Treatment and Prevention of AIDS

John Ziegler, MD

Treatment strategies for patients with AIDS and AIDS Related Conditions (ARC) are aimed at three broad targets: prevention of infection by the AIDS retrovirus; prevention of damage to the immune system; and treatment of complicating illnesses such as opportunistic infections and cancer.

At the present time, the most important and most successful approach is to prevent infection in the first place. We know that the AIDS retrovirus is spread in two ways: by blood or blood products from infected individuals and by sexual transmission. In the United States the epidemic has remained confined to individuals in certain risk groups who may be exposed to the virus through contact with contaminated blood or blood products. These persons include blood transfusion recipients, infants of infected mothers, hemophiliacs, and intravenous drug abusers who share contaminated needles. In this country sexual transmission is most common among gay and bisexual men (particularly those who have had many partners and who have exchanged semen during anal intercourse). Heterosexual transmission is rare in the United States; it seems to occur mostly in female partners of infected males. There is no evidence of casual spread of the virus either within or outside of these risk groups.

The development of a test to detect persons who have antibody to the AIDS retrovirus (and therefore are presumed to be infectious) has permitted screening of blood donors. This measure has effectively safeguarded the blood supply. Blood products are also heat-treated, a process which inactivates the virus.

The prevention of exposure to the virus in other risk groups through education and behavior modification has been more difficult. Public health measures, such as closing bath houses to discourage high-risk sexual activities and supplying sterile needles to intravenous drug addicts, engender social and political controversy. Educational measures, such as pamphlets, media messages, and counseling, have made some headway, particularly in discouraging unsafe sexual activity among gay men. Ongoing studies by the San Francisco AIDS Foundation (1) and by San Francisco researchers (2) have documented substantial changes in reported sexual behavior among gay men. Studies from other American cities report similar shifts to low-risk activities. There remains, however, a great deal more to be accomplished in the area of primary prevention.

In San Francisco the prevalence of AIDS antibody among an estimated 10,000 intravenous drug addicts is about 10%. The Department of Public Health has undertaken programs to prevent further spread of the virus in this group.

The next obvious preventative measure is a vaccine. The phenomenal progress in the field of molecular biology in the last decade has permitted the cloning (obtaining a group of identical items from a single original) and sequencing of the AIDS retrovirus; thus we know its molecular anatomy, or structure, in some detail. The most vulnerable portion of the virus, its outer "envelope" protein, seems to vary considerably in different isolates. Scientists are now searching to find a "constant" portion of the viral envelope that could be used as a vaccine. The development and testing of vaccines may take from several years to more than 5 years. In the test tube, the AIDS virus will kill its host cell, although some cells may escape and enter a state of "latent" infection in which the virus remains but does not actively reproduce. The virus can then be reactivated in these cells by various stimuli.

Although we do not understand what happens in the body, we can infer that the chain of events is similar to what happens in test tubes: infected T-cells producing virus (estimated to be about one in a thousand cells) are killed. Cells containing latent virus may become reactivated with time, so that replicating virus can infect other T-cells. The net result is a slow but relentless destruction of the entire helper T-cell population. Researchers presume that other infections or stimuli that disturb the immune system can act as cofactors and aggravate the latent state by periodically reactivating virus production.

There are a number of other theories that may explain the progressive immune destruction in AIDS. These include an "autimmune" attack by the immune system itself against the infected helper T-cells, alterations of the immune response by viral products released into the circulation, and direct disruption of immune function by the virus. Given the current limitations to our knowledge, it is safe to say that the ultimate cause and course of the immune system dysfunction is unknown. Therefore, it is difficult to devise specific therapies to avert immune impairment.

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Anti-viral Therapy

One potentially promising approach is to inhibit viral reproduction with antiviral drugs or with specific antibodies. There are compounds that inhibit the activity of the viral enzyme, "reverse transcriptase," that is essential for reproduction. Another drug may attack the "proviral" stage when the genetic material of the virus is integrated into host cell DNA. Other agents apparently attack the virus physically and alter its envelope coating. All of these drugs were discovered in the laboratory, and their effectiveness and toxicity in man are unknown. At the same time, many laboratories seek neutralizing antibodies that attach to the virus and prevent its infectivity.

The exact mechanism by which this state of immune dysfunction occurs has been elusive, but all evidence implicates the helper T-cells and another set of cells known as macrophages. In particular, the helper T-cells fail to recognize antigens, or foreign substances, and fail to make an important hormone called interleukin-2 (IL-2). This hormone acts as a signal to other T-cells to respond to the antigen. However, clinical trials of IL-2 treatments have been disappointing. Much more must be known about the cause and course of the immune deficiency in AIDS before other treatments with immune stimulators are tried.

Treatments with the experimental drug or placebo must be made by random methods, since investigators would introduce a bias by selecting patients themselves. While these methods may seem cumbersome to the non-researcher, the inferences made from the trial must be sufficiently convincing to bring about a change in treatment practices.

A patient who agrees to enter a trial must know that the treatments offered are either "state-of-the-art" or an experimental treatment whose effect and toxicity are unknown. As a trial participant, each subject becomes a courageous partner with the investigator in the scientific pursuit of better therapy.

Immunomodulators

Early in the epidemic researchers recognized a progressive imbalance in the T-lymphocyte populations and a wide array of immunologic dysfunctions. Many investigators felt that stimulation of the faltering immune system by various agents known to augment immune reactions might be therapeutic. A large number of such immunomodulators were tested in the clinic, but there were no consistent benefits in any patient. We now know that this approach must be reexamined.

The immune system does not operate in an on-off mode; it is in a state of dynamic equilibrium. When perturbed by any foreign stimulus, a swift response involving several different cooperating cells is set in motion. With AIDS these cells are disoriented and preoccupied.

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Treatment of Illnesses

The final strategy is to treat the many illnesses that result from immune deficiency. The most dangerous of these are the opportunistic infections by microbes that do not cause disease in persons with normally functioning immune systems. Successful treatment for opportunistic infections requires collaboration between antibiotics and host defenses. In an individual with a damaged immune system, treatment must be prolonged and intensive; in AIDS patients these treatments often have significant side effects. Despite these obstacles, a number of clinical trials have succeeded in slowing infections and producing clinical improvement. Unfortunately, relapse and simultaneous infection with several microbes are common. Thus the prognosis for patients with opportunistic infections is poor. Present trials attempt to identify individuals at high risk and to treat them "prophylactically" with suppressive antibiotics to prevent infection.

Patients with AIDS, and particularly gay men, are also plagued by two types of cancer, Kaposi’s sarcoma and non-Hodgkin’s lymphoma, a cancer of the lymph system. These neoplasms prey upon persons with damaged immune systems. Unfortunately, usual treatments involve the use of medications that cause disturbances in the immune system. Thus, physicians must walk the fine line between effective therapy against the cancer avoidance of further damage to the immune system.

Effective treatments for Kaposi’s sarcoma include radiation therapy; various medications such as etoposide, vinblastine, vincristine, bleomycin; or biological agents, such as interferon, that have relatively mild side effects. A new treatment trial for lymphomas has also been developed at UCSF. As in antiviral trials, these studies will require large numbers of patients to draw valid conclusions about the success of treatment.

In summary, the outlook for treatment of AIDS shows early promise in several areas. The most important single objective is to prevent infection in the first place, through education, counseling, and behavior modification of high risk groups. In addition, knowledge of the molecular anatomy of the virus has contributed greatly to vaccine development. A major mystery still surrounds the exact mechanism of immune failure in AIDS, and this gap in understanding has been an obstacle to rational treatment of the immune disorder. Many effective treatments are at hand for the infections and neoplasms that complicate AIDS, but ultimate success will depend on reversing the immune deficiency. In all of these areas, we are entering an era of clinical trials that will involve rigorous, controlled studies in the pursuit of safe and effective treatment.

John Ziegler, MD is the Director of the UCSF AIDS Clinical Research Center. The center coordinates drug trials among its three teaching hospitals and in the community.

REFERENCES:

Diagnosis/Treatment

Four Phases of Testing

Robert J. Wong, Pharm D

Offering clinical drug trials is an important part of medical care for AIDS patients at San Francisco General Hospital. Although the trials of potential AIDS treatments command much media attention and public interest, the procedures for testing these drugs conform to a long-established, scientific regimen for all new medications. New treatments for cancer and heart disease, for example, must undergo the same multi-tiered testing for safety and efficacy as do the several potential AIDS therapies.
Once a new agent has been discovered, researchers subject it to a step-by-step rational investigation that begins with laboratory testing (in vitro studies) and may progress to trials with live subjects (in vivo studies) using animals and then to four phases of tests with human subjects. The pre-clinical trials in the laboratory and with animals help to identify side effects, determine reasonable starting doses, and define the potential activity of an agent. The process helps to focus the goals of future human experimental studies.

Phase I

Once initial information is available from animal studies, drug agents must be tested in a number of studies in order to answer specific well-defined medical questions. The first human trial is classified as a Phase I study, one that looks at drug toxicities and their relationship to medication doses, usually in incremental dosage steps. The initial human dose can be either one-third of the lowest toxic dose (mg/kg) in the most sensitive large animal species (such as a dog or a monkey) or one-tenth the dose (mg/kg) that has been found to be lethal in small animals (such as a rat). The remaining dosage steps may be serially doubled (or increased in a logical fashion) to complete the dosing range to be tested.

Phase I studies define pharmacokinetics (how the drug is handled by the body) in addition to determining the ideal method of administration. Phase I trials are not designed to determine efficacy. Patients eligible are usually those who have been unsuccessfully treated with standard treatments if available, but subjects must have competent organs that are targeted for potential toxicity. An example of an ongoing phase I trial is with the drug HPA-23; the study has four incremental dosage steps and is gathering toxicity information.

Phase II

If phase I trials are successful, phase II trials may be undertaken. Study goals include further monitoring of drug toxicities, defining clinical efficacy and pharmacology. Usually patients are selected based on disease type. Phase II studies may either test the investigational agent alone, test the agent compared to another treatment with known results, or test the agent with the option to offer a patient another treatment if there is no response to the experimental agent.

Four categories of criteria have been established to measure the response in these trials. The criteria range from a complete disappearance of all demonstrable disease to a partial response (up to one-third of the patients may respond on average). The final two criteria involve no changes in the size of any measurable lesions or a response of less than 50% and a response of less than 50% but no more than 50%.

Phase III

Phase II studies compare the new agent to a placebo to insure that the drug has merit over and above the placebo response (up to one-third of the patients may respond on placebo). These studies are usually randomized and double-blinded to decrease investigator bias; thus neither the subjects nor the investigators know who is receiving the new agent or who is getting the placebo. This phase of study is one of the most controversial since half of the patients will not be receiving an active treatment that has proven to be somewhat efficacious.

The trial must also show that the new agent is either more effective than the standard treatment that is currently available, or is equally effective with a lower incidence of side effects. This insures that new agents, if approved by the Food and Drug Administration (FDA), will be a useful addition to the pool of drugs available for treatment of specific diseases. An example of a phase III trial is with Ribavirin. The last phase of study development occurs after the drug is FDA-approved.

Phase IV

Phase IV studies may be conducted to evaluate long-term efficacy and safety. An example of this phase is with patients who have herpetic lesions and are being treated with Acyclovir for more than six months simultaneously.

In conclusion, investigational drug trials are closely monitored to assure that patients receive quality medical care and to guarantee that the study is conducted in a logical fashion to guarantee meaningful results.

Robert A. Wong, Pharm D, is a clinical research pharmacist at San Francisco General Hospital.

REFERENCES:


Protocols and Patients

Deborah A. Hahn

Patient needs for new and improved treatments and for protection as research subjects determine what clinical trials are proposed and what steps must be taken to activate them.

Principles of science and ethics as well as human compassion must be considered in the design of AIDS clinical trials. Investigators must attempt to provide treatment protocols for as many patient groups as possible (for example, those with AIDS Related Conditions, Kaposi’s sarcoma, and Opportunistic Infections) to meet increasing demand. They must also maintain a focus on the scientific questions at hand.

A Brief History

Drug selection for any clinical trial is determined by data from prior animal and/or human studies demonstrating acceptable toxicity and some evidence of efficacy, justifying further investigation. Kaposi’s sarcoma, a type of cancer, was the initially presenting AIDS associated disease, so it was logical to investigate chemotherapy drugs. When the underlying problem was identified as an acquired immune deficiency, drugs believed to stimulate the immune system were tested. With the discovery of the viral etiology of AIDS, investigational antiviral drugs and drugs with antiviral components used as standard treatment for non-AIDS related problems were selected for AIDS trials. Once some patients began to either self-medicate with agents such as vitamin C or received drugs from outside this country such as HPA-23, a few protocols were developed to study these drugs.
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Protocols Development

Physician investigators establish protocols either independently or in collaboration with pharmaceutical companies interested in marketing the drug. Most AIDS drug trials have been sponsored and funded by private industry; in some cases the federal government has provided funding. A few independently generated studies have not been funded at all. SFGH is often one of a number of centers participating in a clinical trial requiring many patients in order to obtain statistically significant results (e.g. randomized placebo controlled efficacy study). All of the participating investigators contribute to the design of the trial, and the sponsor determines the final protocol guidelines.

Investigational drugs must be approved by the FDA for use in clinical trials, and the protocol itself, including the patient informed consent form, must be approved by the UCSF Committee on Human Research, a patient advocacy review board. Two to six months are usually required for the full process from the initial “concept review” of a proposed study to the final approval and activation of the protocol.

Patient Selection

Patients are selected for AIDS clinical drug trials by the written guidelines of the protocol. While every effort is made to offer treatment to as many patients as possible, the goal of clinical research is to collect meaningful data from which more can be learned. Unfortunately many patients may be interested in a specific drug trial for which they are not eligible. The pursuit of knowledge for the benefit of many may not always be the same as providing a last hope for one.

Patients interested in participating in a drug study should be seen in Ward 86 at SFGH (call 821-8830 for appointment). If their doctors or nurse practitioners feel they may be a candidate for a study in development, their names will be added to a list of patients to be contacted and fully evaluated at a later time when the protocol is closer to activation. This is not a “first come, first served” list; all patients are considered. If there are more eligible patients for a study than there are openings, selection is made randomly. If a patient is eligible for an on-going trial, screening and initiation may occur immediately. In addition to being in a certain disease category to qualify, patients must undergo several laboratory tests and an extensive physical exam, meeting certain clinical criteria to qualify. All patients must give written informed consent prior to being entered into the study.

When on study, dosing schedules and other procedures for clinic visits and lab work are clearly explained to the patient by the medical provider and the protocol manager, a person employed at the clinic to ensure that the study operates smoothly. Ward 86 has its own laboratory, pharmacist, and social service/counseling group; and patients are encouraged to contact them with their questions and for support. Most clinical trials are funded well enough that all clinic visits, lab work, and the drug itself are provided at no charge to the patient.

Leaving A Study

Patients can be taken off a study (that is prior to designated termination) for any number of reasons. A patient may simply decide against further participation at any time because of perceived unacceptable effects or for no stated reason. The physician may remove a patient from a study due to objective evidence of unacceptable or life-threatening drug toxicity or because of progression of disease. Having participated in one drug trial does not necessarily disqualify a patient from taking part in another subsequent trial, but usually one to three months must pass before a second drug trial can be initiated.

Current information on the AIDS clinical drug trials program at SFGH can be obtained by calling (415) 821-5531.

Deborah Hahn is Clinical Trials Coordinator of the AIDS Activities Division at San Francisco General Hospital.

BRIEFS

RECENT REPORTS

AIDS Education Survey In SF Schools. The largest and most comprehensive needs assessment conducted by any school district in the United States has revealed the AIDS education needs of San Francisco high school students. More than 1300 questionnaires were completed by students during Family Life Education classes in ten high schools. Although the survey occurred last year and thus does not reflect a likely increase in AIDS awareness since then, the study found that students need AIDS information and that they are willing and eager to receive it.

An overwhelming majority of the students (88%) felt AIDS information should be included in the school curriculum, but only 35% reported that they had received some instruction about AIDS. Most students understood that AIDS was an immune deficiency disease and that it could be transmitted by sexual intercourse and by receiving infected blood transfusions. However, more than one third of the students thought AIDS could be spread by using someone’s personal belongings and 40% were unaware that proper use of a condom during sexual intercourse could lower their risk of getting AIDS.

When the student sample was divided into those who had received AIDS education in school and those who did not, the informed group scored markedly better. The survey was conducted by Dr. Ralph DiClemente and his colleagues at UC San Francisco in conjunction with Joan Haskin of the San Francisco Unified School District.

The amount of research information now appearing in the medical and lay press stagers most AIDS health care and service providers. This newsletter represents an attempt to place much of the data and press reports in a context that will prove meaningful and useful to its readers. Suggestions and comments are welcome and encouraged. Please address correspondence to Editor, AIDS Health Project; 333 Valencia Street, 4th Floor; San Francisco, CA 94103. For information about other AIDS Health Project programs, call (415) 626-6637.

NEXT MONTH

As the AIDS epidemic continues to grow, it impacts all segments of society with complex social, ethical, and psychological challenges. Private practitioners, social workers, and AIDS educators must often struggle with these challenges while working with their clients.

In the April issue of FOCUS Graeme Hanson, MD, Director of Pediatric Mental Health Services at San Francisco General Hospital, will consider how these difficult issues relate to children and infants with AIDS. Hanson, a child psychologist, will address three major and often conflicting needs: the need for research and how it affects children, the need for care and protection of the individual, and the need to protect the general public. He will also analyze the difficulty in separating prejudice from treatment and research.

In addition, FOCUS will present an overview of the epidemiology and immunology of children with AIDS. Included will be discussions of the difficulty of diagnosing AIDS in children, the course of the illness in children, and counselling interventions that may be helpful to women in high-risk groups who are considering pregnancy.