoire, and manifest in diminished immune responses to 
specific pathogens.

If we think of the immune system as a DJ 
at a club, we can think of the T-cell repertoire 
as all of that DJ’s records, and of individual 
T-cells as individual records. Let’s say our DJ 
keeps playing Madonna records, and one Sat-
urd night his own special mix of “Like a 
Virgin” gets broken. This won’t stop our DJ from 
playing next Saturday (the immune system is still 
competent). It won’t stop the DJ from playing 
records of the Madonna phenotype. It will, how-
ever, mean that the next time he wants to play 
“Like a Virgin”, he won’t be able to.

It has been observed that in some people, 
certain records get broken during the course of 
HIV infection, thereby reducing the diversity of 
songs that can be played. In this way, the T-cell 
repertoire gets restricted, and the immune system’s ability to respond to specific patho-
gens (song requests) gets reduced. Studies of 

<table>
<thead>
<tr>
<th>T-cell recovery after HAART follows three phases:</th>
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<tr>
<td><strong>Phase 1 (weeks 1 to 2):</strong></td>
</tr>
<tr>
<td>• rapid decrease in viral load</td>
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<tr>
<td>• increase in T-cells</td>
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<tr>
<td>• immune hyperactivation continues</td>
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<tr>
<td><strong>Phase 2 (week 2 to month 4-6):</strong></td>
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<tr>
<td>• CD4 T-cell elevations are sustained</td>
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<tr>
<td>• CD8 T-cell counts drop</td>
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<td>• CD4/CD8 ratio begins to normalize</td>
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<tr>
<td>• immune activation begins to diminish</td>
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<td><strong>Phase 3 (months 4-6 onward):</strong></td>
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<tr>
<td>“Inverse T-cell kinetics” occur</td>
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<tr>
<td>• immune activation continues to decrease</td>
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<td>• CD4/CD8 ratio continues to normalize</td>
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| • phenotypic reconstitution (increase in pro-
  portion of “naive” CD4 cells; decrease in 
  proportion of memory CD4 cells) in some pa-
  tients                                      |

T-cell diversity consistently demonstrate that 
the T-cell repertoire does get perturbed in HIV 
infection. In addition, test tube studies confirm 
that T-cells from people with HIV can lose 
their ability to respond to specific pathogens 
even when T-cell counts are high and other 
immune responses are strong. Although there 
is preliminary evidence that a small degree of 
T-cell diversity can be restored after HAART, 
it is unlikely that actual ‘holes’ in the reperto-
ire will get filled—that broken records will be 
replaced. Once again, this is probably a func-
tion of peripheral expansion: if it isn’t there, it 
can’t get expanded.

In Summary

Taken together, these findings suggest that 
the immune system can be, but is not always, 
irrevocably damaged by HIV. It is possible, 
however, that with more time (i.e. years) phenoty-
pic reconstitution may occur in a larger 
proportion of patients than has been indi-
cated so far. Similarly, restoration of T-cell 
diversity may also be possible, with time, for 
some people. What remains to be determined 
is what distinguishes immune systems that 
achieve partial reconstitution from those that 
do not.

Duration of HIV infection is a probable factor; 
and most researchers agree that earlier treat-
ment with HAART—i.e. before certain T-cells 
and T-cell phenotypes become depleted—will 
 improve the likelihood of immune reconstitu-
tion.

Thymic function and age are also pos-
sibilities. Because T-cell phenotypes and 
pathogen-specific T-cells eliminated in the 
periphery can be resupplied by what is called 
‘thymic development’ (as opposed to periph-
eral expansion), it is thought that people with 
relatively functioning thymuses (an organ of 
the immune system) will have improved

(Cont. on p. 10)
HAART AND IMMUNE RECONSTITUTION

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chances at immune reconstitution. Unfortunately, it is completely unknown whether adults retain any thymic function at all. There is some evidence that children, who have functioning thymuses, may have improved chances of immune reconstitution after HAART.

It also remains to be seen whether immune systems deemed 'reconstituted' are truly better than those that are not. In theory, it makes sense that an immune system that is more like that of HIV-negative people's will be stronger. But we have to recognize that current assessments of immune reconstitution are based on an artificial index of immune 'completeness'. We will know more when this index is correlated with the clinical outcomes of patients on HAART. Do patients with more 'complete' immune systems stay healthier longer? Do they live longer?

What all of this ultimately suggests is that treatment-related immune improvements are highly variable, and cannot be measured by T-cell counts alone. In this respect, people who experienced dramatic T-cell increases on IL-2 therapy may still have marked defects in their ability to mount immune responses to certain pathogens. This is consistent with IL-2's effects as a stimulator of peripheral expansion: IL-2 induces T-cell increases by expanding what is already present. Accordingly, studies of T-cell diversity show no change in the T-cell repertoire of people before and after IL-2. However, some patients have demonstrated partial phenotypic reconstitution following IL-2 therapy, although this may be an effect of simultaneously administered antiretroviral drugs.

Another point about immune reconstitution is that recovery of immune function may not only result in beneficial effects. A number of reports have surfaced of atypical cases of CMV retinitis, disseminated MAC, and wasting disorders among patients on HAART. What makes these case atypical is 1) they occur at T-cell levels that normally preclude the disorders, and 2) the CMV and MAC cases include an inflammatory component that is not usually seen in these infections. It is possible that in these instances, restored immune reactivity is contributing to the development of illness rather than preventing it.

Future Directions: Immune-based Therapies
It has been suggested that the T-cell repertoire can be repaired in patients who achieve some degree of phenotypic reconstitution. "Naive" T-cells (T-cells that have not encountered their specific antigen) are the main phenotype of T-cell

"What all this ultimately suggests is that treatment-related immune improvements are highly variable, and cannot be measured by T-cell counts alone."

that is preferentially depleted in HIV infection. It is thought that if naive T-cells can be restored, they can then be induced to respond to specific pathogens-- namely, those that the immune system has lost the ability to recognize. This would be accomplished by immunizing patients with vaccines against specific pathogens.

Some researchers are exploring other ways of restoring T-cell phenotypes and/or filling holes in the T-cell repertoire. Thymic transplants, or the use of thymic factors, have been suggested as a possible way to boost the development of naive T-cells. Alternatively, the ex vivo (outside of the body) expansion of selected T-cell phenotypes, or T-cells that target specific pathogens, has been proposed and studied. This "selective expansion" of cells is very different from the "omnichorial expansion" (non-specific expansion of all clones) induced in vivo (inside the body) by IL-2, because omnichorial expansion in the presence of viral replication (and preferential depletion) could theoretically contribute to the crowding out of desirable T-cell phenotypes.

Therapies that reduce the overall degree of immune hyperactivation have also been studied in HIV infection. Indeed, proponents of IL-2 argue that this therapy has normalizing effects upon the immune system, and that these effects may be conducive to phenotypic reconstitution. Another cytokine, interleukin-10, has been found to significantly reduce viral replication via its anti-inflammatory effects. Immune modulators that seek to selectively induce the growth and activity of certain T-cell phenotypes-- such as those that work best against HIV-- have also been proposed. The cytokine interleukin-12 has been studied in this regard. Finally, immunosuppressive therapies-- therapies that dampen immune responsiveness, and therefore hyperactivation-- have been proposed and studied in HIV infection. This counter-intuitive approach to HIV treatment has yielded provocative results, including treatment-related T-cell increases. Craig Sterritt has followed immune-based therapies for the Treatment Action Group since 1993.
CRIA TO STUDY 141W94 PROTEASE INHIBITOR

By Marshall Glessy, MD, PhD

CRIA will be participating in a major new study of 141W94, an investigational protease inhibitor that is being developed by Glaxo Wellcome, Inc. The drug is sometimes referred to as the “Vertex protease inhibitor” or VX-478, as it was initially discovered and synthesized by Vertex Pharmaceuticals but licensed to Glaxo Wellcome for clinical development.

Early studies have suggested that 141W94 is a potent antiretroviral drug. As a single agent, it reduced HIV viral load by about 1.7 logs (50-fold) at 4 weeks in a small number of patients. It has been studied in a range of doses twice or three times a day and may be taken with or without food. The most commonly reported side effects seen in early clinical trials have been headache, rash, nausea, fatigue, diarrhea/loose stools, and numbness around the mouth.

CRIA is participating in a 48-week, randomized, open-label phase III study that will compare the antiviral activity and safety of 141W94 to indinavir (Crixivan™). This international study aims to enroll 460 patients who have taken reverse transcriptase inhibitor drugs (e.g., AZT, 3TC, ddI, d4T, ddC) for at least 12 weeks but have not taken protease inhibitor drugs. To be eligible, patients must be currently taking reverse transcriptase inhibitor drugs and have a detectable viral load (more than 400 copies/ml). There is no restriction on T-cell counts. Patients, in conjunction with their doctors, will be encouraged to change their reverse transcriptase inhibitor drugs at the time of starting the study. Viral load results will be available every 8 weeks during the study, and patients will be able to switch protease inhibitors or their other drugs if certain criteria suggestive of drug failure are met.

For information about this or other CRIA studies, please call Dr. Douglas Mendez or Dr. Avinash Desai at (212) 924-3934.

TREATMENT EDUCATION WORKSHOPS

CRIA is now conducting free treatment education workshops at AIDS service organizations (ASOs) throughout the five boroughs.

Treatment education has emerged as one of the most critical needs among PLWAs and the agencies that serve them. A well-informed patient is better able to access the health care system and make informed decisions with his/her health care provider about treatment options. In the ever-changing world of HIV/AIDS, having information that is up-to-date and easily understandable can give PLWAs a decisive and potentially life saving edge.

As a clinical trials research organization, CRIA is uniquely positioned to disseminate the latest treatment information. Through the use of a workshop format, our program encourages individual participation, which, in turn, facilitates learning. Information presented in the introductory treatment workshop is for people with little or no HIV/AIDS background. More advanced workshops on specific aspects of HIV/AIDS treatment are also offered. Printed materials accompany all workshop presentations.

These workshops are conducted at ASOs city wide for clients and staff. PLWAs who are not connected to an ASO, may schedule an individual treatment education session at CRIA’s offices. This program focuses on providing information to underserved communities including women and people of color.

For more information on this program please call CRIA’s Treatment Education Director, David Pieribone at 212-924-3934.

WOMEN’S STRESS MANAGEMENT PROJECT

CRIA will be participating in the Stress Management and Relaxation Training/Expressive Supportive Therapy Women’s Project (SMART/EST Project) — a multicenter study organized by the University of Miami and the Clinical Directors Network (CDN) and sponsored by the National Institute of Mental Health. The study is designed to test the effectiveness of a 10-week stress management program on quality of life, health, and psychosocial status of women with AIDS. Two approaches — individual and group relaxation training — are being compared. The hope is that participating women will learn how to cope more effectively with their illness, stress, and everyday problems.

We are looking for adult women with a diagnosis of AIDS who might be interested in participating in the study. Free child care and refreshments will be provided, and participants will be reimbursed $25 per visit after enrollment (up to a maximum of $575). For more information about this study, call Debra Munger at (212) 924-3934.
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GENEROUS CONTRIBUTORS

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