AIDS CLINICAL TRIALS AND RESEARCH CONSIDERATIONS FOR PATIENTS AND PRIMARY CARE PROVIDERS

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I. Introduction

The primary purpose of this document is to acquaint the reader with the concepts of a well designed clinical trial. A summary of other types of research--epidemiological, psychosocial, and educational--is included also.

It is hoped that this information will provide a background for counselling patients who may have an interest in participating in a clinical trial or research study.

For your information, the Department of Public Health maintains a registry of clinical trials in Massachusetts for AIDS and HIV-related drugs. Specific information about these trials (e.g., inclusion and exclusion criteria, drugs, dosages, study objectives, locations, and names of research physicians and nurses) is available in a directory, which will be published quarterly beginning in May 1989. Future editions of the directory also will include listings of the other types of research mentioned earlier.

To accompany the directory, the Department has prepared educational material to explain to potential participants the nature and purpose of clinical trials and some of the issues affecting one's decision to participate. Copies of the directory, educational material, and additional information about the clinical trials registry may be obtained by calling 1-800-443-AIDS.

II. Basic Principles of Clinical Investigation

Clinical evaluation of therapeutic agents directed against HIV-related morbidity has been underway since shortly after the epidemic was described in 1981. These studies have contributed significantly to the knowledge of management of patients with HIV infection, and have played a major role in developing a deeper understanding of HIV pathogenesis. Further advances in the clinical management of patients with HIV related morbidity are highly dependent on the continued design and execution of properly drafted clinical trials. This section will focus on some of the elements which are essential to the design of effective clinical studies. Although this discussion will focus primarily on antiviral drug studies, similar principles are applicable to studies of vaccines and studies of drugs to treat opportunistic infections.

Preclinical Studies

Drug discovery and development follow a relatively straight-forward process. Efficient utilization of resources requires an approach that targets aspects of the life cycle of the virus distinct from those of the host. In the case of HIV, a number of stages in the viral life cycle have been identified as potential targets for antiviral drugs. These include but are not limited to: the CD4 molecule, by which the virus enters most susceptible cells; **reverse transcriptase**, the enzyme responsible for converting the viral RNA into double-stranded DNA that is integrated into

the host cell DNA by another enzyme known as **integrase**; **glycosylation inhibitors**, which affect glycosylation of HIV encoded proteins; and **HIV protease**, an enzyme that clips HIV polyproteins into shorter sequences as the virus is assembled (Table 1). **In vitro** systems have been developed by a number of investigators to allow the screening of compounds that might have activity against one or more steps in viral replication. When a compound is identified with activity **in vitro** against one of the steps in viral replication, the compound is then tested against replication of the entire virus in cells of a number of different lineages. If the antiviral activity is confirmed at this level, studies are undertaken that are designed to determine whether the agent has significant anticellular activity. If the agent has significant antiviral activity at a concentration that is not toxic to the host cell, studies are undertaken to determine what toxicities might be observed in animals of various species. Depending on the agent, it also might be studied in animal retroviral model systems. Only after a promising compound has been studied sufficiently in the settings outlined above should human studies be initiated (Table 2).

Clinical Trials

As in preclinical studies, clinical trials proceed through a well-established sequence that begins with small-scale safety studies and ends with large-scale controlled trials designed to evaluate efficacy (Table 3). The initial clinical trials generally are termed "Phase 1" studies. Phase 1 studies are used to establish the dosages and routes of administration by which an agent can be given safely. Hence, phase 1 studies often are termed safety studies. Usually, investigators begin by administering a dose that is several orders of magnitude below the dose established as safe in animal studies. Subjects usually are enrolled in small groups, each of which receives increasingly larger doses until a patient (or patients) at a given dosage experience one or a number of predetermined toxicities. Although some trials involve escalation of dose in individual patients, difficulties in identifying the dose that caused toxicity have led to abandonment of this design by most investigators. The threshold for ending the study depends on the severity of the disease and on the availability of alternative drugs. Before termination of phase 1 trials, in general, less toxicity is tolerated for drugs directed at relatively trivial problems such as baldness or morning sickness than when drugs are being studied for potentially fatal diseases such as AIDS.

Although safety is the primary parameter for phase 1 studies, it is generally prudent at this stage to note pharmacokinetics and desirable endpoints. Because of the heterogeneity of patients in most tolerance trials, one must be wary of preliminary claims of efficacy from phase 1 studies, particularly in the case of an unpredictable disease like AIDS. This caution is true particularly when one takes into consideration the lack of controls, and the placebo effect that easily is evoked in the euphoria of early studies of agents receiving widespread publicity in the lay press on the basis of preclinical studies.

Patient selection for phase 1 studies is often difficult. In general, patients with more advanced disease are asked to volunteer. This approach attempts to spare patients, who might otherwise do well for some time to come, from the risk of being the first humans to receive a new pharmaceutical agent. This bias, in turn, runs the risk of selecting patients who are relatively ill and thus more prone to drug toxicity, or to untoward events related to the underlying disease.

After phase 1 studies have addressed the issue of safety, larger studies are initiated to establish optimal dosing for later studies that will establish efficacy. These studies often are termed dose-ranging studies. In these studies, larger groups of patients receive one of a number of doses of a drug in an attempt to delineate toxicity more fully, and/or to gather evidence related to doses that might produce a desired biologic effect. As in the phase 1 studies, most phase 2 studies are uncontrolled.

When an optimal dosing regimen has been established for a drug in phase 2 studies, it is appropriate to initiate studies designed to assess efficacy. Under most circumstances, it is desirable that these studies be controlled and conducted in a blinded fashion. In order to determine efficacy, it is crucial that crisp, predetermined endpoints be chosen before initiation of the study, and that firm criteria for a response be determined for each variable to be studied. In general, it is easiest to establish a clear effect if entry criteria are relatively narrow so that patients in the trial are fairly homogenous. If there are variables that might lead to a biased result, efforts should be undertaken to "prestratify" patients to be certain that patients in the various arms of the study are likely to be comparable before the study is begun. In the case of AIDS studies, prestratification by CD4 cell number often protects the study from subsequent criticism about non-comparability of the groups. Failure to prestratify adequately has caused skepticism about recent studies of ribavirin and Imreg.

Because phase 3 studies involve comparing a new agent to a placebo or to an established form of therapy, two other considerations are of importance in the study. The first relates to the need to provide for early termination of the study should excessive toxicity (or conversely, convincing efficacy) be observed in any of the study groups. This result is best accomplished by allowing for interim data analysis by an independent data safety monitoring board, which is empowered to stop the study should patients in one or more arms of the study fare statistically better or worse than patients in other arms of the study. The other consideration relates to designing the study to be of sufficient duration, and to including a large enough number of patients so that demonstration of the effectiveness or ineffectiveness of the new drug is likely. This end is accomplished by defining the variables that are of primary interest. Assumptions are made about the rate of occurrence of these variables during the period of study for the control group (a group receiving either placebo or currently accepted therapy). A decision is made about the desired percent reduction of such occurrences that must be observed in order to call the drug a

success. Calculations can then be made that allow definition of the group sizes necessary to see such a percentage decrease with a predetermined degree of certainty. Such "alpha" and "beta" error calculations are extremely important if one is to avoid a study that is inconclusive because too few patients were studied for too short a period of time. The smaller an effect the investigator wishes to detect, the larger and longer the study must be. For example, one may be able to detect a 20 percent reduction in mortality after two years; but it may take five years to detect a 10 percent reduction in mortality.

In the current regulatory climate, it is extremely likely that antiretroviral agents with efficacy demonstrated in one properly designed and conducted phase 3 study will be licensed by the Food and Drug Administration. Although this action renders the drug generally available, it is important that physicians and patients be cognizant of the patient population(s) in which efficacy was established. For example, a drug that is effective in patients with HIV encephalopathy might well not be of benefit to patients with HIV-related thrombocytopenia. Broadening the indications for a new drug generally requires more widespread clinical testing and administration.

III. Considerations Regarding Enrollment in Clinical Trials

It should be apparent from the above section that the clinical evaluation of drugs with putative antiretroviral activity is highly complex and fraught with a number of anticipated and unanticipated pitfalls. A decision to enroll or not to enroll in a clinical trial is also complex and multifactorial. From the patient's perspective or from the perspective of the referring physician, it is extremely important that such a decision be made on the basis of the most complete set of data available. Many of these considerations should be evident from what already has been outlined regarding the drug evaluation process. Several of these considerations are outlined in Table 4. It is important that there be a sound rationale and preclinical data base for the drug before clinical testing. If the study is controlled, the methods for the randomization and the agent(s) to be administered to control patients should be delineated. Provisions for early termination of the study should be apparent. The financial costs of participation should be explicitly outlined. In general, patients or third party payors should not expect to be responsible for payment for the drug or for any costs associated with its evaluation. On the other hand, few studies pay for disease-related medical care, and most have no provision for providing finanial support if an untoward drug-related event occurs.

As with most other medical decisions, joining a clinical trial involves a risk/benefit ratio analysis. The medical risks should be outlined. These include risks from the new drug and those related to not taking drugs that are more established. Finally, concerns about confidentiality, employability and insurability should be addressed. This is extremely important in studies of patients who are healthy.

IV. "Unproven" Therapies

Although a large number of formal drug studies are underway, an even larger number of unproven agents are currently available to individuals with HIV infection. Physicians are asked often by patients to make recommendations for the use of such agents. Although many of the available agents are probably not harmful, the physician must exercise great caution before suggesting the use of such agents. In the absence of scientific data from well designed and monitored clinical studies to support the use of the alternative therapy, the physician must carefully weigh: 1) what data have been accumulated to date about the agent, 2) the rationale for supposing that this agent will have the desired effect, 3) the risk of toxicity and/or interaction with other therapies 4) the financial cost to the patient; 5) the chance that the use of this alternative therapy will discourage the patient from using agents that have been proven effective; 6) the extent to which the physician may be held liable for recommending the use of a treatment for which there are no data on safety or efficacy.

V. Epidemiological Studies and Other Forms of Research

In addition to clinical trials, other types of research that do not involve therapeutics, or basic mechanisms of action of HIV or the immune system, are in progress. Many of the studies are epidemiologic in nature, examining large groups of people over time, rather than focusing on individuals. The groups studied may be specific, e.g., persons who are at increased risk for HIV infection, including gay and bisexual men as well as intravenous drug users, or their sexual partners. Other studies are designed to look at broad classifications of people who are considered to be at lower risk, such as the whole population of certain geographical areas or groups like high school or college students. Epidemiologic studies may involve the administration of a questionnaire to collect information, or may utilize physical examinations and the collection of blood. The latter type of study is called seroepidemiologic and may yield data on the prevalence of HIV, the natural history of infection with the virus, and the transmission of HIV. Studies of the prevalence and incidence (numbers of new cases of HIV infection over a specific period of time) are considered to be surveillance studies and are frequently under the aegis of the Department of Public Health. These types of studies may include persons who come to the alternative test sites, or people who attend sexually transmitted disease clinics or methadone maintenance programs.

Studies that follow cohorts of people for longer periods of time may give more information regarding natural history, i.e. the clinical effects of HIV in large groups of people over time. An example of a natural history study in Boston is the continuing study at the Fenway Community Health Center (FCHC), funded by the Department of Public Health, in which a cohort of asymptomatic gay and bisexual men were recruited in early 1985 to be followed every six months with blood tests. The study seeks to describe the kinds of changes that occur in tests for the specific virus, HIV, as well as in immune systems parameters and to correlate this information

with changes in people's behavior and clinical status over time. Other epidemiologic studies may enroll people who are sexual partners, and thus get information regarding the transmission of HIV. For example, the Centers for Disease Control have funded a study of sexual partners, administered by the Department of Health and Hospitals of Boston and run through the FCHC, in which gay couples have been recruited over time. Data from this study will help answer questions about the efficiency with which HIV is transmitted and why some persons are more or less susceptible to the virus.

In the absence of a vaccine, obviously the major way in which further spread of HIV can be prevented is through behavioral means. There are studies in progress to look at changes in behavior among individuals who are members of higher risk communities, such as gay men and intravenous drug users. Other studies are attempting to assess the ways in which behavior is changing in other groups, either defined ethnically and culturally, e.g., Latino communities, or stratified by age, e.g., high school students. Some of these studies are also looking at the natural history of behavioral change in the absence of interventions, while others are examining whether specific kinds of interventions, such as small group discussion, the provision of increased information, or targeted counseling, make a difference.

Other studies may simply attempt to assess the prevalence of information regarding AIDS and HIV in different populations, and thus are educational surveys. Other studies may attempt to look at the ways in which the health care system or society at large is dealing with information on AIDS and HIV. More specific studies may look at issues around the cost of HIV care and how different aspects of the health care financing system are responding or not responding to the clinical demands raised in the AIDS epidemic.

VI. Conclusion

The evaluation of AIDS therapeutics is a complex, time consuming, costly endeavor. Because the resources to be utilized include not only money and scarce drugs, but also (more importantly) the patients' relatively limited amounts of ambulatory time, it is extremely important that such trials proceed safely, expeditiously, and with great efficiency. Poorly designed or conducted clinical trials expose subjects to unnecessary risks and prolong the search for agents with **bona fide** efficacy. As the therapeutic alternatives proliferate, and as clinical trials increase in availability and sophistication, the ability to make enlightened recommendations about clinical trials will assume increasing importance.

Table 1: Possible Targets for Agents With Antiretroviral Activity

Target	Function	Potential Antiviral Agents
CD4 molecule	Viral entry	Soluble T4
Reverse transcription	RNA to DNA conversion	AZT ddC ddA ddI
Integrase	Integration of viral sequence into host sequence	Under development
Tat-III	Positive regulation of viral transcription	Under development
Cellular glycosidases	Glycosylation of HIV proteins	Castanospermine
HIV protease	Cleavage of HIV polyproteins	Under development

Table 2: Steps in Drug Development

1. Identification of potential targets of action that distinguish HIV from the host.
2. Screening of compounds for agents with activity against these designated targets.
3. Studies of agents with activity against specific steps in viral replication in whole viral systems.
4. Toxicology studies in tissue culture and animal systems.
5. Antiviral studies in animal models (optional).
6. Human Studies.

Table 3: Stages in Drug Development

Phase 1: Initial Toxicity Evaluation

Phase 2: Dose Finding and Preliminary Studies in Efficacy

Phase 3: Larger Scale Controlled Trials With One or More Doses Established in Phase 2.

Table 4: Considerations Regarding Clinical Studies

1. What is the rationale for the trial?

2. What is known about the agent(s) to date?

3. Is the trial controlled? If so, with what? Are there provisions for early study termination?

4. What costs might be expected with or without untoward events?

5. What risks or inconveniences might be expected?

   a. Medical risks
   b. Displaced therapeutics
   c. Social risks

6. What will the role of the primary care provider be in the care of the patient?