The Vaccine Quest
Allan L. Goldstein, PhD and Paul H. Naylor, PhD

The best hope for controlling the spread of HIV is the development of a safe and effective vaccine. Vaccines "prime" the immune system to recognize a specific virus and produce millions of white blood cells in response. The ideal vaccine primes both B-cells, which produce antibodies that neutralize free-floating virus, and CD8+ T-killer cells, which destroy already infected cells.

Priming requires exposure to the virus, which teaches the immune system to recognize the "face of the enemy." Since use of a whole virus vaccine probably carries too high a risk of transmitting HIV and since it appears that injecting certain regions of the HIV envelope coating can exacerbate immunosuppression, many scientists are designing vaccines using only selected pieces, or "epitopes," of HIV. The challenge is to identify the most effective epitopes and the best way to deliver them to the immune system.

Two basic methods of delivery have emerged, both with advantages and disadvantages: infecting an individual with modified virus that contains viral proteins; and injecting synthetic epitopes. HIV presents two other dilemmas. First, there are no perfect animal models in which to test a candidate vaccine, and second, there is no agreement about which viral envelope or core epitopes should be included. The discussion below focuses on the current approaches to these questions.

Why Does the Immune System Fail?

There remain unanswered many questions about how HIV infection destroys immune function. For example, while there are relatively few T-helper cells infected with the virus, why do their numbers decline and why are they not replaced by normal recruitment through the thymus? Why do some individuals exposed to the virus progress to frank AIDS more rapidly than others? Why do the wide variety of antibodies the body generates in response to HIV protein components fail to protect against infection? Why do these antibodies vary in their abilities to neutralize and kill the HIV? Why are antibodies to the p17 and p24 core proteins of the virus the first to decline when individuals progress to AIDS while antibodies to viral envelope proteins remain high?

Despite these uncertainties, it is encouraging to note that for a period ranging from months to years, the body stages an active immune response to HIV. This suggests that manipulation of the immune system with the right vaccine might maintain this immune response and prevent disease in uninfected individuals and perhaps, as first proposed by Jonas Salk, even prevent seropositive individuals from developing AIDS.

Core vs. Envelope Approach

There are two schools of thought regarding protein targets for HIV vaccine development: the "envelope" approach, which has been the most popular, and the "core" approach. These labels refer to the portion of the viral protein targeted by the proposed vaccine. HIV consists of several major proteins, among them an envelope protein (gp120) on the outer coat of the virus, a membrane-spanning protein (gp41), a core or shell protein (p17) under the envelope, and an innermost core protein (p24) surrounding the viral RNA and reverse transcriptase.

The disagreement between the two schools centers around the question of which viral proteins provide the best starting point for the development of an effective vaccine. Clearly, the chosen proteins must be highly "conserved"—that is, remain unchanged as the virus mutates—and must be able to stimulate the production of neutralizing antibodies, or CD8+ T-killer cells, or both. Proponents of each approach suggest that proteins from their sites—the outside or inside of the virus—will meet these conditions. Unfortunately, the lack of an animal model has delayed the development of a consensus about the relative merits of each protein target.

Since previous successes using vaccines against viral diseases such as polio, hepatitis, and measles induced strong antibodies to envelope proteins and produced high concentrations of antibodies that neutralized these viruses, most AIDS experts concluded that an envelope approach had the best chance to combat HIV. This perspective was reinforced by government scientists involved in HIV envelope approaches who influenced government funding policy so that it encouraged envelope-based research to the exclusion of other approaches. Recently, research has uncovered three problems with envelope proteins that seem to make them unsuitable for vaccine development.

Problems with HIV "envelope-only" vaccine approaches, particularly their inability to produce a T-killer cell response, support the reemergence of core-based approaches.

First, the actual amino acid sequence of HIV proteins, identified by immune system cells, changes through a process known as "genetic drift," thus creating a moving target for the immune system. Before the AIDS epidemic, vaccines that primed the system to recognize primarily the envelope were considered effective, since most viruses have a fixed number of proteins on their envelopes, transmit infection as free-floating organisms, and do not mutate rapidly. The protein components of the HIV envelope, however, are like the numbers of a combination lock whose code constantly changes: each infected individual has a different combination, and within each individual the numbers constantly shift. To remedy this, researchers have had to use proteins from more than one strain of HIV, or use envelope epitopes that are less dominant, that is less recognizable to antibodies, but more stable.

Second, there is emerging evidence that certain antibodies raised against some epitopes or domains of envelope proteins (like gp120 and gp160) could actually "enhance" infectivity of HIV. This could lead to increased infection of macrophages and other immune system cells.

Third, researchers have begun to appreciate that antibodies to envelope proteins can neutralize only free-floating virus and will not eliminate already infected cells. These cells can spread HIV to uninfected cells without having to bud a new virus and can be eliminated only by CD8+ T-killer cells.

With the appreciation of the problems associated with "envelope-only" vaccine approaches, particularly the inability to induce a strong CD8+ T-killer cell response, core-based approaches are reemerging. There are two key initiatives: one led by Jonas Salk, continued on page 2
Exploring an inactivated whole virus stripped of its envelope, and the second, led by researchers at George Washington University, who were the first to suggest focusing on core proteins, investigating HGP-30, an epitope of p17. (See sidebar below.)

**Current Vaccine Initiatives and Trials**

Over the past year, a number of studies in chimpanzees and monkeys have shown that vaccination can generate immune responses resulting in protection from HIV infection. Although limited, because animal biology differs from human biology, these models have the potential to define protective responses. There are several interesting reports of chimpanzees protected by vaccines, including by intravenous infection of live virus with a killed envelope-less vaccine (C.J. Gibbs, National Institutes of Health); killed virus later boosted with a complex containing the p17 core protein (M. Girard, Pasteur Institute); and, most recently, gp120 recombinant protein (P. Berman, Genentech).

While chimpanzees are infected by HIV and so offer some information to vaccine researchers, since they do not get sick, chimpanzee trials do not offer insights into the effect of a vaccine on disease progression. In response, an alternative animal model is being developed in monkeys, animals that can be infected with a simian immune deficiency virus (SIV), which is similar but not identical to HIV and has the capacity to cause HIV-like symptoms and death. These monkeys have been protected from SIV when previously vaccinated with whole inactivated SIV. Although so far there have been no published reports of successful SIV vaccines, such research can offer clues to what responses are critical to protection from HIV.

Currently, researchers with the support of pharmaceutical companies are pursuing several vaccines. In clinical trials are three core-based vaccines targeting p17 (HGP-30), p24, and killed virus core proteins, and five envelope-based vaccines, four of which target gp160 and one of which targets gp120. In pre-clinical trials are two combination core/envelope vaccines targeting gp160/gag/p24 and three envelope vaccines, two of which target gp160/120 and one of which targets the V3 loop.

**Perspectives for the Future**

To be effective, an AIDS vaccine may have to induce a large concentration of neutralizing antibodies as well as strong CD8+ T-killer cell responses against epitopes from different envelope or core proteins, or from both. Since T-cell responses are more easily induced by core proteins than envelope proteins, identifying core T-killer cell inducing epitopes and developing novel envelope/core combinations would be the logical next step in vaccine development. The appreciation that combinations may be the answer, however, requires a return to basic research to identify effective combinations and to develop ways to package them so they result in synergistic rather than antagonistic responses.

The complex task of vaccine research must be followed by effective distribution. While formulation and cost remain unknown, it is not too early to consider ways to organize and finance distribution so that vaccines may be accessible to all populations affected by HIV in both developed and developing countries.

**HGP-30: From Discovery to California Trials**

HGP-30 is the first synthetic HIV sub-unit vaccine to enter human testing. Rather than relying on an external envelope protein like other vaccines, the main component is a small man-made reproduction of just part of one of HIV's inner core proteins, p17. The discovery of HGP-30 grew out of the discovery in the 1960s of the thymosins, the family of hormones which stimulate immunity and are produced by the thymus gland. Early in the epidemic, researchers observed that in many who died of AIDS, the thymus was destroyed and there were high blood levels of Tα, a thymus-derived hormone. Investigating this paradox, researchers found an HIV core protein, p17 gag, was cross-reacting with Tα, so that hormonal levels appeared to be higher than they were. The blood test that showed elevated Tα levels was actually measuring viral p17 proteins as well.

Researchers surmised that the virus was using similarities between Tα and p17 amino acids to sneak through the immune system. They concluded that the amino-acid region that p17 shared with Tα, may be the "Achilles heel" of HIV.

In 1986, following this discovery, researchers synthesized this region—dubbed HGP-30 for HIV p17 gag protein of 30 amino acids—and coupled it to a KLH carrier and alum to increase potency. The final vaccine formulation called HGP-30-KLH/ALUM was studied in several non-human species including mice, dogs, monkeys, and chimpanzees. In April 1989, after fruitlessly waiting two years for Food and Drug Administration approval to conduct human trials in the United States, researchers began trials in Great Britain. The London trial enrolled 18 healthy, seronegative adult volunteers all of whom completed immunizations and were monitored for more than one year. The vaccine was safely tolerated and blood chemistries were normal. Researchers observed encouraging immune responses in volunteers, including antibodies to p17, T-cell proliferation, and, most significantly, CD8+ T-killer cells armed to recognize and kill HGP-30 and p17 expressing target cells. However, the trials have not yet shown that HGP-30 stimulates neutralizing antibodies. This suggests that a stronger adjuvant, a different dosage, or more booster injections may be required. To pursue these questions, clinical trials have been initiated at the University of California San Francisco (Paul Volberding and James Kahn) and at the University of Southern California (Peter Heseltine) using seronegative volunteers.
Experiences of a Trial Subject

Chris Adams

The first infusion had gone smoothly enough. During a four-hour process, nearly five milligrams of Compound Q (GLQ 223), a highly purified protein from a Chinese cucumber had dripped slowly into my right arm. I had become the twenty-first trial subject in part two of a Phase One study of this promising, new anti-viral treatment. Over the next 24 hours, after admission into the General Clinical Research Center at San Francisco General Hospital, I would be monitored closely, my vital signs checked regularly, blood drawn periodically from the plastic tubing in my left arm.

The admitting nurse ran down a list of questions. Name? Age? Person to notify in case of an emergency? Quick questions and quick answers until: “What do you expect to get from this trial?” The question threw me. I was excited and I was nervous, more nervous than my confident demeanor let on. But what really did I expect? My battles with HIV have been less often related to physical problems, but rather more with the daunting perplexity of the disease. It’s not knowing what’s around the corner that’s so hard. The trial just added another layer of uncertainty. “I really don’t know,” I finally said, an unsure beginning to this 49-day trial.

A Full-Time Job

I had been diagnosed with ARC in early 1987 when I developed severe complications after routine surgery. I had regained my health and my T-helper cell counts had remained stable in the 200 to 300 range for nearly four years. I had tried ZDV (AZT) at different dose levels until anemia forced me to stop. I had taken ddI but developed severe neuropathy. I was told that ddC would probably lead to the same problems. With stable T-helper cell counts and a sense of physical well-being, I sailed along confidently without any anti-viral therapy. But starting last fall the T-cells began to drop until anemia forced me to stop. I had taken ddI but developed severe neuropathy. I was told that ddC would probably lead to the same problems. With stable T-helper cell counts and a sense of physical well-being, I sailed along confidently without any anti-viral therapy. But starting last fall the T-cells began to drop and I had a series of minor but irritating symptoms of immune compromise. With AZT and its analogues out of the question I had to look elsewhere to fight the virus. Compound Q seemed like a good candidate and a clinical trial was my only means of access.

After waiting two months, I received a call from San Francisco General telling me to come in for a screening. The screening lasted 10 hours. I had 14 tubes of blood taken, and received magnetic resonance imaging (MRI), an electrocardiogram (EKG), an electroencephalogram (EEG), and a complete physical. At the end, there was a four-hour battery of neuropsychiatric tests. I left exhausted, but whatever feelings I had of being a guinea pig were more than offset by knowing that these free tests might uncover a lurking opportunistic condition.

A few days later I returned. The results were in and I had just squeaked by the exacting entry criteria. The nurse handed me a schedule for the next month. A day and a half with overnight in the hospital after each weekly infusion. More hours of blood and neuropsychiatric tests. The trial would be my life for the immediate future, a reality I greeted with equal measures of excitement, apprehension, and resignation.

Permission to Feel Bad

I had been told that after the first few infusions I would feel like I had been in a car wreck. This turned out to be an underatement. There were days when I could hardly roll over. Every joint ached. I was weak and feverish. Several times I tried to open jars or bottles and had to give up. I couldn’t grip a can opener. Staircases became major obstacles. These symptoms would largely disappear just before the next infusion only to return afterwards. I put on fifteen pounds of water weight, the swelling inducing carpal tunnel syndrome that prevented me from typing, playing the keyboard or gardening—important activities that help me through rough times.

A big problem was a psychological battle familiar to anyone with chronic illness. Is what I’m feeling a result of the illness or the medication, or is it in my head? Do I really hurt this badly or am I just feeling sorry for myself? These questions drove me crazy. I realize now that the drug truly hit me hard and left me in bad shape. At the time I was beating myself up. I’m not being strong enough, I thought. I should be out of bed working... What I needed most was permission to feel bad.

This problem was exacerbated by financial concerns. As a self-employed writer, when I don’t work, I don’t get paid. I had to borrow money to make it through the month. In the Research Unit, I remember one man who was in a tobacco study asking me how much I was getting paid. “Well, nothing, I’m doing this to save my life,” I said. But in fact, it was costing me money. I lost more than a month of work time and spent 150 hours in trial-related activities. If a drug company can spend $15,000 to $20,000 on labs and hospitalization for a trial subject, surely they can kick in another $500 to $600 to help them with rent.

The Pay Off

The people conducting the trial put in a strong effort to compensate for the pain and suffering. They made me feel that my well-being mattered more to them than scientific data and without their support I would have dropped from the trial. The supervising nurse, with whom I was in contact almost daily, became crucially important, patiently answering any question and as willing to discuss my emotions as my physical condition. The principal investigator treated me like he had a stake in my overall health, as if I had been under his care for years. Both shared information, good and bad, about other patients’ experiences. There was not a trace of condescension. From the beginning I felt like I was a full partner in the trials and not simply the object of an experiment.

The trial process brings me hope and may help solve the riddle of this disease. To do something is to feel in control. To do nothing is to cede control to the virus.

Each time I arrived for lab work, a copy of the latest results was waiting for me. I know that not everyone wants to track, say, the level of their neutrophils, but for me the sharing of this kind of information is important. It helps me feel like an active player in maintaining my health. By contrast, the neuropsychiatric team informed me they would flag any changes in my cognitive functioning, but they never fully explained their tests and never reported results. I know this affected my attitude. For blood work and the MRIs, tests that I would receive reports on, I was a happy and willing participant. I was grudging and ill-humored about the mysterious neuropsychiatric batteries.

Feeling in Control

The trial has ended, and I have elected to receive maintenance doses of Compound Q. I have free, monitored access to a drug that would otherwise be unavailable to me. The side-effects, as I had been assured, have begun to diminish. And my T-helper-cell counts are showing a marked increase. Was it all worth it? In terms of the disease it will take a while to know, but I could answer that nurse’s question about expectations better today.

It’s not so much that I anticipate something definitive like a cure or boundless energy and the tripling of my T-cells. Rather, my expectations are based on the satisfaction of being part of a process, a process that brings me hope and may help solve the riddle of this disease. To do something is to feel in control. To do nothing is to cede control to the virus. I can see surely now that the uncertainty of an experimental drug is better than the unchallenged course of this capricious disease.

Chris Adams is contributing editor at San Francisco Focus magazine who has written about AIDS for the San Francisco Examiner, Oakland Tribune, San Francisco Business and Stanford Magazine.
Recent Reports


While clinical trials are essential for testing vaccine safety and efficacy, they raise ethical issues that are difficult to resolve. A review of the biological and ethical challenges of HIV vaccine development states that concerns about discrimination and liability thwart efforts to enroll volunteers in HIV vaccine trials.

Uninfected participants may fear negative responses from families, friends, physicians, employers, and insurance companies. These fears are based on the fact that any connection to the epidemic can be stigmatizing, and on the possibility that participants will develop HIV antibodies, which may be detectable for life. The presence of antibodies, even when they result from a vaccine trial, could interfere with employment, insurance coverage, military enlistment, foreign travel, blood donation, and obtaining a marriage license.

Volunteer participants are also forced to assume responsibility for the long-term consequences of a vaccine trial. Researchers offer them limited assurances about the possibility of a vaccine’s harmful effects, including HIV infection, and the extent to which researchers and manufacturers will accept liability. Manufacturers and researchers may have to accept unsecured risks, and these may discourage vaccine development, particularly among small firms.

The federal government can foster vaccine trials by educating the public about the process of vaccine development, establishing a climate free from discrimination, and making a commitment to the long-term welfare of trial participants.

In a second article focusing on evaluating the risks and benefits of vaccine trials, the author presents a risk/benefit formula that offers some basis for gauging whether a vaccine is worth pursuing. Risks may be reduced and recruitment may be enhanced when trials use infected rather than uninfected volunteers.

Finding Out about Clinical Trials. Clinical trials provide access to treatments. The following provide information about such trials:

- AIDS Clinical Trials: Talking It Over is a 28-page primer that explains how clinical trials work, who is eligible to participate, and what are the benefits and risks of entering a trial. Copies can be obtained free by writing: National Institute of Allergy and Infectious Diseases, Office of Communications, National Institutes of Health, Building 31, Room 7A32, Bethesda, MD 20892.
- AIDS Clinical Trials Information Service, operated by the U.S. Public Health Service, provides information in English and Spanish on specific federally and privately sponsored trials, including patient inclusion criteria. Call (800) 874-2572, TTY/TDD (800) 243-7012 between 9:00 a.m. and 7:00 p.m. Eastern time.
- National Library of Medicine On-Line AIDS Trials provides access to the AIDS Clinical Trials Information Service via computer database. Call (800) 638-8480 for details, including cost.
- AIDS/HIV Experimental Treatment Directory, a quarterly directory of disease and treatment information, describes ongoing and future trials across the country. Copies can be obtained for $10.00 each, ($30.00 per year) from: AmFAR, 1515 Broadway, Suite 3601, New York, NY 10036, (212) 719-0033.

In addition, physicians in some parts of the U.S. have formed community consortiums to perform and track drug trials. In San Francisco, Davies Medical Center operates Trial Search, a program that matches individuals in the San Francisco Bay Area to clinical trials for which they qualify. Call (415) 565-6386 for information.


While society should address both social issues, such as discrimination and access to care, and epidemiologic ones, such as infection control, it should address these issues separately, according to an editorial on HIV-related public policy. The federal government should establish and fund a program to expand access to health care and extend benefits to all people with HIV infection. In addition, infected individuals should be protected from employment, housing, and insurance discrimination.

When discrimination is countered by statute and medical care is assured, infection control can be pursued. For instance, sexual partners of infected people can be traced and contacted, a strategy that has been resisted even though it makes epidemiologic sense and is consistent with the response to other sexually transmitted diseases (STDs). All pregnant women and newborns should be screened for HIV antibodies to help them make more informed choices and to provide earlier treatment for infected infants. Health care providers should be screened because patients have a right to know the serostatus of those who perform invasive procedures, and hospitalized patients should be screened to identify those with whom providers must be most careful.

The editorial draws on two commentaries in the journal. The first forecasts an end to HIV “exceptionalisn,” by which HIV disease is viewed differently from other STDs. Exceptionalism is waning; for instance, health officials increasingly endorse reporting seropositive, as well as AIDS, cases to the government. The second commentary supports antibody testing of health care workers, but argues against routine testing of hospitalized patients.

Next Month

The topic of suicide has recently become more prominent in the public consciousness. The Kevorkian “suicide machine,” the Nancy Cruzan right to die case, and the New England Journal of Medicine story of a physician’s dilemma about assisting in a suicide, have all raised public debate. In the August issue of FOCUS, Doug Conaway and David Paisley, BSW, former Director and current Director, respectively, of the AIDS/HIV Nightline in San Francisco, discuss those instances in which suicide is a cry for help and how a suicide prevention hotline acts as an opportunity not only to stop suicide, but also to offer HIV-related counseling.

Also in the August issue, Lee R. Slome, PhD, a Psychology Associate at Pacific Presbyterian Medical Center in San Francisco, and Jeffrey Moulton, PhD, Director of the Psychological Services, HIV Evaluation, and Treatment Team at Letterman Army Medical Center, report on physician attitudes toward facilitated suicide. They also discuss ways medical and mental health professionals can evaluate their options when faced with suicidal patients who ask for assistance in killing themselves.