

AIDS and Changes In Clinical Research Methods

Since it first struck the United States in 1982, the pandemic of acquired immune deficiency syndrome has changed forever the way that biomedical research is done. "We've done a lot of things with the promise that the benefits we reap in HIV will give us new insights into how to solve these problems for others," according to Mark D. Smith. "Now we have to challenge ourselves to see if these benefits and advances really are transferrable to other areas—biomedical research, health policy, society in general."

Smith, who is vice president of the Henry J. Kaiser Foundation, San Francisco, added that "it has become kind of a cliché to say that AIDS is a prism, window, microscope, or mirror to the problems of the larger healthcare system, country, or society." At an October 1992 meeting on AIDS clinical research sponsored by Public Responsibility in Medicine and Research, Smith pointed to positive changes in the way research is conducted, in public policy, and in community involvement in clinical research as a result of HIV (human immunodeficiency virus). But he cautioned those in the research community against adopting an "HIV exceptionist mind-set" and advised instead that they increasingly focus on ways advances in HIV research can be applied to other areas of health policy.

COMMUNITY INVOLVEMENT IN RESEARCH

In the first decade of the AIDS epidemic, the conventional wisdom on how research is conducted had been scrutinized, challenged, and altered. "Until recently mainstream clinical research has been the sole property of academics, of governments, and of industries," explained Lawrence Deyton, assistant director for community research at the National Institute for Allergy and Infectious Diseases. "HIV has catalyzed the real and important role of the regular and constructive voice of persons with HIV disease and the clinicians who care for them in the entire research development and review process."



"We've done a lot of things with the promise that the benefits we reap in HIV will give us new insights into how to solve these problems for others," said

Mark D. Smith.

In the traditional model, Smith noted, it takes researchers several years to write the proposal, get a grant, collect the data, analyze it, present it at a few meetings, send it off to a professional journal, and wait for it to get published. However, the activist community has brought a new sense of urgency to the clinical research enterprise, Smith said. Their commitment and "ability to do their homework" have won them "a seat at the table at which research is designed, carried out, and sometimes analyzed and approved," he added. The changes speed up the processes and involve patients more in the research design and analysis.

The greatest modification has been in where research takes place, according to Deyton. Until 1981, research was conducted primarily by academicians supported by government and industry, based on the assumption that ongoing research should have little impact on primary care. But now, for this disease and others, "the delivery of appropriate primary care can and in many cases should include opportunities for participation in clinical research," Deyton said.

In the current model, primary care providers and groups of clinicians and patients come together solely to do clinical research. With many clinical trial networks and hundreds of community-based organizations doing such research, access to experimental therapy has been greatly improved, Deyton said.

SCRUTINY OF CLINICAL RESEARCH

Until relatively recently, the development of treatments in the rarified environment of scientists and biostatisticians has been subject to little organized scrutiny, Deyton claimed. But that situation started changing in 1972, when the country found out about the Tuskegee syphilis study. "Tuskegee"—now a code word in the research community for unethical, racist practices—was a study of 400 poor black men with syphilis in Tuskegee, AL, that ran for 40 years, beginning in 1932. Without obtaining the subjects' informed consent, the researchers failed to give the men

penicillin (which would have cured the disease) so they could study the progression of the untreated disease.

Media reports and national outrage about Tuskegee in 1972 ultimately led to the National Research Act of 1974, which mandates that institutions conducting research with human subjects establish institutional review boards (IRBs) to oversee such research and prevent fraud or misconduct. However, Deyton noted that this and other regulations to protect human research subjects address the ethical conduct of research and only superficially touch on the scientific merit, development process, or implementation of that research.

Persons with AIDS and their advocates are especially concerned about Tuskegee and the possibility of similar experiments, since the disease is concentrated among vulnerable groups—gays, blacks, Hispanics, drug addicts, prostitutes, and, increasingly, women. However, their concerns go beyond the ethics of study design. As several conference speakers noted, no research is ethical if it is not scientifically sound.

IRBs “formed solely for the purpose of review of AIDS research conducted by research or treatment networks” have expanded their traditional role well beyond the review of ethical issues, Deyton said; they now also explore the design, science, and conduct of these research projects. Most, if not all, IRBs include representatives of the community who have AIDS or HIV infection. And in the clinical trial networks, people with HIV are involved in every protocol development and serve on every committee, Deyton said.

Smith noted that one of the biggest effects of HIV is a change in the “protectionist ethos” of biomedical research. Increasingly, other categories of patients who are research subjects, such as women with breast cancer or families of people with Alzheimer’s disease, are also becoming an integral part of the research process.

TECHNICAL CHANGES IN RESEARCH

One of the primary concerns of persons with HIV and their advocates is that promising treatments be available as quickly as possible. Since, as far as we know, AIDS is universally fatal, persons with the disease cannot afford to wait two to three years for the traditional treatment approval process to run its course.

The AIDS epidemic in the United States first surfaced in 1982, but it was a long haul before the first AIDS drug—the nucleoside analog AZT—was approved in 1987, according to David Feigal, MD, director of the Division of Antiviral Drug Products at the Food and Drug Administration (FDA). It took another two or three years before antiviral therapies became avail-

able, and only last year the FDA approved the first drug for antibiotic prophylaxis of infections.

The approval process for new drugs used to take a median of 22 months, Feigal said. In contrast, the review time for AIDS drugs (from application to approval for marketing) was 3.5 months for AZT (“the record holder”) and about 7 months for the drugs approved in 1992.

This change has been made possible by a number of innovations in the approval process, such as the use of a parallel track method of research and the combination of study phases. Traditionally, Feigal explained, new drugs first go through preclinical studies to find out about issues such as drug metabolism, dosages, and toxicity and carcinogenicity. These studies are followed by three phases of clinical trials to assess toxicity, determine initial efficacy, and obtain widespread, convincing evidence of efficacy.

With AIDS, Feigal noted, “we’ve shifted down most of the preclinical work so that it overlaps with the clinical studies.” This means the clinical trials can begin very rapidly, but the price, Feigal said, is that the trials are not “done as smart or as safe” as possible. For example, the clinical researchers do not know as much about absorption or dosage as in the traditional method, opening the potential for disaster.

Already one problem has occurred, Feigal said. Researchers rapidly advanced the trials of dextran sulfate for AIDS treatment because it was being used widely underground. After a phase III clinical trial, they discovered the drug was not even being absorbed—fortunately, since researchers later discovered dextran sulfate actually accelerates the progression of AIDS.

Another relatively recent innovation to shorten research times is the use of surrogate immunologic markers—instead of death or the opportunistic infections—as endpoints to assess the success of drug trials. As Smith explained, with fatal diseases such as HIV, researchers do not want to wait for death as a measure of the drug’s effectiveness. In addition, a number of other endpoints previously used in AIDS research, such as the development of toxoplasmosis, are either undesirable endpoints because they represent serious morbidity or mortality, or can no longer be used because they can be prevented by other means.

To overcome these obstacles, researchers are now using immunologic markers, primarily CD4 cells, the immune system cells that HIV destroys. By measuring the subjects’ CD4 counts, researchers can assess a drug’s success much sooner than if they had to wait for clinical signs of disease progression. Martin Hirsch, MD, professor of medicine in the Infectious Disease Unit, Massachusetts General Hospital/Harvard Medical

For AIDS and other diseases, “the delivery of appropriate primary care can and in many cases should include opportunities for participation in clinical research,” noted Lawrence Deyton.

School, said that scientists are also looking for a virologic marker to use as an endpoint for clinical trials. And Smith recommended developing other ways of determining a drug's effectiveness, such as measurements of the quality of life and other parameters. Although this science is not well developed yet, Smith predicted that "how well people with AIDS live rather than how long they live will be increasingly important because of our ability to prevent or at least delay many of the endpoints currently used."

The large number of new drugs that need to be tried makes the development of surrogate markers vital. Sandra Lehrman, MD, senior director of

infectious diseases and immunology, Burroughs Wellcome Company, noted that the larger menu of drugs available—26 drugs that can be taken in any combination of up to six drugs—make the choices harder. Separating interactions and drug side effects and analyzing results are complex when patients are taking multiple drugs, including some to manage other conditions. Further complicating the matter are issues of patient compliance. In desperation, some persons with AIDS may discontinue the drug on trial when they fail to see results, or they may take what Lehrman referred to as "the drug of the month and the dose du jour" in hopes of curing their disease or

THE GLOBAL SCOPE OF THE PANDEMIC

As the AIDS pandemic explodes across the world, Jonathan Mann, MD, warns that it is exploiting societal weaknesses. "The central societal lesion behind ill health worldwide is discrimination," he said.

Mann, who is professor of epidemiology in international health at the Harvard School of Public Health and director of the International AIDS Center, Harvard AIDS Institute, explained that, like many diseases, AIDS is most intense among certain segments of the population—"those who are marginalized, stigmatized, or in other important ways not of equal status. In the United States, the early 1980s epidemic among white gay men, which was already a heavily stigmatized group, has become an epidemic which increasingly affects women, African Americans, Latinos, and both the rural and urban poor."

Globally, in 1980, 80 percent of HIV-infected people were men, Mann continued; today, 40 percent are women. In 1990 nearly 80 percent of HIV infection was in the developing world; by 1995 this proportion will increase to about 85 percent, and by 2000 it is expected to exceed 90 percent.

Thus the major impact of the pandemic is yet to come. In the United States, 120,000 to 240,000 new HIV infections are expected in the next three years, Mann said. And HIV is spreading rapidly to communities and countries unaffected just a few years ago. Current

projections are that 20 million people will be infected with HIV by 1995; by 2000 between 40 million and 110 million adults, in addition to 10 million children, will have become HIV infected.

And the number of children orphaned by AIDS will more than double from about 1.8 million today to 4 million by 1995.

Mann expressed concern that, in the face of this expanding epidemic, the societal response to AIDS is declining. A recent report by the Global AIDS Policy Coalition documented that between 1985 and 1991 the industrialized nations provided developing countries a global total of \$864 million for AIDS prevention and care—less than the total spent in New York on AIDS in 1991. And in 1991 for the first time the amount of money rich countries gave to poor countries declined.

Mann pointed to vast inequities in AIDS prevention and care. In 1991, the global coalition estimates, \$1.5 billion was spent worldwide on HIV prevention; of this, only 6 percent was spent in the developing world, where more than 80 percent of the infections are now occurring. In other words, said Mann, in 1991 in the United States \$2.75 per person was spent for AIDS prevention, while 7 cents was spent in Africa and 3 cents in Latin America. And about 90 percent of world spending on care went to people



Mann

with AIDS in North America and Europe, who represent less than 30 percent of the total AIDS population.

These patterns also obtain for other diseases, disabilities, and premature death around the world, Mann noted. To deal with AIDS and other health problems, we have to confront the many forms of discrimination based on race, gender, religion, national origin, sexual preference, and social class, he said. Marginalized groups are at greater risk because their relative lack of resources, information, and social supports decreases their ability to extract the implications of the prevention messages. "Those in full possession of their human rights and dignity are best equipped to contribute to HIV prevention," Mann said.

To move ahead, he continued, we have to confront a paradox of modern global life. "People the world over are concerned about their families and their health, yet it is not a central defining principle of local, national, and global purpose," said Mann. Healthcare workers have contributed to this problem, he added, "for we have accustomed ourselves to playing a minor role in community, national, and global policy." Mann warned that, to combat the AIDS pandemic, healthcare workers must become to some extent revolutionary because the goals—vaccines, care, education, and research on sexual behavior—require changes in the status quo.

at least forestalling death.

To streamline the research process, Hirsch said, researchers in the AIDS Clinical Trial Group (ACTG)—a national research network funded by the National Institutes of Health—plan to use a master protocol consisting of a 24-week trial using measurable clinical markers such as weight change and laboratory markers such as CD4 cell numbers. The researchers use small numbers of patients so they can rapidly screen many combinations of drugs. With the lessons from Tuskegee in mind, these trials do not use a true control group (a group of AIDS patients receiving no treatment), Hirsch said. Instead, each trial group is compared with a “control group” of persons receiving the best standard therapy currently in use, which at this time is AZT, DDI, or a combination of the two. If any drug or combination of drugs looks better than the standard, it will be entered into large-scale efficacy trials, explained Hirsch.

Despite the difficulties in conducting such research, Hirsch noted that researchers have had many successes and have extended the life span of persons with AIDS from an average of six months in 1985 to about three years in 1992.

REGULATORY CHANGES

Despite improvements in HIV research, Smith warned against addressing societal and regulatory issues only in terms of HIV, without considering other conditions as well. For example, he said, recently researchers and AIDS advocates succeeded in securing a change in the definition of AIDS so more people will be considered disabled and hence eligible for government benefits. But this change does not address the basic problem: a policy that requires clinicians to declare their patients “totally, permanently, and completely disabled” so they can receive benefits.

Much of the time, Smith claimed, the patients are not really disabled to that degree. But clinicians sign the papers “because that’s the pipeline to get the benefits.” After patients are declared disabled, they cannot work anymore and suffer loss of self-esteem, purpose, and productivity, Smith said. He advised changing this “nonsensical piece of public policy” to give persons access to these funds without having to give up their jobs.

Smith pointed to another problem that is not limited to AIDS: “the unfettered ability of a private pharmaceutical company to charge what it will for a drug whose development has been at least in part subsidized by the public sector.” This issue has been raised repeatedly with AIDS drugs, since the persons affected are so active and organized. But it is a problem with drugs for other conditions as well, such as Ceredase (aglucerase), used for Gaucher disease, which



“The rise in the price of prescription drugs has increased about three times the rate of the consumer price index over the past 10 years,” said Peter Arno.

costs about \$200,000 per year per patient.

Peter Arno, PhD, associate professor at the Albert Einstein School of Medicine, Montefiore Medical Center, noted that drug pricing is a major factor in the high costs of treating persons with AIDS. Arno said the Association for Health Care Policy Research (AHCPR) recently predicted the cost of caring for persons with AIDS and HIV nationwide would be \$10 billion in 1992 and about \$15 billion by 1995. The estimated lifetime expenditure for someone who got sick with AIDS in 1991 is \$187,000, according to the AHCPR, said Arno. And Blue Cross/Blue Shield data show that outpatient expenditures for a person with HIV and AIDS are going up dramatically, whereas those for inpatient care are falling. The driving force, Arno said, is the price of drugs. For the seven drugs approved by 1991 for treatment of AIDS, the average price per person per year is \$27,000, with a high of \$52,000.

Arno added that the costs of prescription drugs are poorly reimbursed by third-party payers and 55 percent are paid for out of pocket (according to the Health Care Financing Administration). So as drugs are priced higher and higher, fewer and fewer people can get them. Even for FDA-approved drugs used by people with insurance, whether public or private, “I see major problems down the road,” Arno said.

“The rise in the price of prescription drugs has increased about three times the rate of the consumer price index over the past 10 years,” Arno continued. In 1991, he said, the profit rate for Fortune 500 companies was 3.2 percent; for drug companies, 12.8 percent; and for the 20 companies selling the top 20 drugs, 15.1 percent.

Drug companies insist that the drugs are so expensive because of the costs of research and development, said Arno. But he and Karyn L. Feiden have recently released a book disputing these claims (*Against the Odds: The Story of AIDS, Drug Development, Politics and Profits*, HarperCollins, New York City, 1992). For example, with the drug E.P.O. (epoetin alfa, used for treating anemia in patients with chronic renal failure), the pharmaceutical company made \$893 million in sales in 18 months but had spent only \$150 million on R&D. “The industry doesn’t want you to see these figures,” Arno said. “If the country were to find out, we would have drug price controls.”

SCIENCE VERSUS DESPERATION

In the effort to speed the approval of new treatments, one ongoing controversy among researchers and some AIDS advocates is the availability of drugs whose efficacy has not been proven. Smith likened some of the drugs to

laetrile, the useless cancer drug that Americans flew to Mexico to obtain 25 years ago. He called this the "generic" problem of the "contradiction between the deliberateness and caution of the scientific process and people's natural inclination to look for hope and grasp at straws."

This common problem is exacerbated by the legacy of Tuskegee, which has "filtered into the consciousness of the African-American community," Smith said. Many blacks—as well as many whites and gays—would believe the notion that "those in authority might not tell you the whole

truth when it might benefit you but hurt them," he added.

In such a context, it is difficult to dissuade persons from taking useless drugs. It is always hard to prove that something does not work, Smith said, and this is particularly true with AIDS drugs, since none of them are "home-run drugs." However, as the approval process accelerates, with more extrapolation between some laboratory value and the final benefits, he warned that staying true to scientific process will be even more critical.

—Susan K. Hume

AIDS RESEARCH IN WOMEN

Just as HIV and AIDS highlight all the inequities in our society and in our medical care system, HIV in women "emphasizes the somewhat precarious position of women in society," according to Judith Feinberg, MD. Currently 3 million women worldwide are infected with HIV, said Feinberg, who is assistant professor of medicine at Johns Hopkins University. She noted that these numbers are expected to increase as the rates of heterosexual transmission increase. The largest proportional increases will be among women of color. In the United States, black and Hispanic women constitute only 19 percent of the adult female population, but 74 percent of the women with AIDS. Feinberg noted that AIDS is now one of the five leading causes of death of women of reproductive age, and in some cities it is the leading killer of women.

"This portends a social catastrophe of enormous proportions," warned Feinberg. "Women are really the glue of this society that holds many of the largest social structures together—family, the community." In addition to the devastating effect on the women themselves, 25 percent to 30 percent of children born to women with HIV also carry the virus. And Feinberg noted that we are heading toward a frightening era of AIDS orphans—between 50,000 and 82,000 in New York City alone within seven years, according to recent estimates.

Despite this alarming picture, women have been almost entirely ignored by the AIDS research community. "How can you take care of these women if you

don't study them?" Feinberg asked. "Are there gender-specific aspects of the HIV infection? Do women react to the treatments in different ways?"

Feinberg recently measured participation of women in clinical trials using demographic data by the AIDS Clinical Trial Group (ACTG), a federally-funded research network made up of 47 university medical centers and about 150 clinics. In the first four years of ACTG's operation (from December 1986 to December 1990), 12,084 participants were enrolled in the trials nationwide. Of these, only 801 (6.7 percent) were women, even though women with AIDS made up 9.8 percent of the population. More than half the women were white, compared with a fourth of the women with AIDS nationwide; and less than a fourth of the women had a history of intravenous drug use, compared with more than half the women with AIDS nationwide. "The demographic distribution of women who were in the trials was clearly not representative of the women with AIDS in the U.S. Plus, women with AIDS are only a proxy for those with HIV infection itself," said Feinberg.

One major reason researchers are failing to study enough women with HIV is fear of possible teratologic effects of the drugs under study. But many speakers at the conference urged researchers to allow the women to decide for



Feinberg

themselves whether to risk harm to future children. "It's very dangerous to assume that women will not have the wits to understand the issues involved and make these decisions," said Paula Schuman, MD, assistant professor of medicine at Wayne State University.

Other factors also have combined to keep women out of clinical trials. Special personnel for patient advocacy and peer counseling are needed to help women understand the study, to search them out when they move and encourage them to continue the study, and to discuss compliance with them, Schuman said. Other limiting factors, Feinberg noted, are study eligibility criteria that are not designed to accommodate women; competing needs and concerns, such as children and sick parents; difficulties getting to and from the clinic at the increased frequency required; and the need for other support services such as drug treatment.

Feinberg noted that women's lack of access to clinical trials has long-term implications. "Access to research is access to care," she said. Patients in research projects get free medications and a degree of clinical care and scrutiny they could not obtain elsewhere. They also receive potentially useful drugs early in their development. Beyond personal benefits, omission of women from clinical trials limits their opportunities to play an altruistic role, and it limits AIDS researchers' abilities to know about gender-related differences in effectiveness and toxicity, Feinberg said.