FOCUS A GUIDE TO AIDS RESEARCH

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Whether to Take Experimental Drugs: Counseling Issues

William J. Woods, PhD

Almost from the very beginning of the AIDS epidemic hopes and expectations have been placed on promising treatments. Though the media continually reminds us that AIDS has "no known cure" and is "100% fatal," those closer to the epidemic realize that the true picture is not quite so simple.

With increasing knowledge about the disease, its cause, and its many manifestations, patients and their health care providers now face increasingly complicated medical options related to HIV infection. For many, these expanded treatment options result in more conflict and confusion than comfort.

Conflicts and Confusion

Previously only people diagnosed with AIDS struggled with the decision to take drugs; now people at all points in the spectrum of HIV infection face this question. At least three recent developments pressure seropositive individuals to consider treatments: (1) several studies indicating that, over time, most seropositive people will develop symptoms; (2) recommendations by treatment information groups and several physicians for testing and early treatment intervention; and indirectly, (3) efforts to lobby the government and pharmaceutical companies for treatment research.

Despite the developments, no consensus has developed on major issues related to experimental treatment. Discussion of these issues is influenced by the distrust felt by segments of at-risk populations for the established medical and political forces responsible for testing and marketing treatments. Without consensus on treatment approaches and timing, individuals infected with HIV often feel that time is running out while they struggle with a decision.

Treatment Classifications

At this time there are several treatment alternatives which an individual infected with HIV may consider. These include antivirals, immune stimulants, and prophylactic treatments for specific opportunistic infections. Antivirals are expected to improve the medical condition of the individual by fighting HIV at some stage in its reproduction. Many people infected with HIV, hoping to increase fighting power of a given treatment, take more than one antiviral at a time but these combinations may be antagonistic. For example, ribavirin should not be taken with AZT because it has been shown (in vitro) to interfere with AZT's activity in fighting the virus.

The purpose of immune stimulants is to rebuild what the virus has destroyed, since HIV causes destruction of immune cells. Though many immune stimulants are currently under investigation, there is controversy about their use. For instance, some physicians theorize that immune stimulants may provide fuel for the virus by stimulating the cellular machinery that facilitates viral replication. There is also debate about the quality of the new cells produced in terms of their ability to fight the virus. There is a general consensus among health care providers and treatment advocates that antivirals should be used before starting any of the immune stimulants.

There are many therapies under consideration which show promise for preventing the onset of certain opportunistic infections, specifically, aerosol pentamidine for *Pneumocystis* pneumonia and clofazimine for *Mycobacterium avium-intracellulare*. These drugs can usually be prescribed by a physician outside a clinical trial.

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Treatment Options

There are six viable treatment options for people infected with HIV and living in developed countries: (1) enter a clinical drug trial, (2) obtain prescriptions from private physicians for treatments already approved for use with either HIV-associated or other illnesses, (3) join a "buyers' club" or "guerrilla clinic" (organized individuals who provide as yet unproven treatments and information), (4) import treatments not yet approved in their own country, (5) take approved or experimental treatments to prevent the development of opportunistic infections, or (6) "wait and see."

Most physicians are comfortable with either prescribing a drug approved by the Food and Drug Administration (FDA) or entering a patient in a clinical trial since they consider these options responsible and reasonable. Nevertheless, people entering clinical trials should realize that they may be given a placebo, or another drug of unproven efficacy.

The widespread use of experimental drugs outside of clinical trials in many countries creates some concern that the validity of research trials has been compromised. Often, if participants determine that they are on the placebo (or the unproven treatment), they make decisions to use other treatments as well or instead, without informing the researchers. Individuals considering participation in a clinical trial should fully understand the elements of the study and commit themselves to observing the restrictions of the trial.

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THE AIDS HEALTH PROJECT

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Experimental Drugs . . .

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Using experimental treatments outside of supervised clinical trials is less comfortable for many people; somehow it seems "wrong." Much of the media coverage of these alternative treatments implies that they are underground, illegal or black market. While there may be some cases in which people are engaging in illegal activity, the vast majority of those acquiring, importing and using these treatments are doing so legally. To continue to treat such use as legally questionable is misleading and unfair since it further burdens the individual's already difficult medical situation. For patients, the clear advantage to obtaining experimental treatments outside of supervised clinical trials is knowing they are getting the specific substance under investigation rather than a placebo.

Finally, many individuals after consideration of the options choose to "wait and see." There are many possible reasons for this outcome: getting lost in the thicket of decision-making, procrastination, using denial as a primary coping skill, or deciding the potential risk of taking a particular treatment is not outweighed by the potential benefit. At this point all treatments are experimental. Even the highly toxic AZT, though approved by the FDA, may be considered experimental in some circumstances since little is known about its long-term use, especially for people who are infected but asymptomatic. Clearly, individuals may choose to wait for evidence that a particular treatment does in fact make a difference and is safe to use.

Counselors can help insure that their clients make informed choices that fit their understanding of the disease and their view of how to be responsible for their own health. These clients need support and encouragement to take as much time as they need to make decisions and to do so on their own without undue influence from others.

Risks and Benefits

Health care providers can help their clients by assessing the benefits and risks of using experimental treatments. Benefits to taking experimental treatments may include:

(1) the possibility that one is, in fact, slowing the disease progress;
(2) a sense of doing something, of taking responsibility, to slow the progress of HIV;
(3) lessening of isolation by feeling a part of a "social movement" and not being "left behind"; and
(4) the positive psychological effect of observing possible improvements.

Risks to taking experimental treatments include:

(1) wasting time, energy and money on useless treatments;
(2) losing hope if a treatment used is shown to be ineffective;
(3) creating tensions between the patient and physician in treatment decisions;
(4) toxic drugs may do more harm to the individual than to HIV; and
(5) drug combinations may do nothing or, instead, worsen the condition.

Structure of the Decision-Making Process

The first stage of decision-making is to acquire information. Delaney, Goldblum & Brewer (1987) suggest several important questions to consider regarding any treatment: (1) What evidence is there that the product works? (2) What is known about its side effects? (3) What is being done to get the product licensed for use? (4) What are the motives and background of the suppliers? (5) What does the official medical establishment think of the solution being offered, and why? (6) Who can I talk to who has used the product, and how long have they used it? Also, most people will want to consider how much time and money it will cost to use a treatment. Stretching limited resources for unproven treatments may be detrimental to the overall quality of life.

After learning about various alternative treatments, counselors might assist individuals by determining what other information or guidance is needed before a decision can be made, establishing a follow-up review date to consider whether circumstances have changed, and discussing under what circumstances (for example, increased anxiety or appearance of new symptoms) treatments would likely be pursued.

For those who decide to pursue treatment, the structure of the process depends on the individual's medical status. If they are infected, they should establish the medical facts as soon as possible: what do antibody, antigen and t-cell count test results suggest about their medical status? Those who choose to wait until after an AIDS or ARC diagnosis should continue to learn about treatment alternatives and signs and symptoms of the various opportunistic infections. The decision-making process is dynamic due to the mutable nature of the information base and the individual should work with a physician who is willing to assist with this process and to monitor the use of *all* treatments used.

Action Plan

Because working closely with a physician is imperative for everyone using treatments, clinicians will sometimes need to assist in identifying available and knowledgeable physicians for their clients. Most physicians are willing to work with their patients to try to understand the very complicated situation of HIV infection and treatment. Mental health professionals may be useful resources in teaching patients and physicians to negotiate these new, more active and responsible roles.

Depending on the treatment regimen chosen, the task of acquiring the treatment can range from very simple to very difficult. AZT is now a prescription drug as are many of the other available experimental treatments. Clinical trial participation can also provide easy access to the treatment, depending on the site of the trial. However, many of the available experimental treatments are more difficult to acquire. Some require contacting special groups organized to make the product available, while others require relatively frequent travel to foreign countries. Finally, the cost of treatment itself or of obtaining it may be prohibitive.

Support from other people who are seropositive, or who have AIDS or ARC, can be an important part of both the decision-making and action plan. Most large American and European cities have organizations and support groups where people with similar health status can meet and share information and experiences. These meetings can help also to reduce the sense of isolation and fear.

Conclusions

Decisions about medical interventions for HIV require knowledge of one's medical status, information on available treatment options, and awareness of the mechanisms for appropriate use and monitoring of treatments. Until definitive medical answers for treatment are found, the individuals faced with these decisions will look to professionals for assistance in this important decision-making process.

Some of the militancy that many gay men express about the AIDS treatment issue is due to the perception, and emerging scientific opinion, that without an effective treatment a whole generation of gay men will likely die of AIDS. There is a sense that the whole community, an extended family, is being wiped out. Thus, health care providers and their clients continue to place their hopes and expectations on promising treatments. Clinicians, then, might see their role not only as one of providing information and structure for the decision-making process, but also as one of promoting and maintaining hope.

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Delaney, M., Goldblum, P., & Brewer, J. *Strategies for Survival: A Gay Men's Health Manual for the Age of AIDS.* New York: St. Martin's Press, 1987.

Helquist, M. "The Helquist Report: Experimental Treatments," *Advocate*, Dec. 8, 1987.

INFORMATION AND RESOURCES:

1. *AmFAR Directory of Experimental Treatments for AIDS and ARC* (40 W. 57th St., Ste 406, New York, NY 10019; 212-333-3118)
2. Project Inform's Hotline (US: 800-822-7422; CA: 800-334-7422)
3. *AIDS Treatment News* (415-282-0110)
4. Gay Men's Health Crisis (132 W. 24th, New York, NY 10011; 212-807-6664)
5. New York PWA Coalition (Box 234 70-A Greenwich Ave., New York, NY 10011; 212-995-5846)

Diagnosis/Treatment/Prevention

The Value of T-Cell Testing in HIV-Infected Patients

John F. Krowka, PhD

Laboratory analysis has revealed multiple abnormalities in the immune systems of individuals who have been infected by the human immunodeficiency virus (HIV). One of these abnormalities, a reduction in the number of helper T-cells, is characteristic of exposure to HIV and is used commonly as a marker of the progression from primary HIV infection to AIDS. An understanding of helper T-cells in HIV-infected individuals can be useful for health care providers and patients in making informed decisions about disease progression and use of experimental treatments. It should be noted, however, that helper T-cell testing alone is not a surrogate marker for HIV infection and results should be interpreted in light of knowledge of the patient's HIV status.

What are Helper T-Cells?

The immune system is basically a defense system that functions to eliminate microorganisms and cancer cells from the body. It is composed of various types of white blood cells that have distinct and coordinated defensive functions. Cells of the immune system that mature in the thymus gland before being released into the blood are called T lymphocytes. One type of T-cell, the helper T-cell (also called a CD4 or T4 lymphocyte), provides essential supportive functions for many of the other cell types in the immune system. Helper T-cells rarely participate directly in the elimination of foreign substances from the body. However, without their assistance many other cell types of the immune system are unable to function successfully.

Helper T-cells are the major targets for infection by HIV. The outer coat protein of HIV is physically complementary to the CD4 protein located on the surface of helper T-cells and several other cell types in the body. These two proteins fit together in a lock-and-key fashion, enabling HIV to selectively infect these cells. Then the virus slowly multiplies and progressively destroys other helper T-cells. Although helper T-cells constitute only about one-sixth of the white blood cells, their destruction by HIV profoundly impairs the defensive functions of the entire immune system. Monocytes are another type of white blood cell that have the CD4 protein on their surfaces and are also susceptible to HIV infection. This infection of monocytes by HIV may also contribute to immunologic abnormalities in infected individuals.

Laboratory methods have been developed during the last decade to count the numbers of helper T-cells in blood samples. After the red blood cells are removed, the remaining white blood cells are mixed with a fluorescent compound that binds specifically to the CD4 protein on the surface of helper T-cells. Under ultraviolet light, these labelled helper T-cells glow brightly and can be counted using a microscope or by semi-automated methods. Variations in the details of this procedure may contribute to differences in test results from different labs. The immune system is dynamic, adapting the numbers of some cell types in its arsenal in order to meet the body's changing defensive needs, so the absolute number varies from day to day. Five hundred to 1500 helper T-cells per microliter (μl) of blood constitutes the normal range for healthy people who have not been infected by HIV.

Lower Helper T-Cells = High Risk For AIDS

Studies of gay men in San Francisco [1] demonstrate that there are subnormal numbers (less than 500/μl) of helper T-cells in many HIV-infected individuals. In contrast, the numbers of helper T-cells in HIV-infected hemophiliac patients and infants are more variable. In both gay men and patients with hemophilia, the numbers of helper T-cells are associated with the duration of time since exposure to HIV. The San Francisco studies indicate that these men lost a median of 107 helper T-cells per μl each year [1]; individuals, however, may vary greatly from this rate of decline. In general, most HIV-infected individuals lose helper T-cells with the passage of time.

The association of low helper T-cell numbers and the appearance of HIV-related symptoms is not absolute.

The decline in helper T-cells often parallels the appearance of many types of HIV-related disease symptoms in infected individuals. These symptoms include persistent fevers, sweats, fatigue, weight loss, oral lesions, diarrhea, herpes zoster (shingles) and other disease manifestations that are generally categorized as AIDS-related conditions (ARC). These symptoms often occur in HIV-infected individuals with 400 or more helper T-cells per μl but are more frequently observed in persons with lower numbers of helper T-cells. Many studies indicate that HIV-infected people with less than 400 helper T-cells per μl are very likely to develop AIDS. In San Francisco, 78% of HIV-infected gay men with less than 200 helper T-cells per μl developed AIDS within three years. Thirty-five percent of individuals with 200-400 helper T-cells and 12% with more than 400 at the beginning of this study developed AIDS during this period of time. [1] The survival times of patients diagnosed with AIDS are generally longer in individuals with higher helper T-cell numbers.

The association of low numbers of helper T-cells and the appearance of HIV-related disease symptoms is not absolute. Some asymptomatic HIV-infected individuals have less than 200 helper T-cells per μl; rarely, some persons with AIDS may have more than 500 helper T-cells per μl. The progressive decline of helper T-cell numbers in many HIV-infected individuals cannot be charted along a straight line. Many "peaks and valleys" are seen in helper T-cell numbers during the years after HIV infection, though as time progresses the peaks become fewer and a trend toward chronically decreasing helper T-cell numbers becomes predominant.

Uses of Helper T-Cell Tests

Helper T-cell tests constitute an important part of the immunologic evaluation of HIV-infected individuals. These tests are most useful when evaluated by a knowledgeable physician in the context of other symptoms of HIV infection. These tests should be performed in the same lab at about six-month intervals or more frequently if disease symptoms are progressing. Testing at multiple time points can indicate trends and rates of immunological deterioration. Helper T-cell tests are not a substitute for regular physical exams; however, they may help

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detect individuals at very high risk of developing AIDS who would not be identified by physical examination alone.

Currently, HIV-infected individuals with less than 200 helper T-cells per microliter may be eligible to obtain the antiviral drug, AZT. Helper T-cell tests are useful as an indicator of immunologic improvements in HIV-infected individuals who are receiving AZT or other therapies. If helper T-cell levels continue to decline in the presence of increasing symptoms of HIV-infections or side-effects of drug therapies, modifications of therapeutic regimens may be warranted.

Conclusions

The decision to undergo helper T-cell testing can be an empowering experience for HIV-infected individuals. Testing can help individuals realistically confront the prognosis of their HIV infection and the results can be used to make informed decisions. Some HIV-infected individuals with relatively high helper T-cell numbers may wish to wait until more is known about experimental therapies before beginning treatment, while those with documented decreasing trends may wish to begin treatment. Counseling is advisable for HIV-infected individuals to understand the results of helper T-cell tests and to use them in an appropriate manner. Although helper T-cell test results need to be interpreted cautiously, the usefulness of these tests makes them advisable for everyone who has been infected by HIV.

John Krowka *is an Assistant Research Immunologist in the Department of Laboratory Medicine at UCSF and is supported by a grant from the California Universitywide AIDS Task Force.*

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BRIEFS

Recent Reports

Improvements Reported with Regimen of AZT and Acyclovir. As earlier laboratory studies showed that the anti-Herpes drug, acyclovir, potentiates the antiviral activity of AZT, researchers evaluated the results of treatment of eight ARC or AIDS patients with a combination of AZT and acyclovir (*Annals of Internal Medicine*, April 1988). If equivalent anti-HIV activity was obtained with this drug combination, the likelihood of serious side effects would be diminished with a lower dose of AZT.

Eight individuals participated in the study, two of whom dropped out after the first week due to opportunistic infections. The remaining subjects were treated with AZT alone the first week and with a combination of AZT and acyclovir the following nine weeks.

The researchers reported that AZT and acyclovir acted independently of each other, showing no added toxic effects. No adverse neurological side effects were reported other than minor and reversible complaints. There was an overall mean weight gain after 10 weeks and most felt subjectively improved. All six patients elected to continue treatment. In the weeks subsequent to the initial testing period, two patients developed hematological toxicity, one of whom required a transfusion. Both participants subsequently were issued dose reductions, while the other four remained on the original regimen.

The results of this small study suggest that the lowered doses of AZT, when combined with acyclovir, induced virological, clinical, and laboratory improvements. These included an increase in the number of helper T-cells, greater skin test reactivity, and the clearing of HIV p24 antigen (in the two patients who originally had measurable p24). The reasons for the potentiating capacity of acyclovir are unknown. However, the authors repeatedly stress that this is too small a number of subjects from which to base definitive conclusions and strongly recommend that these combinations not be used except as part of research protocol.

HIV Antigen Level in AZT Treatments of Asymptomatic Individuals In the February 20, 1988 issue of *Lancet*, researchers from the University of Amsterdam reported the effects of a lower, less frequent dosage of AZT, with or without acyclovir, on eighteen HIV-infected, asymptomatic individuals. The study demonstrated that frequent dosage is not necessary to inhibit replication of HIV; the amount of HIV antigen declined in blood samples from all but one patient treated with AZT. Additionally, there was a striking regression of lymph node sizes in the patients treated with AZT and a modest increase in the helper T-cell population.

Toxicity was reported to be mild and infrequent. Two patients required a transfusion of packed red blood cells, one of whom had a history of needing transfusions. In this study, acyclovir did not seem to influence serum antigen levels, though the authors acknowledge that the subject size was too small to reach firm conclusions about the efficacy of a treatment regimen of acyclovir administered in combination with AZT.

Next Month

There is a large group of people experiencing severe stressors associated with the epidemic in addition to those actually sick with AIDS: those who know and are close to people with AIDS. In the June issue of **FOCUS, John L. Martin, PhD, MPH** will discuss the impact of AIDS-related deaths and illnesses on gay men in New York City. John Martin is the Director of the AIDS Research Unit at the Columbia University of Public Health. In addition, **Kitsy Schoen, LCSW** and **Ellie Schindelman, MPH** will provide information on the grief process, including some of the more serious problems which can develop, and discuss how caregivers can help. Kitsy Schoen is the Bereavement Coordinator for the AIDS Homecare and Hospice, Visiting Nurses and Hospice of San Francisco and Ellie Schindelman is a Health Education, Training and Organizational Development Consultant in Berkeley, California.

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