

HIV and the Immune System

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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

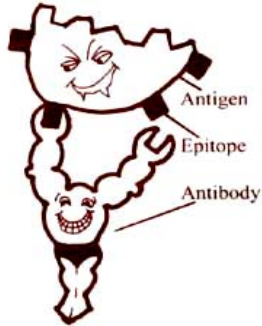
By Rich Lynn, PhD

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.

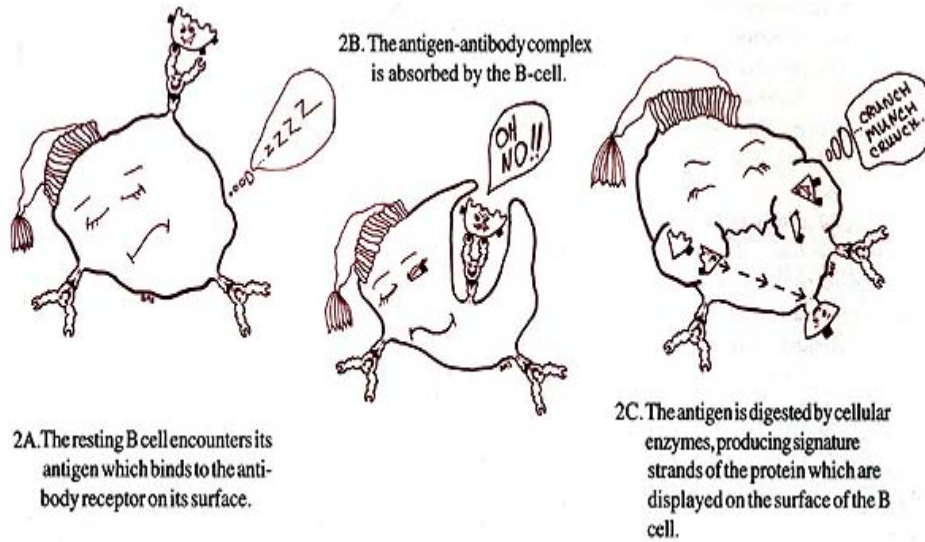
Cellular Invaders



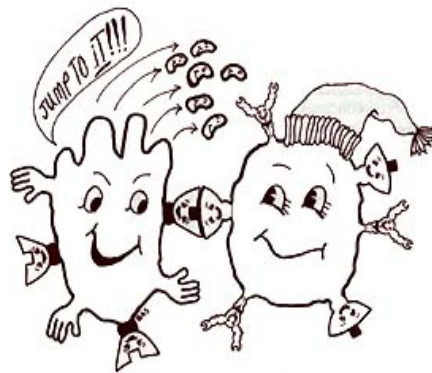
For example, if the attack is by a cellular agent, such as the bacteria that cause pneumonia, the primary response comes from antibodies.

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). Millions of different B cells capable of making millions of different antibodies exist in a resting state in the body. When the body is exposed to a particular antigen, the B cells capable of making the necessary antibodies need to be stimulated from the resting state and turned into antibody factories. This stimulation process involves both the B cell and a type of T cell called a T-helper cell. The process is initiated

by the binding of antigens to antibodies that are attached to the surface of B cells and function as antigen receptors. Once a B cell's surface antibody binds to its antigen, the resulting complex is absorbed by the B cell. The complex is then chewed up with enzymes, producing strands of protein, which are distinctive signatures of that particular invader. These signature strands are transported to the surface of the cell and then displayed, where the T-helper cell recognizes

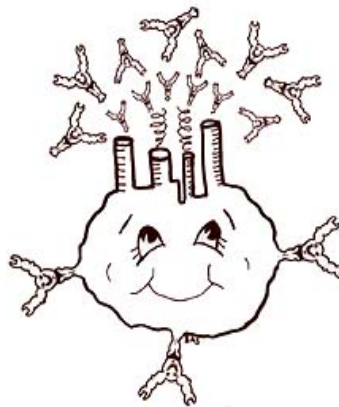


them.



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.

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



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. The invader is then chewed up with special digestive enzymes.

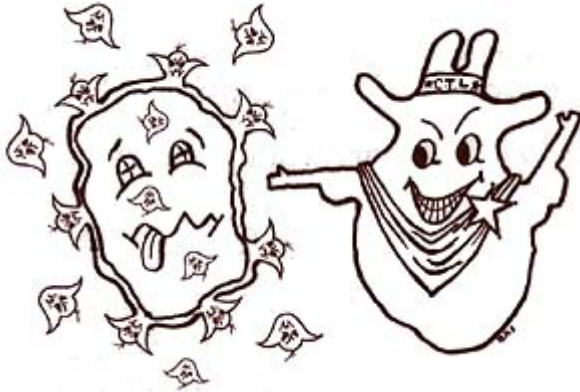
Viral Invaders

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 virus factories spewing 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 CTLs 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. 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.

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, 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-cells 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 immune regulation weren't universal: some people's cells performed just great, while others' flagged. It was therefore hypothesized that early regulatory defects occurred in some people with HIV, but did not occur in others. Moreover, it was predicted that people with poorly functioning T-cells would progress more rapidly to AIDS. Scientists mobilized to discover how HIV infection caused immune dysregulation, and how immune dysregulation resulted in AIDS.

The concepts of "functional depletion" and "immune dysregulation" finally got distilled into what is known as the "TH1-TH2 shift" hypothesis. Fortunately, all we need to squeeze out of this hypothesis is that it got people thinking in terms of `these' T-cells and `those' T-cells. Researchers recognized that not all T-cells are created equal: different T-cells did different things, and individual cells could be classified according to functional characteristics, or phenotype. Some T-cells produced IL-2 and IFN-gamma (TH1 phenotype), while others had different immune regulation responsibilities (TH2 phenotype). A big lesson in immunology was learned: perhaps functional defects didn't reflect a generalized weakening of garden-variety T-cells, but reflected a

change in T-cell populations. It wasn't that all T-cells were producing less IL-2 and IFN-gamma. It was that fewer T-cells of the IL-2 and IFN gamma-producing phenotype were present.

This revelation introduced the investigation of "population dynamics" that is very much in vogue today.

Whereas studies of functional defects suggested that HIV somehow sabotaged T-cells without actually destroying them, or that the immune system somehow gets confused, population or phenotypic studies suggest that certain T-cells are simply killed off earlier in the course of HIV infection.

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 play (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 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 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 mellows out because it no longer needs to intensely struggle to combat HIV and restore T-cells (phase 2). As a result, the immune system attempts to recuperate 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 phenotypic 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 immune activity and the beginning of a trend towards normalization. Phase 3, which began about 4-6 months post-HAART, was characterized 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 pathogens-- 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 a decrease in general immune function. Rather, such T-cell deletions are defined as perturbations 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 Saturday 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, however, 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 pathogens (song requests) gets reduced. Studies of 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 repertoire will get filled-- that broken records will be replaced. Once again, this is probably a function of peripheral expansion: if it isn't there, it can't get expanded.

T-cell recovery after HAART follows three phases:

Phase 1 (weeks 1 to 2):

- rapid decrease in viral load and increase in T-cells
- immune hyperactivation continues

Phase 2 (week 2 to month 4-6):

- CD4 T-cell elevations are sustained
- CD8 T-cell counts drop
- CD4/CD8 ratio begins to normalize
- Immune activation begins

diminish

**Phase 3 (months 4-6 onward):
"Inverse T-cell kinetics" occur**

- immune activation continues to decrease
- CD4/CD8 ratio continues to normalize
- phenotypic reconstitution (increase in proportion of "naive" CD4 cells; decrease in proportion of Memory CD4 cells) in some patients

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) phenotypic reconstitution may occur in a larger proportion of patients than has been indicated 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 treatment with HAART-- i.e. before certain T-cells and T-cell phenotypes become depleted-- will improve the likelihood of immune reconstitution.

Thymic function and age are also possibilities. 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 peripheral expansion), it is thought that people with relatively functioning thymuses (an organ of the immune system) will have improved 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 cases 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 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 "omniclonal expansion" (non-specific expansion of all clones) induced in vivo (inside the body) by IL-2, because omniclonal 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.

Preventive Vaccines For HIV

By Sam Avrett

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 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:

Type of Vaccine	Whole Killed	Live Attenuated	Recombinant Subunit
Mechanism of Action (How it works)	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.	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.	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.
Stage of Development	No private sector company is developing these vaccines for preventive trials despite data demonstrating that HIV can be safely inactivated and	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	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.

	despite the success of whole-killed vaccines in feline retroviral diseases.	of humans naturally infected with an apparently attenuated strain of HIV.	
Comments	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.	Studies of live attenuated Simian Immunodeficiency Virus (SIV) in macaques have shown unparalleled protections 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.	The recombinant subunit approach was first used against hepatitis B virus, where viral envelope produced in yeast cells proved very effective in clinical trials.

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

Therapeutic Vaccines

By Marshall Glesby, MD, PhD

Several types of HIV vaccines have been studied as treatments rather than for prevention of HIV infection. The goal of vaccinating an HIV-infected person (immunotherapy) is to induce an immune response that will fight the existing HIV infection and delay the progression of disease. Since the progression of HIV disease depends on the balance between viral replication and the body's immune response, boosting the immune response could be used in theory as an adjunct to antiretroviral therapy. Most of the vaccines studied to date have been well tolerated and have elicited antibody and cellular responses to the vaccine. Although beneficial effects on CD4 cell counts and HIV viral load have been suggested in a few small studies, the data are limited and controversial.

Presently, a therapeutic vaccine called Remune (often referred to as the "Salk vaccine") is undergoing a Phase III study. Remune is composed of inactivated HIV mixed in mineral oil and is injected every 3 months. In March 1996, a double-blind, placebo-controlled study of Remune was initiated involving 2,500 HIV-infected persons with T-cell counts between 300 and 549 cells/mm³. The participants, who may take antiretroviral drugs concomitantly, will be studied for up to three years and will be monitored for the development of AIDS. More information about this trial can be obtained from the AIDS Treatment Data Network (800-734-7104) or the AIDS Clinical Trials Information Service (800-TRIALS-A).

CRIA NEWS

CRIA to study 141W94 Protease Inhibitor.

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 ACRIA 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, ACRIA 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 ACRIA'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 ACRIA's Treatment Education Director, David Pieribone at 212-924-3934.

CRIA TRIALS NOW ENROLLING

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, d4T, 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. ACRIA 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. ACRIA 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, d4T) 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 \$575). Free child care and refreshments will be provided. For more information, call Debra Munger at (212) 924-3934.

CRIA UPDATE

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

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acknowledging our friends...

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