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Keystone National Policy Dialogue on Expanded Access to Promising Therapeutic Drugs for HIV Infection and AIDS with Implications for Other Life-Threatening Diseases

Final Report

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The Keystone Center, founded in 1975, is a national non-profit organization located in the Rocky Mountains at Keystone, Colorado, 75 miles west of Denver. The Center is organized around three major programmatic areas: (1) The Keystone Science and Public Policy Program, which facilitates the resolution of national public policy conflicts through the use of an innovative consensus dialogue approach; (2) The Keystone Science School Program, which provides residential natural science education programs for students of all ages with emphasis on sound scientific understanding of nature and our relationship to the environment; (3) The Symposia on Molecular and Cellular Biology, which offers an annual series of colloquies addressing critical developments in science and research. The Center's programs are funded by grants from foundations, corporations, government, individuals, and in the case of the Science School Program, fees paid by students.

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Dedication

This report is dedicated to the memory of
Sonia Singleton,
whose commitment to education, information and prevention of AIDS
made a significant contribution
to the Keystone Dialogue Group's efforts,
as well as the overall fight against HIV disease.
Sonia's energy, humor and courage are enduring inspirations.

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Table of Contents

I. **Executive Summary** **1**
Introduction 1
Definitions 2
Relevance to Other Diseases 2
The Current Situation 3
Problems with the Current Situation 4
Education & Information Recommendations 5
Research & Development Recommendations 7
Resource & Finance Recommendations 8
Conclusion 10

II. **Introduction** **11**
Participants & the Process 11
Changing Context 12
Goals & Objectives 12
Relevance to Other Diseases 13
Health Care Reform 13
Definitions 14

III. **Importance, Need & Barriers** **15**

IV. **Current Situation** **19**
Drug Development & Approval Process 19
Expedited Development 22
Broadened Pre-Approval Access 23
Current Programs for Pre-Approval Access 23

V. **Recommendations for an Improved Expanded Access System** **27**

Role of Education & Information in Expanded Access **29**
Information to Communities 29
Information to Primary Caregivers 30
Information to Expert Clinicians 34
Information to the Public Health System 36
Information to Public & Private Insurers 36
Information from the Pharmaceutical Industry 37

Clinical Research & Development Design **39**
Continuation of Clinical Evaluation 39
Broader Representation of Patient Populations 40
Optimal Use of Early Data Collection 41
Expedited Development 41

Financing Expanded Access & Resource Issues 43
Overview of the United States Health Care Financing System 43
Assessment of the Existing Financing Situation for Expanded Access 45
Issues & Recommendations 46
Additional Finance & Resource Issues 50

VI. Conclusion 51

VII. Appendices
Appendix A Glossary 53
Appendix B Liability Issues 54
Appendix C Participant List with Ground Rules & Keystone Center Staff 57

Executive Summary

Introduction

This report summarizes the discussions which took place in the Keystone Policy Dialogue on Expanded Access to Promising Therapeutic Drugs for HIV Infection and AIDS with Implications for Other Life-Threatening Diseases. The report and recommendations contained within are important not only for their substance, but because of the varied perspectives and opinions that converged to develop them.

For the past 30 years, the marketing of drugs has depended upon a relatively high degree of certainty of both safety and efficacy. In the past 10 years, patients with HIV infection and AIDS have indicated their willingness to assume a larger degree of risk in exchange for access to not yet available promising drugs at the earliest indication of safety and efficacy. In other words, they view the risk-benefit ratio differently than what has been used historically for pre-approval access and full marketing approval. This willingness to accept a greater degree of risk stems from the fact that the availability of effective therapies is currently quite limited. For patients who do not respond to commercially available therapies, earlier access to promising but not proven drugs may offer the best hope. Access to a greater number of options, even though substantial information concerning safety and efficacy has not been accumulated, is desirable as long as no fully satisfactory treatment has been found that is available to all patient populations. Two related benefits that groups would like to see as a result of a shift in this risk-benefit ratio include: 1) increased industry investment in drug development because of earlier "payoff"; and 2) more therapies available earlier in the research and development or pre-approval process, and ultimately in the marketplace to patient populations who lack satisfactory alternatives. With greater interest and research and development activity, the chances of more effective therapies becoming available are increased.

In addition to regulatory restrictions to access, the traditional clinical research process for drug development was never intended to include wide access to experimental therapies as a primary goal of its design and function. Clinical trial design methodology has evolved over the past few decades to construct the most efficient means of determining an experimental therapy's safety and efficacy. In order to draw clearer conclusions from data, trials are typically designed with narrowly defined entry criteria to minimize the number of external variables potentially impacting the results. In addition to clinical research development and design, other factors reduce the likelihood that a broad base of patients desiring access to promising or new therapies will obtain them. These barriers include financing issues, access to medical care in general, and access to information that allows patients to make fully informed choices.

The sections that follow examine the challenges presented by expanded access from varying perspectives, but always with the same ultimate goal: to give the broadest group of patients

without satisfactory alternatives new chances for prolonged and improved quality of life while continuing to pursue clinical research that will provide more definitive data on the usefulness of new and promising therapies. This report is a summary of discussions surrounding these issues and the recommendations that emerged.

Definitions

The Dialogue Group used the following definitions and related terms throughout their discussions and this report:

> **Expanded Access:**
> Making therapeutic agents available at the time of the earliest evidence of safety and efficacy to the broadest possible patient populations, or to very targeted groups, who lack satisfactory therapeutic alternatives. Expanded access can be achieved by two general routes: pre-approval access, and expedited development and regulatory review and approval.
>
> > **Pre-approval Access:**
> > Making drugs available before marketing, during the phase of research for establishing safety and efficacy. (This includes parallel track.)
> >
> > **Expedited Development and Regulatory Review and Approval:**
> > Through potentially new protocol design and a different regulatory standard, increasing the speed of research, development, review and approval, and thereby shortening the time to market availability.

(See Appendix A for a complete Glossary of terms used in this report.)

Relevance to Other Diseases

The principles discussed here deal specifically with HIV infection and AIDS. Although the Dialogue focused primarily on this problem, the issues and approaches seem broadly applicable to other disease settings where therapeutic options are limited and the disease process is life-threatening or leads to serious implications. Patients with cancer and Alzheimer's disease, for example, are becoming increasingly vocal in their willingness to assume a shift in the risk-benefit ratio in exchange for hope, and the regulatory and financing concerns of these patients have many parallels to those identified for HIV disease. It is the hope of the Dialogue Group that the experience of this Dialogue and the recommendations contained within this report can serve as a foundation upon which discussions of expanded access programs for other life-threatening diseases can begin.

The Current Situation

Discovering and developing safe and effective new medicines is a long, difficult and expensive process. On average, it takes 12 years and $231 million to get one new medicine from the laboratory to the pharmacist's shelf, according to an industry-funded 1990 study conducted by the Center for the Study of Drug Development at Tufts University[1]. For every drug which ultimately reaches the market, many do not. The research-based pharmaceutical industry will have invested approximately $9.2 billion in research and development in 1992, and that investment has been doubling every five years. Drugs intended for serious and life-threatening diseases do not take this long, on average, but have not been separately analyzed. AZT, for example, began pre-clinical development in 1985 and was approved for marketing by FDA in March 1987, a little over two years.

The United States system of new drug approvals has been designed to provide the public with the safest and most effective drug development system in the world. While approval of AZT reflected flexibility in the review of approval of drugs for AIDS, it has been recognized that this system does not always meet the needs of those with serious or life-threatening diseases. Although modifications to the system have allowed additional availability and approval of promising therapeutics such as ddI and ddC, continued efforts were necessary to provide a more specific regulatory structure to offer earlier and broader access to those with life-threatening diseases with no alternatives. For this reason, a variety of mechanisms have been implemented by the Food and Drug Administration (FDA) to modify the system for serious and life-threatening diseases. Mechanisms constructed to meet these needs have concentrated on access to promising therapies through two routes: 1) pre-approval access, and 2) expedited development and regulatory review and approval.

Pre-approval access can provide availability of promising therapies to those individuals without satisfactory treatment alternatives during the research and development process. Access is offered prior to approval (either traditional approval or accelerated approval) and while the clinical trials to meet the regulatory standard of safety and efficacy continue. Examples of this approach have included treatment, compassionate and emergency IND (investigational new drug) applications. Primary care physicians aware of new therapies for life-threatening diseases being developed that may be of therapeutic value to their patients who have no satisfactory alternatives can apply for their patient to acquire these therapies.

Expedited development, as it is defined in this document, incorporates elements of accelerated approval and an expedited process of review and approval, and potentially allows for the approval of a therapy for a life-threatening disease earlier in the research and development process. This decision can be based on less comprehensive data and by accepting less rigorous criteria for safety and efficacy (i.e., the use of surrogate endpoints such as CD4

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[1]DiMasi, J.A., Hansen, R.W., Grabowski, H.G., et al, "The Cost of Innovation in the Pharmaceutical Industry," *Journal of Health Economics* 10:107-142, 1991.

count and condensing the usual 3 phases of a clinical trial into 2). The drug is sometimes brought to market with less certainty about its value and potential side-effects. The process of expedited development can begin even before the IND application is submitted to FDA. The product sponsor, FDA and others can meet frequently to assure that trials are designed with the maximum likelihood of producing clinically relevant data. As results are obtained, expedited development allows FDA to use surrogate endpoint data, historical controls and other innovative mechanisms to evaluate safety and effectiveness. Research on the drug may continue during the post-approval or marketing phase to monitor for unexpected effects and continue studies of efficacy, but, because earlier approval has been achieved based upon surrogate versus certain clinical data endpoints, access to the therapy is no longer constrained by lack of FDA approval for marketing.

Problems with the Current Situation

Current treatment options available for a person with HIV infection depend upon the individual's knowledge and sophistication regarding treatment options, access to information on clinical research and drug development, and the individual's available resources to pay for care. They also depend on whether FDA has approved the drug for clinical trials.

Gaining access to investigational treatments through clinical research protocols may be problematic for many patients due to a variety of factors. These factors include the location of trials, (i.e., significant travel distance considerations); stringent patient eligibility criteria; a care provider unaware of currently available trials for which his/her patients might be eligible; and, a patient's lack of adequate personal resources or insurance to cover some costs of treatment, even though the costs of the actual drug in clinical trials is almost always free of charge.

The issues and circumstances that continue to restrict access of HIV-infected people to promising agents fall into three main categories:

1) Information and Education
2) Research and Development Design
3) Finance and Resource Issues

Regulatory issues are significant to each of these areas and are also addressed in this report. However, while regulatory issues initially were a driving force in launching this project, the subsequent changes and modifications to the regulatory system that have occurred during the course of the project allowed the participants to concentrate on these other areas of concern. During the course of this year and a half effort, the Public Health Service and Food and Drug Administration announced proposed regulations for parallel track and accelerated approval. As a result of this progress in the regulatory arena, the emphasis of the discussions moved more toward the implementation of these mechanisms and barriers that prevent those in greatest need from receiving promising therapeutics.

Role of Education and Information in Expanded Access

AIDS research and treatment are rapidly evolving. Current information is essential for all parties involved in providing patients with care. In general, few educational resources are available regarding AIDS treatments. Key constituencies, such as community-based groups, primary care physicians, nurses and pharmacists, and others who come in contact with those with HIV infection and AIDS, do not have information which would enable them to provide optimal care to patients infected with HIV. Recommendations for improving education and information efforts were directed towards specific parties.

1. Information to Communities

People with HIV need access to timely and accurate information about treatment options available to them.

A mechanism should be fostered for pooling funds from both the public and private sectors for community-specific, treatment-related education and information dissemination concerning the benefits of treatment and the available options. Additionally, programs must be developed to ensure that all HIV-infected individuals are linked to these community-based groups. This education function can best be accomplished through already existing community-based organizations which have established good working relationships with targeted populations.

2. Information to Primary Caregivers

Primary caregivers on the front line of health care delivery in the United States are becoming increasingly responsible for care of patients who are HIV-infected. In order for them to provide comprehensive health care to all their patients, primary care providers need information about available HIV and AIDS treatment options.

Widely accepted guidelines for appropriate care need to be developed. Relevant and useful guidelines must be made available to primary care practitioners in simple, concise and highly usable formats including tables, decision trees and algorithms. A systematic distribution of these guidelines should be undertaken.

3. Information to Expert Clinicians

Expert clinicians require information on relevant scientific and clinical findings regarding new treatments to allow the appropriate incorporation of this information into both clinical and educational activities.

Mechanisms need to be established to ensure rapid dissemination of clinically relevant information, including pre-publication reporting of clinical trial results. Current incentives and prohibitions with respect to the dissemination of information for

manufacturers, regulators, journals, and investigators should be restructured to allow earlier dissemination of clinically useful information. All groups involved with the development, oversight and dissemination of these kinds of materials must cooperate in establishing guidelines for this kind of information to become available.

4. Information to the Public Health System

Pre-approval access is an effective instrument to increase availability of promising drugs which have not yet been approved by FDA. Low visibility has prevented more patients from being aware of and participating in pre-approval access mechanisms.

The public health system, such as national and state governmental agencies, should provide leadership in facilitating exchange of information regarding treatment options by arranging conferences, and other educational and informational forums. The public health system should also promote the education of individuals with HIV infection and AIDS regarding expanded access models, local standard drug trials, and specific protocols as they arise.

5. Information to Public and Private Insurers

Insurers, both public and private, tend not to pay for services considered investigational or experimental, including services for people with HIV infection and AIDS.

Insurance companies must be aware of the state-of-the-art information concerning treatment options for people with HIV infection and AIDS so that reimbursement decisions can be appropriately made. The insurance industry should work with the other groups identified in this report to assure that the potential recipient of care has access to information concerning all available treatment options, including expanded access.

6. Information from the Pharmaceutical Industry

Pharmaceutical companies have established roles in providing information and educational materials to health care providers. By Federal statute these companies are limited to providing this information for only on-label indications for approved products.

Pharmaceutical companies should, to the greatest extent legally possible, work to build on earlier success and continue to inform both patients and providers about available expanded access options. The pharmaceutical industry and FDA need to work together and with other groups to develop innovative ways to disseminate information.

Clinical Research and Development Design

The clinical trials process for development of new therapeutic agents is statutorily designed to determine safety and effectiveness, and as structured, does not support the primary goal of expanded access for those with HIV infection and AIDS. The historical structure of clinical trials has tried to create the fastest route to approval ensuring a high level of certainty regarding safety and efficacy defined by a very high benefit to risk ratio. Consequently, the design of clinical trials has encouraged a focus on homogenous patient populations in order to reduce the number of variables considered in assessing clinical data and to determine the safety and effectiveness of a drug as quickly as possible. The result of this structure is that early information gleaned from these early clinical trials is restricted to the homogenous population that takes part in the trial.

Recognizing that many different populations are affected by HIV infection and AIDS has encouraged a different view of clinical trial structure. Acknowledging the diversity of the populations affected by HIV infection has highlighted the need to incorporate different groups into new trial designs in order to encourage equal access and information among all patient groups as early as possible. While this may potentially impact the speed with which therapies are approved, a balance should be struck so that more groups are included in clinical trials. In addition, new methods of analysis may be developed to make the tradeoff less significant in terms of diversity versus faster market approval.

Ultimately, encouraging greater access to promising therapies in development must be balanced with maintaining the basic integrity of clinical research and development. Four key areas to concentrate change in order to better support expanded access are the following:

Continuation of Clinical Research For pre-approval access, efforts must be made within both expanded access and clinical research development programs to maintain incentives for participants, investigators, sponsors and regulators to complete the process of clinical evaluation.

Broader Representation of Patient Populations Early development plans should be formulated with the additional goal of including all potential patient groups. Innovative trial design mechanisms should be explored in conjunction with this goal.

Optimal Use of Early Data Collection To achieve expanded access, use of information on intermediate outcomes (e.g., early symptoms, serum marker levels, etc.) could help foster confidence in the decision-making process by considering such outcomes obtained from short-term studies at the early end of the drug development process as a basis for expanding access. Larger, more definitive studies would be implemented concurrent with the expanded access program. Maximization of data could also be promoted in other stages of development. For example, post-approval efforts such as heightened monitoring of patient experience shortly after approval, and consideration of data derived from outside of the United States could help confirm clinical benefit

and bring these agents to market through expedited approval. Information from expanded access protocols also could be reviewed to enhance data assessment and evaluation of a promising therapy.

Expedited Development Some additional innovations in research design could include more flexible eligibility requirements for clinical trial protocols, use of surrogate markers, and new, novel and more creative analytical techniques. Industry and FDA have been pursuing these new approaches and FDA has, in fact, granted approval to some therapies for HIV infection for which use of some of these mechanisms were employed. Continued efforts are encouraged. Some mechanisms will help promote more rapid product availability, while others will focus most directly on a more inclusive pre-approval drug development process.

Financing Expanded Access and Resource Issues

Costs of expanded access programs include: 1) research and administration; 2) drug production and distribution; and 3) patient care. Current mechanisms for financing health care services often do not specifically address early availability of new drugs and services. As a result, deficiencies in financing care services prevent some individuals with serious and life-threatening diseases from having investigational therapies available to them.

Issues and Recommendations

1. Many people have inadequate or no health insurance. This situation is devastating for individuals with advanced HIV infection who require a significant amount of care and do not have the personal resources to obtain the care they need.

   Alternative funding mechanisms should be developed for the under and uninsured.

2. Medicare does not reimburse for self-administratable drugs provided outside institutional, in-patient settings, or for experimental therapies.

   Public and private third-party payers should neither deny coverage, nor reject claims for health care services, when such care is provided to a payer's beneficiary under an FDA approved and supervised expanded access program, or when such care is otherwise determined to constitute the current standard of care. This provision should apply to in-patient and out-patient therapies and include both experimental and approved drugs.

3. Some private insurers remain reluctant to pay for expanded access care due to the uncertainty about the added and unanticipated costs, and the precedent such payment might establish.

Costs of all necessary and reasonable medical care should be covered by public and private payers (including self-insurers). Further, a protocol should be developed to appropriately distribute costs among the various parties involved, including government agencies, third-party payers and pharmaceutical sponsors.

4. Private health care coverages are designed and administered by literally thousands of independent third-party payer organizations, including insurance companies, health maintenance organizations (HMOs), third-party administrators (TPAs) and employers. There are currently no industry mechanisms for specifically evaluating and approving expanded access programs and considering the appropriateness of third-party payment for related health care services. Absent such mechanisms, or multiple legislative mandates, significant change in third-party payer participation in expanded access will likely remain problematic.

   The Health Association of America (commercial insurers), the Group Health Association of America (HMOs), the Blue Cross and Blue Shield Association (Blue Plans), the ERISA Industry Committee (self-insured employers), and representatives from other appropriate groups should be encouraged to jointly consider the establishment of a Payers Commission on Expanded Access to represent their respective memberships in making recommendations concerning payer participation in specific expanded access programs.

5. Expanded access entails additional costs to pharmaceutical companies that go beyond research, development and production, such as additional data collection, patient monitoring and administration. Costs of expanded access might prevent pharmaceutical companies or emerging biotechnology companies from entering the field of HIV drug development. Also, the pharmaceutical companies fear losing proprietary information and control of their respective research and development programs to outside (i.e., patient) groups.

   Research costs should be covered by drug sponsors and should be clearly delineated from care costs. Existing provisions allow for companies to charge to cover their drug costs in expanded access and possibly other costs such as data collection. The costs of expanded access should be kept as low as possible by keeping data requirements to the minimum needed for safety and efficacy information. Financial incentives, tax relief, and increased patent exclusivity should be considered as ways of offsetting expanded access costs. Use of a participatory protocol development process referred to above, where all of the affected interests are represented, can also help put realistic limits on expectations and concerns regarding expanded access.

Conclusion

Action directed by these recommendations for change in information and education initiatives, research design, and financing mechanisms, as well as continued efforts to further refine and address these difficult issues, is imperative in order to facilitate access to promising agents for those with HIV infection and AIDS, and those with other serious and life-threatening diseases who currently have no satisfactory alternatives. The Dialogue Group was unanimous in its consensus that constructive steps in all areas are feasible and should be undertaken.

Introduction

The Participants and the Process

The AIDS crisis has raised a number of challenging scientific, ethical and public policy questions, including issues associated with early or expanded access to potentially therapeutic drugs. The crisis has created a conflict between society's obligation to ensure that products are safe and effective before they are marketed, and the obligation to make promising therapeutics for people with HIV infection and AIDS available as soon as possible, especially in situations where alternatives are limited or do not exist. Traditionally, the primary driving force of regulation has been to protect the desperately sick from false hope and potential harm. The AIDS crisis has highlighted the emotional and financial costs of withholding approval until an extensive understanding of the clinical benefit of a therapy has been reached. Acknowledgement of these costs has sparked action for exploring the need for shifting the risk-benefit ratio used by the regulatory process surrounding promising therapies for AIDS. This shift does not mean abandoning efforts to ensure that marketed drugs are safe and effective, but rather recognizing the need for addressing the significant cost of delaying access to those without adequate alternatives.

Determining the appropriate change in the risk-benefit ratio highlights several issues such as the potential impact on the current structure of drug development for all life-threatening diseases, including clinical trials; the appropriate allocation of the financial costs of early and broadened access programs; the potential implications of treating AIDS differently from other life-threatening diseases within the regulatory context; and, the critical need for information exchange and dissemination early in the drug development process.

At the request of governmental agencies, pharmaceutical companies, congressional staff, researchers and public interest groups involved with the AIDS crisis, as well as advocates for other life-threatening diseases, The Keystone Center initiated a project to clarify issues and explore consensus on public policy surrounding the expedited development and broadened pre-approval access to promising therapeutic drugs for AIDS (see below for definitions of these terms). Key decision-makers, including those who actively participated in the project as well as others interested in the results, helped define the scope of the Dialogue, identify participants, and establish goals and objectives for this effort.

The initial impetus that drew these diverse interest groups together (see Appendix C for the list of participants) was to explore new and improved mechanisms for making drugs more widely available to people with HIV infection. The barriers that prevent those in greatest need from receiving promising agents are more complex and extensive than initially realized. While regulatory mechanisms have been developed to pursue expanded access, other issues, such as research design, information exchange and communication, and financing problems have not been incorporated into a comprehensive approach or effort to facilitate access to promising agents. While various groups, organizations, agencies and companies have been

working on issues relevant to expanded access, their efforts have been primarily focused on their respective areas of interest, and many overlapping or related issues have not been addressed.

The diversity of interest groups that participated in this effort and the broad scope of issues the Group discussed strengthen the recommendations contained in this report. The process and structure of the discussions made this effort unique. It is the hope of the participants that the analysis and recommendations generated during this Dialogue will continue to have an impact beyond the project and offer a foundation from which current and future decision-makers draw and build upon to resolve these critical and timely issues pertaining to AIDS and, potentially, other serious and life-threatening diseases.

This final report reflects the culmination of the participants' deliberations and a consensus overview of their efforts to address policy issues and concerns surrounding expedited development and regulatory review and approval, and broadened pre-approval access to therapeutic drugs for HIV infection, with implications for other life-threatening diseases.

Changing Context

During the course of this year and a half effort, the Food and Drug Administration announced proposed regulations for parallel track and accelerated approval. As a result of this progress in the regulatory arena, the emphasis of the discussions moved more toward 1) the implementation of these mechanisms and 2) barriers that prevent those in greatest need from receiving promising therapeutics.

The context of the Dialogue was also altered with the approval of two antiviral therapeutics for persons with HIV infection: dideoxyionosine (ddI, Videx®), and dideoxycytidine (ddC, Hivid®) in combination with zidovudine (AZT, Retrovir®). As more therapeutics reach the marketplace, the pressure for faster approval will shift from expanded access to improving upon available alternatives and removing the economic and other non-regulatory barriers some groups face in gaining access to therapies. However, as the participants noted, the need for better and more effective therapies will continue to exist until a cure is found, as will the need to help diverse populations gain access to promising therapies early in the drug's development. Interest in broadened and accelerated access mechanisms will persist as long as serious and life-threatening diseases with no immediate cures exist.

Goals and Objectives

The goals and objectives of the Dialogue were: 1) to clearly articulate and foster understanding of different perspectives on issues surrounding expanded access; and 2) to propose options for achieving expanded access and make recommendations for action. The

following key questions focused the issues that were most important to accomplish expanded access:

1. What are the current mechanisms available for pursuing expanded access and how do they accomplish this goal?

2. What are the shortcomings of these established mechanisms?

3. What options could be developed to achieve expanded access more effectively, and what are their respective benefits and potential problems?

    a. How will expanded access mechanisms and procedures be structured and implemented?

    b. Who will participate in expanded access programs, both as providers and recipients of therapeutics?

    c. Who will bear the costs of early or expanded access programs, and how?

Focus on HIV Infection and Relevance to Other Diseases

The Dialogue Group decided the discussion would focus on promising agents (therapeutic drugs) associated with HIV infection. This focus was chosen because the most current context in which many of these issues have evolved has been the AIDS crisis, and the experience of most of the participants has been with AIDS. However, an explicit commitment was made by the Group to note and discuss the relevance for other life-threatening diseases. While the specific recommendations of this report are focused on HIV infection, it is the hope of the Group that the insights and recommendations made in this context will be useful in encouraging discussions and actions regarding other life-threatening diseases.

Health Care Reform

The Group acknowledged, and where possible highlighted, the tremendous need for change in the health care system to more fully address the barriers that prevent people from receiving adequate basic care, let alone access to promising therapies that are in early stages of development. However, given the significant and complex issues surrounding health care reform and cost containment, and the pressing urgency of the AIDS crisis, the Group determined that their discussions would be focused on expanded access. The Group felt that any progress concerning policy on expanded access will contribute to the future shape and structure of an improved health care system.

Definitions

"Expanded access" is a term that has taken on a variety of meanings. The Keystone Dialogue participants thought it best to establish a concise definition that would be used throughout the report in a uniform manner. The definitions agreed upon by the participants and utilized in this report are as follows:

> **Expanded Access:**
> Making therapeutic agents available at the time of the earliest evidence of safety and efficacy to the broadest possible patient populations, or to very targeted groups, who lack satisfactory therapeutic alternatives. Expanded access can be achieved by two general routes: (1) pre-approval access and (2) expedited development and regulatory review and approval.
>
> > **Pre-Approval Access:**
> > Making drugs available before marketing, during the phase of research for establishing safety and efficacy. (This includes parallel track.)
> >
> > **Expedited Development and Regulatory Review and Approval:**
> > Through potentially new protocol design and a different regulatory standard, increasing the speed of research, development, review and approval, and thereby shortening the time to market availability.

(See Appendix A for a complete Glossary of terms used in this report.)

Expanded Access - Importance and Barriers

For the past 30 years, the drug approval process has depended upon a relatively high degree of certainty of both safety and efficacy through a fairly standardized set of clinical study phases. Cooperative interaction among pharmaceutical manufacturers, clinical investigators and federal regulators has resulted in a well-defined drug development system that has been designed to substantially reduce the risk of unsafe and ineffective products.

In the past 10 years, patients with Human Immunodeficiency Virus (HIV) disease and Acquired Immune Deficiency Syndrome (AIDS) have indicated their willingness to assume a larger degree of risk in exchange for earlier access to investigational therapeutic alternatives whose safety and efficacy are less certain. In other words, they place a higher degree of value on having access to a promising therapy than on having comprehensive data available on a promising drug. They are willing to accept a greater degree of risk because the number of therapeutic options is currently extremely limited. Having an increased number of options and a reduced threshold for access is desirable as long as no cure or highly successful therapy has been found that is available to all patient populations.

The traditional clinical research system for drug development, necessary for determining the clinical relevance of a product, has permitted only limited access to investigational therapies. Clinical trial design, which typically has narrowly defined entry criteria, various laboratory requirements, and a limited geographic availability of study sites present barriers to access; clinical trials are typically conducted in urban teaching hospital settings where there is a large population of potential research subjects.

Over the last ten years, attempts have been made to make both the regulatory system and the clinical research system more flexible for those with life-threatening diseases who need alternatives to ineffective existing therapies. HIV and the later stages of the disease's progression, AIDS, have brought special urgency to this issue. While the traditional conservative risk-benefit assessment has not been applied to approval of AIDS' drugs, interest in formalizing flexibility in the system has become more acute. The result has been broader support for reassessing the risk-benefit ratio that usually governs drug development, and regulatory review and approval, as well as pre-approval access which is a new approach. The goal of the Expanded Access Dialogue project is to combine the best of a system based on proven safety and efficacy while allowing the flexibility for access to promising new experimental therapies for those who have no satisfactory alternative therapies.

Throughout the discussion of expanded access issues, the Group sought to remain focused on how best to address the drug treatment needs of people with HIV infection and AIDS. These needs are most acute in patients for whom standard therapy has failed or is no longer effective, or who experience drug intolerance. Expanded access, as the Dialogue participants defined it, encompasses the mechanisms by which patients can obtain access to promising medical alternatives, which do not have well-defined safety and regulatory profiles, without

having to await the outcome of ongoing clinical trials required by the traditional drug approval process.

Expedited development allows for approval of a therapy for life-threatening diseases earlier in the FDA-approval process. Early approval may be granted on the basis of interim results of controlled trials. Research on the drug continues during the post-approval phase to further define its therapeutic index and profile of indications, but access to the therapy is no longer limited to investigational settings.

Pre-approval access provides access for those without approved treatment alternatives during the research and development process prior to approval (either traditional approval or accelerated approval). The clinical trials, necessary to demonstrate the traditional regulatory standards of safety and efficacy, continue.

Beyond the legal barriers to access and the limited scope of clinical trials, other barriers exist that decrease the likelihood that a broad base of patients needing access to promising or new therapies will obtain them. These include financing issues, access to basic medical care, and access to information that allows patients and their care providers to make fully informed choices.

The many important financial issues are especially critical when drugs are distributed in pre-approval access programs, such as parallel track. For example, third-party payers may deny reimbursement for care to patients receiving unapproved therapies, or the associated or ancillary care costs that are specific to these programs. From the pharmaceutical company perspective, there are certain administrative and data collection costs which are over and above those usually involved in clinical research.

Some of these same financial issues may arise when drugs are marketed after accelerated approval. Payers may consider such drugs, whose safety and efficacy have not been fully established by conventional standards, to be "experimental", although FDA said these drugs, once approved, are not experimental. Will third-party payers continue their practice of covering all approved uses? Given limited resources, will government programs, such as the drug purchase assistance program funded under the Ryan White CARE Act, cover these therapies?

Pre-approval access is also affected by the availability of basic medical care services. Many people with HIV infection and AIDS do not have primary care providers. Without such care, programs for access to new or experimental therapies create only the illusion of choice. Similarly, even where primary care services are available, providers and patients must have access to the information so that they can make informed choices of experimental or newly approved therapeutic options.

The sections that follow examine the challenges presented by expanded access from varying perspectives, but always with the same ultimate goal: to give the broadest group of patients

with no satisfactory alternatives new chances for prolonged and improved quality of life, while continuing to pursue clinical research which will provide definitive data on the usefulness of new and promising therapies.

The Current Situation

To identify key issues and develop recommendations for change, the participants first discussed the current situation regarding access to therapies for those with HIV infection or AIDS. The Dialogue Group outlined the basic or typical process of drug development and compared it to accelerated approval and parallel track development in order to understand the differences.

The Drug Development and Approval Process[2]

The United States system of new drug approvals is perhaps the most rigorous in the world. On average, it takes 12 years and $231 million to get one new medicine from the laboratory to the pharmacist's shelf, according to an industry-funded 1990 study conducted by the Center for the Study of Drug Development at Tufts University. The discovery and development of safe and effective new medicines is a long, difficult and expensive process. The research-based pharmaceutical industry will invest $9.2 billion in research and development in 1992, and that investment has been doubling every five years.

In the drug development process for non-life-threatening diseases, new medicines are generally developed as follows:

Preclinical Testing Laboratory and animal studies are done to show biological activity against the targeted disease and the compounds are evaluated for safety. These tests vary widely, but average about three and one-half years to gather adequate safety data to support filing an IND (see below).

Investigational New Drug Application (IND) After completing preclinical testing, the sponsor files an IND with FDA and begins testing the drug in people. The IND becomes effective if FDA does not disapprove it within 30 days. The IND describes results of previous experiments; including how, where and by whom the new studies will be conducted; reveals the chemical structure of the compound; suggests how it is thought to work in the body; indicates any toxic effects or pharmaceutical data from animal studies; and, discusses how the compound is manufactured. In addition, the IND must be reviewed and approved by the Institutional Review Boards where the studies will be conducted, and progress reports on clinical trials must be submitted at least annually to FDA. While basic preclinical work is still mandatory in any accelerated approval scenario, the specific requirements may be modified to minimize the time required to complete them.

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[2]Gordon, C., and Wierenga, D., "The Drug Development and Approval Process," *New Drug Approvals in 1991* (Washington, DC: Pharmaceutical Manufacturers Association, January 1992).

Clinical Trials, Phase I These tests may average about one year and involve 20 to 80 volunteers. In a drug development process for non-life-threatening diseases, these tests involve healthy volunteers (i.e., those without illnesses relevant to the drug's intended effects), however, in an accelerated drug development process the volunteers are infected with the disease the drug is designed to combat. The tests study a drug's safety profile and gather preliminary safety data, including the safe dosage range. The studies also determine how a drug is absorbed, distributed, metabolized and excreted, and the duration of its action.

Clinical Trials, Phase II In this phase, which may take approximately 2 years, controlled studies involving approximately 100 to 300 volunteer patients (i.e., people with the disease) take place in order to confirm the drugs activity against the disease process.

Clinical Trials, Phase III This phase may last about three years and usually involves 1,000 to 3,000 patients in clinics and hospitals. Physicians monitor patients closely to determine efficacy and identify adverse reactions.

New Drug Application (NDA) Following the completion of all three phases of clinical trials, if the data successfully demonstrates safety and effectiveness, the sponsor files an NDA with FDA. The NDA must contain all the scientific information that has been gathered. NDAs may run 100,000 pages or more. By law, FDA is allowed six months to review an NDA. In almost all cases, the period between the first submission of an NDA and final FDA approval exceeds that limit; the average NDA review time for the 30 new molecular entities approved in 1991 was 30.3 months. Under an accelerated drug development process, approval of a drug usually takes between several months and one year after an initial NDA filing. During this time, substantial additional information is submitted by the drug sponsor.

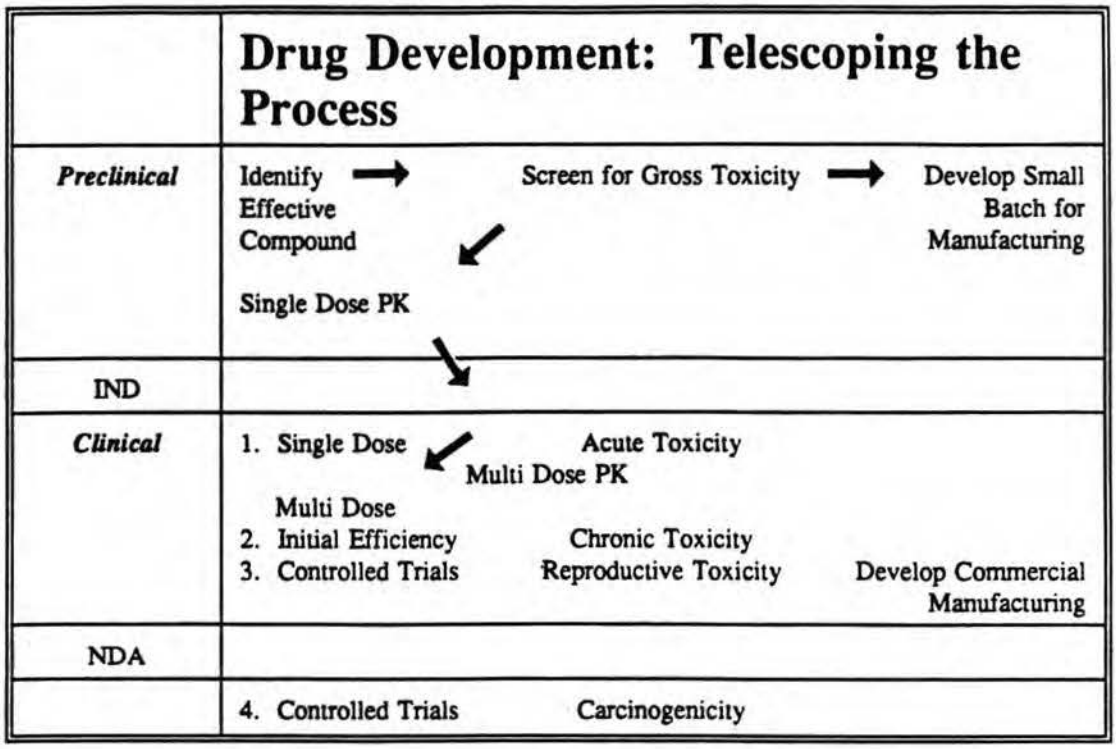
Product License Application (PLA) Biological products, including the majority of medicines produced through biotechnology, are reviewed and approved by FDA in a manner similar to drugs. Instead of an NDA, a PLA is submitted. However, there is no statutory mandate for biologics to be reviewed within six months. The average approval time for PLAs in 1991 was 23.3 months, and only two were approved while 21 were pending.

Approval Once FDA approves the NDA or PLA, the drug may be marketed. The company must continue to submit periodic reports to FDA, including any cases of adverse reactions and quality-control records. For some drugs, FDA requires additional studies to evaluate long-term effects.

	Drug Development
Preclinical	Identify Effective Compound → Screen for Gross Toxicity → Develop Small Batch for Manufacturing Single Dose PK Multi Dose PK → Acute Toxicity Chronic Toxicity
IND	
Clinical	1. Single Dose ← Reproductive Toxicity Multi Dose 2. Initial Efficiency 3. Controlled Trials Carcinogenicity Develop Commercial Manufacturing
NDA	
	4. Controlled Trials

DRUG DEVELOPMENT FOR NON-LIFE-THREATENING DISEASES[3]

[3]*Ibid.*



EXPEDITED DRUG DEVELOPMENT
FOR SERIOUS AND LIFE-THREATENING DISEASES[4]

Expedited Development

Under a plan implemented by FDA, the various pre-approval phases may be combined to shave years from the development process for those medicines that show sufficient promise in early testing and are targeted against serious and life-threatening diseases, such as cancer. Approval is accelerated on the basis of the drugs effect on a non-clinical marker. These sorts of "surrogate endpoints" data are often available during the earlier phases of the drug development.

Expediting the drug development and regulatory review and approval process is one means of providing increased access to promising therapeutics. Whether the current process of evaluation and approval can be significantly accelerated, however, remains unclear for at least some of the following reasons:

1. Clinical trials depend upon the passage of some amount of time to reach their

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[4]*Ibid.*

clinically significant endpoints, time which varies with the diseases and cannot be accelerated.

2. The utility of surrogate markers as endpoints in establishing a drug's effectiveness in HIV infection remains unclear.

3. Incomplete trial results, while often showing some promise for the drug, may provide inadequate information to the clinician concerning how to use the drug.

4. Expedited development and approval will likely mean that additional post-approval monitoring will be imposed.

5. Withdrawal criteria and marketing limitations may be seen by potential sponsors as disincentives to participate in expedited development.

6. There may be concerns with potential liability in the pharmaceutical industry if efficacy standards are perceived by some to be lessened.

7. There are logistical, staffing and resource limitations, as well as competing priorities affecting FDA's ability to further accelerate the review and approval process.

Broadened Pre-Approval Access

Broadened pre-approval access provides opportunities for those in greatest need to have access to promising therapies during the developmental phases of research on the drug, prior to FDA approval. This aspect of expanded access will only be achieved if the criteria for participating in the clinical trials or pre-approval access programs are broad enough to include significant numbers of patients.

Current Programs for Pre-Approval Access

There are at least three existing formal and informal mechanisms for pre-approval access to experimental therapies: 1) Clinical Trials (i.e., Open Label Protocols, Treatment INDs and Emergency INDs), including Parallel Track; 2) Importation for Personal Use; and 3) Underground Buyers' Clubs. The last two of these mechanisms have the primary explicit goal of providing investigational therapies for treatment. Clinical trials may provide such access, but their primary goal is to provide definitive data by which to determine safety and efficacy (often, but not always, in the service of obtaining marketing approval).

1. Clinical Trials See description under Current Situation, page 19.

Open Label Protocol This is an uncontrolled clinical study that may be used to assess the safety of an investigational drug in very ill patients for whom there are no other reasonable alternative therapeutic options, or who do not qualify for formal clinical trials, or for whom there is inadequate evidence to support approval of a treatment IND. Open label studies are performed under an IND with appropriate informed consent and may run concurrently or follow a well-controlled clinical trial.

Treatment IND This mechanism provides a bridge between completion of clinical trials and approval for marketing. Treatment INDs have also been used to provide access earlier in the development process. To date, over two dozen drugs, including ten for AIDS or AIDS-related conditions, have been made available under treatment IND protocols.

Emergency IND The emergency IND mechanism may provide for the use of an investigational drug for an individual patient in an emergency treatment situation when time does not allow prior submission of an investigational new drug application.

Parallel Track Parallel track, announced in the April 15th, 1992 Federal Register, is a policy statement of the United States Public Health Service Agency that permits the distribution of drugs for HIV during the development phase when there is a lack of satisfactory alternative therapies. Clinical and laboratory data must show promising evidence of safety and efficacy. Controlled trials must be underway, and patients in parallel track must be ineligible for those trials because they do not meet criteria for inclusion in the study, or have other reasons they cannot enroll in the standard clinical trials such as geographic distance. Parallel track drugs are distributed by the sponsor under a protocol which is run "parallel" to the clinical trial being conducted to collect the safety and efficacy data necessary for approval, and participating physicians are required to report data from the parallel track trial. The amount of data which must be reported will vary from drug to drug. Parallel track protocols are subject to approval by local Institutional Review Boards or by a National Human Subjects Review Panel.

2. Importation for Personal Use FDA may permit individuals with serious illnesses to import unapproved medications, by person or by mail, provided that the amount imported does not exceed a three month supply; the individual is under the care of a physician licensed in the United States; the medication is for personal use only; there is no promotion or commercialization of the product; and, the product does not pose an "unreasonable safety risk."

3. Underground Buyers' Clubs Certain community-based organizations provide nutritional supplements and other non-validated therapies and can sometimes assist clients in obtaining medications that are approved overseas. The legal status of certain of these activities is unclear. In some cases, commercial enterprises, sometimes engaged in illicit or fraudulent activities, have characterized themselves as *buyers' clubs* in order to avoid scrutiny by FDA.

These mechanisms permit early distribution of promising drugs for HIV to patients without therapeutic alternatives. However, experience with these formal mechanisms suggest various difficulties which limit their usefulness or broad application. Moreover, even when such programs are undertaken, not all eligible patients will be enrolled. The informal mechanisms have been somewhat successful in the distribution of drugs, but there are also substantial risks associated with these mechanisms.

Recommendations for an Improved Expanded Access System

The primary areas which prevent HIV-infected people from having access to promising agents fall into three main categories:

1) Information and Education
2) Research and Development Design
3) Finance and Resource Constraints

Regulatory issues are significant to each of these areas and are also addressed in this report. However, while regulatory issues initially were a driving force in launching this project, the subsequent changes and modifications to the regulatory system that occurred during the course of the project allowed the participants to concentrate on these other areas of concern.

The Dialogue participants identified several themes that were relevant in shaping the recommendations, including the following:

- The scientific integrity of research and development of new therapeutics must be protected while at the same time a broader cross section of the affected population must have access to promising new therapeutics. Increased acceptance of informed risk should be permitted particularly by those with life-threatening conditions for whom approved treatment options are limited or alternatives.

- Clinical trials should be complemented by the expanded access system and operated in tandem. The data requirements of the expanded access system must not be so extensive as to discourage either pharmaceutical manufacturers or providers from participation. Establishment of some minimum data set is important and consideration of innovative analytical tools should continue.

- Individuals who have neither personal resources nor health care coverage should have the opportunity to participate in all facets of an improved expanded access system.

- Payers, both public and private, should cover the costs for medically necessary services provided to insured individuals and/or policy holders during treatment in a clinical trial or an expanded access program.

- Effective communication and mutual education must be encouraged, enhanced and facilitated between and among primary care providers, specialty clinicians, research scientists, patients/recipients of care, AIDS service providers and educators, and, to the extent permitted by law, between payers and pharmaceutical manufacturers.

- Leadership must come from all affected groups, including the Administrative Branch, such as the Department of Health and Human Services, Congress, pharmaceutical companies, public and private third-party payers, primary and clinical care representatives, and patient advocacy groups.

Role of Education and Information in Expanded Access

Affected groups, including patients, community-based organizations, primary caregivers, expert clinicians, the public health agencies, private and public health insurers, and the pharmaceutical industry do not have the information necessary to provide optimum care to patients infected with HIV. All of these groups have a role and a responsibility to become involved in education and information dissemination. Because the groups are diverse, a single general model cannot be applied to every situation. The diversity of patients and provider groups require that information and education programs be tailored to fit local circumstances and needs.

Information to Communities

People with HIV need access to information about treatment options available to them. To ensure that any form of expanded access will be successful, patients and their care providers must be involved in as many aspects of decision-making as possible. They must become partners with the traditional players, including pharmaceutical companies, regulators and researchers. Mechanisms are needed to adequately educate people with HIV regarding standard and experimental treatments; from clinical trials and pre-approval access programs to newly approved therapies. These education programs must be structured to enable HIV-infected people to discuss alternative treatments with their health care providers.

This education function can best be accomplished through already existing community-based organizations who have established good working relationships with targeted populations. Treatment education should be incorporated into existing education and case management programs. As with all HIV-related education, this effort must be targeted and culturally sensitive to the diversity and needs of people with HIV. While no one model will apply to all communities, a number of organizations have developed structures for information dissemination to targeted communities or groups.

Some service providers and educators have shown strong resistance to taking on treatment education and advocacy work. Some believe that the subject matter is too technical and that it is unethical for groups outside the medical profession to provide medical opinions. Others disagree with this assessment. All of the AIDS issues that many groups without formal scientific training have grappled with are complicated. Many of those same issues concerning ethics and responsibility are now being discussed around treatment education. The question should not be whether to provide information, but rather how to provide information.

Recommendations

Certain ground rules should be set for quality information dissemination. First, AIDS service providers are not in the business of providing medical opinions. Treatment information programs should serve to inform people so that they are able to make educated decisions about their treatment. Second, information must be unbiased. Third, education programs should be linked to HIV testing, T-cell and other diagnostic testing, drug availability, reimbursement options and primary care.

The expansion of treatment education efforts will cost money and cannot be developed at the expense of other existing services and educational efforts. The development of these new programs provides an excellent opportunity to build a better working relationship between communities affected by AIDS, the pharmaceutical and insurance industries, and governmental entities.

Funding mechanisms should be established to encourage development and delivery of information to communities. A mechanism should be created for pooling funds from both the public and private sectors for community-specific education and information dissemination concerning the benefits of treatment and the available options. These education and information dissemination activities should be directed toward specific populations. The organizations funded should be well integrated into their communities to enable them to accomplish this goal. The funding from the pooling mechanism should be used as seed money for these organizations.

The pooled funding mechanism would not promote any particular treatment. Rather the goal would be to provide unbiased information about all available treatments. Because the information will be developed independently, FDA should not automatically regard the programs as improper promotional activity. The activities of this pooled funding mechanism should be coordinated with the efforts of the Public Health Service and other entities of the public health system to ensure the greatest efficiency and avoid unnecessary duplication of efforts.

Information to Primary Caregivers

Currently, the average primary care provider receives HIV information sporadically and, therefore, the caregiver's knowledge of advances in research and development is delayed. The result is often confusion or ignorance about the range of treatment options available, including expanded access.

The types of information needed are summarized below as guidelines for assuring that health care workers with primary patient contact are able to provide appropriate diagnostic and therapeutic medical care and/or referral for their HIV-infected patients. Although the guidelines in this section are drafted to refer to primary care physicians, many of these

recommendations are applicable to other primary caregivers including nurses, pharmacists and other health care providers.

Tremendous advances in the management of people with HIV infection have been made by AIDS researchers and practicing specialists. However, many primary care providers, particularly those in areas with smaller HIV-infected populations, have not benefitted from these advances and do not have access to the medical expertise and resources routinely available to specialists and primary care physicians in areas with larger HIV-infected populations. These recommendations are intended to describe how primary care providers can better benefit from the clinical advances being made in the care of HIV-infected individuals.

Recommendations

The goal is for all primary care physicians[5] within the scope of their clinical practices and as is appropriate to their professional training, to be able to:

a) Recognize risk factors for, and/or early clinical symptoms of, HIV-related disease.

b) Conduct or arrange appropriate pre-test counselling and HIV antibody testing and post-test counselling.

c) Conduct or arrange appropriate risk reduction counselling and periodic follow-up of at-risk but HIV-uninfected individuals.

d) Conduct or arrange for conduct of appropriate risk-reduction and medical counselling for HIV-infected individuals.

e) Be aware of newly available therapeutics, both approved and on expanded access.

f) Provide appropriate periodic laboratory and clinical monitoring of, and health and risk reduction education for, HIV-infected individuals. This includes both HIV-specific health care such as CD4 monitoring and routine health care such as immunizations for children, regular Ob/Gyn care for women and, as appropriate, referral for substance abuse treatment.

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[5]For purposes of this document, "Primary Care Physician" should be interpreted broadly, to include Family Practitioners, General Practitioners, Pediatricians, Obstetrician/Gynecologists, and Internists practicing in a variety of clinical settings ranging from private practice and public health/community health clinics to prisons and substance abuse treatment centers.

g) Begin appropriate prophylactic treatment for HIV-related infectious diseases, including, though not necessarily limited to, antiretroviral treatment and anti-Pneumocystis carinii treatment.

h) Be able to consult with, and, as appropriate, refer to appropriate infectious disease specialists or regional centers those HIV-infected individuals with more advanced disease for:

1. entry into on-going controlled clinical trials;
2. treatment of advanced, complex or progressive disease; and,
3. sophisticated diagnostic and/or therapeutic interventions.

i) Provide on-going medical care for HIV-infected individuals with advanced disease between visits to, and in conjunction with, specialists or regional centers.

j) Understand the process of gaining access to treatment IND and expanded access products and on-going clinical investigations (including community-based research) for appropriate patients.

k) Be aware of, and able to refer patients to, local support organizations, community groups, social service agencies, etc.

l) Understand the need for appropriate policies for local hospitals, hospices, home care agencies, nursing homes and schools regarding:

1. provision of service to people with HIV infection;
2. maintenance of confidentiality; and,
3. infection control practices.

For the above goals to be reached, three steps could be considered:

1. Widely accepted guidelines for appropriate care, including risk identification, counselling, monitoring, prophylaxis, and referral criteria need to be identified and developed.

a) These guidelines must be made available to primary care practitioners in simple, concise and highly usable formats including tables, decision trees and algorithms.

b) A systematic distribution of these guidelines should be undertaken. This dissemination effort could include any or all of the following:

1. a mailing to all appropriate physicians;

2. a systematic series of presentations at appropriate professional assemblies

and society meetings, hospital staff meetings, etc.;

3. a systematic publication of guidelines in appropriate professional publications;

4. training of local health care workers (e.g., Area Health Education Consortia, or "physician trainers" such as infectious disease or AIDS referral specialists), to conduct presentations for practicing physicians in their catchment area; and,

5. incorporation of guidelines into medical school and appropriate residency training curricula.

2. Greater emphasis should be placed on education and information delivery for primary caregivers.

a) State-based or national toll-free help lines connecting physicians and other health care providers to the expertise available at AIDS Clinical Treatment Units (ACTUs), AIDS treatment centers, hospitals and other resources should be created.

b) Statewide or regional medical, health and social service resource directories should be developed and widely distributed.

c) State medical, dental and nursing societies should be involved in actively designing, providing and funding education programs, especially about access to experimental products.

d) State licensing boards and professional (e.g., pharmacist) societies should consider developing incentives to encourage HIV-related courses in professional education programs.

e) The resources of the regional Health Resources and Services Administration (HRSA)-funded AIDS education and training centers should be utilized to educate physicians and other primary care providers.

f) Local Ryan White planning consortia should be used to help identify physician education needs and work with all available resources (e.g., ETCs, AHECs) to meet those needs.

g) Information about expanded access programs and new product approvals should be communicated as broadly as possible to practicing physicians by a variety of mechanisms, including notifications in journals and by direct mailings.

The single most important step to be taken in educating primary care providers is the development and widespread distribution of the above mentioned guidelines. Guidelines are

envisioned as different from the currently produced "consensus" standards of care being developed by both federal agencies and local medical and community-service organizations. These latter standards are developed primarily for AIDS-sophisticated physicians. The guidelines for primary care physicians should: 1) be simple and direct; 2) allow the primary care physician to use his or her existing skills to provide the best possible primary care services to HIV-infected individuals; 3) provide a full explanation for the physician and his or her patient of treatment options that include clinical trials and expanded access; and 4) enable the physician to know when to refer these individuals to more specialized levels of care. Without such guidelines it is unlikely that those physicians who currently are unable, unwilling or uncomfortable providing services to HIV-infected individuals will change their practice.

3. Where appropriate clinical guidelines do not already exist, the most efficient mechanism for their development is probably through a small working group of knowledgeable and respected clinicians who come from both research and practice settings. The organizing body could be either a federal agency (e.g., the Agency for Health Care Policy and Research or the National AIDS Program Office); a professional society (e.g., the American Medical Association or the American Public Health Association); or an independent body (e.g., the American Foundation for AIDS Research, Physicians Association for AIDS Care, the Institute of Medicine, or others). These guidelines should not be developed as static documents, should encourage both diverse participation and geographic diversity, and will need to be updated as new therapies evolve.

Information to Expert Clinicians

Expert clinicians serve as a resource for patients under their care as well as for other providers in their community by providing consultation and teaching. Thus, the expert clinician requires information on relevant scientific and clinical findings regarding new treatments on an ongoing basis and in such a fashion as to allow the appropriate incorporation of the information into both clinical and educational activities.

This task is fundamentally different from providing basic guidelines or treatment algorithms to non-expert primary providers. The latter task requires a synthesis of aggregate and scientifically-sound information while the former is one of adding the best available (usually incomplete) new information to a substantial personal knowledge framework in a timely fashion.

Medical journals are official records of scientific medicine that generally present completed work after a sometimes lengthy peer review process. Excluded from publication are reports which are preliminary and incomplete. Yet these preliminary and incomplete reports often represent most of the available experience with a new therapeutic agent.

Newsletters, which are produced both commercially and by interest and professional groups, are generally good at collating widely available information, but are of uneven quality and often have limited access to important new information, and, in the case of commercial efforts, can be quite expensive. Continuing Medical Education (CME) programs have similar shortcomings and may have poor geographic distribution.

For many providers the major source of new drug information is the manufacturer. However, manufacturers are prohibited from distributing early positive information because of FDA proscriptions on promotion of unapproved compounds. Manufacturers may also be reluctant to release early negative information because of fears that research and commercial prospects may be harmed even if the negative information is not borne out when adequate studies are complete. The duty of the manufacturer to inform investigators of significant findings and events mitigates these problems for providers already using an unapproved agent under an expanded access program or in formal clinical research. However, information is generally provided with a regulatory rather than clinical perspective and often does not reliably reach providers for whom knowledge of the appropriate use of the agent is most important.

Recommendations

Communication regarding new treatments should be increased through changes in incentives. Consideration should be given to restructuring incentives and prohibitions relative to information dissemination for manufacturers, regulators, journals and investigators. Incentives could focus on encouragement of and recognition for articles and information dissemination concerning early clinical data experience. Solutions could incorporate the use of a clearing-house which would likely need to be run by, or with the cooperation of, the public sector according to principles that would protect both patient interests and investigator's and manufacturer's intellectual property. Reports from the clearinghouse could be electronically distributed with commentaries by professional staff via a regular journal or newsletter, and through release to appropriate medical journals and the popular press. All groups involved with the development, oversight and dissemination of these kinds of materials must cooperate in establishing guidelines for this kind of information to become available.

Further, more rapid release of summary results and editorial comments could be accomplished by using a publication in the fashion of Mortality and Morbidity Weekly Report (MMWR) or MMWR itself with accompanying brief mention in major clinical journals after the fashion of the "From the CDC" or "From the Assistant Secretary for Health" features in the Journal of the American Medical Association (JAMA) or other journals.

Information to the Public Health System

Groups that make up the public health system, including the administrative branch (i.e., Health and Human Service agencies), state agencies and others, have an ongoing responsibility to adequately address the needs of those for whom standard therapies are no longer effective. Currently,

1. Community-based clinics and public health facilities lack information regarding drugs which are available through expanded access mechanisms and clinical trials.

2. Patients lack information regarding the option of receiving drugs through expanded access mechanisms.

3. Community-based clinics and public health facilities lack information regarding inclusion criteria for agents on expanded access.

There are many areas in which the public health system provides a potential network to address information needs.

Recommendations

The public health system should play a leadership role in fostering information exchange. Components of the public health system should work to arrange conferences and other educational and informational forums. These activities should be specifically targeted toward public health facilities and community-based care providers to promote a better understanding of the purpose and operations of the expanded access model and available therapies.

Further, the public health system should also promote the education of individuals with HIV infection and AIDS regarding expanded access models, local standard drug trials, and specific protocols as they arise. These efforts should involve community-based organizations to ensure that diverse populations have access to information and educational resources.

Also, the United States Public Health Service should serve a coordinating role to ensure that their information and education activities are carried out efficiently and that duplication of efforts is avoided.

Information to Public and Private Insurers

Insurers, both public and private, tend not to pay for services considered investigational or experimental, including services for people with HIV infection and AIDS.

Recommendations

The standards of care for HIV infection and AIDS are evolving rapidly. The information which is made available to health care providers and community-based organizations regarding standards of care and expanded access programs should also be provided to insurers. Insurers should take a more active role in enhancing and benefitting from information exchange. Insurance companies must be aware of the state-of-the-art treatment options which are available to health care providers and community-based organizations so that reimbursement decisions are appropriately based on standards of care and not simply approval status. Mechanisms for gathering and exchanging this information could be established through efforts outlined in the Finance section of this report, such as a Payers Commission (see page 48).

The insurance industry should work with the other groups identified in this section to assure that the public has access to information concerning all available treatment options.

Information from the Pharmaceutical Industry

Pharmaceutical companies have established roles in providing information and educational materials to health care providers. By federal statute companies are limited to providing only information concerning on-label indications for approved products. In addition, pharmaceutical companies have a limited and tightly regulated ability to advertise directly to patients for prescription products.

Recommendations

Regulatory barriers preventing critical information exchange should be reformed. Pharmaceutical companies should, to the greatest extent legally and ethically possible, work to build on earlier success and continue to identify appropriate mechanisms to inform patients and providers about available expanded access options. The pharmaceutical industry and FDA need to work together and with other groups to develop innovative ways to disseminate information. An example of this would include the support of community-based organizations through a pooled funding mechanism as recommended earlier in this report.

Beyond these efforts, additional creative mechanisms should be explored and consideration should be given to federal rule-making or legislation to address these problems where appropriate.

Clinical Research and Development Design

The clinical trials process for development of new therapeutic agents is statutorily designed to determine safety and effectiveness, and as structured, does not support the primary goal of expanded access for those with HIV infection and AIDS. The historical structure of clinical trials has tried to create the fastest route to approval ensuring a high level of certainty regarding safety and efficacy defined by a very high benefit to risk ratio for drugs for non-life-threatening diseases. Consequently, the design of clinical trials has encouraged a focus on homogenous patient populations in order to reduce the number of variables considered in assessing clinical data and to determine the safety and effectiveness of a drug as quickly as possible. The result of this structure is that early information gleaned from these early clinical trials is restricted to the homogenous population that takes part in the trial.

Recognizing that many different populations are affected by HIV infection and AIDS has encouraged a different view of clinical trial structure. Acknowledging the diversity of the populations affected by HIV infection has highlighted the need to incorporate different groups into new trial designs in order to encourage equal access and information among all patient groups as early as possible. While this may potentially impact the speed with which therapies are approved, a balance should be struck so that more groups are included in clinical trials. In addition, new methods of analysis may be developed to make the tradeoff less significant in terms of diversity versus faster market approval.

Ultimately, encouraging greater access to promising therapies in development must be balanced with maintaining the basic integrity of clinical research and development. Four key areas to concentrate change in order to better support expanded access are the following:

1. Continuation of Clinical Evaluation
2. Broader Representation of Patient Populations
3. Optimal Use of Data Collection
4. Expedited Development

Continuation of Clinical Evaluation

As expanded access programs provide mechanisms for obtaining new agents outside of traditional clinical trials, it is essential that the primary research continue in order to fully define the new agent's relative safety and efficacy. If data indicate that a therapy is not effective, a mechanism or procedure must be in place to remove the agent from this expedited development.

Recommendations

The pursuit of expanded access should be balanced with the need for medical knowledge. Efforts must be made to ensure that incentives remain for participants, investigators, sponsors and regulators to complete the process of clinical evaluation. Attention should be given to ensuring that expanded access protocols are not excessively cumbersome but remain likely to significantly contribute to medical knowledge.

Procedures should be in place for restricting marketing and use if early promise is not expeditiously confirmed. If further clinical evaluation, following expedited approval, indicates negative impacts such as unsafe or harmful impacts to the patient or potentially misleading statements regarding a drug that has little or no efficacy, then authorities must continue to be able to restrict distribution of the drug. Mechanisms are in place for post-approval monitoring, and this is an important component in any expanded access effort due to the critical need for continued data collection regarding clinical application and patient response and safety.

Broader Representation of Patient Populations

Early phases of clinical research are currently designed to support further development efforts rather than provide widespread clinical use of new agents. That is, traditional Phase I studies are designed to collect data on metabolism, distribution, bioavailability, safety and tolerance of single agents at various doses in a small and relatively homogeneous population. This design has been constructed to promote a more certain assessment of a drug's safety and efficacy at a high benefit to risk ratio and in a relatively advanced time-frame. The conclusions and information generated from early development efforts are used to support and construct later clinical development and research. However, with AIDS as well as other life-threatening diseases, clinicians and patients need early information on the likely consequences of use in diverse populations. While attention to broadening the participation of diverse populations may result in slowing the research and development, or pre-approval process, equity in access also is critical. Also, more extensive experience with diverse patient groups can produce important clinical data helpful in the review and approval process.

Recommendations

Design of Phase I trials should be more inclusive of all patient populations. Early development plans should be formulated with the understanding that the results of early trials may be used to support wider access to investigational agents. This can be accomplished by a number of mechanisms, including increasing the diversity and possibly size of populations studied early in development; giving attention to the development of more useful surrogate markers; and, studying protocols incorporating features such as use of randomization, active control arms, and early evaluation of drug combinations.

Optimal Use of Early Data Collection

Mechanisms for early decision-making regarding clinical development and judging safety and efficacy in the past have not optimally used information available from early data collection, or from information gathered from post-approval monitoring or clinical studies conducted overseas. Current changes have made significant progress in maximizing use of data. These efforts and others should be applauded and further encouraged.

Recommendations

To achieve expanded access, use of information from early short-term studies at the front-end of the drug development process should be more fully incorporated into the decision-making process to help foster and expedite the development process for a promising agent. Maximization of data should also be promoted in other stages of research and development. For example, post-approval monitoring of patient experience shortly after approval, and consideration of data derived from outside the United States could help confirm clinical benefit and bring these agents to market through expedited approval. Information from expanded access protocols also could be reviewed to enhance data assessment and evaluation of a promising therapy, especially if such protocols were implemented as simple randomized studies of two or more dose levels of the new agent. Clinicians, patient groups, primary caregivers, government agency representatives, insurers and others should work together in exploring options for optimizing data collection and use to maximize informational benefits and minimize costs.

Expedited Development

Moving a drug candidate more quickly through the research and development phases will expand access. Compressing the traditional development and review steps so that the approval threshold is crossed earlier maximizes the use of the marketplace as a means of access, and minimizes the need to create new distribution systems. Also, the need to redefine the role of third-party payers would be less critical because current protocol is to pay for FDA-approved agents, regardless of how slow or fast the approval process might be. Another consideration is the costs associated with clinical trial expansion in the context of pre-approval access as compared to the basic costs of doing research and development. New and proven efficiencies and innovations in clinical research protocols also should be explored and introduced into each of these systems and may be used without compromising the overall integrity of the system, while favorably streamlining it. FDA, in cooperation with many interest groups, has made progress and furthered efforts in incorporating new approaches to develop and establish an accelerated approval process.

Recommendations

The Group supports the rule for accelerated approval issued by FDA. Some efficiencies which might achieve more rapid product availability include more flexible eligibility requirements for clinical trial protocols, use of surrogate markers, and new, novel and more creative analytical techniques. For example, FDA recently issued final regulations to expedite review and approval of drugs for life-threatening diseases through an accelerated approval rule (published in the Federal Register on December 11, 1992). This rule provides market approval based upon surrogate endpoints that will be confirmed through subsequent studies conducted after approval. The Group recommends further consideration and application of these efforts.

Financing Expanded Access and Resource Issues

Finance issues have had the least amount of attention in the public policy debate surrounding expanded access to promising therapies and have become a major source of frustration for those dissatisfied with the progress of providing access to therapies earlier. Attempts to develop a more effective financing model that acknowledges limited resources is challenging, as well as efforts to develop agreed to priorities among different funding and funded entities. Policies vary dramatically not only between public and private insurers, but also among private insurers. The insurance industry has begun to address some of these issues, but change is slow. Some members of the private industry sector are trying to move at a more rapid pace, but what might become policy for one company is not necessarily adopted by all companies. For those whose insurance policies will not pay for costs associated with an expanded access program, the financing component may be their biggest barrier to receiving therapies prior to FDA approval.

Below is a description of issues the Dialogue Group discussed, and suggestions for how these financing and resource problems might begin to be addressed.

Overview of the United States Health Care Financing System

A variety of public and private mechanisms are used to finance health care in the United States. Below is a brief description of the major forms of public and private health care coverage.

Public Sector

The two main public insurance programs are Medicaid and Medicare, both of which were established in 1966 to provide medical care coverage for the poor and elderly, respectively. The military health system and Veterans Administration are additional sources of publicly-financed care.

Medicaid: The Federal/State Medicaid program assists the states in financing health care for eligible low-income individuals. The program covers health care expenses for all recipients of Aid to Families with Dependent Children (AFDC), and, in most states, the program covers the needy elderly, blind, and disabled who receive cash assistance under the Supplemental Security Income (SSI) program. Coverage is also extended to certain low-income individuals with high medical bills who qualify as medically needy. States may also extend Medicaid eligibility, for the payment of group health insurance premiums only, to certain individuals with low income and resources who are entitled to continue their employer-based policies after they leave employment.

The Medicaid program is administered by the states and financed jointly with the federal government. Federal law requires States to provide a minimum benefit package for AFDC

and SSI recipients that includes hospital inpatient and outpatient services, home health care for those eligible for nursing facility care, prenatal care, pediatric and family nurse practitioner services and certain federally qualified health center services, laboratory and x-ray services, nurse midwife services, family planning services and supplies, and rural health clinic services. States can also elect to cover a wide variety of other benefits.

Medicaid, designed as it is to help eligible low-income people with their health care expenses, does not provide medical assistance to all low-income people. Generally, it serves certain designated groups, primarily the ones mentioned above, and the states have broad discretion in deciding (within federal guidelines) which groups their Medicaid programs will cover, and what financial criteria will apply. In addition to covering people who receive federal or certain state income-maintenance assistance payments and some related groups not getting cash payments, many states also cover the medically needy.

The option to implement a program for the medically needy allows states to extend Medicaid eligibility to certain individuals (including those with AIDS and HIV infection) and families with high medical costs, specifically, those who meet the eligibility requirements except that they have more income or resources that are otherwise allowed. These people may "spend down" to Medicaid eligibility by incurring medical expenses that reduce their incomes to a state-specified level. Thirty-six states and the District of Columbia provided Medicaid benefits through a medically needy program in 1992.

Medicare: Medicare is a federal program composed of two parts: A and B. Coverage under Part A includes inpatient hospital care and some home health, hospice and skilled nursing facility care. Part B generally covers services such as outpatient hospital care, physicians' services and durable medical equipment. Of particular note is the fact that prescription drugs are not covered by Medicare, except those which are provided while in an institutional setting (e.g., hospitals), or which require a physician's involvement (e.g., intravenous chemotherapy).

The following groups are eligible for Medicare coverage: people who are aged 65 or older, totally or permanently disabled, or who have end-stage renal disease. For individuals who qualify for Medicare as a result of disability, they must wait 29 months before they are entitled to receive Medicare coverage. That is, once an individual is disabled, he or she must wait five months before receiving disability cash payments and then another 24 months before being eligible for Medicare benefits.

The Medicare program has tentatively determined that there will not be payment for drugs used in most expanded access programs. An exception exists with regard to the program's coverage of certain oncologic drugs classified as "Group C" by the National Cancer Institute in cooperation with the Food and Drug Administration. Drugs are so classified only if there is sufficient evidence demonstrating their efficacy within a tumor type and that they can be safely administered.

Private Sector

Employer-based group health plans are generally the most common form of private health insurance. Most large companies in the United States offer some type of health care coverage to their employees, usually without any medical screening. Small firms (i.e., under 15 employees), however, may not offer health insurance to their employees, or the group health plan that is provided may have restrictive coverage policies (e.g., exclusion of employees with particular health problems or health risks). Alternatively, individuals may purchase health insurance on their own. Most insurance companies who offer individual health coverage have restrictive underwriting policies, which means that individuals with significant health problems or risks may face expensive premiums if they successfully obtain insurance, or may simply be denied coverage based on their medical history (i.e., declared "medically uninsurable").

Many large firms are self-insured, which means that they fund employee health benefits from their own assets rather than purchase health insurance from a private insurance company. Currently approximately half of the health benefit claims paid are paid through these self funded health coverage arrangements. While many of the self-funded plans may be administered by insurance companies, the benefit design does not have to comply with state legislative mandates for coverage. These programs, as is the case for all private insurers, vary in terms of the benefits packages they offer and are exempt from some regulation.

Assessment of the Existing Financing Situation for Expanded Access

Costs of expanded access programs are comprised of three types: 1) research and administration; 2) drug production and distribution; and 3) patient care. When pre-approval access has been pursued, the costs for research and administration, and drug production and distribution have been borne overwhelmingly by drug manufacturers and, to a lesser degree, by entities such as the National Institutes of Health. Under a treatment IND, a company may be given permission to charge for the costs of the drug. Thus far, few companies have exercised this right for HIV-related drugs in part because they are reluctant to provide the cost justification information a company must provide when seeking to recover those costs.

For all companies, but more so for smaller companies, the expenses of expanded access can be an economic disincentive to develop programs. Consequently, one of the main concerns when considering financing of pre-approval access is how to provide financial incentives to companies that result in more drugs developed under expanded access programs and more drugs available to needy patients.

Further, primary care providers may be reluctant to participate in expanded access programs because traditionally they have not been compensated for the care they provide, or, under Medicaid, reimbursement rates have been inadequate.

Issues and Recommendations

The current mechanisms for financing health care services do not specifically address innovations such as early availability of new drugs and services. As a result, certain deficiencies remain that prevent individuals with serious and life-threatening diseases from having available to them therapies still under investigation.

1. Perhaps the most difficult financing issue is not a pre-approval access issue, but a health care issue. Many patients will not have access even when drug sponsors and insurers are willing to share the added costs of pursuing expanded access because they are not insured and do not have access to basic health care, let alone expanded access. Moreover, even when a drug is approved, some payer policies do not include pharmaceutical coverage, and for categorical programs, some state payers have been slow to put approved drugs for HIV on their lists of reimbursable care costs.

Many individuals infected with HIV have inadequate or no health insurance. Federally funded block grants for HIV treatment and education are generally thought to be underfunded relative to the need, both in terms of the levels of service and the numbers of HIV-infected patients reached.

Further, due to the economic and political climate throughout the country, many states are cutting back on payment for drugs and health care services for indigent populations that lack access to Medicaid or other sources of third-party payment.

Recommendations

Alternative funding mechanisms should be considered to create better funding sources for the HIV patients in need of clinical services. Possible mechanisms could include access to, and expansion of, Ryan White funds, pooled funds from potential payers, and money from private foundations.

2. Medicare provides reimbursement only for drugs administered in institutional, in-patient settings, or when a physician's involvement is required. The expected increasing numbers of HIV-infected individuals covered by Medicare will have no coverage for HIV drugs under this financing mechanism.

Recommendations

Public and private third-party payers should not deny coverage for medically necessary therapy. It is recommended that public and private third-party payers should not deny coverage on the basis of contract language excluding investigational drugs and therapies, when such care is provided under an FDA approved and supervised expanded access program or when such care is otherwise deemed to

represent the current standard of care.

3. Current payment for ancillary patient care costs (i.e., costs associated with the patient's medical care which would be incurred regardless of particular treatment) and costs arising from unintended side effects are often covered by public and private third-party payers although there are variations among payers and types of coverage. A growing number of insurers are not willing to cover these costs. This is due to uncertainties surrounding distinctions between research costs and health care costs. These insurers believe that research costs are being shifted to them disguised as health care costs. Increased pressure to contain costs may also result in fewer insurers being willing to pay for any costs related to expanded access.

Expanded access programs contain elements of both research and treatment. It is difficult to clearly distinguish the costs of treatment, which many third-party payers would cover, from the costs of research, which historically they have not covered.

Further, some private insurers remain reluctant to pay for expanded access care due to the uncertainty about the added and unanticipated costs, unpredictable results, and the precedent such a payment might establish.

Recommendations

Costs of ancillary care, and necessary and reasonable medical care for unintended side effects should be covered by public and private payers (including self-insurers) for patients in expanded access protocols.

a) Expanded access protocols should clearly define "ancillary costs" (e.g., blood tests, X-rays, etc.).

b) A clear statement of current federal policy should be established. HCFA should clarify Medicare coverage policy regarding payment for unapproved therapies so that it can be uniformly implemented by carriers and intermediaries. Also, HCFA should inform states of the flexibility they have to cover such costs under Medicaid.

c) Private payers should be encouraged to give clear policy statements as well. The National Association of Insurance Commissioners and the Health Insurance Association of America should encourage their members to adopt appropriate policies.

The protocol development process can be used to allocate costs among potential payers (in addition to insurers) and to gain realistic expectations of, and address concerns surrounding, expanded access. To this end, the development of a research protocol to define and determine the research and administrative costs of an expanded access program should have 1) credibility; 2) consensus; and 3) coordination.

a) Insurers need confidence in the sponsor of an expanded access protocol as well as in the hospitals and doctors. Managed care formats, such as case management care, can provide some assurance that payers will not be paying for unnecessary costs. Treatment facilities agreeing to participate in expanded access programs might agree to managed care plans.

b) A consensus process should be used by relevant parties to determine how much of an expanded access program is research and how much is health care. Such information could then be used to determine cost allocation between the sponsor and payers. Consensus approaches could help determine if patients should receive a specific treatment, separate from the drug. Only after some type of agreement has been reached would the expanded access program begin.

c) Coordination among all involved in an expanded access program, both in the design of the program and in the various efforts to administer it, would be necessary to the development of consensus on a protocol. A protocol, developed through a consensus approach, could result in a program agreeable to most and the best use of resources.

The protocol should also include provisions which determine when an expanded access program should be terminated.

4. Private health care coverage is designed and administered by literally thousands of independent third-party payer organizations, including insurance companies, health maintenance organizations (HMOs), third-party administrators (TPAs) and employers. There are currently no industry mechanisms for specifically evaluating and approving expanded access programs and considering the appropriateness of third-party payment for related health care services. Absent such mechanisms, or multiple legislative mandates, significant change in third-party payer participation in expanded access will likely remain problematic.

Industry trade associations do exist, however. Each of them has the potential for representing their members' interests in assessing the appropriateness of payer participation in expanded access programs. The Dialogue Group is unaware of any industry efforts to do so to date. In addition, the Dialogue Group has been made aware of a reluctance on the part of some insurers to engage in discussions and deliberations through their trade associations that they feel might conflict with anti-trust prohibitions.

Recommendations

The Health Insurance Association of America (commercial insurers), the Group Health Association of America (HMOs), the Blue Cross and Blue Shield Association (Blue Plans), the ERISA Industry Committee (self-insured employers), and representatives from other appropriate groups should be encouraged to jointly consider the establishment of a Payers Commission on Expanded Access to

represent their respective memberships in making recommendations concerning payer participation in specific expanded access programs.

The mission of such a Commission might be to perform the following functions, among others:

a) Establish industry criteria for reviewing and approving expanded access programs.

b) Review individual FDA approved expanded access programs.

c) Recommend to payers whether third-party payment should be made for health care services provided to beneficiaries under specific FDA approved expanded access programs. (The Dialogue Group recognizes that not all health benefit plans provide coverage for prescription drugs, and that this lack of coverage would not be addressed by the foregoing recommendations.)

5. The costs of expanded access in terms of resources and possible impacts on a pharmaceutical company's internal research and development programs might prevent companies from entering the field of HIV drug development. These costs go beyond current costs of traditional research, development and production, such as extra ordinary data collection, patient monitoring, potentially larger and higher risk trials, and program administration. The high costs of expanded access might prevent pharmaceutical companies or emerging biotechnology companies from entering the field of HIV drug development. Also, the pharmaceutical companies fear losing proprietary information and control of their respective research and development programs to outside (e.g., patient) groups.

Recommendations

The costs of expanded access should be kept as low as possible. Data requirements should be kept to the minimum needed for safety and enhanced efficacy information.

Research costs should be covered by drug sponsors. Research costs should be clearly delineated from care costs.

Consideration should be given to financial incentives for pharmaceutical companies to seek pre-approval access and assume its attendant costs. These incentives could include tax incentives, patent extensions, and a pre-approval fund generated by a nominal drug surcharge that could be accessed for funding expanded access costs.

Additional Finance and Resources Issues

The Dialogue Group identified other important finance and resource issues, including the following:

1. Not all health insurance policies cover prescription drug costs, and generally those that do cover only the costs of FDA approved drugs or uses.

2. Inconsistency in health benefit plans and their administration by public and private third-party payers creates confusion among patient populations and providers, and fosters an impression that fewer services are covered than is the case.

3. The group is concerned that, in the context of formularies, "prior authorization" will be required of potential recipients of a promising therapeutic drug for reimbursement for expensive and investigational drugs and therapies. As a consequence, new financial barriers to expanded access drugs may arise. It is anticipated that access to approved drugs, let alone drugs under expanded access, may be restricted by new drug pricing legislation and increased use of formularies with their attendant prior authorization. Policy makers should carefully consider the implications of such policies on access to new drugs.

4. For drugs that are not under a treatment IND, it is difficult for a company to recover costs for a drug under investigation. Cost recovery requires FDA approval even for investigational drugs under a treatment IND.

5. Patients should recognize that an insurer's agreement to pay for the cost of care will not increase the insurer's obligation beyond existing coverage caps.

6. Although liability issues have not yet assumed central importance in the development of drugs for AIDS, concerns over liability could become more important and potentially interfere with the development and availability of these products in the future. (See Appendix B for a discussion of liability issues.)

These issues require continued debate among, and efforts by, all interested and involved parties in order to resolve them. The Keystone Expanded Access Dialogue Group's recommendations are a first step in understanding the complex relationships between the health care financing system and making therapies available to more people in need of care.

Conclusion

The AIDS crisis continues to raise many challenging scientific, societal and public policy issues. The Keystone National Policy Dialogue on Expanded Access to Promising Therapeutic Drugs for HIV Infection and AIDS with Implications for Other Life-Threatening Diseases provided an opportunity for people with different perspectives and expertise to come together in an effort to productively discuss and address some of these issues. It is hoped that these recommendations will encourage and facilitate earlier and greater access to promising therapies for those who are HIV-infected and have no satisfactory alternatives. Many more issues remain and work must continue. It is hoped that the groundwork constructed through this project will serve as a resource for future and continued work on expanded access issues surrounding HIV infection and AIDS, as well as for consideration by those working on expanded access issues for other life-threatening diseases.

Appendices

APPENDIX A

Glossary

ACTU	AIDS Clinical Trial Units
AFDC	Aid to Families with Dependent Children
AHEC	Area Health Education Consortia
AIDS	Acquired Immune Deficiency Syndrome: the specific criteria for the diagnosis of AIDS has changed over time. The official definition is determined by the CDC.
AZT	zidovudine (Retrovir®)
BCBSA	Blue Cross Blue Shield Association
CDC	Center for Disease Control & Prevention
CME	Continuing Medical Education
ddC	dideoxycytidine (Hivid®)
ddI	dideoxyionosine (Videx®)
ERIC	ERISA Industry Committee
ERISA	Employee Retirement Income Security Act of 1974
ETC	Education and Training Centers
FDA	Food and Drug Administration
GHAA	Group Health Association of America
HCFA	Health Care Financing Administration
HHS	Department of Health & Human Services
HIAA	Health Insurance Association of America
HIV	Human Immunodeficiency Virus
HRSA	Health Resources and Services Administration
IND	Investigational New Drug
IRB	Investigational Review Board
NDA	New Drug Application
NIH	National Institutes of Health
OI	opportunistic infections
PHS	Public Health Service
PK	pharmacokinetic
RCT	Randomized Clinical Trials
SSI	Supplemental Security Income

APPENDIX B

Liability Issues

Although liability issues have not yet assumed central importance in the development of drugs for AIDS, concerns over liability could become more important and potentially interfere with the development and availability of these products in the future. Because a key goal of the Expanded Access Dialogue Project has been to encourage companies to invest in research and development of therapeutic drugs for HIV infection, the Group believes that the issues should be given more attention if companies become deterred from investing the sums necessary to discover, test and distribute drugs for AIDS and related illnesses due to liability concerns.

Limited clinical trials of investigational drugs have not historically presented substantial liability risks. Patients are carefully screened prior to entry, their medical condition is frequently monitored, and study size is only gradually increased as greater experience is gained with a particular drug. Although AIDS drugs have been tested in larger populations more quickly than is typically the case for other drugs, persons involved in the studies have been fortunate that few unexpected adverse effects have surfaced.

As further progress is made, however, liability issues can potentially be expected to play a more important role in research and investment decisions, particularly for smaller companies. There is a greater likelihood of unanticipated adverse effects as drugs are made available to greater numbers of patients through expanded access protocols. Expanded access programs also may involve less demanding entry criteria and less rigorous monitoring of patients' medical status. This loss of control also may increase the risk of injury.

Accelerated approval procedures may present additional liability risks. Under these procedures, drugs may enter widespread and essentially unrestricted distribution after testing in fewer subjects and for a shorter period of time than has traditionally been the case. These circumstances increase the risk of missing serious adverse events that might have been discovered in the clinical trials.

The Group discussed but did not come to any conclusions or make any specific recommendations regarding liability risks facing companies that develop AIDS drugs. Among the ideas raised by the Group was a review of the standard for liability for drugs approved by FDA subject to accelerated approval procedures. In addition, some members of the Group expressed an interest in a change in the law in order to permit and give binding effect to clauses in informed consent agreements. The structure of the informed consent process is critical to the level of interest in pursuing this change. Some participants also suggested a review of alternative compensation systems, such as a no-fault compensation fund, and the consideration of caps on compensatory and punitive damages. Many of these changes would be considered only if definitive data demonstrated that companies were not investing in research and development of AIDS therapies expressly for reasons of liability concerns. Finally, patients in expanded access programs may suffer injuries possibly related to the

administration of the drug and require subsequent medical treatment, which sometimes may not be reimbursed by third parties. The group believes that drug companies, physicians, patients, IRBs and possibly others should consider appropriate and fair arrangements to ensure the coverage of such unreimbursed treatment for patients who have volunteered to participate in clinical trials.

APPENDIX C

Participant List

The people listed below participated in the Keystone Expanded Access Dialogue Project. Their discussions and deliberations resulted in this report. The participants conducted their deliberations under the following ground rules.

Ground Rules

In order to enhance discussions among the participants of the Expanded Access Dialogue, ground rules were established, as they are with all Keystone Center dialogue projects. The ground rules governing the Expanded Access Dialogue were the following:

1. All participants attended as individuals, not as formal representatives of their respective organizations, agencies, or companies.

2. All comments and sessions were off-the-record and not for attribution.

3. No document produced by the Group was made public without the full consent of the Group.

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UNDERSTANDING HIV PATHOGENESIS: IMPLICATIONS FOR DRUG AND VACCINE DEVELOPMENT

Summary of a Workshop
July 26, 1991

Institute of Medicine
Roundtable for the Development of
Drugs and Vaccines Against AIDS

INSTITUTE OF MEDICINE

Roundtable for the Development of Drug
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Since the human immunodeficiency virus (HIV-1) was first isolated and identified as the etiologic agent of acquired immune deficiency syndrome (AIDS), biomedical researchers have made substantial gains in defining important aspects of the genetic structure and *in vitro* biology of the virus. Yet progress in elucidating the natural history and pathogenesis of HIV infection has proceeded more slowly. Emerging scientific data are now illuminating a preliminary, but increasingly, coherent framework for understanding the pathogenesis of HIV-associated disease. A more complete description of the pathogenesis and natural history of HIV infection is likely to facilitate the development and application of improved therapeutic interventions.

VIRAL PATHOGENESIS OF HIV INFECTION AND AIDS: CURRENT UNDERSTANDING AND UNRESOLVED QUESTIONS[1]

To understand more fully the pathogenesis of HIV infection, researchers will need to define the level of viral burden and expression that are present at various stages of disease. They will also need to describe further the various factors that regulate the level of viral replication. The prediction, based on early studies, that few target cells in HIV-infected individuals actually harbor and express the virus has remained a fundamental difficulty in understanding the pathogenesis of infection. The recent application of more sensitive methods of viral detection, however, indicates that both the viral burden and magnitude of expression may be substantially higher than previously believed. The level of replication *in vivo* appears to represent a balance between the complex viral mechanisms that regulate HIV gene expression and the ability of the host immune system to recognize and eliminate infected cells. Activation and attenuation of HIV production also appear to depend on important cellular factors involved in the normal host response to immunologic or inflammatory stimuli.

Studies of the HIV-1 life cycle have demonstrated that the character of viral gene expression differs at various points following viral infection. The expression of HIV-1 genes assumes two essential stages—early and late—that are distinguished by the pattern of viral ribonucleic acids (RNA) present in infected cells. In the "early" stage, shortly following infection, the predominant viral RNA transcripts are the multiply-spliced transcripts that encode the viral *tat*, *rev,* and *nef* gene products. It is thought that this "early" pattern derives from the paucity of HIV *rev* protein present shortly after infection. The *rev* protein plays an essential role in viral replication and regulates the pattern of viral RNA transcripts that are synthesized. The *rev* gene acts, in an incompletely defined manner, to regulate either the splicing or nuclear to cytoplasmic transport of specific viral RNA pieces. In the absence of *rev*, only the multiply-spliced transcripts that encode the viral regulatory gene products are available for translation in the cytoplasm. As time passes following infection and as *rev* protein accumulates, the "late" stage of gene expression occurs during which the unspliced or singly-spliced viral RNAs are expressed. These transcripts encode the virion structural and enzymatic constituents, and their expression allows viral assembly and subsequent transmission to proceed. Additionally, recent evidence suggests that the complex viral regulatory process, which underlies transition from the "early" to "late" stages of the HIV-1 life cycle, may also play an important role in the virus's ability to assume an attenuated or latent state of infection.

Studies of HIV-infected individuals indicate that far more CD4+ lymphocytes may be infected in the peripheral blood than those that actually express detectable levels of viral RNA or protein. Experiments in tissue culture models of HIV latency suggest a possible explanation for this observation, which derives from an intricate interplay between viral and cellular regulatory factors. HIV transcription and production are activated by antigenic, mitogenic, or inflammatory stimuli. This transcriptional activation is mediated in large part by the cellular transcription factor referred to as NF-κB. This factor serves an important function in activating the expression of a number of cellular genes that are essential to

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[1]This section is based on material presented by David Baltimore.

generate an immune response. In an inactivated state, a cell infected with HIV may contain little active NF-κB and, thus, HIV transcription is limited. When the level of HIV transcription is low, only a small amount of *rev* protein is produced. As a result, the pattern of viral transcripts resembles the "early" phase of gene expression—that is, the stage during which the multiply-spliced messenger RNAs that encode the regulatory gene products are preferentially produced and those that encode the virion constituents are rare. With immunologic or inflammatory stimulation, the NF-κB is activated, resulting in increased HIV transcription. As HIV transcription accelerates, the level of *rev* protein that is synthesized also increases. HIV-1 gene products that are characteristic of the "late" stage of the viral life cycle can then be synthesized, and viral assembly can proceed. By remaining in the "early" stage of its life cycle in quiescent cells, the virus synthesizes little of the immunogenic structural proteins that target an infected cell for immunologic elimination. Further, because expression of the HIV envelope glycoprotein (a "late" gene product) can result in direct cytopathic consequences for an infected cell, carefully regulated control of its expression may be essential. Both of these factors may serve to facilitate viral persistence in an infected host.

UNDERSTANDING THE VIRAL PATHOGENESIS OF HIV INFECTION AND AIDS[2]

Definition of the range of cells that are targets for HIV infection is essential to elucidate the process of viral pathogenesis. The CD4+ T lymphocyte (or so-called, helper-inducer T cell) is known to be the prime target for HIV infection in the peripheral bloodstream, while macrophages are important targets for viral infection in the peripheral tissues, the central nervous system, and perhaps, the lymphoid organs. Recent attention has also focused on the possibility that follicular dendritic cells play an important role as early targets of HIV infection, although this is still controversial.

The CD4 cell surface molecule that phenotypically defines the helper-inducer population of lymphocytes, which is profoundly depleted in persons with AIDS, is, in fact, the receptor that HIV uses to gain entry into its target cells. The CD4 molecule serves as the viral receptor on both lymphocytes and macrophages. The process of HIV infection is initiated when the virus particle binds to CD4 present on the surface of a cell via the viral envelope glycoprotein, gp12O. The virus then gains entrance to the cell through a process of membrane fusion mediated by the HIV envelope protein, gp41, which is physically associated with gp12O. (Both proteins are encoded by a single gene whose translation product, gp16O, undergoes proteolytic processing to the two constituent parts—gp12O and gp41).

Although lymphocytes and macrophages can both serve as targets for HIV infection, by virtue of their expression of the CD4 molecule, certain isolates of HIV will preferentially infect one or the other of these cell types. The genetic basis of the preferential tropism of HIV isolates for specific target cells has recently been mapped to a region of gp12O, known as the V3 loop. This region also represents the principal neutralization domain that is recognized by antiviral antibodies, which block HIV infection *in vitro*. Although the envelope glycoprotein has been clearly implicated in effecting viral tropism, the mechanism by which this occurs has not yet been described.

With the identification of CD4 as the HIV receptor, biomedical researchers proposed an imaginative approach to antiviral therapy, whereby soluble versions of CD4 were produced to competitively block the process of virus binding to potential targets. In fact, this approach worked well in tissue culture models that utilized standard laboratory isolates of HIV and immortalized T cell lines. However, soluble CD4 was without demonstrable antiviral effect *in vivo*. The apparent explanation for this discrepancy is

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[2]This section is based on material presented by Robert Gallo.

that primary isolates of HIV, as opposed to those adapted for growth *in vitro*, are poorly inhibited by soluble CD4. This experience highlights the difficulties in extrapolating certain aspects of *in vitro* studies to the complexities of HIV biology *in vivo*.

In addition to mediating HIV binding and entry into target cells, the gp12O/gp41 envelope glycoprotein complex also plays a major role in the cytopathic consequences of HIV infection. Expression of the gp12O/gp41 complex in a CD4+ T cell can result in a process of membrane fusion between neighboring cells, which is termed syncytia formation. Although this is an obvious result of HIV infection *in vitro*, its role in the process of CD4+ T cell depletion *in vivo* is not known. Other mechanisms for T cell depletion have been proposed: the possible influence of the HIV *nef* gene on T cell growth and the inappropriate targeting of uninfected CD4+ lymphocytes for immune clearance through an "innocent bystander" mechanism when lymphocytes bind free gp12O to their cell surface. An essential aspect of future investigations should be an improved understanding of the respective contributions of the direct and indirect mechanisms of T cell depletion that follow HIV infection.

The factors that underlie the loss of CD4+ lymphocytes, following HIV infection, are not clearly understood nor are the factors that contribute to the immune system's failure to replace these lost cells. This may be due, in part, to a fundamental limitation of T cell repopulation in adult humans, although little is known about this important process. Alternatively, HIV infection may result in direct damage to the thymus where T cell differentiation and production occur. A critical goal for future studies is to define the kinetics of the loss and replenishment of T cells following HIV infection.

Further information is needed regarding the important effects of HIV-associated disease that occur outside the T lymphocyte population. Such manifestations include the neurological sequelae of HIV infection, as well as two types of malignancies—B cell lymphoma and Kaposi's sarcoma (KS)—often seen among persons with AIDS. Aggressive B cell lymphoma is emerging as a prominent and increasingly frequent AIDS diagnosis, although its etiology is unknown. Several possible etiologies, however, have been offered. B cell lymphomas may be the result of an as yet unidentified infectious agent or the outcome of polyclonal B cell activation that occurs in HIV-infected persons. Or, these lymphomas may arise due to the failure of immune surveillance against malignant transformation. Kaposi's sarcoma, the other characteristic HIV-associated malignancy, is also poorly understood. The role of HIV in the etiology of KS, acting in either a direct or indirect role, is not well defined but remains an active area of research.

ACCESSORY GENES OF HIV[3]

Three structural and enzymatic gene products—*gag*, *pol*, and *env*—are common to all retroviruses. In addition to these gene products, lentiviruses (such as HIV-1 and HIV-2) encode an array of other products. These auxiliary genes are termed: *tat*, *rev*, *nef*, *vif*, *vpr*, *vpu*, and *vpx*. Of these genes, *tat*, *rev*, *vif*, and *nef* are present in all lentiviruses. *Vpu* is present in HIV-1 but absent from all other members of the lentivirus subfamily. *Vpx*, on the other hand, is present in all of the immunosuppressive lentiviruses, except HIV-1 and the simian immunodeficiency virus (SIV) isolate from mandrills. Based on gene sequence comparisons, scientists have postulated that *vpx* is a duplicate *vpr* gene, and that the presence of *vpr* in HIV-1 and SIV from mandrills may compensate for the absence of *vpx*.

The *tat* and *rev* gene products are essential for HIV replication. *Tat* is required to efficiently synthesize viral RNA and to facilitate elongation of HIV RNA transcripts. *Rev*, as previously discussed, controls the pattern of spliced HIV RNA transcripts that are expressed in infected cells. This process

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[3]This section is based on material presented by Ronald Desrosiers.

occurs either through regulation of the splicing of viral RNA transcripts or through selective control of viral RNA transport from the nucleus. Because both of these gene products are essential for HIV replication, they provide promising targets for future development of antiviral agents.

Scientists have had difficulty in determining the function of the remaining "non-essential" gene (i.e., *nef*, *vpr*, *vpx*, *vpu*, *vif*) products, in part because they are not critical to viral replication. Furthermore, no assays have been identified, to date, for measuring the function of these gene products *in vitro*. In the absence of reliable, reproducible assays, various studies of their function have produced conflicting results. Although these gene products are not essential for viral replication in tissue culture, their conservation among the diverse members of the lentivirus subfamily of retroviruses suggests that these gene products play important roles in the *in vivo* processes of infection and pathogenesis.

Convincing evidence for this view comes from recent analyses of the *nef* gene. As previously noted, *nef* is dispensable for viral replication *in vitro*. Scientists have reported that *nef* binds GTP, acts as a GTPase, and undergoes autophosphorylation, but these findings have been disputed. Scientists have also reported that *nef* has a negative, positive, or no effect on viral transcription. The acronym, nef, derives from earlier suggestions that it served as a *Negative Factor*. Recent studies in the SIV model, however, have indicated that although mutation of the *nef* gene has no appreciable effect on SIV replication *in vitro*, it destroys the ability to cause disease in the rhesus macaque. *Nef* plays an as yet unidentified function required for the maintenance of a high virus load and for disease development in infected animals. Determination of the *in vivo* function of *nef* remains a critical area for future investigation.

The *vif* (Virion Infectivity Factor) gene is present in all primate lentiviruses. Mutation of *vif* substantially decreases but does not abolish viral replication in tissue culture. The magnitude of this effect, however, depends on the target cells that are used. *Vif* seems to be particularly important for cell-free virus transmission. Preliminary studies have shown that *vif* may be associated with the Golgi apparatus and may affect the processing of the viral gp41 envelope glycoprotein.

The *vpr* gene is present in all primate lentivirus groups, except SIV_{agm}. The *vpr* protein is found in detectable quantities in virions, although its function is unknown. Mutation of *vpr*, however, has no apparent effect on viral replication. Some scientists believe that it may play a role in viral infection of macrophages.

The *vpx* gene is found in HIV-2 and SIV_{mac} virus groups. The *vpx* protein is associated with the virion, perhaps in high concentrations. As previously discussed, however, this gene is dispensable for virus replication in tissue culture and may have originated via duplication of the *vpr* gene. It is hoped that future studies will clarify the function of *vpx*.

The *vpu* gene is present only in the HIV-1 group. The *vpu* protein has been reported to increase the export of virus from infected cells, perhaps by influencing the formation of intracellular complexes between gp12O and CD4 molecules.

As the preceding discussion indicates, the function of the "non-essential" gene products of the immunosuppressive lentiviruses is unclear. A more complete description of their function is essential to future progress in understanding viral transmission, disease pathogenesis, and in developing antiviral drugs that are specifically designed to target their function.

BIOLOGICAL VARIABILITY OF HIV[4]

The mutation rate of retroviruses, including HIV-1, over a single replication cycle is quite high—estimated to be between 10^{-3} to 10^{-5} per nucleotide per round of replication. When this rate is extrapolated to project the mutation rate that occurs *in vivo*, it is estimated that the rate of change is 0.1 to 1 percent per year. The high mutation rate of retroviruses stems from the lack of a "proof-reading" function in the viral reverse transcriptase, such that polymerase errors cannot be corrected. The biological significance of HIV-1 sequence variation is not well understood but is likely to be important in understanding the basis of viral persistence and pathogenesis.

A confounding feature in the experimental design of early studies of HIV-1 genetic variability was the reliance on *in vitro* propagation of viral isolates prior to genetic or biologic characterization. Only later was it discovered that the process of culturing HIV *in vitro* rapidly selects for viral variants, which may not accurately represent the population of viruses present in the original inoculum. Thus, the isolates that were typically studied frequently did not reflect the distribution or character of viral variants present in an HIV-infected individual. The subsequent development of the polymerase chain reaction (PCR) technique has permitted the direct cloning and sequence analysis of viruses as they exist *in vivo*.

A fundamental question concerning the nature of sequence variation *in vivo* is whether the process is random, or whether it reflects the influence of selective pressure exerted by the host immune system. Resolution of this question is important for future understanding of the immunopathogenesis of infection and the mechanism of HIV persistence *in vivo*, as well as for vaccine development efforts.

In the few instances in which primary HIV infection has been studied in detail, it appears that viral sequence variation can occur quite soon after establishment of infection. The evolution of viral populations in infected individuals is the focus of a number of ongoing descriptive analyses. Viral variation is thought to play an important role in the virus's escape from immune surveillance, although this is not yet clear. Biological variation may also be of pathogenic significance, particularly if early suggestions concerning the possible acceleration of immunodeficiency coincident with the appearance of more highly replicative viruses prove correct. Sequence variation is known to play a role in determining the cellular tropism of a given isolate. In this instance, sequences within the V3 loop of gp12O appear to be responsible for determining a variant's tropism for T cells or macrophages.

The pronounced sequence variability of HIV-1 also has important practical implications for drug and vaccine development efforts. Rapid sequence evolution of HIV plays a critical role in the development of drug resistance. In addition, candidate HIV vaccines will need to accommodate the range of sequence variation in their design, testing, and application.

IMMUNOPATHOGENESIS OF HIV INFECTION AND AIDS: CURRENT UNDERSTANDING AND UNRESOLVED QUESTIONS[5]

The profound, deleterious impact that HIV has on the human immune system may reflect the susceptibility of the essential population of CD4+ lymphocytes and macrophages to viral infection and killing. Lymphocytes and macrophages play essential functional and regulatory roles in the human

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[4]This section is based on material presented by Irvin Chen.

[5]This section is based on material presented by Max Cooper and Anthony Fauci.

immune system. The impairment of these important functions would be expected to have numerous and potentially deleterious effects. The varied pathology resulting from HIV infection validates this expectation.

Progressive loss of CD4+ lymphocytes following HIV infection indicates that the capacity for T cell replenishment is ultimately outstripped by the process of lymphocyte depletion. Currently, scientists' limited knowledge about the balance and control of lymphocyte production in adult humans presents a challenge in understanding the kinetics of CD4+ lymphocyte loss associated with HIV infection.

The progress of HIV infection almost certainly represents a balance between immunologic containment of viral replication and the control of viral gene expression. The details of this process are unclear, but important insights have recently emerged. Shortly following exposure to HIV, an acute viral syndrome, which represents primary HIV infection, occurs in some individuals. In the absence of preexisting antiviral immunity, HIV can initially replicate to high levels and become readily detectable in cell-free plasma and in a substantial proportion (up to one percent) of peripheral blood lymphocytes. During this period, there is a transient drop in the number of CD4+ lymphocytes, which may result from lymphocyte redistribution or loss. It is possible that much of the damage to the host immune system, which may presage future deterioration, occurs during this period of primary infection.

The high level of virus expression that occurs during primary infection declines with the appearance of antiviral antibodies. The development of antiviral cytotoxic immune responses is also likely to play a role in decreasing the extent of active viral replication, although little information on this important topic is currently available.

With the decline of virus replication following the acute viral (or seroconversion) syndrome, the chronic phase of infection begins. This period was previously considered the "latent" stage, but such a characterization represents some confusion of the definitions of clinical and microbiological latency. Recent research results have convincingly shown that HIV replication and expression continue at all stages of the disease process and, thus, HIV is never truly latent (from a microbiological perspective).

During the chronic phase of infection, the number of infected cells present in the peripheral blood and the magnitude of plasma viremia are both low. Within the peripheral bloodstream, CD4+ T cells constitute the predominant reservoir of HIV-infected cells. Monocytes in the peripheral blood apparently are not major target cells.

In asymptomatic HIV-infected individuals, an estimated one in 10,000 to one in 100,000 CD4+ T cells in the peripheral blood are infected with HIV-1, and only very low levels of plasma viremia can be detected. The subsequent increasing viral burden heralds the development of progressive immunologic impairment. The proportion of infected CD4+ lymphocytes frequently rises coincident with an accelerated decline in total number. During this period of evolving immunodeficiency and progression to clinical AIDS, viral expression increases with the recrudescence of significant plasma viremia, elevated p24 antigen levels, and increased viral RNA synthesis. An increasing viral burden can herald the development of clinical AIDS; it may also reflect the failure of the immune system to contain HIV infection.

Early investigations of viral burden and expression during various stages of HIV disease have relied primarily on studies involving peripheral blood cells. Recent work, however, shows that lymphoid tissues exhibit a high viral burden and increased levels of viral expression. The localization of viral replication in the lymphoid tissues may have significant implications for disease pathogenesis. As previously noted, immunologic or inflammatory stimuli [including the cytokines known as tumor necrosis factor (TNF), interleukin 6 (IL-6) and granulocyte macrophage colony stimulating factor (GM-CSF)] enhance HIV production in infected cells. These cytokines all activate expression of the cellular transcription factor, NF-κB, which in turn augments HIV gene expression.

Concentration of HIV-infected cells at the anatomic sites of the immune response may also enhance viral expression. T cells involved in the generation of an immune response to a given antigen may thus bear the brunt of the cytopathic consequences of HIV-1 infection. In addition, recent evidence indicates that viral infection of the thymus itself may be important in understanding the failure of the immune system to compensate for T cell loss due to HIV infection.

IMMUNE DEFICIT ASSOCIATED WITH HIV INFECTION[6]

Depletion of CD4+ lymphocytes is a hallmark of HIV infection and AIDS, but this process is not fully understood. In addition, there is substantive evidence that demonstrable defects in T cell function are present before the decline in CD4+ lymphocytes occurs. HIV-infected individuals exhibit a selective impairment in their response to antigens to which they have been previously exposed through infection or vaccination. Such antigens are referred to as "recall" antigens. The immune response to recall antigens requires a subset of CD4+ lymphocytes bearing the cell surface markers CD29 and CD45 RO, which phenotypically define "memory" T cells. Recent studies suggest that this important population of memory T cells may be preferential targets for HIV infection both *in vitro* and *in vivo*. Exposure to a given antigen may stimulate an immune response in an HIV-infected individual, which may, paradoxically, result in depletion of the responding cells. Constriction of the T cell repertoire of specific antigenic recognition may thus occur prior to the depletion of total CD4+ lymphocytes. If this hypothesis proves to be correct, it would provide further support for early antiviral treatment of infected individuals. The impaired ability to respond to recall antigens also has important implications for therapeutic vaccination of seropositive individuals—a strategy designed to boost their antiviral immune response. HIV-infected individuals may be stratified to receive such immunization based on their ability to respond to other antigens.

REVERSING THE IMMUNE DEFICIT: CAN IT BE DONE?[7]

Numerous gaps remain in our knowledge of the immunopathogenesis of HIV infection and AIDS. The role of immune activation and the existence of possible cofactors for disease progression, such as coexisting viral (e.g., cytomegalovirus, Epstein-Barr virus) infection, require more complete description. The challenges faced in defining the pathogenic mechanisms of HIV infection highlight limitations in the current understanding of the human immune system.

Studies of T lymphocyte development in humans have been hampered by the inability to perform adaptive transfer studies, which have yielded essential insights into lymphoid differentiation in animal models. Recently, however, scientists have developed several models for the study of human lymphocyte development based on transfer of human lymphocytes, or their progenitors, into immunodeficient mice. These systems provide useful information regarding the identity of the human hematopoietic stem cell. Characterization of this stem cell is essential to many of the proposed strategies (such as autologous transplantation of genetically modified stem cells) for immunologic reconstitution of HIV-infected individuals. Gene therapy for HIV infection (so-called, "intracellular immunization") will require resolution of several outstanding concerns. Among them are: documentation that the pluripotent stem cell is not itself a target for HIV infection and the development of an efficient means to genetically modify

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[6]This section is based on material presented by Gene Shearer.

[7]This section is based on material presented by Irving Weissman.

stem cells. Further investigation is needed to define the developmental potential of T lymphocytes in adult humans, as well as to understand the consequences of viral infection of important lymphoid organs, such as the thymus.

IMMUNE RESPONSE TO HIV[8]

The fluctuation in virus production at various stages of the disease process indicates that the immune system may contain, albeit temporarily, HIV replication. Studies of the immune response to HIV infection have shown that both humoral and cytotoxic responses are directed against viral antigenic determinants. Researchers have devoted substantial effort to defining the HIV antigens (and epitopes) that antibodies and cytotoxic T cells recognize. Yet, at present, knowledge is limited regarding the potentially protective components of the antiviral immune response. Identifying these protective determinants, as well as the agent of host immunity that may effectively respond to them, is an essential challenge for future HIV vaccine development efforts.

Scientists have focused considerable attention on the phenomenon of antibody-mediated neutralization of HIV-1 *in vitro*. The primary neutralization domain has been mapped to a region of the gp12O envelope glycoprotein, referred to as the V3 loop. A large proportion of the antibodies in naturally infected humans or experimentally immunized animals, which are able to neutralize HIV-1 infectivity *in vitro*, do so by binding to the V3 loop. The precise mechanism of neutralization is as yet unclear. Antibodies experimentally generated against the V3 loop are generally type-specific; that is, they are only able to neutralize the viral isolate from which the sequences used for immunization were derived. Sera from HIV-1 infected patients generally display more broadly reactive neutralizing abilities. The V3 loop designation refers to the third variable region of the gp12O molecule. It, by definition, displays considerable sequence variation among viral isolates. Because such variation may frustrate vaccine development efforts, immunogens that elicit broadly neutralizing antibodies are being investigated. Effective immunogens may be identified through the study of conserved elements within the V3 loop or through population studies to define the extent and localization of HIV-1 variants. Challenge studies conducted among chimpanzees have shown that monoclonal antibodies with strong reactivity to the V3 loop can prevent infection. These studies offer provisional support for the potential of vaccination with the V3 loop to protect against viral infection. Similar experiments conducted using human immune sera with *in vitro* neutralizing activity, however, have been unsuccessful.

Specific cell-mediated immune responses to HIV-1 are believed to be mediated by CD8+ T cells, which recognize peptide antigens bound to class I MHC (Major Histocompatibility Complex, also known as HLA in humans) molecules expressed on the surface of infected cells. Additional antiviral effector cells include natural killer (NK) cells and cells that carry out antibody-dependent cytotoxic activities. CD8+ T cells that react with HIV-1 antigens have been identified in a variety of tissues, including the peripheral blood, lymph nodes, skin, central nervous system, and lung. In certain instances, these cells may contribute to the pathologic consequences of HIV-1 infection in affected tissues. However, the balance between the protective or possibly pathogenic role of CD8+ antiviral T cells is not known.

Because human T cell populations are genetically heterogeneous and CD8+ T cells recognize antigens only in the context of HLA (MHC Class 1) molecules, the identification of viral epitopes that are recognized by CD8+ T cells depends on the host cells' MHC haplotype. Although current evidence

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[8]This section is based on material presented by Barry Bloom, Norman Letvin, and Wayne Koff.

suggests that CD8+ T cells can inhibit HIV-1 replication *in vitro*, the *in vivo* contribution of these cells to containment of HIV-1 infection is not known. Experimental resolution of this essential question will likely rely heavily on studies performed in primate animal model systems.

As discussed earlier, HIV-1 exhibits considerable sequence variation among isolates derived from different individuals. Sequence variation is also seen among different viruses within an individual over the course of infection. It is unclear whether the antiviral immune response selects for (or against) variation, or whether genetic drift permits HIV-1 to escape from immune surveillance. In the chimpanzee model, sera derived late in infection can neutralize early but not late viral isolates, which provides evidence for a process of viral escape. Whether this phenomenon exists in infected humans is uncertain. At present, the evidence regarding potential escape of viral variants from cytotoxic T cell recognition is both preliminary and conflicting.

Results from a variety of animal model systems are relevant to the development of a vaccine to prevent HIV-1 infection. In the SIV system, vaccines based on whole, inactivated virus have successfully protected immunized animals from intravenous experimental viral challenge. Subunit vaccines, which consist of the envelope glycoproteins alone, have been unsuccessful to date. In the chimpanzee model of HIV infection, animals immunized with recombinant HIV-1 gp12O or gp16O have been protected from experimental challenge. Important caveats must, however, accompany the results cited above. These experiments were performed under ideal conditions, which may bear little resemblance to prevention of natural HIV infection. All viral challenges in these experiments were of relatively low dose and consisted of free (not cell-associated) virus. In addition, they were delivered intravenously (not mucosally), at the height of the immune response, and they consisted of the same viral isolate used for immunization. Further vaccine studies will need to be performed under circumstances relevant to natural human exposures. Also critical to these efforts is an understanding of the nature of the protective immune response in immunized animals.

NEW AVENUES FOR DEVELOPING POTENTIALLY EFFECTIVE THERAPY[9]

Efforts directed toward the development of effective antiretroviral drugs are an essential part of the medical and scientific response to the HIV epidemic. Recent history in this area highlights both challenges and opportunities for future drug development efforts. Clinical experience with zidovudine (AZT) suggests one challenge—namely, therapeutic efficacy may require more than *in vitro* antiretroviral activity. Drug toxicity and potential development of drug-resistant viral variants are critically important considerations in developing drugs to treat a chronic disease.

Viral isolates with decreased sensitivity to zidovudine have been identified in treated patients. Although the clinical implications and correspondence of drug resistance are uncertain, it is a troubling development. The genetic alterations in HIV-1 isolates with decreased sensitivity to zidovudine have been mapped to a range of specific sites in the reverse transcriptase gene. The precise mechanism of zidovudine resistance induced by these mutations is not yet known.

Drug resistance has also emerged in HIV-1 infected patients treated with ddI, ddC, as well as with the non-nucleoside TIBO reverse transcriptase inhibitors. In some instances (e.g., TIBO drugs), resistance develops shortly after initiation of therapy. The phenomenon of antiviral drug resistance has prompted the application of combination therapy with simultaneous or alternating agents. The rationale for this therapeutic approach stems from the recognition that distinct genetic alterations are responsible for the

[9]This section is based on material presented by David Barry and Edward Scolnick.

development of resistance to particular antiviral agents, the varying toxicities of specific agents and, in some cases, their different mechanisms of action. It is hoped that combination therapy will be less toxic, more effective, and more likely to inhibit the emergence of drug-resistant viral variants. More definitive answers regarding combination antiretroviral therapy await the completion of ongoing clinical trials.

To date, many of the agents that are active against HIV infection have been identified through random screening of previously synthesized compounds. Exploitation of these compounds, however, depends on existing technology and expertise that derive from prior basic research efforts. Basic research, therefore, provides essential support for applied studies. Future progress in drug development efforts, including realization of the promise of "rational drug design," will depend on continued advances in basic science research.

Institute of Medicine

Roundtable for the Development of Drugs
and Vaccines Against AIDS

Understanding HIV Pathogenesis: Implications for Drug and Vaccine Development

July 26, 1991

Lecture Room, National Academy of Sciences
2101 Constitution Avenue, N.W.
Washington, D.C.

REVISED AGENDA

8:00 am	Continental Breakfast
8:15 am	Welcome and Introduction — Sheldon Wolff, Physician-in-Chief, New England Medical Center and Cochair, Roundtable
8:30 am	**VIRAL PATHOGENESIS OF HIV INFECTION AND AIDS: CURRENT UNDERSTANDING AND UNRESOLVED QUESTIONS** *Moderator*: David Baltimore, President, The Rockefeller University
8:35 am	Understanding the Viral Pathogenesis of HIV Infection and AIDS — Robert Gallo, Chief, Laboratory of Tumor Cell Biology, National Cancer Institute
8:55 am	Accessory Genes of HIV — Ronald Desrosiers, Chair, Department of Microbiology, New England Regional Primate Research Center
9:10 am	Biological Variability of HIV — Irvin Chen, Professor of Microbiology, Immunology and Medicine, UCLA School of Medicine
9:25 am	Discussion
10:25 am	Break
10:40 am	**IMMUNOPATHOGENESIS OF HIV INFECTION AND AIDS: CURRENT UNDERSTANDING AND UNRESOLVED QUESTIONS** *Moderator*: Max Cooper, Investigator, Howard Hughes Medical Institute, University of Alabama, Birmingham
10:45 am	Toward an Understanding of the Immunopathogenesis of HIV Infection and AIDS — Anthony Fauci, Director, National Institute of Allergy and Infectious Diseases

11:05 am	Immune Deficit Associated with HIV Infection — Gene Shearer, Chief, Section on Cell-mediated Immunity, Experimental Immunology Branch, National Cancer Institute
11:20 am	Reversing the Immune Deficit: Can It Be Done? — Irving Weissman, Professor, Department of Pathology, Stanford University School of Medicine
11:35 pm	Discussion
12:35 pm	Lunch
1:30 pm	**IMMUNE RESPONSE TO HIV** *Moderator*: Barry Bloom, Professor and Chairman, Department of Microbiology and Immunology, Albert Einstein College of Medicine
1:35 pm	Viral Targets for Cellular and Humoral Immune Response — Norman Letvin, Chair, Division of Immunology, New England Regional Primate Research Center
2:10 pm	Defining a Protective Immune Response — Wayne Koff, Chief, Vaccine Research and Development Branch, Division of AIDS, National Institute of Allergy and Infectious Diseases
2:25 pm	Discussion
3:30 pm	Break
3:45 pm	**NEW AVENUES FOR DEVELOPING POTENTIALLY EFFECTIVE THERAPY** *Moderator*: David Barry, Vice President of Research, The Wellcome Research Laboratories, Burroughs Wellcome Co.
3:50 pm	Identifying Novel Targets for Antiviral Intervention — Edward Scolnick, President, Merck Sharp & Dohme Research Laboratories
4:05 pm	Discussion
4:45 pm	Concluding Remarks — Sheldon Wolff, Physician-in-Chief, New England Medical Center and Cochair, Roundtable
5:00 pm	Adjourn

Report of a Workshop

THE POTENTIAL VALUE OF RESEARCH CONSORTIA IN THE DEVELOPMENT OF DRUGS AND VACCINES AGAINST HIV INFECTION AND AIDS

The Roundtable for the Development of Drugs and Vaccines Against AIDS

INSTITUTE OF MEDICINE

Washington, D.C. 1989

These proceedings of a workshop were prepared by the Institute of Medicine's Roundtable for the Development of Drugs and Vaccines Against AIDS, chaired by Harold Ginsberg and Sheldon Wolff and directed by Richard Berzon. Major themes are reported to provide highlights of the workshop discussions; however, they do not represent policy statements by the Institute of Medicine.

The Institute of Medicine was chartered in 1970 by the National Academy of Sciences to enlist distinguished members of appropriate professions in the examination of policy matters pertaining to the health of the public. In this, the Institute acts under both the Academy's 1863 Congressional charter responsibility to be an advisor to the federal government, and its own initiative in identifying issues of medical care, research, and education.

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THE POTENTIAL VALUE OF RESEARCH CONSORTIA IN THE DEVELOPMENT OF DRUGS AND VACCINES AGAINST HIV INFECTION AND AIDS

CONTENTS

	PAGE
INTRODUCTION	1
THE NATURE AND STRUCTURE OF CONSORTIA	1
THE NIH NATIONAL COOPERATIVE DRUG DISCOVERY GROUPS-AIDS PROGRAM	3
POTENTIAL TARGETS FOR RESEARCH CONSORTIA	4
Animal Models	4
Opportunistic Infections	4
Exchange of Reagents	5
Basic HIV Pathogenesis	5
Clinical Research Network	6
Policy-level Consortium	7
REFLECTIONS ON RESEARCH CONSORTIA	7
CONCLUSION	8

APPENDIXES (Background Material Provided to Workshop Participants)

Introduction
Questions for Roundtable Discussion
Opinions Expressed During Telephone Conversations
Letter from Edward Scolnick

PL97-414, Orphan Drug Act, Letter to "Inquirer" from Marlene Haffner, FDA
PL98-462, National Cooperative Research Act of 1984, Press Release from the Department of Justice
PL99-502, Federal Technology Transfer Act, Summary

S2889 - Use of Consortia for Research and Development
A New Spirit of Cooperation - Joint Projects Aid Industry, by Andrew Pollack, New York Times
Hurdling R&D's Gaps: U.S. Companies are Sharing Some of the Risks and Costs, by Therese Welter, Industry Week
Cooperative Industrial R&D: Funding the Innovation Gap, by Lansing Felker

NIAID Backgrounder - NCDDG-AIDS
Organizing Committee for the Second NIH AIDS NCDDG Meeting - Background Information on the Developmental Therapeutics Branch, AIDSP, NIAID
AIDS Drug Discovery and Development, by John McGowan and Daniel Hoth

MCC (Microelectronics and Computer Technology Corporation) - Fact Sheet
MCC: A Progress Report, by Damond Benningfield, Austin
Sematech: Progress and Prospects. Report of the Advisory Council on Federal Participation in Sematech
Cooperative R&D in Industrial Competitiveness, by the U.S. Department of Commerce

INSTITUTE OF MEDICINE

Roundtable for the Development of Drugs and Vaccines Against AIDS

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INTRODUCTION

The Roundtable for the Development of Drugs and Vaccines Against AIDS was established in 1988 by the Institute of Medicine (IOM), National Academy of Sciences (NAS). The Roundtable is composed of leaders from government, pharmaceutical industry, academia, and the public. Its mission is to identify and offer suggestions to help resolve impediments to expeditious AIDS drug and vaccine development and availability. The Roundtable accomplishes its mission through regular meetings of its members, in which urgent issues are identified and discussed, and through public conferences and workshops that explore scientific and policy matters central to the development of AIDS therapeutics. This publication is the report of a workshop held June 26, 1989 in Washington, D.C.

The Health Omnibus Extension Act of 1988 (S.2889) directs the Secretary of the Department of Health and Human Services to ask the National Academy of Sciences to assess the potential value of research consortia in the AIDS drug and vaccine development process (this portion of the bill is included in the appendix). Because the Roundtable was established to consider just such matters, the request from DHHS was directed to this IOM committee. The Roundtable provides a forum for government policymakers to meet with their counterparts from the private sector, to exchange views, and, it is hoped, to influence each other's actions. With this role in mind, the Roundtable cochairs and staff prepared a workshop for the group, for which background material on consortia was presented as a prelude to a consideration of the issue at hand: would the government's encouraging the formation of research consortia hasten the development of drugs and vaccines for HIV infection and AIDS? As set out in Senate Bill 2889 (pp. 78-79), the term consortia was understood to mean entities or relationships "(A) designed to combine and share resources needed for such research and development; and (B) consisting of businesses involved in such research and development, of nonprofit research institutions, or of combinations of such businesses and such institutions. . . ."

This report consists of two major sections. The first section is a summary of the workshop, which provides highlights of the discussion and emphasizes the major themes that emerged. The second section (appendixes) contains the background material gathered and distributed by IOM staff in preparation for the workshop.

The workshop discussion was focused on three major areas: (1) the nature and structure of research and development consortia generally, their performance in non-biomedical fields, and some basic principles to consider in establishing consortia; (2) a review of the National Institutes of Health (NIH) National Cooperative Drug Discovery Groups-AIDS (NCDDG-AIDS) Program, a venture that is an example of a consortium approach to research; and (3) particular research topics that may derive special benefit from a consortium approach, because funding and/or interest is inadequate despite a clear need for progress.

This one-day workshop was meant to give some initial direction to further, in-depth exploration of the consortium approach if it is to be pursued. While mention is made in this report of the important relationship between vaccine development and the existence of good animal models, the subject of vaccine development is one that requires more attention than it received during the course of this workshop. The state of research on vaccines against HIV will be pursued in future Roundtable activities.

THE NATURE AND STRUCTURE OF CONSORTIA

Lansing Felker, deputy director of the Office of Technology Policy, Department of Commerce, provided an overview of government policy on consortia and the development of research consortia in a variety of fields. More than 128 research consortia, including some in the biomedical field, have been registered under the National Cooperative Research Act (NCRA) of 1984. This act limits the potential antitrust liability of collaborating firms by reducing treble

damages to actual damages, thereby removing the incentive for third parties to sue. Prior to the NCRA, the law encouraged third-party suits by providing for treble damage awards. As a result, collaborative research and development was limited. Passage of the act has reduced perceived antitrust obstacles to consortia, and cooperative research and development (R&D) ventures are now rapidly becoming common business practice.

Mr. Felker emphasized the importance of the active involvement of firms, especially their business planners, in initiating and structuring consortia. This level of involvement enhances members' feelings of ownership and encourages them to incorporate the expected output of the consortium into their business plans for future products. Thus, the probability of successful transfer and commercialization of the resulting technology increases. Other experts have alluded to the essential need for passion on the part of the private sector participants--a passion that cannot be generated by government.

Mr. Felker listed four factors that affect the specific design of a consortium: (1) what the firms involved are trying to accomplish; (2) what stage of R&D the consortium's agenda is concerned with; (3) who the consortium members are in relation to the technology (are they future manufacturers, users, suppliers?); and (4) who the consortium members are in relation to each other. Mr. Felker described two types of consortia. Horizontal consortia typically include firms from the same industry that may be competitors, e.g., two pharmaceutical firms. Vertical consortia are generally composed of firms in different industries that are not competitive but rather have a complementary relationship, e.g., a pharmaceutical firm and a medical device firm. Horizontal consortia are effective vehicles to cofund the creation of generic technology that will benefit the entire industry. Vertical consortia, on the other hand, are best suited to producing breakthrough technology because they are less encumbered by antitrust concerns and, therefore, may be better able to carry a new technology to manufacture and sale.

Mr. Felker said that horizontal consortia tend to function best when the goal is generic research that will apply to a wide range of industries and products. Consortia make less sense when a specific type of product is the goal. Collaboration among competitors becomes more difficult and risky the closer the collaboration gets to a proprietary product.

When planning the development of a consortium, Mr. Felker advised considering all possible stakeholders. One way to go about this is to create a checklist of all those who might benefit from the consortium's accomplishments. For example, in the instance of AIDS, in addition to persons with HIV infection or AIDS, health and life insurance companies (as well as government, in its role as a third-party payer) may be prime beneficiaries of a therapeutic breakthrough and therefore may have an interest in participation in a consortium for AIDS drug research.

Because, in Mr. Felker's opinion, the typical innovation pattern in the pharmaceutical industry involves highly focused R&D and often results in a single patent, he suggested that pharmaceutical firms may be less used to thinking and working collaboratively either within or outside of their own industry. Product innovation in the pharmaceutical industry appears to occur with fewer participants than in many other industries. Therefore, the pharmaceutical industry may be less suited to the development of consortia. Such characteristics may also tend to make that industry less open to collaborative possibilities when they are appropriate. He contrasted this to technologies, such as semiconductors, that require the involvement of several industries to bring a product to market, thereby providing a strong incentive for companies to work together.

Observing that Mr. Felker's discussion of consortia was focused up to that point on what is good for the industry or the nation's economy, a Roundtable member questioned whether the discussion's proper focus ought to be on what would benefit the health of the population or in this case, persons infected with HIV. Mr. Felker responded that, however lofty the goal, focusing on the common good will not repeal the laws of business and economics. When the market fails

to produce sufficient incentive for R&D for a product, or where a firm cannot capture the benefit of an R&D investment, then government subsidy traditionally has filled the gap. That is the reason the government funds so much biomedical research. In Mr. Felker's opinion, government should only have a funding role when commercial incentive is insufficient. In the case of AIDS drug development, he said, the fact that pharmaceutical firms appear to be disinterested in collaboration suggests that there is a strong commercial incentive: the expectation that one of the firms may win the race to develop an effective AIDS drug.

When asked whether a horizontal consortium of competitors would be viable in producing a single product (such as a drug), Mr. Felker replied that antitrust laws offer no protection for this type of activity, although there is consideration being given to further changes in the antitrust laws that would give some protection to joint production ventures. Even without these protections, however, Mr. Felker speculated that some types of multifirm initiatives could work. However, he said that the goal of creating a proprietary product would not be the optimal use of a horizontal cooperative venture.

THE NIH NATIONAL COOPERATIVE DRUG DISCOVERY GROUPS-AIDS PROGRAM

John McGowan, director of the National Cooperative Drug Discovery Group-AIDS Program, National Institute of Allergy and Infectious Diseases, described the NCDDG-AIDS Program. This program was established in 1986 to encourage scientists from academia, industry, and government to work together in groups to develop treatment for AIDS (see the appendix). Dr. McGowan explained that NCDDG-funded groups are mini-consortia already operating successfully to hasten drug development. Twenty-eight groups are currently funded, with 21 firms from the private sector participating. NCDDG groups have identified the following compounds: soluble CD4, CD4-ricin, benzyl-CD4 (83-94), d4T, CS-87, A-69992, castanospermine, protease inhibitor, and others.

Under the NCDDG program, any scientist in academia, a nonprofit institution, or a commercial organization (such as a drug company) can organize a group and apply for a grant. The groups are funded as cooperative agreements so that the academic and industrial partners in each group define and manage their research programs. The NCDDG program also requires scientific exchange through local and national meetings.

Dr. McGowan believes that additional consortia would be appropriate for particular types of research, such as research in animal models and opportunistic infections (OIs). He outlined a "model consortium"--a detailed proposal for a consortium for animal model studies that would require participation from private industry, government, and academic or nonprofit institutions. He suggested that private industry would provide capitalization costs for the construction or renovation of facilities; government would provide research investigators and core resources for basic research on models and for the testing of candidate drugs and vaccines (drug candidates would be selected by an advisory committee); and academic and nonprofit institutions would provide land and the administrative structure. In return for this investment, the benefits for participating firms would include guaranteed access to the resources of the consortium, the possibility of specific studies paid for by NIH, potential tax advantages, and the absence of long-term obligations. For government, the advantages of the consortium would include better use of NIH funds for research, guaranteed access to the resources of the consortium, ability to rank drugs (in animal tests) for clinical study, and a base of highly qualified experts across different disciplines. The participating academic and/or nonprofit institutions would gain new facilities, as well as personnel and research resources. These institutions would be responsible for the animal care and use.

POTENTIAL TARGETS FOR RESEARCH CONSORTIA

Telephone conversations with Roundtable members and others (see the appendix) suggested a general reticence on the part of industry to support an all-out "Manhattan Project" style of research consortium for AIDS. Yet many consultants acknowledged that there may be particular research topics amenable to a consortium approach because, for one reason or another, such topics are not attractive to any one company.

Animal Models

Several Roundtable members suggested that the development of animal models was an example of research that might benefit from collaborative effort and funding. The development of animal models requires great resources, and it is not in the interest of firms individually to make such great investments on animal research when a new model may have to be shared with everyone.

The development of animal models, however, was identified as crucial for both AIDS drug and vaccine research. "We desperately need inexpensive, valid, and predictive animal models for AIDS research," said Roundtable member David Martin.

> In vitro tests for anti-HIV activity are useful, but not predictive of the in vivo response of patients with AIDS. The situation is becoming critical because as the clinical evaluation system becomes saturated with drugs, there is no way to screen candidate therapeutics for efficacy in order to take only the most promising to human trial. Developing a valid animal model will help solve the clinical trials problem because it will allow for the selection of the best candidates of drugs and biologics very early on and can be used to assign priorities for human trials.

Opportunistic Infections

Research on treatment for some bacterial, viral, and fungal opportunistic infections--particularly mycobacterium avium-intercellulare (MAI)--was identified by some Roundtable members as "high need," an area that requires more attention. The following issues were raised regarding treatment for OIs:

o Opportunistic infections are not the subject of major research and development programs in many pharmaceutical firms because the potential information to be gained is not seen as highly valuable from a marketing standpoint. "Many pharmaceutical companies tend to favor research on antivirals over, and possibly to the exclusion of, research on OIs," contended Jay Lipner. "There are many OIs, for instance MAI, for which treatment is desperately needed and for which there is little or no research currently underway because the universe of people who would be candidates for these drugs is relatively small. Thus, the drugs are not seen as potentially profitable." Scientists from the pharmaceutical industry responded that some research on OIs is being conducted and that there is a recognized medical need for better agents to treat OIs and therefore a market. Dr. Martin said that less overall research investment on OIs is the result of a company's balancing priorities and conserving resources. Patrick Gage suggested that some firms have decided that the most productive use of resources in the long term is to focus on the underlying cause of the disease and the development of antivirals directed towards HIV.

o But other conferees emphasized the importance of research on OIs. Mr. Lipner said, "The inability to treat HIV in the short term means that people are suffering and dying from these untreatable bacterial and fungal infections. As each day passes, the number of people vulnerable to these OIs grows larger, and the development of drugs to treat them has not kept pace with the need."

o Also contributing to the paucity of research on OIs is the limited number of trained investigators focusing on these previously rare diseases. Doubts were raised about the usefulness of forming consortia for research on OIs, when the real issue may be that there are too few investigators in the field to "consort with." Attracting knowledgeable people to the field may be the most effective way to further research on OIs; incentives may be necessary to draw researchers to the field.

o The term "opportunistic infection" includes a broad array of infections that have different etiologies and that require different scientific approaches. For many bacterial OIs, given their broader occurrence beyond the population of AIDS patients, there seems to be a significant body of science and therapies, according to Dr. Martin. Other conferees observed that certain fungal infections, and atypical mycobacterial infections that affect AIDS patients almost exclusively, may be receiving less research attention relative to other infectious diseases.

o Questions were raised about scientists and drug companies not having made a concerted effort against MAI. A conferee suggested that perhaps the technology for developing an agent against MAI may not yet have reached a sufficiently advanced stage. Dr. Martin explained that, although a very large number of compounds were reported to be active against MAI in vitro, current research reveals that the compounds do not seem effective for patients, even when administered in combinations with four or five other drugs that were all effective in vitro. "Perhaps efforts should be redirected towards the whole body's response, particularly immunologic response, to these organisms and to cells infected with these organisms," he said.

o A survey was suggested to determine if in fact there is a paucity of research in the area of antifungals.

Exchange of Reagents

The exchange of research reagents was suggested as a potential consortium focus. Dr. McGowan reported that since the publication of the first and second catalogues of the NIH AIDS Research and Reference Reagent Program, the number of reagents requested and the sharing of reagents have greatly increased. Researchers are now receiving the reagents they want, according to Dr. McGowan, and he sees no need for consortia to produce reagents.

Basic HIV Pathogenesis

Roundtable members discussed the importance of research on basic HIV pathogenesis for AIDS drug development and whether a consortium approach would contribute to scientific progress.

"A knowledge of basic HIV pathogenesis is crucial so that scientists can have a better understanding of how the virus causes disease," said Patrick Gage. "This understanding will allow us to predict better which targets will be most appropriate for the development of drugs and also may reveal appropriate surrogate endpoints for clinical studies in humans which can be utilized to accelerate the development process."

Roundtable member Martin Delaney voiced frustration about the lack of basic knowledge on the pathogenesis of HIV infection. "It seems to me that we are still shooting in the dark and that perhaps we need a greater sharing of minds on the pathology of the disease," he said. Mr. Delaney proposed a formal collaborative relationship to investigate basic pathogenesis because "nobody is getting there on their own."

Although other conferees agreed that progress in understanding pathogenesis is of the greatest importance, they expressed reservations as to whether that type of fundamental biomedical research could be accomplished better through a consortium. Anthony Fauci observed that, traditionally, the best research on basic pathogenesis has come from the classical investigator-initiated approach. He said that a consortium approach at a later stage of research may be useful; but he believes that would occur naturally under existing NIH programs.

David Barry suggested that one problem with a consortium to conduct research on pathogenesis would be identifying a research target:

> If we wanted to set up a consortium to study the pathogenesis of AIDS, I am not sure what the target should be, probably not AIDS. If you look at what we have learned about the most heavily studied target to date, called reverse transcriptase, it had nothing to do with HIV or even viral pathogenesis. It really had to do with cancer; so there are serendipitous observations that can end up being very important. What we think we know now about the pathogenesis of HIV infection, at least what I think is responsible for the drop in T4 cells, may have little to do with the virus per se or even viral infection. It has more to do with indirect and rather complicated effects of lymphokines on cells within the immune system. I think that more money and more emphasis at the basic level is critical, but I think trying to target the research too narrowly is not going to be as productive as putting the money in very good fundamental research. Then, when an observation is made regarding an important fundamental issue of pathogenesis, it would be appropriate to pull together various skills and experiences. I just think it is probably premature to do that now at the fundamental level.

Clinical Research Network

Concerns about a potential saturation of the clinical trial mechanism in the near future and the need for additional clinical investigators led to the discussion of whether consortia for clinical research may help fill future needs.

In considering the topic of consortia for clinical research, Samuel Thier, president of the Institute of Medicine, said that the following questions must be asked: Is the existing network and structure for testing drugs adequate now and will it be adequate in the next three years? Is the system adequate for answering the question of testing the models of pathogenesis? If it is foreseeable that the strategies, personnel, and population available for testing will be inadequate in the future, does this create a basis for some kind of cooperative venture?

Conferees expressed the following points of view:

o Clinical trials have been proceeding well and have been reasonably organized. There has been a good mixture of private industry working with individual investigators as well as through NIH's AIDS Clinical Trials Group (ACTG), according to Dr. Martin. He said,

> There is concern, however, that soon the system may become saturated with a large number of potential compounds and limited by the availability of patients who are good candidates for drug studies, i.e., those with early AIDS, who are antigen positive, not terminally ill, and not on multiple drugs already. In the future, the trend will be testing combinations of compounds, as was done in the 1960s and 1970s with experimental therapy for childhood leukemia. Difficult decisions will have to be made, not only in the selection of compounds, but also regarding how . . . thoroughly each component will have to be tested in order to satisfy the Food and Drug Administration's combination drug policy. Many thousands of patients will have to

be involved to determine whether each component clearly and statistically has an effect of its own.

o There is reason for concern that there will be inadequate personnel and facilities for clinical trials even sooner than two years from now. "There actually will be in short order a mismatch of resources and needs, given the growth of the epidemic and the increase in clinical load, the increasing number of compounds, and the complexity of clinical trials involving combination therapies," said Roundtable member Gerald Friedland.

o Inadequate personnel, in particular, is a critical problem. Although there is a large group of investigators devoted to AIDS, the number of trained people at all levels, including investigators, clinicians, nurse practitioners, etc., is limited and is not expanding at the same rate as the need for them. "We may soon reach a situation where there will not be enough qualified investigators to conduct the clinical trials," said Dr. Friedland. Although Mr. Felker advised that education was a legitimate mission of consortia in other industries, Dr. Fauci questioned how a consortium would help in the context of AIDS. "I can't see how the problem of lack of trained investigators is going to be solved by forming a consortium," he said. "I think it can be solved by just training new investigators."

o Conferees discussed whether a consortium might facilitate the process of bringing drugs into clinical trials. Soluble CD4 was cited as an example of a compound that several companies have been able to produce in large amounts and are putting into clinical trials. Each version is slightly different pharmacologically. Dr. McGowan said that the two companies that have put CD4 into clinical trials so far did so as quickly as possible and that he did not think a consortium would have expedited the entry of CD4 into clinical trials.

o Cooperative clinical trials would create practical problems regarding proprietary rights, patent rights, choice of a company to pursue the IND and the NDA, and of which company would be responsible for reporting to the FDA. FDA regulations would have to be adjusted for clinical testing by consortia.

o While some viewed clinical trials as outside the topic that Congress requested be examined, Mr. Lipner maintained that, absent specific congressional language to the contrary, the common sense understanding was that research on and development of drugs includes clinical trials.

Policy-level Consortium

A policy-level consortium was proposed to unite and coordinate the overall effort to find a cure for AIDS. Such a consortium would bring together the scientific community, industry, the government, and the patient community to look broadly, rather than narrowly, at all of the policy issues related to AIDS research as they arise. Others pointed out that creating a policy-level consortium was an appropriate task for the new National AIDS Commission appointed jointly by Congress and the President.

REFLECTIONS ON RESEARCH CONSORTIA

Although drug company representatives seemed receptive to the possibility of contributing resources to a consortium for animal models, they did not express interest in, or willingness to

contribute resources to consortia on drug development and clinical trials. Dr. Gage summed up the view this way,

> I don't sense that there is a feeling within the industry that there is a benefit of consortia at the development end. I think we feel that any one of the companies that identifies a compound that looks promising has the capability of developing it on its own. I think the problem has been that the clinical development experience in AIDS to date has been disappointing; but once some good drug candidates on the horizon start coming out, the whole program will look better. Where we do see opportunities for consortia are in the precompetitive side. For instance, certainly animal models could be studied more effectively. So at least for my company, no matter what incentives one might come up with, I do not think we feel there is any rationale for having consortia on the development end.

Pharmaceutical industry representatives also challenged the suggestion that consortia would be a way to raise additional funding from their industry for AIDS drug development. Dr. Barry explained: "Even though pharmaceutical firms have a large research and development budget, the amount is finite. What a firm spends on consortia is that much less spent on either the same research internally or on funding for an individual academic investigator. Most firms would tend to want to spend money on their own research because they feel more confident about accountability."

Seymour Cohen expressed concern about the duplication of scientific research, as happened, for instance, with viral protease, and whether such duplication might be avoided with a consortium approach. Using the protease example, Dr. Gage pointed out that there is value in duplication. He explained,

> Protease is one of the few targets besides reverse transcriptase where one can design inhibitors based on the substrate structure. If everyone got together and proposed a single research program, it would probably result in one chemical class of inhibitor compounds, rather than the four or five different chemical classes now being investigated independently by the companies currently involved. There are many factors that determine the success of drugs in humans, only some of which can be explored in experimental models. An advantage of independent development of several inhibitors is that there is a higher likelihood of success. A disadvantage of a consortial approach in this case is that the focus would have been restricted to one or two inhibitors, reducing our chances of success.

The NIH was characterized as a type of consortium, similar to the consortia that private industry in other fields have to create on their own. Dr. Barry observed: "We don't have a national institute of cement or plastic. In other industries, there is no group that is supported heavily by the government to produce that science and then share it with others. In one sense NIH is a rather large consortium and the AIDS program within it is a good example of a consortium designed to address an individual problem. Therefore, the question should be, how many more consortia do we need?" Others noted the varieties of consortia in drug development in existence under NIH's NCDDG program and proposed looking into ways to strengthen the existing program. Catherine Wilfert suggested thinking more broadly about additional sources of support for consortia, such as the health insurance industries or the health care support industries.

CONCLUSION

Research on drugs and vaccines for the treatment of AIDS is being pursued on many scientific fronts and in various settings, including investigators working individually in pharmaceutical firms, and scientists from industry, academia, and nonprofit institutions working

together in groups, or "mini-consortia," funded through NIH's NCDDG-AIDS Program. In addressing the issue of whether the government's encouraging consortia would enhance AIDS drug development, Roundtable members spoke of the advantages of the current pluralistic multi-center approach to AIDS research, and noted that collaboration on specific projects is already taking place under existing programs. One conferee pointed out that there is value in the duplication that results from multiple investigations because, using the example of viral protease, it can lead to the four or five different chemical classes now being investigated independently. Others observed that there seemed to be a general reticence on the part of industry to support an all out "Manhattan Project" style of research consortium for AIDS drug development.

Yet, many Roundtable members acknowledged that there may be particular research topics amenable to a consortium approach because, for one reason or another, the topics were not attractive to any one company. Most conferees agreed that the development of animal models, which are important to both drug and vaccine development, was appropriate for a consortium because it requires great financial investment and benefits the entire field. Others discussed a consortium approach for research on certain opportunistic infections because there now seems to be insufficient market incentive, and a lack of trained scientists and information necessary to search for new drugs for some OIs. Roundtable members also discussed the pros and cons of a consortium approach for research on the pathogenesis of HIV infection, for clinical trials, and for the training of clinical investigators. There appeared to be little support for development of consortia in these three areas.

Institute of Medicine

Surrogate Endpoints in Evaluating the Effectiveness of Drugs Against HIV Infection and AIDS

September 11-12, 1989
Conference Summary



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Robin Weiss and Leah Mazade, editors

The Roundtable for the Development of Drugs
and Vaccines Against AIDS

Institute of Medicine

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This conference summary was prepared by the Institute of Medicine's Roundtable for the Development of Drugs and Vaccines Against AIDS, chaired by Harold Ginsberg and Sheldon Wolff and directed by Robin Weiss and Richard Berzon. The document reports major themes of the conference discussions; these themes, however, do not represent policy statements by the Institute of Medicine.

This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

The Institute of Medicine was chartered in 1970 by the National Academy of Sciences to enlist distinguished members of appropriate professions in the examination of policy matters pertaining to the health of the public. In this, the Institute acts under both the Academy's 1863 Congressional charter responsibility to be an advisor to the federal government, and its own initiative in identifying issues of medical care, research, and education.

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PREFACE

The Roundtable for the Development of Drugs and Vaccines Against AIDS was established in 1988 by the Institute of Medicine. Composed of leaders from government, the pharmaceutical industry, academia, and the public, its mission is to identify and help resolve impediments to the speedy availability of safe and effective drugs and vaccines for human immunodeficiency virus (HIV) infection and acquired immune deficiency syndrome (AIDS). The Roundtable accomplishes its mission through regular meetings of its membership, during which urgent issues are identified and discussed, as well as through public conferences and workshops that explore scientific and policy matters central to the development of AIDS therapeutics. This publication is the report of a conference held September 11 and 12, 1989, in Washington, D.C.

At the first meeting of the Roundtable, Frank Young, then commissioner of the Food and Drug Administration (FDA), identified surrogate endpoints as a topic that could benefit from the Roundtable's attention. He suggested that two issues be considered: first, whether any surrogate endpoints are ready to be used as the basis for evaluating the effectiveness of drugs for marketing approval, and second, the standards governing the acceptance of any particular marker as an alternative to the "true" clinical endpoints (in the case of AIDS, serious morbidity and mortality) that are ordinarily used in drug efficacy trials. The committee agreed to hold a public conference at which scientists, physicians, patients and their advocates, and policymakers could exchange the latest information and opinion on this topic and thereby contribute to the FDA decisionmaking process. The presentations at the conference varied from summaries of already published data and conclusions to presentations of prepublication data and, in some cases, very preliminary analyses of research results. The summary presented here is not intended to replace information that will become available in peer-reviewed scientific papers published in journals. Nevertheless, the committee believes it is important to convey the general sense of the conference on the major issues discussed, although such a summary can never capture the full richness of the presentations and discussion.

The Roundtable and staff wish to thank the presenters for their generosity in sharing early research results and for their careful and thoughtful presentations. We also thank those who attended for their contributions to the discussions and to the lively, cooperative, and constructive spirit that prevailed throughout the event.

INSTITUTE OF MEDICINE

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CONTENTS

Conference Program	vi
Conference Participants	viii
Introduction	1
Virologic Markers	3
Immunologic Markers	4
Special Issues in the Maternal and Pediatric Population	7
Endpoints, Trial Design, and Regulation	10
Summary	12

SURROGATE ENDPOINTS IN EVALUATING THE EFFECTIVENESS OF DRUGS AGAINST HIV INFECTION AND AIDS

September 11-12, 1989

PROGRAM

Monday, September 11

8:00 ***Welcome and Opening Remarks***
- Samuel O. Thier
- Harold Ginsberg
- Sheldon Wolff

8:15 ***Surrogate Endpoints in Clinical Drug Trials***
- James Bilstad

8:30 ***Surrogate Endpoints in AIDS Drug Trials***
- Paul Volberding

8:45 ***Laboratory Predictors of Progression to AIDS: The Epidemiological Data***
- Andrew Moss

9:15 ***Virologic Markers: p24 Core Antigen, Quantitative Plasma Cultures, and Polymerase Chain Reaction***

Moderator: Thomas Merigan

Panelists	**Discussants**
Henry Balfour	Paul Beninger
Douglas Richman	Lawrence Corey
Robert Coombs	Blaine Hollinger
Stephen Wolinsky	

11:00 Break

11:15 ***Immunologic Markers: CD4, CD8, Beta-2 Microglobulin, Neopterin, and Soluble Interleukin-2 Receptors***

Moderator: Anthony Fauci

Panelists	**Discussants**
John Phair	John Fahey
Margaret Fischl	Janis Giorgi
Mark Jacobson	Gerald Quinnan
	Fred Valentine

1:00 Lunch Break

2:00 ***Special Issues in the Maternal and Pediatric Populations***

Moderator: Stanley Plotkin

Panelists	**Discussants**
Gwendolyn Scott	Edward Connor
Catherine Wilfert	John Modlin
Karina Butler	Paul Parkman

3:30 Break

3:45 ***Endpoints, Trial Design, and Regulation***

Moderator: Frank Young

Panelists	**Discussants**
Ellen Cooper	Peter Barton Hutt
Martin Delaney	Stephen Lagakos
Sandra Lehrman	
Daniel Hoth	

5:30 Adjourn

Tuesday, September 12

8:30 ***Panel Summaries***
- Thomas Merigan
- Anthony Fauci
- Stanley Plotkin
- Frank Young

9:15 ***WORKSHOP: Which Surrogate Endpoints are Ready for Use in Evaluating AIDS Clinical Drug Trials?***

Moderator: Martin Hirsch

Discussants	**Discussants**
Samuel Broder	Jay Lipner
Ellen Cooper	Thomas Merigan
Anthony Fauci	Stanley Plotkin
Gerald Friedland	Stephen Sherwin
Clifford Lane	Frank Young

10:30 Break

11:00 ***Discussion***

12:00 ***Summation***
- Sheldon Wolff

12:30 Adjourn

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INTRODUCTION*

In the search for effective therapies against infection by the human immunodeficiency virus (HIV), patients and their care givers have increasingly called for a shortening of the testing and approval process that has traditionally brought drugs from development to market. As regulated by the Food and Drug Administration (FDA), this process often takes from 7 to 10 years and involves preclinical testing and a phased series of clinical trials of increasing size and complexity to investigate a new drug's potential toxicity and effectiveness. In the drug approval process, FDA has sought to achieve a balance between requiring definitive, large-scale, carefully monitored clinical trials to determine the safety and efficacy of new drugs and ensuring that patients receive helpful medicines at the earliest possible time. Yet in the case of HIV infection, that balance has proved elusive. The protracted course of the disease and the fact that patients may be infected but remain asymptomatic for a relatively long period compound the difficulties of large-scale trials and could lengthen even more the time required under traditional methods to establish the efficacy of a drug. The pressure for more rapid approval of effective therapies has led to a search for appropriate ways to shorten the time it takes to establish drug efficacy. One such mechanism that has been used by FDA in other drug classes and that may hold promise for HIV infection is the surrogate endpoint.

To define a surrogate endpoint, it is first necessary to define the "true" clinical endpoint for which the surrogate will substitute. A true endpoint, often termed the significant clinical endpoint, is that outcome measure by which therapies are deemed efficacious or inefficacious in clinical trials. In the case of AIDS it is generally death (mortality) or serious disease (morbidity—usually, an opportunistic infection). A surrogate endpoint, then, is a substitute for these later, definitive outcomes that nevertheless correlates with disease progression and shows changes as a result of drug effects.

A surrogate endpoint can involve determining a laboratory measurement or marker (e.g., CD4+ cell counts, levels of p24 antigen) that reflects in some manner the status of the disease process. Clinical conditions (e.g., changes in weight, fever, neuropsychiatric functions) may also be measured, and, to the extent that they predict more severe disease or survival, some researchers consider them surrogate markers as well. (An important difference between laboratory and clinical measures is that clinical measures may have independent significance for patient well-being as well as usefulness for predicting later disease.) Although there is no universally accepted definition of a surrogate endpoint, there is a distinction to be made between a surrogate endpoint and a laboratory marker of disease progression. A particular laboratory measurement may be a good predictor of the course of the disease, but it may not necessarily be an appropriate surrogate endpoint for drug efficacy trials. There is no guarantee that a marker that predicts progression of disease in an untreated patient will respond in a reverse fashion to therapeutic intervention.

One of the primary benefits of establishing a surrogate endpoint for drug trials is that any effects of a particular therapy can be seen earlier in the course of clinical trials before patients progress to a more severe disease state. This early determination of effects allows for quicker approval and more widespread availability of an effective treatment. Surrogate endpoints also have other advantages. In some cases, they may be easier to measure than the significant clinical endpoint; in addition, drug development costs may be lower because long, complex drug efficacy trials with large populations are shortened or simplified. Surrogate endpoints may also be used at different stages of the clinical trials process. They can serve as the primary endpoint in Phase I trials of drug activity or as secondary endpoints in efficacy trials to support mortality and morbidity findings. In addition, they can be used as stratification criteria to divide a population into groups for consideration of drug effects on different levels of the marker being used.

In addition to benefits, however, there are risks to be considered in replacing clinical endpoints with surrogates that rely on measurement of laboratory markers. A drug that was actually useful

*This section is based on material presented by James Bilstad, Paul Volberding, Andrew Moss, and Lawrence Corey.

might be rejected (or considered to be of little interest) simply because it showed no effect on the particular marker chosen as a surrogate. The reverse also applies: a drug that actually produced little clinical benefit might nevertheless be considered efficacious because it affected the marker favorably. These considerations argue for great care in choosing and validating surrogate endpoints.

Another factor to be considered is that good markers have characteristics that may vary from population to population. For example, it appears that beta-2 microglobulin is not as strongly predictive of disease progression among intravenous drug users as it is among homosexual men. Also, p24 antigenemia shows population variability: the marker appears to be found less frequently among blacks than among whites. This type of variability increases the difficulties already inherent in the task of identifying an appropriate surrogate for the true clinical endpoints of AIDS drug efficacy trials.

An appropriate surrogate endpoint must satisfy a number of criteria:

1. The marker must be biologically plausible; that is, it must be consistent with what is known about the pathophysiology and pathogenesis of the disease. If a marker is central to the pathogenesis of the disease, then regression of the marker (i.e., the reversal or stabilization of an adverse trend) should occur with therapies that have different mechanisms of action.
2. The marker must be present or abnormal in a large percentage of people who have the disease. Preferably, it would be present in all persons with HIV infection.
3. The marker must be a good predictor of disease progression and should correlate closely with the significant clinical endpoint.
4. There should be a correlation between the quantitative aspect of the marker and the progression of the infection, i.e., the more severe the infection, the more deviant the marker from normal.
5. The regression of the marker should be significantly associated with clinical improvement (i.e., those with the greatest improvement in the marker should also show the greatest clinical effects). Conversely, the lack of regression of the marker should be commonly associated with a lack of clinical improvement.
6. The incidence of regression or improvement in the laboratory marker should be significantly greater in treated than in untreated patients.

Whether a marker holds up as a surrogate for the clinical endpoint in a drug trial is eventually determined by validating the marker through well-designed, carefully conducted, prospective clinical studies that establish correlations between surrogate and clinical outcomes. Such validation means that the drug must be studied for its effect on both the clinical endpoint and on the surrogate marker. The current trend toward informal or truncated clinical trials is of some concern as it may damage the potential for obtaining the required correlations. Once a drug is approved with well-designed studies that validate the surrogate endpoint, it may be easier to demonstrate the effectiveness of subsequent drugs of the same class on the basis of the surrogate endpoint. The weight given to any particular marker depends on how well it correlates with the clinical endpoint and the degree to which it has been validated. Some markers may be useful for determining drug activity or dose ranges in early clinical studies, but they may not be useful as primary efficacy endpoints for approval of the drug for marketing. In addition, a marker may be validated for use as a surrogate endpoint for one stage of the disease but not for all stages. For instance, a marker may be valid and valuable in asymptomatic infection but lose its value in later stages of disease. Some of the drug classes in which FDA has accepted surrogate endpoints as a basis for approval include antihypertensive drugs, drugs to treat osteoporosis, vaccines, lipid-altering drugs, antiarrhythmic drugs, and alpha-1 proteinase inhibitors. With HIV infection, however, the question is whether a drug should be approved now on the basis of a surrogate endpoint that may or may not be validated by future studies.

Sometimes a candidate surrogate endpoint is initially identified through epidemiological studies in which it is found to be a strong predictor of disease progression. During clinical trials (where the bulk of experience so far is with nucleoside analogues), reproducible, measurable clinical benefits

(e.g., improved neurological status) other than the primary endpoints of interest may also be observed, offering another way to measure drug efficaciousness. Predictors of progression to AIDS gleaned from epidemiological data include both virologic markers (e.g, p24 antigen levels, plasma viremia) and immunologic markers (e.g., CD4+ cell counts, beta-2 microglobulin, neopterin). The potential use of these various markers as surrogate endpoints for drug efficacy trials is discussed in the following sections.

VIROLOGIC MARKERS*

In the search for surrogate endpoints of drug efficacy against HIV, researchers have quite naturally looked to the virus itself for a virologic marker of disease progression. They have investigated viral burden using a number of different techniques and considering several specific elements of the virus. Particular attention has centered on p24 antigen, the major viral core protein of HIV. As a result the measurement of p24 has been included in clinical trials to determine whether the administration of a particular agent appears to affect levels of the antigen. Indeed, such measurement was used to advantage in the Phase II trial of AZT. The p24 antigen is relatively easy to detect and quantify, and measurement methods have been standardized and validated largely as a result of the work of the Virology Committee of the National Institutes of Health (NIH) AIDS Clinical Trials Group (ACTG). Measurable levels of the antigen have been shown to correlate with stages of disease and disease progression. For example, one study showed more symptomatic disease among hemophiliacs with detectable levels of p24 antigen than among those who were not antigenemic. In addition, p24 levels have been shown to decrease with the administration of antiretroviral drugs—to the point that in some studies a dose-response relationship has been seen. Furthermore, several drugs that have failed to affect serum or plasma levels of p24 antigen have shown few indications of efficacy by other laboratory or clinical measures.

Despite these advantages, the use of p24 levels as a surrogate endpoint in drug trials has several major drawbacks. First, the antigen is not present in all HIV-infected persons; in fact, the percentage of individuals who show p24 antigenemia at any stage of infection, and particularly in asymptomatic infection, is relatively low. Any clinical trial enrollment limited to p24 antigenemic persons would be severely constrained in its population. Moreover, although a reduction of p24 levels following the administration of AZT has been correlated with clinical response, this remains only an association. There is no guarantee that an antigen response to therapy will consistently predict a clinical response or that failure to decrease the level of p24 antigen correlates with a poor prognosis.

From a biological perspective, it is premature to accept p24 antigen as a surrogate endpoint for drug efficacy. For one thing, it is not known which cells in vivo produce the antigen or what the reduction of p24 after therapy means at a cellular level. Consequently, although many researchers display some confidence that the reduction of p24 with the use of nucleoside analogues (e.g., AZT, ddI, ddC) reflects antiretroviral activity, they are unable to explain why this reduction occurs. Also unknown is the route by which the antigen enters the circulation or why many HIV-infected individuals develop AIDS—and die—without ever generating measurable antigen levels. When researchers measure p24 antigen, they are really measuring only one component of a dynamic system comprising antigen, antibody, and immune complexes (which may interfere with measuring free antigen). So far the majority of attention has been focused on free antigen. Yet some investigators have proposed that the drop in antibody seen in later stages of HIV infection may actually be a better predictor of disease progression than antigen levels, especially when used in combination with other indicators. A further limitation to the use of p24 antigen as a surrogate

*This section is based on material presented by Thomas Merigan, Henry Balfour, Douglas Richman, Robert Coombs, Stephen Wolinsky, Paul Beninger, Lawrence Corey, and Blaine Hollinger.

endpoint is that criteria for what constitutes a significant decline in p24 levels in clinical trials have not been established. This limitation, as well as the drawbacks noted earlier, must be addressed before p24 antigen can serve as a major surrogate marker of drug efficacy.

Virus cultured from peripheral blood mononuclear cells, although often considered by virologists to be a "gold standard" against which to measure other markers, has not proved particularly useful in the case of HIV infection. Current measurement techniques are so sensitive that the virus can be reliably isolated from the great majority of antibody-positive individuals, regardless of the stage of their disease. Once the culture is positive, it remains so, and there has been no evidence to date that AZT reverses this result. The lack of change with therapy in the ability to culture cell-associated virus suggests that, despite therapeutic progress, either drugs with greater antiviral effects are needed or culturing techniques amplify latent virus that antivirals in theory cannot eradicate.

Unlike p24 antigen, plasma viremia (as measured by virus cultured from plasma) is highly prevalent in persons with AIDS. In recent cross-sectional studies that quantified plasma viremia by serial dilution, plasma viremia rose from approximately 20 percent in asymptomatic subjects to 90 percent in AIDS patients. Moreover, a prospective study by the same investigators showed that the appearance of plasma viremia was associated with progression to symptomatic disease and declines in CD4+ cell counts. In preliminary data presented at the conference, oral zidovudine therapy did not significantly reduce the titer or frequency of plasma viremia, although there was a downward trend with therapy. The same patients displayed a significant decline in antigen level with therapy. Because plasma viremia is a useful marker of disease progression, delay in the progression of plasma viremia may become a valuable means of evaluating response to antiviral therapy early in infection.*

Another area of exploration that appears promising is the use of polymerase chain reaction (PCR) to establish and measure viral burden. PCR is a gene amplification technique that detects proviral sequences in the peripheral blood mononuclear cells of HIV-infected persons. Thus far, PCR has been used mainly to establish the presence of infection. Its use as a marker of drug efficacy is more problematic. For example, any alterations in the efficiency of the process may substantially affect the reliability of quantification. In addition, the technique is not yet widely available, and laboratories have yet to standardize procedures and establish reliability. PCR has been used to study a few patients before and after AZT therapy, and the studies suggested decreases in the amount of detectable provirus after AZT administration. Such efforts, although in their infancy, point to the value of continuing investigation of PCR and suggest it may be a technique that holds promise for the future.

IMMUNOLOGIC MARKERS**

The common denominator of HIV infection is a progressive diminution of immune function. It is thus appropriate to consider a variety of immunological variables as surrogate endpoints in efficacy trials for drugs against AIDS and HIV. Data have been gathered on several markers of immune system activation, such as beta-2 microglobulin, neopterin, and soluble interleukin-2 receptors. Yet

*As evidence of how quickly the field is developing, soon after this conference, two studies were published that amplify these conclusions. In one (Ho, D.D., T. Moudgil, and M. Alam, "Quantitation of human immunodeficiency virus type 1 in the blood of infected persons," *New England Journal of Medicine*, vol. 321, no. 24, pp. 1621-1625 [1989]), both plasma and peripheral blood mononuclear cell end-point-dilution cultures were found to vary in titers with stage of disease. In Ho's study, the HIV-1 titers of seven patients with AIDS or ARC (AIDS-related complex) treated with AZT declined significantly in plasma but not in peripheral blood mononuclear cells. Coombs and colleagues (Coombs, R.W., A.C. Collier, J.-P. Allain, B. Nikora, M. Leuther, G.F. Gjerset, and L. Corey, "Plasma viremia in human immunodeficiency virus infection," *New England Journal of Medicine*, vol. 321, no. 24, pp. 1626-1331 [1989]) elaborated on the results presented here. Both studies raise the possibility of a role for plasma viremia as a surrogate marker of drug efficacy.

**This section is based on material presented by Anthony Fauci, John Phair, Margaret Fischl, Mark Jacobson, Janis Giorgi, Gerald Quinnan, and Fred Valentine.

the marker that continues to hold the most promise as a surrogate endpoint is the number of CD4+ cells. This immunological indicator reflects an essential component of the human immune system that is affected directly by HIV and that shows a clear relationship to disease pathogenesis. In addition, studies have increasingly shown the value of this measure as a predictor of clinical outcome.

The CD4+ cell is a T lymphocyte (its precursors lie in the thymus) that expresses the cell surface marker CD4 to which HIV binds. Thus, it is the primary target for HIV. CD4+ cells are also essential in the coordination of many critical immune system functions. Many of the immunological abnormalities in individuals with HIV infection are secondary to the lack of an appropriate inductive signal from the CD4+ cell. Measurement of CD4+ cell counts has become embedded in clinical management and clinical trials, and data on this marker over a relatively long period are now available. They show that there is an unequivocal association between low levels of CD4+ cells and measurable deleterious events (i.e., initial AIDS-defining events such as *Pneumocystis carinii* pneumonia [PCP] or wasting, as well as their recurrence) over the course of HIV infection. The reverse also appears to hold: the higher the CD4+ cell count, the better the prognosis.

Although more remains to be learned about the patterns and mechanisms of CD4+ cell depletion in HIV disease, studies have identified several periods during which CD4+ cell patterns change. At HIV seroconversion, for example, a rapid fall occurs in CD4+ cell levels. During the period of seropositivity, cell levels often remain stable, but they generally fall rapidly just prior to the development of AIDS. During AIDS, depending on therapy, cell levels usually continue to fall to very low levels. As noted earlier, a strong correlation is seen between CD4+ cell numbers and deleterious events.

One of the studies that has been instrumental in establishing this correlation is the Multicenter AIDS Cohort Study (MACS), an ongoing prospective investigation of the natural history of HIV infection in approximately 5,000 homosexual and bisexual men. Begun in 1984, cumulative data from the MACS indicated that seropositive persons with higher CD4+ counts had a lower risk of developing PCP, whereas those with CD4+ cell counts of less than 200 had a markedly increased risk of developing it. These findings served as the basis for the Public Health Service's recommendation that prophylaxis against PCP should be begun for patients with CD4+ counts of less than 200.

Data are also available on the effects of AZT on CD4+ cells. The National Cancer Institute's (NCI) original Phase I AZT study showed that CD4+ counts increased with administration of the drug, then declined slowly. At the highest doses of the drug, however, CD4+ levels decreased, perhaps as a result of toxicity. In the double blind, placebo-controlled trial of AZT, CD4+ cells increased in the treatment group and then declined slowly, as opposed to the pattern of progressive decline in cell counts seen in the placebo arm of the trial. The preliminary analysis of data from a study investigating progression to AIDS or advanced ARC in individuals with early ARC treated with AZT versus placebo found differences in drug effect between lower and higher CD4+ cell strata. Individuals with CD4+ counts of 200 to 500 treated with AZT showed a mean increase of approximately 50 cells, followed by a slow, progressive decline. Individuals in the higher stratum (CD4+ counts greater than 500) showed only a nominal increase compared to controls, also followed by a slow decline.

An important question that remains unanswered is the meaning of the decline that occurs following the initial increase in CD4+ cells on therapy. Is the decline a reflection of the lymphosuppressive effects of nucleoside analogues, or does it reflect the possibility that the immune system may not be able to reconstitute itself because it has undergone irreparable damage to the thymic precursors of mature CD4+ cells? Further data that have recently become available from a multicenter ACTG study investigating two different doses of AZT in the treatment of AIDS found no difference between the two doses in their effects on CD4+ cells (i.e., CD4+ cells increased early in therapy and then slowly declined). More important, however, these data suggest that the absolute number of CD4+ cells at any one point in time, the latest measurement, is the most important predictor of survival, regardless of how the individual achieved that level (through therapy or by

starting at a different baseline level from which progression or regression occurred). This study also suggested that relatively small shifts in the number of CD4+ cells can be very important if they bring an individual's cell count into a better prognostic category. From these findings comes the hypothesis that a stable CD4+ level indicates that HIV disease is not progressing; therefore, a halt in the decline in the number of CD4+ cells is viewed as meaningful. Such a halt becomes especially important if it prevents an individual from moving to a CD4+ cell count that predicts a deleterious event.

The ability to reliably measure small changes in the number of CD4+ cells is crucial to this marker's use as a predictor of disease progression and potential surrogate endpoint. However, because CD4+ cell absolute values are obtained from three different laboratory measures using three separate instruments, reliable measurement has been a problem. There have been concerted efforts to standardize such measurements and implement quality control in laboratory testing, and a number of laboratories have been certified for such testing. Nevertheless, reliability remains an issue.

In addition to measurement problems, several factors in individual patients may affect CD4+ values. Diurnal variations may occur, or concurrent common viral infections may cause a transient depression of the number of CD4+ cells. The difficulties involved in determining absolute CD4+ cell counts have led some researchers to suggest that more reliable measurements might be obtained by measuring CD4+ cells as a percentage of total lymphocytes (there appears to be less day-to-day fluctuation in measuring the percentage). Another alternative is to use a combination of several measures—for example, cell count, percentage of total lymphocytes, and the CD4+/CD8+ ratio.

Unlike CD4+ cell counts, the other immunological markers noted earlier in this discussion—beta-2 microglobulin, neopterin, and soluble interleukin-2 receptors—are relatively easy to measure and show a smaller degree of variability from assay to assay. Beta-2 microglobulin (part of the major histocompatibility complex class I antigen), neopterin (a product of stimulated macrophages), and soluble interleukin-2 receptors are all markers of immune activation. Moreover, these markers are systemic measures and may reflect the whole pool of cells affected by the disease, including macrophages. Of the three, beta-2 microglobulin has been found to be the most powerful predictor of progression to AIDS, although elevation of any of the three markers has been shown to be prognostic. Beta-2 microglobulin and neopterin are both abnormally elevated in more than 90 percent of people with symptomatic disease and in more than 40 percent of those with asymptomatic infection. With AZT therapy, all three have shown significant decreases and trends toward normalization. Indeed, some data have indicated that a decrease in beta-2 microglobulin early in the course of AZT therapy predicted the longer term clinical outcome. However, therapeutic studies of these markers are limited, which precludes judgments on whether drugs that influence the marker also affect adverse outcomes. In addition, the nonspecificity of these markers (they are elevated in the presence of numerous other viral, bacterial, and protozoan infections, as well as HIV) and their uncertain relationship to disease pathogenesis are major drawbacks to their use as surrogate endpoints in efficacy trials. Their use in combination with other markers (e.g., CD4+ cells, p24 antigen, IgA) has been proposed, and early studies have shown some promise.*

The markers considered to this point all have qualities that support their potential use as surrogate endpoints for drug trials.** It is well to reiterate, however, that any laboratory marker (or clinical marker, for that matter) being considered for such use should reflect an important physiological phenomenon related to the pathogenesis of the disease. Given the current state

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* Fahey and coworkers recently evaluated three cellular markers and five serologic markers for their ability to predict progression to AIDS. They found that progression to AIDS was predicted most accurately by the level of CD4+ cells in combination with the serum level of either neopterin or beta-2 microglobulin (Fahey, J.L., J.M.G. Taylor, R. Detels, B. Hofmann, R. Melmed, P. Nishanian, and J. Giorgi, "The prognostic value of cellular and serologic markers in infection with human immunodeficiency virus type 1," *New England Journal of Medicine*, vol. 322, no. 3, pp. 166-172 [1990]).

** Other interesting but relatively less investigated surrogate endpoints were also mentioned during the conference discussion

of knowledge about the pathogenesis of AIDS, it is impossible to state absolutely that CD4+ lymphocyte decline reflects both necessary and sufficient factors in such pathogenesis. The caveats noted by researchers concerning whether the actual effect of a drug on CD4+ lymphocyte counts are really related to the pathogenic mechanisms of HIV infection should not be dismissed out of hand. Yet what must also be taken into account is the definitive finding that CD4+ cells are necessary for survival. In addition, although any one individual may be an exception, for populations of HIV-infected persons studies have shown an unequivocal association between low levels of CD4+ cells and measurable deleterious events that are AIDS-defining phenomena and, by extrapolation, predict survival. Thus, if one considers phenomena that are associated directly with deleterious events and that are found in everyone who is infected with HIV, one is left with a virus, the markers for which were summarized in the discussion on virology, and the CD4+ cell count, which invariably declines in HIV-infected individuals.

It may well be that damage occurs to the precursors of CD4+ cells during the initial precipitous drop in cell count following seroconversion and that this damage makes the loss of CD4+ cells inevitable and irreversible. If this were true, a steady, sustained increase in CD4+ cells might be too much to ask of any therapy. Perhaps, rather, the prevention of a decrease in such cells would be a more reliable indicator of the blunting of the effects of HIV. Many issues involving this marker remain to be resolved; nevertheless, with regard to the immunological parameters under discussion as surrogate endpoints, the CD4+ cell count must certainly stand out as the primary measurement of significance. Indeed, in some respects, patients have already accepted the CD4+ cell count as the major determination by which they judge drug efficacy in trials and decide when to end their participation in tests of what they believe are nonefficacious treatments. These very pragmatic judgments on CD4+ cell counts may bear increasingly on any policy regarding its use as a surrogate endpoint in efficacy trials.

SPECIAL ISSUES IN THE MATERNAL AND PEDIATRIC POPULATION*

AIDS in children and AIDS in adults differ in several respects, and these differences may affect the use of surrogate endpoints in general and the choice of any one endpoint in particular. For example, in the groups of infants and young children who have been identified as infected with HIV, the incubation period to AIDS—and, indeed, the whole course of the disease—is shorter than for adults: the median incubation in these groups of infants with either perinatally acquired or transfusion-associated AIDS is about two years. In addition, B lymphocytes in children appear to be more affected by the virus than are B cells in adults. The two groups are also susceptible to different types of opportunistic infections: severe bacterial infections are more common in childhood, although PCP and thrush, the most common opportunistic infections in children, are common to both groups. These factors affect the design and conduct of clinical trials, as does the fact that the pediatric AIDS population is substantially smaller than the population of adults with AIDS. Yet perhaps the most important difference between children and adults with AIDS is that infants and children are still developing. Thus, changes in the clinical markers of physical and mental development in children may have promise as early indicators of the action and efficacy of therapeutic drugs.

A number of natural history milestones are thought to have some prognostic value and may be useful to consider in the search for surrogate markers of drug effect in the pediatric population.

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periods. One such candidate is delayed type hypersensitivity skin testing, particularly Candida skin testing, as a method for assessing immunocompetence in HIV-infected patients.

*This section is based on material presented by Stanley Plotkin, Gwendolyn Scott, Catherine Wilfert, Karina Butler, Edward Connor, John Modlin, and Paul Parkman.

These factors can be divided into three types: immunological, virological, and clinical. The immunological and virological aspects of AIDS in children have much in common with the disease in adults; however, as noted above, the clinical picture in children varies substantially.

Of the immunological factors that seem to have prognostic value in children with AIDS, immunoglobulin levels appear to be one of the most significant. Most children with HIV disease have significantly elevated levels of immunoglobulin that may occur as early as three months of age and persist for long periods. Anecdotal information suggests that, late in the course of illness, the decline of these elevated immunoglobulin levels is associated with clinical deterioration in untreated children. Also, the small minority of children found to be hypogammaglobulinemic early in the course of disease seems to have a worse prognosis. However, as shown in the Phase I AZT trials, with therapy the majority of children in the trials had prompt and dramatic declines in measurable IgG and IgM toward normal levels. Thus, a decline in immunoglobulin levels associated with clinical improvement appears to be a marker of change when children are receiving drug therapy.

The prognostic relevance of CD4+ cell counts in children is more ambiguous. Lymphocyte counts in all children are higher than those of adults in the first year of life, and normal subset values have not been defined. At birth or during the first year, infected children who subsequently develop AIDS may have CD4+ cell counts of greater than 1,000. There may also be a significant increase in CD8+ cells, which produces the characteristic reversal of the CD4+/CD8+ ratio that in adults foreshadows the progression of clinical disease.

Several studies have shown drug effects on CD4+ cell counts in pediatric trials. Data from the Phase II pediatric AZT trials showed an initial increase in CD4+ counts with therapy. Preliminary data from the National Cancer Institute study that investigated a regimen of alternating ddC and AZT indicated that CD4+ cell counts increased and the CD4+/CD8+ ratio improved with therapy. In addition, preliminary results of a trial of ddI in children showed a similar improvement. Yet despite these promising results, the absence of data on normal CD4+ counts in children during the first year of life complicates the ability to determine abnormal levels. More data are needed on levels of CD4+ cells in children who are not HIV infected and in children with AIDS, over the course of the disease. Describing CD4+ cell values as percentages rather than as absolute numbers may also prove useful because, although children have approximately four times as many lymphocytes as adults, the percentage of CD4+ cells to total lymphocytes in children is comparable to that in adults.

In addition to CD4+ cell levels, several other immunological factors have been considered as laboratory markers in pediatric populations (and thus as potential surrogate endpoints for drug trials). These factors include tumor necrosis factor, beta-2 microglobulin, and soluble interleukin-2 receptors. Only limited data are available on the association of changes in these markers with disease progression; thus, no conclusions may be drawn regarding their value as surrogate endpoints in drug trials.

As in the case of immunological markers, virologic markers in children have not yet proved very useful for understanding prognosis and disease progression. Viral culture in children is used mainly for diagnosis rather than prognosis. Furthermore, as in adults, virus can be cultured from children on therapy. PCR studies in children (see the general discussion of this technique under the virological panel) are limited and have concentrated on the early neonatal period, once again, mainly for the purposes of diagnosis. This method needs further quantification and standardization before it is ready for use in drug evaluation.

Among children as among adults, the virologic marker that so far has stirred the most interest regarding its possible use as a surrogate endpoint of drug effect is the level of p24 antigen. In spinal fluid, p24 antigen has been recognized as an early indication of HIV infection. Other data relating to p24 antigen in children suggest a correlation between quantitative levels of antigen and disease stage. Studies in New York, New Jersey, and the Netherlands have found a correlation between the presence of high levels of antigen and disease progression. The p24 antigen has also shown changes in the presence of drug therapy, declining in response to AZT therapy in Phase I and II trials. The

NCI study of ddC plus AZT reported brisk falls in levels of the antigen. In addition, data from the collaborative AZT studies indicated that essentially all of the children who had detectable p24 antigen in spinal fluid at the onset of therapy had reductions of the antigen to undetectable levels by 24 weeks. These reports are promising; however, as in adults, a major drawback to the use of p24 antigen levels as a surrogate endpoint is that not all children with HIV infection have detectable antigenemia.

Certain clinical aspects of AIDS in children have been shown to have prognostic value in the course of untreated infection; however, their utility as surrogate markers of drug effect is unclear. Prognostic clinical factors include age at presentation of clinical disease, the type of disease with which the child presents, and the development of opportunistic infection. The particular type of opportunistic infection developed by a child may also be a key to the rate of disease progression. In general, children who present with AIDS at less than one year of age have a shorter median survival than those who present after one year. The type of clinical disease with which the child presents also appears to predict prognosis: for example, survival following PCP is dismal. In adults, the presence of PCP is associated with low CD4+ cell counts; in children, there is less correlation with the absolute number of CD4+ cells (children have died with CD4+ counts of 1,000 to 2,000). On the other hand, children who develop lymphoid interstitial pneumonitis (LIP) have a longer median survival. (Although children with LIP meet the CDC case definition for AIDS, they are actually less symptomatic and are sometimes combined with ARC patients in clinical trials.)

Finally, a unique aspect of children is that the "business" of infancy and childhood is growth and development. These processes in children are predictable and well-described; because they also proceed rapidly, changes can be detected early. Loss of appetite, wasting, and neuropsychological impairment (detectable in 40 to 95 percent of HIV-infected children) are hallmarks of HIV infection in this population. Consequently, measurements of linear growth and weight gain and assessments of neurobehavioral function through tests of motor skills and cognitive ability can be used to evaluate the action of a drug.

Several studies have shown what many researchers believe is evidence of drug efficacy using these developmental measures. Data from the multicenter Phase I trial of AZT in children showed that administration of the drug was associated with weight gain in a population of children that had shown an abnormal distribution of weights by percentile at their enrollment in the trial. The evidence of growth that occurred when the children were placed on therapy was an indication that their disease had undergone alteration. Changes were also reported following AZT therapy in tests of both gross and fine motor skills and cognitive function. Before therapy, the distribution of children in the trial by percentile on a scale measuring cognitive function was abnormal; following therapy, the distribution was much more in line with normal values. In a similar Phase I study of AZT at NCI, 13 of 21 children had neurological impairment on entering the trials, and all 13 showed neurologic improvement with AZT. However, this neurologic improvement appeared to be independent of other disease symptoms and was not always accompanied by improvement in immunologic function.

One important feature of these data is that, although some children on therapy may not have actually improved their status, very few children continued to show declines in development. Thus, the stability of neurobehavioral status and the stabilizing power of a pharmacological agent should be considered both in conclusions about efficacy and discussions of appropriate indicators of drug action. Many pediatric researchers see these types of developmental measures as some of the most promising candidate markers, although there are some drawbacks to neurodevelopmental tests. For example, they are more reliable in children who are older than two or three years, and they are extremely expensive to administer. In addition, interobserver variability may be a problem, particularly in multicenter trials.

Some pediatric researchers have called for the development of a comprehensive, well-designed clinical scoring system as a potential outcome measure for drug effect. Such a system could incorporate growth, neurological development, development of opportunistic infection, and dysfunction

of particular organ systems (e.g., heart, lungs, liver, and kidneys). There is precedent for employing a clinical scoring system that reflects overall well-being in evaluations of interventions for patients with cystic fibrosis.

Any discussion of treatment for pediatric AIDS would be incomplete without considering prevention or interruption of perinatal transmission using chemotherapeutic modalities. Vertical transmission of HIV from infected mothers to their infants accounts for 80 percent of all childhood cases of AIDS. Studies are currently planned to investigate chemoprophylaxis against in utero transmission (i.e., prophylaxis of the fetus) and intrapartum transmission (prophylaxis of the newborn). Clinical endpoints of drug efficacy in such studies would be the presence or absence of established infection in the infants.

With the apparent short incubation period of pediatric HIV infection (in those children observed thus far) and a generally short disease course characterized by early clinical signs and symptoms, the question arises: Is there a need for surrogate markers to speed definitive drug trials in children? The consensus of the conference was that surrogate markers are important for trials in children because analysis of early trends in responses to experimental drugs can identify drugs that merit further evaluation and direct future research. Moreover, as in adults, the hope is that new drugs can eventually be approved sooner on the basis of surrogate endpoints.

Indeed, the speed and sequencing of pediatric (versus adult) drug trials have become issues of some debate with the advent of AIDS, and several points are worth noting. More than two years have passed since AZT was approved for adults; yet at the time of the conference it had not received full approval for marketing in children. The conditions that promote such a substantial, and, as many conferees expressed it, unacceptable lag in drug availability for children are forcing a reconsideration of the drug approval process for this population. In the past, sponsors and researchers have waited for evidence of efficacy from adult trials before commencing trials in children. Now, however, many in the field agree this should no longer be the case; rather, Phase I studies for safety, tolerance, and pharmacokinetics, as well as preliminary evidence of efficacy, generally should proceed in parallel in adults and children. (In some instances, preliminary studies to establish general parameters of dosage and safety in a small number of adults may be useful, particularly in new classes of drugs and to serve as a basis of selection for Phase I trials in children among a number of candidate drugs.) All drugs that will be prescribed for children should be tested in children for safety and pharmacokinetics (Phase I trials). On the other hand, some efficacy trials may be easier to conduct in adults, by virtue of the larger number of adult patients, and these efficacy trials (Phases II or III) should not necessarily require duplication in children before a drug is approved for pediatric use. For example, data from adult studies on the efficacy of AZT in infected persons with CD4+ counts of less than 500 have been applied to children to support the practice of treating symptomatic children and infected children with CD4+ counts of less than 500 with AZT. (Future studies may reveal that a higher CD4+ count would be a more appropriate cutoff in infants.) Furthermore, there may, in the future, be drugs particular to pediatric AIDS that may never undergo evaluation in adults. Randomized, controlled clinical trials will continue to be essential in most cases in children and can be efficiently conducted because of the apparent short incubation period and rapid progression of perinatally acquired infection. Trials using placebo are ethical at this time only for newborn infants of infected mothers.

ENDPOINTS, TRIAL DESIGN, AND REGULATION*

Using surrogate endpoints for drug efficacy trials raises the additional problem of how to design such trials to show the effects of a drug in an era of combination chemotherapy, prophylaxis for some

*This section is based on material presented by Frank Young, Ellen Cooper, Martin Delaney, Sandra Lehrman, Daniel Hoth, Peter Barton Hutt, and Stephen Lagakos.

opportunistic infections, and an established standard (AZT). The development of AZT has ended the days of placebo-controlled trials for antiretroviral agents in symptomatic patients. The urgency of the epidemic, and the recent appearance in some patients of virus with in vitro resistance to AZT, has brought increasing pressure for quick approval of any drug that appears to proffer benefits. This force in turn has created a dynamic tension between the traditionally measured response of regulators, who are responsible for careful review of the data that seek to establish drug safety and efficacy, and patients and their advocates, whose overriding concern is to provide promising therapies to infected persons as quickly as possible. Balancing the requirements of both these groups in the search for ways to speed drug approval has led to the recent focus on the potential use of surrogate endpoints in clinical trials.

The current regulatory position is that no single marker has been sufficiently well validated to be used as a surrogate endpoint for drug efficacy trials. Rather, FDA sees the use of combinations of markers, including intermediate clinical endpoints (less severe or life-threatening clinical illness), as the direction it would prefer continuing studies to take. Its present policy is to encourage the investigation of these markers within clinical trials as a way to gather the additional data needed to assess their validity as endpoints. One of the factors working against any quick decision on the use of such endpoints is the chronic aspect of HIV infection; the safety and efficacy of drugs must be assessed over the length of what is now known to be a long disease course. Consequently, it is virtually impossible to provide the quick answers desired by those who have the disease or who must treat patients daily.

Technically, there is nothing in any of the regulatory statutes governing the drug approval process that precludes FDA's approving a drug on the basis of its effect on a surrogate endpoint. From the FDA's point of view, however, the establishment of such an endpoint or endpoints is premature at this time. Further progress in the following areas is needed before surrogate endpoints can be established: the ability to detect and measure markers reliably, the establishment of standards for significant changes in markers, the possibility of using different markers at different phases of drug development or with different classes of compounds, and, most important, the correlation of changes in these markers with both short- and long-term clinical outcome. To address these issues requires the prospective collection of more data that consistently establish the relationship between changes in clinical condition and changes in surrogate markers over time at different stages of disease and with different classes of drugs. In such an effort, proper statistical analysis is critical, especially in light of the great variability observed in all of the laboratory markers currently under consideration.

AIDS patients and advocates argue that the use of surrogate endpoints will speed the availability of drugs and in clinical studies may provide a type of "safety net" for patients by defining a threshold below or beyond which patients should not be allowed to progress without the opportunity to receive therapeutic interventions. In particular, AIDS patient advocates argue for the acceptance of measures of intermediate clinical endpoints as surrogates, including the so-called quality-of-life indicators. Some have proposed using such indicators for a form of conditional licensing for a promising therapy whose effectiveness could then be confirmed (or disproved) in postmarketing surveillance. In addition, they suggest the possibility of revisiting and reviewing past studies and data in the light of new knowledge to ensure that no promising drug has been overlooked or rejected on the basis of what is now known to be inaccurate or incomplete information.

FDA officials have stated that the agency would approve a drug that had been shown to have a clearly beneficial effect on intermediate clinical variables, even though the drug had not been shown to affect the virus. The issue turns, however, on how definitively clinical benefit has been demonstrated. The results of small uncontrolled trials to measure improvement in these clinical phenomena could well be confounded by operation of the placebo effect (patients improve because they think they are receiving an effective therapy). As a way to facilitate decisions regarding surrogate endpoints for drug trials, FDA officials expressed the need for a public consensual process. Most FDA decisions are fundamentally driven by the current standard of opinion in the

medical community about a particular issue. Once this standard has been more clearly defined and enunciated—that is, once the data are available from which to develop such a standard—the use of surrogate endpoints in drug efficacy trials may be more widely implemented and carry more weight in judging the effectiveness of a therapy against HIV and AIDS.

As in many aspects of HIV infection and AIDS, the lack of data on the mechanisms of action of the laboratory markers restricts both the ability of researchers to reach conclusions on the advantages of any particular marker and the ability of regulators to help speed drugs to the marketplace and into the hands of patients. As one way to address the data problem the ACTG has now moved to more multicenter trials of drugs and dosages. Still, at least for the present, there will continue to be a number of factors that are not well understood but that may have a substantial effect on whether and how a particular surrogate marker is used. For example, HIV infection is not a single entity—it manifests differently in different individuals and at different stages of disease. There is also some evidence that demographic factors may affect prognosis, an aspect of the problem that continues to surface but that has not as yet been substantially investigated. Furthermore, as in any new area of medicine for which remedies are being sought, the question of the individual patient looms large. The available studies of markers deal, as they must, with populations; the use of markers for clinical staging of individual patients requires further study.

Decisions regarding the use of any of the markers discussed at the conference rest on determining what level of risk is tolerable and at what point the medical and regulatory communities should stop seeking perfection in the state of knowledge and make decisions based on the data that are available. There can be no doubt that what might be called the classic, large-scale controlled trial produces the best information on the efficacy of a drug; without such a trial, AZT would not have been approved as quickly nor could it be prescribed for AIDS as confidently. The heavy demands of the disease, however, argue for thoughtful consideration of less traditional methods that may speed drug approval and make effective therapies available to patients. Surrogate endpoints merit study and development as one such approach.

ROUNDTABLE SUMMARY*

In the climate of urgency that surrounds the search for efficacious therapies against a deadly disease, surrogate markers of drug effectiveness have great appeal as a mechanism for speeding determinations of efficacy and safety. Their utility, however, is not limited to the arena of drug regulation. Clinical management of patients, for example, will also be influenced by the information collected about surrogate endpoints. Indeed, CD4+ cell counts are now widely used to evaluate individual patients' disease status and their suitability for medical interventions. Choosing among the candidate markers that have been identified as possibly useful thus assumes great importance, especially considering that those surrogates identified today by researchers as most promising will influence future clinical trial design. The costs of clinical trials and the need to separate less promising endpoints from those that are most closely related to the pathogenesis of the disease and correlate most strongly with the true clinical endpoints of morbidity and mortality argue for careful consideration of the endpoints that may currently be considered candidate surrogates.

Of the laboratory markers of disease progression that have been considered so far, the CD4+ cell count is preeminent. Drugs may have two types of beneficial effect on CD4+ cell counts. In patients with low CD4+ cell counts, they may produce a rise in CD4+ cells. In patients whose CD4+ cells indicate that they are not yet at high risk for deleterious events, beneficial drugs may decrease the rate of decline in CD4+ cell counts. For that period of time during which these patients have higher CD4+ counts than they otherwise would have had, their risk of adverse outcomes is

* This section is a synthesis of the information presented at the conference based on the Roundtable members' discussion of the material immediately after the conference concluded.

presumably diminished. Although the data on the relationship between CD4+ cell count and prognosis in the natural history of HIV infection are much stronger than those for the significance of CD4+ changes in studies of drug effect (in which analyses are still preliminary), the early evidence is promising. In addition, the clear relationship of CD4+ cell counts to disease pathogenesis adds weight to this conclusion. Data collected and analyzed in the future, of course, may modify this assessment of the marker's promise. In addition, as is the case for all surrogate endpoints, clinical measurements of significance must always take precedence in assessing the effectiveness of a drug. Nevertheless, with this caveat in mind, and all other things being equal, the available evidence suggests that any drug that raises CD4+ cell counts significantly or delays their decline to a level predictive of adverse events should be considered effective for that measure, and therefore for the disease. This finding should be an important consideration in the drug approval process for AIDS therapeutics.

Other markers of immune activation—neopterin, beta-2 microglobulin, and soluble interleukin-2 receptors—are also of interest. These markers correlate with disease activity and deserve further study to establish how they perform in therapeutic studies. At this time, however, their relationship to the pathogenesis of HIV disease is less clear than that of CD4+ cell counts. Thus, their best use may be in combination with CD4+ cell counts, percentages, or CD4+/CD8+ ratios.

Because there is substantial variation in viral burden during the course of disease, measuring the virus itself may be the most direct link to disease pathogenesis and offers promise as a surrogate endpoint of drug effect. Until recently, viral cultures have not appeared to be useful surrogates because they gave only a yes/no answer to the question of whether virus was actually present (current techniques are sensitive enough to allow investigators to culture virus from peripheral blood mononuclear cells at all stages of disease) and could not be used to quantify viral burden. Now, however, promising early results have appeared showing that the magnitude of plasma viremia correlates well with disease stage. In addition, some researchers have now demonstrated that plasma viremia titers decline in response to AZT therapy.

As a measure that reaches to the heart of disease pathogenesis, quantification of viral burden offers clear promise as a marker of disease progression and a possible surrogate endpoint of drug effect. Further development of good quantitative viral assays should be encouraged. The technique of quantitative polymerase chain reaction (PCR) also shows substantial potential for quantitating viral burden. However, its early stage of development and lack of standardization preclude its immediate use as a definitive measure of drug effect.

Another virological marker investigated for its potential as a surrogate endpoint is p24 antigenemia. Although levels of p24 antigen do seem to correlate with drug effect, there are some important limitations to their usefulness. For one thing, only a small proportion of HIV-infected persons has measurable p24 antigen levels. Therefore, using p24 as the major indicator of drug effect would severely restrict the population of patients eligible for drug trials. On the other hand, measurement of p24 antigen is relatively inexpensive and easy to perform, and in patients in whom p24 is present it does correlate with drug effect. For these reasons, further information on the response of p24 antigen levels to therapy will be valuable to collect.

Less severe or life-threatening clinical illness may offer another realm of opportunity in the search for appropriate measures in drug trials. An essential distinction between clinical and laboratory endpoints is that, although less severe clinical endpoints may be considered surrogates insofar as they correlate with disease progression and regression, they may have important significance for patient well-being by themselves. Therefore, any drug that has beneficial effects on an intermediate clinical marker may be important in two discrete ways: for its effect on the clinical condition as an end in itself and for its effect on further disease progression. For example, a drug that effectively delays the onset of bacterial infections would be important for those effects as well as any effect it might have on delaying overall disease progression. For this reason, some people object to labeling any clinical measure a surrogate endpoint. The natural history of HIV infection indicates that earlier clinical illness is detectable and that such illness itself predicts more severe subsequent

clinical outcomes. For example, tuberculosis, particular bacterial infections such as pneumonia, skin infections, diarrhea, fever, weight loss, minor cognitive changes, changes in Karnofsky scores, and objective measures of quality-of-life outcomes demand further study for their relation to disease progression and for their potential role as early indicators of drug effect.

Of necessity, the conference purview was limited mainly to consideration of laboratory surrogate markers. In the pediatric population, however, persuasive evidence that clinical endpoints may be the most powerful predictors of drug effect in infants and children overrode that limitation. Pediatricians are accustomed to measuring growth and development; thus, the capability for accurate quantification is already in place. In addition, studies have shown that the well-documented failure to grow normally that is found in infants and young children with HIV infection is clearly altered with antiretroviral therapy. Researchers in this area take this phenomenon to mean that antiretroviral therapy has had an effect on overall disease progression. Reverses in neurobehavioral abnormalities, which are more specific to HIV infection than are growth abnormalities, also provide objective, measurable evidence that antiretroviral therapy has affected disease progression.

Most studies of the relations between laboratory markers and disease progression and regression have used adult populations. Consequently, although certain trends in such relations are comparable from adults to children, the predominant theme here is the paucity of data from sequential studies in infected children. One problem in understanding the importance of CD4+ cell counts for pediatric patients is the lack of established norms in infancy and early childhood. Because normal levels of these cells are higher in infants than in adults, the meaning of exact numbers of CD4+ cells and their relation to disease progression (for example, the often-used level of 500 CD4+ cells) may differ in these populations. One potential solution to this problem may be for researchers to adopt the convention of expressing CD4+ cells as a percentage of total lymphocytes rather than as an absolute value.

In some respects, the exigencies of AIDS and HIV infection have produced a change in thinking about clinical trials, especially in the case of pediatric populations. Fueling such a reconsideration of traditional methods and established practice has been the realization that those mechanisms designed to protect infants and young children from the potentially damaging effects of drugs have paradoxically retarded the delivery of effective therapy to this population. For example, in the past, trials in children with any particular agent were not initiated until the drug had been proved effective through large-scale efficacy trials in adults. Now, however, a consensus is forming that the initiation of clinical trials in infants and children with HIV infection and approval of drugs for them should not await action in the adult population but may proceed in parallel. Because toxicity of drugs may differ in children and adults, Phase I pediatric trials to establish safety are always necessary; however, when evidence from large-scale adult trials shows the effectiveness of a drug, large-scale Phase II and III studies for efficacy do not necessarily require duplication in children. In other cases, randomized controlled clinical trials in children will continue to be practical and important, especially in those cases in which a particular drug is only being considered for use in the pediatric age group.

The search for surrogate endpoints of drug efficacy as a way to shorten clinical trials of drug safety and effectiveness is impelled by the understandable urgency that attends a disease such as AIDS. On the basis of currently available evidence, CD4+ cell counts appear to be the marker most immediately applicable to the drug approval process. In addition, plasma viremia holds great promise. It is now essential to pursue the clinical studies that will clarify the value of these and other potential surrogate markers and their relationship to ultimate clinical outcome by incorporating their analyses into drug trial design.



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INSTITUTE OF MEDICINE

CONFERENCE SUMMARY

Expanding Access to Investigational Therapies for HIV Infection and AIDS

1991



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March 12-13, 1990
Conference Summary

Eve Nichols

Roundtable for the Development of Drugs
and Vaccines Against AIDS

Institute of Medicine

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This conference summary was written by Eve Nichols for the Institute of Medicine's Roundtable for the Development of Drugs and Vaccines Against AIDS, chaired by Harold Ginsberg and Sheldon Wolff and directed by Robin Weiss. The document reports major themes of the conference discussions; these themes, however, do not represent policy statements by the Institute of Medicine.

The report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

The Institute of Medicine was chartered in 1970 by the National Academy of Sciences to enlist distinguished members of appropriate professions in the examination of policy matters pertaining to the health of the public. In this, the Institute acts under both the Academy's 1863 congressional charter responsibility to be an advisor to the federal government, and its own initiative in identifying issues of medical care, research, and education.

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The image adopted as a logotype by the Institute of Medicine is based on a relief carving from ancient Greece, now held by the Staatlichemuseen in Berlin.

ROUNDTABLE FOR THE DEVELOPMENT OF DRUGS AND VACCINES AGAINST AIDS

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PREFACE

The Roundtable for the Development of Drugs and Vaccines Against AIDS was established in 1988 by the Institute of Medicine. Composed of leaders from government, the pharmaceutical industry, academia, and the public, its mission is to identify and help resolve impediments to the speedy availability of safe and effective drugs and vaccines for human immunodeficiency virus (HIV) infection and acquired immune deficiency syndrome (AIDS). The Roundtable accomplishes its mission through regular meetings of its membership, during which urgent issues are identified and discussed, as well as through public conferences and workshops that explore scientific and policy matters central to the development of AIDS therapeutics. This publication is the report of a conference held March 12 and 13, 1990, in Washington, D.C.

The call for a "parallel track" for AIDS drug development—a proposal that would allow the early distribution of AIDS drugs to large numbers of patients in parallel with the conventional clinical trials that assess the drugs' safety and efficacy—has sparked controversy within the scientific community. Questions have arisen about the risks to patients of such a plan, about its potential effect on the successful completion of standard controlled trials, and about whether the parallel track will generate useful data. Larger questions have also been raised about whether the parallel track heralds fundamental changes in the philosophy underlying drug regulation in the United States, about the costs and financing of investigational therapies and associated medical costs, and about the role of expanded access mechanisms for drugs in reaching those whose health care generally is inadequate. The Roundtable sought to illuminate these issues by inviting knowledgeable speakers and the public to a two-day conference to examine proposals for expanded access to investigational drugs and possible repercussions of such an action.

Two months after the conference was held, in May 1990, the parallel track proposal was published in the *Federal Register* and comments were

sought. A meeting was held in September 1990 by the Public Health Service (PHS) to discuss the comments. As this report goes to press, the PHS is finalizing the document, which, when completed, will constitute a written PHS policy. As the policy takes effect, many of the issues raised in this report will serve as valuable guideposts in evaluating the parallel track experiment.

A note on terminology: Although the word *effectiveness* rather than *efficacy* was used by Congress in the Drug Amendments of 1962, we have chosen in this report to conform to the definitions of the two terms as they are commonly understood in the field of medical technology assessment. Here, the term *efficacy* refers to what a method (e.g., a drug) can accomplish in expert hands when correctly applied to a patient; *effectiveness* refers to its performance in more general routine applications.[1] Therefore, most randomized clinical trials assess efficacy; the Food and Drug Administration, in reviewing the results of these trials, is evaluating the efficacy of the drugs under investigation.

This report seeks to summarize the conference presentations. It contains no recommendations or conclusions, and the Roundtable has neither altered nor commented on the views and opinions expressed by the speakers, except for purposes of clarity. The Roundtable and staff wish to thank Eve Nichols, whose capable hands crafted the transcript of the meeting into a smooth narrative. We also thank, once again, the conference speakers for their thoughtful presentations, and all participants for the lively and challenging discussions throughout the conference.

[1]Institute of Medicine, *Assessing Medical Technologies* (Washington, D.C.: National Academy Press, 1985).

CONTENTS

	CONFERENCE PROGRAM	1
1	**HISTORICAL PERSPECTIVE**	5
	Early Development of Expanded Access	6
	Drug Amendments of 1962	7
	Modern Clinical Trials (Non-AIDS Drugs)	9
	The Advent of AIDS	11
	Broadening Participation	11
	Accelerating the Pace of Drug Development	12
	Expanded Access	14
2	**RIGHTS AND RESPONSIBILITIES**	19
	Freedom of Choice	19
	Informed Consent	20
	Information Resources	20
	Access	22
	Competing Rights	24
	Institutional Review Boards	24
	New Attitudes	25
3	**EVALUATION OF EXPANDED ACCESS PROGRAMS**	27
	Treatment Investigational New Drugs	27
	Potential Risks	28
	Examples from the Past	28
	The Target Population	29
	Safety Data	30
	Impact on Conventional Randomized Trials	31
	The Parallel Track Experiment	32

4 CREATIVITY IN CLINICAL TRIALS 35
The Changing Environment 35
Conventional Trials 36
Preference Trials 38
Large, Simple Randomized Trials 39
Physician Participation 40
Quality Control 41
Data from the Parallel Track 41
Efficacy Data 41
Safety Data and Related Information 42
Expectations 43

5 DRUG INNOVATION AND THE PHARMACEUTICAL INDUSTRY 45
Time to Commercialization 46
Direct Costs of Expanded Access 46
Manpower Needs 47
Drug Costs 48
The Small Manufacturer 48
Product Liability 49
Concerns Specific to the Parallel Track 50
Potential Solutions 50

6 THIRD-PARTY PAYERS 53
Blue Cross and Blue Shield 55
Health Insurance Association of America 56
Health Care Financing Administration 58
Medicaid 58
Medicare 60
Resources for Clinical Investigation 60

7 IMPROVING ACCESS TO CARE 63
People of Color 65
Resource Considerations 65
Suspicion 67
Informed Consent 67
Women 68
The Gender Perspective 68
A New Approach 70
The Pediatric Population 71
Scientific Issues 72
Social Issues 72

EXPANDING ACCESS TO INVESTIGATIONAL THERAPIES FOR HIV INFECTION AND AIDS

EXPANDING ACCESS TO INVESTIGATIONAL THERAPIES

March 12–13, 1990

PROGRAM

Monday, March 12

8:15 **Welcome and Opening Remarks**
– Harold Ginsberg, Eugene Higgins Professor of Medicine and Microbiology, College of Physicians & Surgeons, Columbia University, and Co-chair, AIDS Roundtable

8:20 **Expanding Access to Investigational Therapies: The Challenges Ahead**
– Samuel O. Thier, President, Institute of Medicine

8:30 **A Lucid Explanation and Brief History of Food and Drug Administration Policy on Investigational Drugs for Treatment Purposes**
– Peter Barton Hutt, Partner, Covington & Burling

9:00 **The Promise of Treatment Investigational New Drug Regulations: Have They Done What They Were Supposed to Do?**

Moderator:
J. Richard Crout, Vice President, Medical and Scientific Affairs, Boehringer Mannheim Pharmaceuticals

Panelists:
Robert Temple, Director, Office of Drug Evaluation I, Food and Drug Administration
Jay Lipner, Partner, Silverstein Langer Lipner & Newburgh
Stephen Sherwin, Vice President for Clinical Research, Genentech, Inc.

Lawrence Corey, Professor of Laboratory Medicine, Microbiology, and Medicine, University of Washington
Raphael Dolin, Head, Infectious Diseases Unit, University of Rochester School of Medicine and Dentistry

10:00 **Discussion**

10:45 **The Philosophy of Drug Regulation in the United States: Is It Changing from Beneficence to Patient Autonomy?**

Moderator:
Dan Brock, Professor of Philosophy, Brown University

Panelists:
Harold Edgar, Professor of Law, Columbia University School of Law
Bernard Lo, Director, Program in Medical Ethics, University of California
Daniel Wikler, Professor, Department of Philosophy, University of Wisconsin
Carol Levine, Executive Director, Citizens Commission on AIDS

12:00 **Discussion**

1:45 **Issues of Cost and Coverage: How Will the Changes Affect the Drug Industry, Payers, and Patients?**

Moderator:
Patrick Gage, Executive Vice President, Genetics Institute, Inc.

Panelists:
Jerome Birnbaum, Executive Vice President for Research, Bristol-Myers Squibb Company
Paul De Stefano, Chief Corporate Counsel, Genentech, Inc.
David Higbee, Branch Chief, Catastrophic Medical Services, Office of Coverage Policy, Health Care Financing Administration
Susan Gleeson, Executive Director, Technology Management, Blue Cross and Blue Shield Association
Steven Peskin, Vice President and Medical Director, CIGNA Healthplan of Texas, Inc.

Lee Mortenson, Executive Director, Association of Community Cancer Centers

3:00 **Discussion**

3:45 **Expanding Access and Gathering and Analyzing Data: Can You Have Your Cake and Eat It Too?**

Moderator:
Lincoln Moses, Professor of Statistics, Stanford University

Panelists:
Melanie Thompson, President, AIDS Research Consortium of Atlanta, Inc.
Marvin Zelen, Chair, Department of Biostatistics, Harvard School of Public Health
Floyd J. Fowler, Senior Research Fellow, Center for Survey Research, University of Massachusetts
Susan Ellenberg, Chief, Biostatistics Research Branch, Division of AIDS, National Institute of Allergy and Infectious Diseases

5:00 **Discussion**

5:30 **Adjournment**

Tuesday, March 13

8:15 **Reaching the Disenfranchised: What Role for Clinical Trials?**

Moderator:
Gerald Friedland, Professor of Medicine, Epidemiology, and Social Medicine, Albert Einstein College of Medicine

Panelists:
Lawrence Brown, Jr., Senior Vice President for Research and Medical Affairs, Addiction Research and Treatment Corporation
Mark Smith, Associate Director, AIDS Service, Johns Hopkins University School of Medicine
Deborah Cotton, Clinical Director for AIDS, Beth Israel Hospital

Philip Pizzo, Chief, Pediatric Branch, National Cancer Institute

9:30 **Discussion**

10:15 **Parallel Track: An Update**
– James Allen, Director, National AIDS Program Office, Public Health Service

10:30 **Parallel Track: What Should It Achieve?**

Moderator:
Anthony Fauci, Associate Director for AIDS Research, National Institutes of Health, and Director, National Institute of Allergy and Infectious Diseases

Panelists:
Louis Lasagna, Dean, Sackler School of Graduate Biomedical Sciences, Tufts University
James Eigo, Member, Treatment and Data Committee, AIDS Coalition to Unleash Power
Daniel Hoth, Director, Division of AIDS, National Institute of Allergy and Infectious Diseases
Ellen Cooper, Director, Division of Antiviral Drug Products, Food and Drug Administration

11:45 **Discussion**

12:15 **Expanding Access and the Needs of the Traditional Primary Care Provider**
– Harvey Makadon, Assistant Professor of Medicine, Harvard Medical School, and Executive Director, Boston AIDS Consortium

12:35 **Discussion**

12:50 **Summation**
– Sheldon Wolff, Endicott Professor and Chairman, Department of Medicine, Tufts University School of Medicine, and Co-chair, AIDS Roundtable

1:00 **Adjournment**

1

HISTORICAL PERSPECTIVE

In the second week of March 1990, headlines across the country described an unusual scientific controversy over the distribution of an investigational drug called dideoxyinosine (ddI) to thousands of patients with acquired immune deficiency syndrome (AIDS). Newspapers reported that patients receiving the drug through a new expanded access program had a much higher death rate than patients enrolled in conventional clinical trials of the drug. In one case, a Harvard faculty member was quoted as saying that death rates in the expanded access program were "a disgrace, an absolute disgrace." But many physicians advised their HIV (human immunodeficiency virus)-infected patients to keep taking the drug. Officials at the Food and Drug Administration (FDA), advocates for people with AIDS, and the drug's sponsor, Bristol-Myers Squibb, attributed most or even all of the disparity in death rates to the fact that patients enrolled in the expanded access program were sicker to begin with than those in the clinical trials.

The ddI controversy exposed sharp differences of opinion within the medical community about the appropriateness of making investigational drugs—drugs not yet approved for marketing by the FDA—available for therapeutic purposes. In August 1989, the Public Health Service (PHS) convened a committee to formalize procedures for making promising investigational agents available to people with AIDS and other HIV-related disorders who could not participate in controlled clinical trials and who had no therapeutic alternatives. The committee's recommendations were still in draft form seven months later,

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This chapter is based primarily on the presentation of Peter Barton Hutt. Other contributors include Jay Lipner, Lawrence Corey, James Allen, Louis Lasagna, James Eigo, Daniel Hoth, and Ellen Cooper.

but many people regarded the ddI trial as the prototype of the new "parallel track system." (On May 21, 1990, the Department of Health and Human Services published a proposed policy statement, "Expanded Availability of Investigational New Drugs Through a Parallel Track Mechanism for People with AIDS and HIV-related Disease," in the *Federal Register*.)

The controversy continues today. Opponents of the parallel track worry that it will disrupt efforts to assess the safety and efficacy of drug candidates through conventional clinical trials. They question the value of information gathered through the parallel track system and express concern about exposing large numbers of people to relatively unknown agents. Advocates of parallel track acknowledge that increasing access to investigational drugs without definitive evidence of either safety or efficacy carries serious potential risks, but they believe that many desperately ill patients are willing to assume such risks. After all, they say, investigational drugs are the only hope for thousands of AIDS patients who either cannot tolerate or fail to respond to zidovudine (commonly known as AZT), the only anti-HIV drug licensed in the United States.

One fact often ignored by both sides is that access to investigational drugs for therapeutic purposes is not new in this country. In fact, it is as old as the history of drug regulation itself. Two features that make the current situation somewhat different from the past are (1) the desire to establish a written policy and (2) the large number of people who could receive a single investigational drug in a short period of time. A brief review of earlier approaches to expanded access and a summary of the drug approval process prior to the start of the AIDS epidemic help place the debate over the parallel track mechanism in perspective.

EARLY DEVELOPMENT OF EXPANDED ACCESS

Modern drug regulation in the United States began in 1938 with enactment of the Federal Food, Drug, and Cosmetic Act, prompted by the elixir sulfanilamide tragedy of November 1937 (more than 100 people died when a drug containing the poisonous solvent diethylene glycol was marketed without animal tests). The new act contained one brief section, labeled 505(i), in which Congress authorized the FDA to issue rules governing investigational use of drug candidates. The FDA regulations that resulted from this authorization contained four requirements: (1) an experimental drug had to be labeled "for investigational use only"; (2) the drug could be delivered only to

experts and could be used by them solely for investigational purposes; (3) each expert had to have adequate facilities for investigation; and (4) the sponsor had to have a signed statement from the investigator indicating that the drug would be used solely for investigational purposes until it had been fully licensed.

The regulations did not describe "expert" qualifications or specify the nature of "adequate facilities." In fact, they did not even define "investigational use." Thus, in practice, the sponsor could provide an investigational drug to any physician who was willing to sign the required statement. Questions of expanded access did not arise because there were no substantive barriers to obtaining investigational drugs for therapeutic purposes.

Drug Amendments of 1962

Public attention did not focus again on the drug regulatory apparatus until July 1962, when a story in the *Washington Post* disclosed links between the experimental drug thalidomide and severe birth defects. Three months later, the U.S. Congress unanimously passed the first major drug amendments.

Surprisingly, the 1962 amendments did not radically alter section 505(i). They authorized regulations for investigational new drugs but did not require the submission of study plans, record keeping, or statements from investigators. The only mandatory provision was that investigators had to obtain informed consent from every subject.

The regulations issued by the FDA in response to the thalidomide tragedy and the new statute provided the first formal structure for the drug development process. Before beginning clinical trials, all sponsors would have to submit an investigational new drug application, or IND. The IND would describe the chemical structure of the new compound and its probable mode of action in the body, identify investigators, describe the results of laboratory and animal tests, and outline specific elements of the study protocol.

Access for Therapeutic Purposes

The FDA press release that accompanied the final regulations in January 1963 addressed for the first time the issue of access to investigational drugs for therapeutic purposes. In an analysis of objections that had been raised to the regulations in draft form, the press release noted, "The proposed regulations were said to deny

extremely important new drugs not yet approved for general distribution to patients who might need them urgently as a lifesaving measure."

The FDA's response set the tone for the next two decades. The press release explained, "The increased flexibility in the regulations will allow the sponsor of a new drug investigation to add new investigators after the program is started. There is no bar in the regulations to giving the necessary instructions to, and obtaining the necessary commitments from, a new investigator by telephone in case this is needed to save a life."

Growing Confusion

From 1962 until the beginning of the 1980s, access to investigational drugs was an informal process governed primarily by telephone. The FDA had no written policies. If a physician determined that a severely ill patient had no recourse other than an experimental drug, the physician called the FDA and requested access to that drug. Medical officers in the agency evaluated each situation separately and either approved or denied the request. The criteria were simple. Approval required four basic elements: a manufacturer willing to supply the drug, a physician willing to prescribe it, a patient willing to give informed consent, and some basis for believing that the treatment was not an outright fraud or poison.

The flexibility of this system enabled many very sick patients to receive drugs with a minimum of delay and paperwork. But there were also drawbacks to the informal approach. First, the system only worked for patients whose physicians knew what drugs were under investigation; patients treated by physicians outside the mainstream of academic medicine were less likely to have access to experimental therapies. Second, some ineffective or even toxic drugs, such as DMSO (dimethyl sulfoxide), attained widespread distribution among patients whose original illnesses did not justify extreme measures. Finally, the lack of written policies spawned a confusing array of terms and concepts that still cloud discussions and interfere with efforts to develop a more uniform approach to the access problem.

In the 1960s, FDA medical officers permitted access to investigational drugs under several mechanisms: orphan drug INDs, individual investigator INDs, and compassionate use INDs. The orphan drug concept actually predated the 1962 amendments and remains in use today. It refers to drugs developed to treat rare or unusual conditions. The "permanent" orphan drug IND was conceived to provide

access to drugs that would never meet licensure requirements because there were simply too few patients to collect adequate data. (In 1983, Congress passed the Orphan Drug Act to provide certain tax and other financial incentives to the sponsors of therapies for rare diseases.)

The individual investigator IND enabled physicians to obtain experimental drugs for therapeutic purposes when it was not possible to enroll their patients in existing clinical trials. By the end of the 1960s, this concept had been incorporated into the compassionate use IND, which also covered the provision of experimental drugs to patients during FDA review of a new drug application, or NDA (the document submitted by a sponsor after the completion of clinical trials to request permission for marketing).

Two more expanded access concepts arose during the 1970s. Sponsors of controlled trials were permitted to develop concurrent open-label safety studies (also called open enrollment or open protocol). Through these studies, which continue today, thousands of patients received access to experimental drugs at various stages of investigation. Although the FDA requires sponsors of these studies to collect safety data, many observers of FDA policy believe that the primary purpose of the open-label studies is to provide therapy to patients. In 1976, the FDA also accepted the concept of the Group C cancer drug IND, which provides increased access to certain investigational cancer drugs distributed by the National Cancer Institute.

It is important to remember that all of these concepts evolved in the absence of any written policy. Over the years, several groups in Congress and the FDA attempted to develop a more rational approach to the use of investigational drugs for therapeutic purposes, but changes in administration and other political events intervened. Meanwhile, the drug development and approval process itself grew increasingly formal. By 1980, it took an average of 10 years for a new drug to progress from the laboratory to the medicine chest.

Modern Clinical Trials (Non-AIDS Drugs)

With some important exceptions, the basic framework of the drug evaluation process today is similar to that of 10 years ago (although a study by the Pharmaceutical Manufacturers Association suggests that the average time to FDA approval now may be closer to 12 years). If preclinical investigations indicate that a drug has biological activity against a targeted disease and does not cause unacceptable damage to healthy tissues, the drug sponsor requests permission from the FDA

to begin the first of three phases of clinical trials—that is, the sponsor files an IND.

Phase 1 studies usually take a year and may involve up to 50 normal, healthy volunteers. These are short-term tolerance and clinical pharmacology studies; their goals are to begin to establish the drug's safety in human beings and to determine appropriate dose levels and routes of administration. (Phase 1 studies of drugs for life-threatening conditions, such as AIDS and cancer, or of drugs that are very toxic may involve patients with the target disease rather than healthy volunteers. Patient studies are also preferred when investigators shorten preclinical studies to speed drug development. As a result of the shortened preclinical studies, the potential for toxicity may be too great to justify giving the drug to someone who has no chance of benefiting from it.)

Phase 2 trials, which usually take two years or more, involve 100 to 300 consenting patients. Investigators gather additional information about possible adverse effects and begin to assess a drug's clinical potential. Most phase 2 studies are randomized, controlled trials. A group of patients receiving the drug, a "treatment" group, is matched with a group that is similar in important respects, such as age, gender, and disease state (factors that could affect the course of the disease or the effect of the investigational drug). The second, or "control," group receives another treatment such as standard therapy or a placebo (an inert substance). Many phase 2 studies are double blind—that is, neither the patient nor the researchers know who is getting the experimental drug. The purpose of double-blind studies is to reduce errors in interpretation caused by unwarranted enthusiasm or other forms of bias.

Phase 3 clinical trials involve many more volunteer patients—several hundred to several thousand—and last about three years. The larger trials allow researchers to acquire more information about efficacy and to identify some of the less common side effects associated with an experimental drug.

If the net results of all three phases of clinical trials are favorable and the sponsor decides to market the drug, it submits a new drug application to the FDA. The NDA must contain all the scientific information gathered in the previous years and typically runs 100,000 pages or more. The average time between the submission of an NDA and final FDA approval is close to three years.

THE ADVENT OF AIDS

The AIDS epidemic has drawn unprecedented attention to the entire drug approval process and prompted or accelerated a variety of changes—some of which were under consideration before the epidemic began. These changes fall into three categories: efforts to broaden patient and community involvement in developing and testing new products, efforts to shorten the overall development and review process, and efforts to increase access to promising drugs before FDA approval (expanded access).

Broadening Participation

Throughout most of the 1980s, people with AIDS and their advocates were highly critical of the FDA and other government agencies involved in drug development. There was a perception that government scientists were more interested in maintaining the scientific standards of clinical trials than in providing new options for the thousands of patients who were dying as a result of HIV infection. Government scientists, on the other hand, were frustrated by misconceptions surrounding the drug development process. For example, the role of the FDA is to ensure that drugs marketed in the United States meet established standards of safety and efficacy; the FDA could not initiate or conduct clinical trials on its own, as some patient advocates were suggesting.

Over time, the adversarial relationship has relaxed somewhat, although strong disagreements remain. Persons with AIDS and their advocates now participate on advisory committees within the Public Health Service to provide practical advice about the optimal design and implementation of clinical trials from the patient's perspective. In addition, scientists at the helm of the research effort in AIDS have recognized the need for creative approaches to the problems associated with HIV infection.

One result of this cooperation was the establishment in October 1989 of a new AIDS treatment research initiative called Community Programs for Clinical Research on AIDS (CPCRA), funded by the National Institute of Allergy and Infectious Diseases (NIAID). Before the advent of CPCRA, all federally funded clinical trials of experimental AIDS drugs were conducted by investigators at the National Institutes of Health or at the 47 university-based research hospitals associated with the AIDS Clinical Trials Group (ACTG). (Of course, pharmaceutical companies and community-based physicians have also

conducted important clinical trials of AIDS drugs.) The ACTG consortium was created by NIAID in 1986 to perform the complex multidisciplinary clinical and laboratory studies required for development of new antiviral drugs.

Although AIDS activists and community care providers recognized the contributions made by ACTG investigators, they questioned the need to restrict federally funded clinical trials to university medical centers. They claimed that many important research and clinical questions could be addressed in settings that lacked the technological sophistication of the ACTG institutions. Also, demographic information on patients in ACTG studies revealed that, although some of the large medical centers are also inner-city hospitals that treat underserved patient populations, other ACTUs (AIDS clinical trial units) were not reaching certain patient groups. (Underserved populations have included people of color, women, and intravenous drug users infected with HIV.) As a result, these groups did not have access to potentially beneficial investigational drugs.

CPCRA was designed to address these issues. The 18 diverse CPCRA sites give community care providers and their HIV-infected patients opportunities to participate in clinical trials. The program is designed to take advantage of the clinical expertise acquired by physicians in private practice, in community clinics, and at larger inner-city hospitals. In addition, NIAID seeks, through these new sites, to increase access for underserved populations to experimental therapies. As noted in Chapter 7, however, much more work remains to be done to solve the access problem.

Accelerating the Pace of Drug Development

One of the hardest messages to convey to desperately ill patients has been that no changes in regulations or clinical trials can increase access to drugs unless potential drug candidates are already in the pipeline. Historically, medical science has not fared well in the battle against chronic viral infections such as herpes, hepatitis B, cytomegalovirus, and AIDS. The successes against HIV infection—represented by zidovudine, and perhaps ddI—have resulted from very recent advances in virology, cell culture, and molecular biology.

In 1986, NIAID started the National Cooperative Drug Discovery Group to stimulate new research on targeted development of AIDS drugs. The group's efforts have complemented work by the Preclinical AIDS Drug Development Program at the National Cancer Institute, which screens thousands of natural and synthetic compounds each year

for activity against HIV. As of January 1990, the FDA had granted permission for IND studies involving more than 80 different AIDS-related antiviral or immunomodulating drugs. Experience suggests, however, that fewer than 20 percent of these will survive the trials and approval process.

Improving Response Capabilities

Recognizing that FDA would be called upon to respond rapidly to the new challenges posed by AIDS, then commissioner Frank E. Young made a number of administrative and organizational changes at the agency. First, he assigned all AIDS treatments a special 1-AA designation, giving them top review priority. This meant that the FDA intended to act on all AIDS-related NDAs within 180 days of their submission. A new division of antiviral drug products was created within FDA's Center for Biologics Evaluation and Research to expedite the review and evaluation of potential AIDS therapies. In addition, FDA established the AIDS Coordination Staff to integrate the agency's various AIDS-related activities and to interact with other agencies and outside groups interested in AIDS drug development.

Expedited Development

Perhaps the most fundamental change, however, involved the clinical trials process itself. In October 1988, Dr. Young announced immediate implementation of a formal plan to reduce the time required for human testing of drugs for life-threatening and severely debilitating diseases, such as AIDS, Parkinson's disease, and certain aggressive cancers. The primary effect of the new "expedited development" process is to eliminate phase 3 clinical trials for drugs shown to improve survival or prevent irreversible morbidity. By planning the critical phase 2 studies well, the development and review process might be shortened by two to three years.

Expedited development follows a pattern established by the development of zidovudine. In February 1986, after a promising phase 1 trial at the National Cancer Institute and Duke University, researchers started a phase 2 study of zidovudine at 12 medical centers across the United States (the placebo-controlled randomized trial involved patients with AIDS or advanced AIDS-related complex [ARC]). The phase 2 study was stopped in September of that year, when an independent data safety monitoring board found a dramatic

difference in outcomes between the 145 patients receiving zidovudine and the 137 patients receiving placebos (19 patients in the placebo arm of the trial had died, compared with only a single death in the zidovudine group). Burroughs Wellcome, the manufacturer, submitted a new drug application for zidovudine in December 1986. The FDA approved the NDA without a phase 3 clinical trial on March 20, 1987. At the time, officials explained that one reason for the rapid approval of zidovudine was that FDA scientists had had an opportunity to work closely with the drug's sponsor from the very beginning of the development process.

Current procedures for expedited development specify that the FDA will meet with drug sponsors to help devise efficient animal and human studies—studies that answer vital questions about safety and efficacy in the least amount of time possible. The FDA also monitors the progress of clinical trials and, if necessary, helps the sponsor develop appropriate postmarketing studies to provide additional information about risks, benefits, optimal uses, and dosages. The FDA approval process for drugs in the expedited pathway takes into consideration the severity of the disease being treated and the availability of alternative therapies, as well as the statutory criteria for approval.

Expanded Access

The urgency created by the AIDS epidemic also has focused attention on two approaches to expanded access: the treatment IND and the parallel track protocol. These mechanisms, which incorporate the expanded use practices that began in the 1960s, evolved from a growing awareness on the part of drug sponsors, government scientists, and others that the informal procedures of the past would not be sufficient to handle the distribution of investigational drugs to AIDS patients. The complexity of HIV infection and the potential toxicity of some drug candidates discouraged FDA medical officers from approving expanded access protocols for AIDS drugs on the basis of a few quick telephone conversations. There also was concern that the volume of requests might become overwhelming.

Treatment Investigational New Drugs

The treatment IND first emerged as part of a long-term effort to incorporate the concept of expanded access into the IND regulations.

In June 1983, the FDA issued proposed regulations that included a very broad interpretation of the use of investigational drugs for therapeutic purposes: at any time during the investigational process, the FDA could approve a treatment protocol for any patient with a serious disease (the definition of "serious" was left to the discretion of the patient and physician). The proposed interpretation would have incorporated virtually all of the older versions of expanded access, including the compassionate use IND and the orphan drug IND.

Some critics believe that when the final IND regulations emerged in 1987, the definition of treatment IND was much narrower. The treatment IND mechanism allows patients suffering from serious or life-threatening conditions for which there is no satisfactory alternative therapy to obtain a promising experimental drug. Clinical evidence must be available to show that the drug is relatively safe and that it "may be effective." In addition, controlled clinical trials must be completed or ongoing and the sponsor must be pursuing marketing with "due diligence." Others at the FDA argue that the only real difference between the 1983 and 1987 versions of the regulations was that the 1987 announcement received a great deal of publicity, which reminded the public that the treatment IND was an available mechanism.

A government scientist reports that, as of March 12, 1990, the FDA had approved 18 treatment INDs for conditions ranging from AIDS to respiratory distress syndrome in infants. Almost 20,000 patients had obtained access to drugs not yet approved for marketing. Nevertheless, persons with AIDS and their advocates say that the treatment IND has fallen far short of their expectations. They suggest that the FDA's interpretation and implementation of "may be effective" have been too rigorous—too close to the standard used for final approval of a drug. With one exception, they say, treatment INDs have simply bridged the gap between the end of clinical trials and full FDA approval. They have not increased access to drugs at earlier stages of development or helped patients who were ineligible for conventional clinical trials.

Another criticism of the treatment IND regulations has been that they increased, rather than decreased, confusion about the parameters of expanded access. People inside and outside the government had hoped that the regulations would furnish a framework for all of the different approaches to providing experimental drugs to desperately ill patients. Instead, the regulations defined one particularly narrow approach and left other options open. Early dissatisfaction with the

treatment IND led to calls for a more flexible solution to the access problem.

Parallel Track

For almost a year after the release of the new IND regulations, patient advocates, community physicians, and government scientists exchanged ideas about other possible ways to expand access to experimental drugs. Finally, at a meeting in San Francisco in June 1989, Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases, presented the concept of the "parallel track" protocol. The parallel track would make selected drugs available to HIV-infected patients who could not participate in conventional clinical trials and who had no therapeutic alternatives, without disrupting the progress of controlled clinical trials. Parallel track protocols could be approved for promising investigational drugs when the evidence for effectiveness was less than that required for a treatment IND.

Several months later, an FDA Advisory Committee meeting convened by the FDA and a subgroup convened by the National AIDS Program Office began efforts to define the structure of the parallel track system. After a lengthy review process, they decided that parallel track protocols could be implemented within the framework of existing regulations. In December 1989, they submitted a proposed policy statement explaining the basic outlines of the parallel track to the Office of the Secretary of Health and Human Services. Drugs would be considered for the new track only if manufacturers could provide the following:

1. information showing promising evidence of efficacy based on an assessment of all available laboratory and clinical data, as well as sufficient information to recommend an appropriate starting dose and preliminary pharmacokinetic and dose-response data;
2. evidence that the investigational drug is reasonably safe, taking into consideration the intended use and the prospective patient population;
3. a description of the intended patient population;
4. evidence that the defined patient population lacks satisfactory alternative therapies;
5. assurance that the manufacturer is willing and able to produce sufficient quantities of the drug for both controlled clinical trials and the parallel track;

6. a statement of the status of existing controlled clinical trial protocols (drugs will be considered for parallel track only after protocols for phase 2 controlled clinical trials have been approved by the FDA; also, patient enrollment in phase 2 controlled trials must start before or concurrently with the release of drugs for parallel track);
7. an assessment of the impact that the parallel track study may have on patient enrollment in controlled clinical trials and a proposed plan for monitoring progress of the controlled trials; and
8. information describing the educational efforts that will be undertaken by the manufacturer or the sponsor to ensure that participating physicians and potential recipients have sufficient knowledge of the potential risks and benefits of the investigational agent.

Evidence for safety and efficacy might come in part from expanded phase 1 trials. As noted earlier, phase 1 trials for drugs for AIDS and other life-threatening diseases often involve persons with the disease instead of healthy volunteers. The expedited development process and the potential increase in the number of people who might get very early access to an experimental drug for therapeutic purposes have placed pressure on investigators to get as much information as possible from phase 1 trials. For example, the authors of the proposed policy statement on the parallel track indicate that expanded phase 1 trials should provide some information about potential interactions between an investigational drug and other drugs commonly used in the patient population. Other physicians suggest that expanded phase 1 trials should compare different doses of an experimental drug, primarily to avoid problems similar to those that arose with zidovudine. (Two years after the FDA approved zidovudine, a randomized trial carried out by the ACTG revealed that patients taking 600 milligrams per day of the drug did as well as patients taking the recommended dose of 1.2 grams per day. If this had been known sooner, some patients might have avoided adverse reactions, and many more would have been spared unnecessary expense.)

The proposed policy statement on parallel track also outlines eligibility requirements for patients. First, patients must have clinically significant HIV-related illness or be at imminent health risk as a result of HIV-related immunodeficiency. Second, patients must be unable to participate in related controlled clinical trials, either because they do not meet entry criteria (for example, laboratory test results are not within specified limits), because they are too sick, or because

participation would create undue hardship (the nature of possible hardships, such as travel time to a research center, must be described in the parallel track protocol). Finally, physicians who wish to enroll a patient in the parallel track must provide evidence that existing FDA-approved therapies for the condition are contraindicated for that patient, that the patient cannot tolerate them, or that they are no longer effective.

Close monitoring of the parallel track will be essential to ensure that serious adverse effects (or, conversely, unexpected benefits) are recognized at the earliest possible moment. According to the proposed policy statement, sponsors will be required to establish a data and safety monitoring board (DSMB) with responsibility for overseeing the parallel track protocol and for comparing information gathered from the parallel track with information gathered from related clinical trials. The recent experience with ddI, described at the beginning of this chapter, underscores the importance of reviewing all available materials. Although data collection in the parallel track will be minimal compared with data collection in controlled trials, the DSMB should have a sufficient basis for comparison. If necessary, the DSMB or its equivalent may recommend to the FDA, to the sponsor, or to the NIAID AIDS Research Advisory Committee that the parallel track protocol—and possibly related clinical trials—be terminated.

In conventional clinical trials, educational materials and informed consent documents that describe the potential risks and benefits associated with an experimental drug must be approved by an institutional review board (IRB) at each participating institution. The PHS working group, however, determined that such an arrangement might be impractical for parallel track protocols, in part because many community physicians who wished to participate in the parallel track would not have access to IRBs. In addition, the time required to provide sufficient information to hundreds of IRBs around the country would defeat the main purpose of the parallel track—rapid dissemination of investigational drugs to desperately ill patients.

To overcome this problem, the working group has proposed a national human subjects protection review panel to provide continuing ethical oversight of all parallel track protocols. The panel would have a diverse membership, including persons with AIDS, physicians, government scientists, and others. It would be responsible for establishing the types of information that must be given to patients and for approving all informed consent procedures.

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RIGHTS AND RESPONSIBILITIES

The philosophical debate over expanded access to investigational drugs takes many forms. People often try to reduce the standard arguments to simple dichotomies; for example, the "mind versus heart" approach pits the scientific discipline of clinical trials against the compassionate use of experimental drugs for therapeutic purposes. The "beneficence versus autonomy" approach suggests that providing protection to people with HIV infection must conflict with respect for their individual rights.

In fact, most efforts to simplify the debate over expanded access do a disservice by diverting attention from a host of complex issues that must be considered in any discussion of increased access to AIDS drugs. These issues concern (1) the need for constraints on freedom of choice, (2) the capacity for informed consent in an environment characterized by restricted access to health care, (3) the potential for setting the rights of today's patients against the rights of future patients, (4) the shifts in concerns of institutional review boards, and (5) the problems that could arise from early and close collaboration between the FDA and drug sponsors.

FREEDOM OF CHOICE

The expedited review process, treatment IND regulations, and recent efforts to establish a parallel track system for AIDS drugs (all described in Chapter 1) have led some people to suggest that the FDA is moving away from its traditional role of consumer protection

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This chapter is based on the presentations of J. Richard Crout, Dan Brock, Harold Edgar, Bernard Lo, Daniel Wikler, and Carol Levine.

toward a new vision of patient autonomy. Scientists involved in these programs indicate, however, that they were never intended to promote freedom of choice as an independent value in drug development. Instead, they were designed to increase options for desperately ill patients with no therapeutic alternatives.

The extreme argument for freedom of choice has been that persons infected with HIV have "little or nothing to lose," so why limit their access to any drugs? The problem with this argument is that it fails to recognize the association between desperation and vulnerability. Exploitation of people with HIV infection by unscrupulous vendors with worthless products has been a significant problem. People with HIV infection do have something to lose: they can waste time, energy, and hope—or even become sicker—on substances that would never reach the marketplace through normal channels.

Totally free access to substances that may or may not be fraudulent is quite different from the opportunity to make informed, reasoned choices about products for which there is a reasonable expectation of effectiveness (based on preclinical or early clinical data). Clearly, persons with life-threatening illnesses are willing to assume greater risks in exchange for smaller potential benefits than other groups of patients. Expanded access programs recognize the right to assume such risks—with the advice and assistance of a personal physician—without abandoning the individual to the forces of the marketplace.

INFORMED CONSENT

Early experiences with both treatment INDs and the parallel track approach have demonstrated that several external factors can limit a person's ability to make informed, reasoned choices about participation in experimental protocols. Two of the most troublesome factors are the lack of adequate information about drug products and the shortage of health care options—for some people with HIV disease, clinical trials may represent the only opportunity for access to a knowledgeable medical team.

Information Resources

For most persons with HIV infection and their physicians, the first encounter with a new drug or treatment alternative occurs through

the lay press. Traditional attitudes within the medical establishment about publishing first in the medical literature and then in the press have been tempered with regard to AIDS because of the recognized need to get information out "on the streets" as quickly as possible. News about successful studies fosters hope and gives patients a sense of control that they might not otherwise have.

But there are also disadvantages to this strategy. Physicians who treat HIV-infected patients complain that news reports do not have sufficient clinical detail to allow them or their patients to make informed decisions. For example, the patient may be especially concerned about one particular side effect of a drug, such as fatigue. News reports rarely present specific information about the incidence of an adverse effect unless the problem is severely debilitating.

The long delay between publicity about a new therapy and the publication of peer-reviewed journal articles limits the physician's ability to add substance to the decisionmaking process. Events surrounding the establishment of a treatment IND for aerosolized pentamidine illustrate this concern. The treatment IND was issued in February 1989, simultaneously with a press release announcing the effectiveness of the therapy as prophylaxis for *Pneumocystis carinii* pneumonia. San Francisco investigators presented a formal abstract describing community trials of the treatment at the international AIDS meeting in Montreal several months later, and by late June the FDA had approved the drug for marketing. As of March 1990, however, data from the community trial of aerosolized pentamidine still had not been published in a peer-reviewed journal.[1]

Another problem with depending on the media to disseminate information is the potential for bias. Reporters may have difficulty achieving objectivity in a news report based on a press conference called by a drug manufacturer, a funding agency, or an investigator who has devoted several years to a drug study. The need for eye-catching headlines also hinders efforts to place new discoveries in perspective.

Physicians who treat HIV-infected patients have suggested several ways to improve communication about promising new drugs. One suggestion has been to encourage a standard format for press releases

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[1]Results of this trial appeared in G. S. Leoung, D. W. Feigal, A. B. Montgomery, D. Corkery, L. Wardlaw, M. Adams, D. Busch, S. Gordon, M. A. Jacobson, P. A. Volberding, D. Abrams, and the San Francisco County Community Consortium, "Aerosolized pentamidine for prophylaxis against *Pneumocystis carinii* pneumonia: The San Francisco Community Prophylaxis Trial," *New England Journal of Medicine*, vol. 323, no. 12, pp. 769–775 (1990).

that includes basic information about study subjects, methodology, endpoints, and results (the same type of information that would be included in a formal abstract). Another option is to speed up journal publication. Alternatively, an independent group could be designated to review data and present key results in an informational letter to physicians, perhaps in the *FDA Drug Bulletin*. Other options include a mechanism similar to the "Clinical Alert System" adopted by the National Cancer Institute, or a federally sponsored on-line data base that would provide relevant data from clinical trials to HIV-infected patients and their physicians.

The proposed policy statement for parallel track protocols emphasizes the development of appropriate mechanisms to educate potential drug recipients and their physicians. Initially, the sponsor must provide patients with enough information to compare the potential risks and benefits of a new drug with the risks and benefits of other treatment options. The sponsor also has the more difficult task of ensuring that information acquired during the course of a parallel track protocol—especially with regard to adverse effects—is relayed to participants as quickly as possible. Physicians involved in the early days of the parallel track protocol for ddI report that lack of such information sometimes hampered their efforts to provide appropriate care for their patients.

Access

Two different access problems may distort decisions about participation in conventional clinical trials, as well as in expanded access protocols. The first involves access to health care in general (see Chapter 7). The second involves access to specific drugs.

Primary Care

The AIDS epidemic has had a disproportionate impact on the urban poor in the United States. Socioeconomic factors associated with high rates of intravenous drug abuse, such as poverty, unemployment, and inadequate education, are also associated with higher rates of HIV infection, especially in the major population centers of the Northeast. Repeated studies have shown that access to primary medical care is inadequate for the impoverished men, women, and children who are most likely to become infected with HIV. Contributing to access difficulties is the fact that the proportion of physicians

practicing primary care specialties has dropped precipitously in this country over the past two decades. The number of physicians who are willing to provide primary care for Medicaid patients with HIV infection is extremely small.

One dilemma created by this situation is that patients may have to enter drug trials to obtain basic health care. All of the efforts by institutional review boards and others to ensure that participation in randomized clinical trials is voluntary may mean very little if the patient has no alternative form of care. Similarly, the patient's right to withdraw from a trial at any point is jeopardized if dropping out means losing touch with essential health care providers.

Parallel track protocols are unlikely to ease this situation because the primary care provider is the fundamental link between the patient and the drug sponsor. A patient cannot participate in a parallel track protocol unless his or her primary care physician certifies that the patient meets the requirements of the protocol and that all efforts have been made to use standard therapies. The physician also must agree to participate fully in patient education and to monitor the patient closely for adverse effects of the investigational drug.

Difficult Choices

Patients who are fortunate enough to have a primary care physician have an advocate in the search for an appropriate experimental therapy. Sometimes, however, a physician will learn that a patient is not eligible to receive a desired drug because he or she does not meet the entry criteria for relevant protocols. A San Francisco physician who encountered this situation recently polled his colleagues about how they would handle it. A surprisingly large number replied that they would ignore the entry criteria and, if necessary, falsify laboratory data rather than deny the patient access to a potentially beneficial drug.

Discussions about misrepresentation in clinical trials have focused mainly on patients who knowingly take drugs that are not authorized by a study protocol or who surreptitiously have their drugs analyzed to determine whether they have received the investigational drug or a placebo in a blinded study. The informal poll described above indicates that the problem could go much deeper. Open-label studies, such as the parallel track protocol, are especially vulnerable to misrepresentation because regulators and sponsors keep reporting requirements to a minimum.

COMPETING RIGHTS

Every time a patient or physician misrepresents a patient's clinical status to enroll the patient in a drug trial, the quality of data collected in that trial diminishes. For example, a study protocol might be designed to assess whether patients who have failed to improve on standard therapies benefit from a new investigational drug. If a patient gained entry to such a study without trying standard therapies, information related to that patient would distort conclusions drawn from the entire trial. Improvement in the patient's condition would be regarded as evidence that the drug had the potential to help a certain group of patients—those who had failed to respond to other measures—when in fact the evidence did not pertain to that group at all.

If many patients and physicians choose to follow this course, future patients will not have accurate information on which to base their own choices about treatment alternatives. The tension between the needs and rights of today's patients and the needs and rights of future patients is an unfortunate corollary of the drug evaluation process. The only way to obtain accurate information about the risks and benefits of an unknown agent is to introduce it through a series of careful, methodical clinical trials. Understandably, however, today's patients often view immediate access to a potentially beneficial drug as a higher priority than the gathering of information for future patient populations. (Sometimes, however, participants in trials are also direct beneficiaries of the results. For example, when the recent trial of AZT in patients with asymptomatic HIV infection was terminated, more than 90 percent of the participants had not yet developed AIDS and were immediately offered AZT.)

Organized expanded access may help resolve this conflict, but only if parallel track protocols do not interfere with enrollment in conventional clinical trials. Patient advocates suggest that one way to increase patient accrual in conventional trials and to decrease the risk of misrepresentation is to include patients, their advocates, and their primary care physicians in the planning of each protocol. Patient representatives can provide important insights into the factors that make a particular trial more or less appealing to the target population.

INSTITUTIONAL REVIEW BOARDS

Expanded access reflects some underlying changes in the philosophy of drug regulation, and these changes will be mirrored in the functioning of institutional review boards, the local organizations charged with protecting the rights of individuals who participate in clinical trials. These changes are subtle and do not call for eliminating the traditional concerns of IRBs; they may, however, challenge IRBs to modify and revise some commonly held principles.

First, there has been a shift in emphasis from nonmaleficence to beneficence; that is, from preventing harm by protecting patients from risk to actively promoting patients' welfare by providing them earlier and broader access to experimental drugs.

Second, a different aspect of patient autonomy is receiving more emphasis. IRBs have always been concerned with patients' rights—to be free from subtle or overt coercion in making decisions about whether or not to participate in a research protocol, to have full information to make informed choices, and to take the risks associated with participation in protocols, as long as those risks are understood. Recently IRBs have had to recognize that many patients are more concerned with their right to take serious risks than with their right to be free from coercion.

Finally, IRBs will have to adjust their perspective on the selection of subjects for participation in trials. Traditionally, IRBs have acted to protect individuals and groups from being included in trials simply because they were easily accessible—for example, prisoners—or because they were vulnerable—for instance, drug users or pregnant women. Today, when patients believe that participation in clinical trials offers substantial promise of benefit, these restrictions may be viewed as discriminatory rather than as protection from harm.

NEW ATTITUDES

The effect of the AIDS epidemic on drug regulators has not received a great deal of attention, but some observers suggest that calls for expedited development and early expanded access could have a major impact on the way regulators view their own responsibilities. For decades, regulators and drug sponsors have had an almost adversarial relationship. Sponsors produced and organized huge amounts of data and presented it to the FDA for evaluation. The FDA played the devil's advocate, often focusing more on the potential for adverse effects than on the potential benefits of a candidate drug. Regulators were rewarded for refusing marketing privileges to a drug or device that later turned out to be harmful; there were no comparable rewards for making a beneficial drug available quickly.

Advocates for patients with many different diseases have complained that the traditional system placed too much emphasis on caution. But some scientists and legislators worry that new procedures could err in the other direction. If FDA officials become deeply involved in the design of drug protocols, will they still be objective when the time comes to evaluate the data generated by those protocols? If a protocol does not exactly answer the questions that must be addressed to assess safety and efficacy, will the regulator who helped shape the protocol be willing to turn to sponsors and suggest starting over?

Identifying promising drugs and getting them to the marketplace as quickly as possible are extremely worthwhile goals, but everyone should be aware of the potential costs as well as the potential benefits. For example, the new emphasis on expedited development greatly increases the demands on postmarketing testing and surveillance systems. Drugs could be approved for marketing even if some questions remained about the most effective ways to use them. Physicians who treat patients with drugs approved through expedited review must understand the importance of responding quickly to all requests for information and of relaying all questions and concerns to drug sponsors as they arise.

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EVALUATION OF EXPANDED ACCESS PROGRAMS

Scientists have only begun to formulate the questions that will need to be addressed to determine whether the benefits of very early access to AIDS drugs exceed the risks. Experience with the treatment IND program and with other forms of early access may help guide the evaluation process.

TREATMENT INVESTIGATIONAL NEW DRUGS

The treatment IND regulations issued by the FDA in May 1987 were greeted with great enthusiasm by persons with AIDS and their advocates. They viewed the regulations as a dramatic shift in FDA policies that would allow hundreds or thousands of patients to gain access to investigational drugs. Three years later, however, many AIDS activists consider the program a failure. Although six treatment INDs for AIDS-related drugs have been approved, the activists say that the treatment IND accomplishes too little, too late.

The underlying problem, described in Chapter 1, is that patients and FDA officials had very different expectations about what the treatment IND would accomplish. FDA officials regarded the rules as an opportunity to make drugs available to patients with life-threatening conditions and no treatment alternatives, but only after the acquisition of clinical evidence that a drug was relatively safe and probably effective. Early charts produced by the FDA showed that approval of a treatment IND would be most likely for drugs nearing the end of the traditional phase 2 clinical trial; or, if the condition

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This chapter is based on the presentations of Robert Temple, Jay Lipner, Lawrence Corey, Raphael Dolin, Bernard Lo, Jerome Birnbaum, and Susan Ellenberg.

was "serious" but not life-threatening, the treatment IND might be approved during the phase 3 trial. AIDS patients, on the other hand, expected the treatment IND to make drugs available at a very early stage of development.

Problems with the treatment IND demonstrate the importance of early and consistent communication. Efforts to include patients, primary care physicians, and AIDS activists in the planning process might prevent similar problems from arising with the new parallel track program.

POTENTIAL RISKS

Drug regulators have indicated their willingness to begin parallel track programs concurrently with the beginning of phase 2 trials. Patients and their physicians must understand, however, that scientists may have very little information about the potential adverse effects of a drug at that time.

Consider, for example, a phase 1 trial involving 20 patients. Statisticians explain that even if no serious toxicities were observed in those 20 patients, the upper 95 percent confidence limit for the true serious toxicity rate would be 17 percent (as many as 1 in 6 patients might experience a severe toxic reaction). Even if the phase 1 trial were expanded to 40 patients with no adverse effects, the true toxicity rate could be as high as 9 percent.

If physicians observed one serious reaction among 20 patients in a phase 1 trial, the observed rate would be 5 percent, but the true rate could be as high as 25 percent. A patient considering enrollment in a parallel track protocol might feel very differently about a 1-in-20 chance of a severe adverse reaction than about a 1-in-4 chance.

Examples from the Past

A study in the early 1970s of a potential treatment for herpes encephalitis provides a more graphic illustration of some of the problems that can arise with expanded access protocols. Herpes encephalitis is a life-threatening infection of the brain caused by the herpes simplex virus. In the late 1960s and early 1970s, about half a dozen case reports in the medical literature described treatment of this disease with a new drug called 5-iododeoxyuridine (IUDR). Scientists had a strong rationale for IUDR's antiviral effects and there were no treatment alternatives, so the FDA quickly approved an

open-label IND. Infectious disease specialists came to regard IUDR as the treatment of choice for herpes encephalitis and administered it to more than 70 patients under the open-label IND.

After several years, however, investigators decided to take a closer look at the drug's effects. Despite the objections of some early pioneers in the field, they organized a small placebo-controlled, randomized study. (The pioneers had believed that a placebo-controlled trial would be unethical because of existing clinical evidence in favor of the drug.) The results of the placebo-controlled study were striking. Of the 12 patients who received IUDR, 9 had some evidence of serious toxicity (an estimated 3 to 5 died as a direct result of the drug's adverse effects on bone marrow). Moreover, autopsy results in 4 patients who received IUDR showed that the patients had virus in the brain at the end of therapy. This example shows that even those who are acknowledged experts in a medical field may have difficulty predicting the benefit/risk ratio for a new investigational drug.

The Target Population

Physicians enrolling patients in expanded access protocols also should understand the potential impact of demographic differences on the outcome of clinical trials. These differences are important first in interpreting risk based on phase 1 trials and later in comparing phase 2 clinical trials with corresponding parallel track protocols.

Conventional clinical trials generally have very specific requirements with regard to the health status of prospective subjects. Scientists want to be able to see the effects of an investigational drug with a minimum of interference from other drugs, from confounding diseases, or from other risk factors. In HIV infection, age and overall health status affect survival and the rate of progression of disease; nutrition, past smoking history, and past occupational status affect the frequency of disseminated opportunistic infections (especially fungal and mycobacterial infections). To control for these differences among patients, differences that could confound the findings of a study, most investigators attempt to make their study populations as homogeneous as possible. In contrast, parallel track protocols enable thousands of patients with diverse backgrounds and medical histories to get access to drugs after minimal testing in a highly selected subgroup. The incidence of adverse effects in patients weakened by repeated battles with *Pneumocystis carinii* and other microorganisms, or by the effects of intravenous drug abuse, could be very different from that observed

in the relatively healthier population characteristic of the phase 2 trial.

The recent controversy over ddI illustrates some of the problems that can arise when people try to make direct comparisons between expanded access programs and conventional phase 2 trials. In March 1990, a spokesman for Bristol-Myers Squibb told a reporter from the *New York Times* that the death rate among patients in the parallel track protocol for ddI was 10 times higher than the death rate among patients enrolled in phase 2 trials of the drug. Of the almost 8,000 patients enrolled in the expanded access program, 290 had died; in contrast, only 2 of 700 patients in the phase 2 trials had died.

These figures were used to illustrate the dangers of expanded access, and physicians received hundreds of telephone calls from worried patients. Yet initial reviews of the data indicated that most or even all of the disparity might be due to the fact that patients in the expanded access program were sicker to begin with than patients in the clinical trials. With the exception of six deaths from pancreatitis (five in the expanded access program and one in the phase 2 trial), the deaths seemed to result from natural progression of the disease. (However, complete data from both protocols have not yet been published.)

The expanded access protocols for ddI were designed for patients who could not meet eligibility requirements for participation in the clinical trials. The majority have been intolerant of or unresponsive to zidovudine (AZT). Many cannot participate in the conventional trials because they are taking medications such as gancyclovir to fight severe opportunistic infections. Others are too sick to undertake the time and travel commitments necessary for participation in a traditional drug trial. All of these characteristics are indicative of progressive disease.

Safety Data

The proposed policy statement on the parallel track developed within the Public Health Service indicates that all physicians participating in a parallel track protocol should be required to report safety data (the collection of efficacy data depends on the specific protocol; see Chapter 4). Some observers have suggested that this requirement is too stringent—that mandatory reporting should not be part of a program designed primarily to increase access to therapy for desperately ill patients with no treatment alternatives. They worry that even minimal reporting requirements will discourage participation

by physicians and by drug sponsors (who assume financial responsibility for data collection).

Although these concerns are genuine, they represent a failure to appreciate the risks involved in widespread use of minimally tested agents. Failure to request reports of serious events in the parallel track could delay recognition of severe side effects for months or even years, increasing potential risks for patients enrolled in both research and open protocols.

IMPACT ON CONVENTIONAL RANDOMIZED TRIALS

In addition to worries about safety, critics of the parallel track have expressed great concern about its effects on enrollment in traditional clinical trials. Randomized, controlled trials provide definitive information about the relative risks and benefits of new therapies. Sponsors must have such information to seek approval for marketing from the FDA. Marketing, in turn, is the most efficient way to make a drug available to large numbers of people.

The critics are concerned that patients will enter the parallel track to avoid the uncertainty of a randomized trial. They refer to news articles about individuals who have sought outside help to identify drugs they receive in blinded studies as evidence that patients will not participate in a traditional clinical trial if other options are available. Supporters of the parallel track believe that current screening mechanisms are sufficient to separate people who are eligible for clinical trials from those who are eligible for the parallel track. They suggest that improved patient education and better trial design (see Chapter 4) will ensure patient accrual in the randomized trials and, at the same time, allow patients who are ineligible for clinical trials to receive experimental drugs through expanded access programs.

The experience with ddI highlights some early mistakes. Bristol-Myers Squibb received the exclusive license for ddI from the National Cancer Institute (NCI) in mid-1988. During the late summer and early fall of 1988, the NCI and Bristol-Myers Squibb sponsored four separate phase 1 trials of the drug. These trials produced a reasonable expectation that ddI was efficacious against HIV and that it was safe enough to allow expansion of a clinical program.

The company worked with the NCI, the National Institute of Allergy and Infectious Diseases (NIAID), and the FDA to develop appropriate phase 2/3 trials. At the FDA's request, the company submitted a proposal for a treatment IND; it also worked closely with AIDS patients and their representatives to develop a prototype

parallel track protocol. The FDA approved the phase 2/3 trials and the expanded access protocols on September 28, 1989. The first patient was placed on the expanded access protocol on October 12. The drug was shipped to the first phase 2 investigators on October 11, but actual enrollment of patients did not begin until October 20.

Many observers believe that the lag time between the start-up of the parallel track and the beginning of the phase 2/3 trials may have distorted the enrollment process. Patients who were eligible for the clinical trials entered the parallel track because ddI was not available any other way (excessive expectations for ddI created by the news media may have been partly responsible for this problem). An important lesson for future parallel track programs has been learned, that is, to ensure that enrollment in clinical trials precedes or coincides with the release of drugs through the parallel track protocol.

To this day, much controversy remains over the question of whether or not the availability of ddI through the parallel track has adversely effected accrual to the three clinical trials of ddI (protocol 116, a comparison of AZT versus ddI in recently diagnosed AIDS and ARC patients; protocol 117, a comparison of AZT versus ddI in patients who have been on AZT for longer than 12 months; and protocol 118, a dose-escalating trial of ddI in AIDS-intolerant persons). Views range from the belief that the expanded access program had very little effect on accrual to the trials, to the belief that the expanded access program has had a disastrous effect. As of January 1991, there were more than 14,000 patients receiving ddI through expanded access programs and approximately 1,600 patients participating in the trials, which are about 75 percent filled. Most scientists associated with the trials seem to feel that some eligible patients must have been diverted from the trials by expanded access. They assert that, although the rates of accrual to the ACTG trials of ddI have been similar to rates for trials of other AIDS drugs, without the competing availability of ddI through expanded access these trials would have recruited patients much more quickly.

THE PARALLEL TRACK EXPERIMENT

Although expanded access has been part of the drug evaluation system for many years, the formal parallel track approach is new. The proposal for the approach states that the entire parallel track program for AIDS drugs should be regarded as a pilot test. Many investigators would like to see mechanisms built into the program to answer questions about differential toxicity rates and about the impact

of the parallel track on clinical trials. The Public Health Service plans to organize a working group to assess the parallel track concept, but their task will be quite difficult unless data collection and certain evaluation strategies are incorporated into parallel track protocols from the beginning.

The extent of data collection efforts to be included in the parallel track is a complex issue. Ideally, basic demographic data and some clinical indicators of efficacy and toxicity should be collected in a format similar to that used for conventional clinical trials. It may be difficult, however, to convey state-of-the-art staging information to the broad spectrum of physicians who wish to enroll patients in the parallel track. Given that the primary goal of the parallel track is to make drugs accessible to desperately ill patients, sponsors must strive to obtain basic information without discouraging physician participation.

One option may be to arrange for a subset of patients in the parallel track to be followed by persons or institutions who are also involved in conventional trials of a candidate drug. Academic medical centers, CPCRA groups (members of the Community Programs for Clinical Research on AIDS), and other community-based research groups could be recruited for such a task. Data collection on these patients would be more comprehensive than that required for other parallel track participants but not as extensive as that specified for the ACTG trials. This strategy would permit comparisons of outcome and toxicity on two different levels: (1) between subjects enrolled in clinical trials and the subgroup of parallel track participants followed in a fairly rigorous fashion and (2) between the subgroup and the larger population of parallel track patients. The results could give government scientists, drug sponsors, and HIV-infected patients and their physicians a foundation for evaluating the parallel track program.

4

CREATIVITY IN CLINICAL TRIALS

Each month physicians participating in the expanded access protocols for ddI submit status reports on their patients to the drug sponsor and, in return, receive new supplies of the drug. The clinical and laboratory data enable the sponsor and government scientists to monitor the course of the protocols—especially with regard to safety concerns as described in Chapter 3. But the availability of these data also raises questions about the role of expanded access in the drug evaluation process. Can the information gathered through expanded access be used to speed or enhance the evaluation of AIDS drugs?

The answer to this question depends on a host of medical, scientific, and financial issues. Chapters 5 and 6 examine the costs of the parallel track approach for drug sponsors, patients, and third-party payers. This chapter explores the drive for innovation in clinical trials and the possibility of including expanded access protocols as part of the broad spectrum of drug evaluation mechanisms.

THE CHANGING ENVIRONMENT

Since the beginning of the AIDS epidemic, persons infected with HIV and their advocates have complained about the conservative nature of the drug development and evaluation process. Many have viewed the strict entry criteria for these clinical trials as an unreasonable barrier to participation. The problem grows worse as greater numbers of patients reach the advanced stages of HIV

This chapter is based on the presentations of Lincoln Moses, Lawrence Corey, Melanie Thompson, Marvin Zelen, Floyd J. Fowler, Susan Ellenberg, and Ellen Cooper.

infection. Each new opportunistic infection decreases the chances that a patient will qualify for entry into a desired clinical trial. One physician reports screening 80 to 100 patients to find 5 who qualified for any of the formal clinical trials of ddI. Another physician screened 275 patients to enroll 35 in the ddI trials. The extensive screening procedures slow patient accrual and lengthen the time required for completion of clinical trials. Moreover, when patients are excluded from a trial investigators lose the opportunity to learn anything from those patients, including information about drug-drug or drug-disease interactions, and how sicker patients respond to the drugs under study.

Some scientists also question the relevance of clinical trials conducted with a highly selected subgroup of the population. As HIV-infected patients live longer, their clinical histories become more diverse; they have different opportunistic infections and receive different combinations of drugs. Clinical trials that ignore these differences—that focus exclusively on a homogeneous group of patients—may not provide an accurate perspective on the drug's performance in the real world.

Most government scientists, academics, and patient representatives agree that there are many opportunities for greater creativity in the clinical trials process. Scientists are exploring new ways to modify the standard three-phase approach to drug evaluation—to improve efficiency without undermining the reliability of results. Other proposals include establishing preference trials, devising large-scale trials with broad eligibility requirements and limited data collection (similar to the International Studies of Infarct Survival in Europe), and gathering data through the parallel track.

CONVENTIONAL TRIALS

Decades of experience indicate that conventional randomized controlled clinical trials (RCT) are the most reliable and informative way to obtain information about the safety and efficacy of an investigational drug. The IUDR story in Chapter 3 is just one example of a situation in which randomized study of a small group of patients revealed that a highly regarded treatment was not accomplishing its goal. The Cardiac Arrhythmia Suppression Trial, or CAST, provides another relevant case history.

The CAST effort involved two drugs, encainide and flecainide, both known to suppress irregular heartbeats in patients with heart disease. Many physicians believed that these drugs should be administered widely to patients who had suffered a heart attack (because deaths following a heart attack often result from irregular heart rhythms) and that it would be unethical to conduct a placebo-controlled trial in which some patients would not receive the drugs. A randomized trial was begun, however, and the results were startling. The trial demonstrated that the drugs did, indeed, reduce irregular heartbeats compared with placebo, but they also increased mortality among patients who had symptomatic but not life-threatening rhythm abnormalities.

The strength of RCTs lies in the fact that they are structured to eliminate as many extraneous differences as possible between the groups being compared. This can be accomplished by applying very carefully devised inclusion and exclusion criteria, carefully following a protocol, and, of course, assigning patients randomly to treatment arms. These procedures are especially important in HIV infection, which has an erratic clinical course and many different patterns of illness.

The challenge for AIDS investigators is to retain the advantages of traditional clinical trials and at the same time reduce entry restrictions. The AIDS Clinical Trials Group has established a Protocol Evaluation Subcommittee to explore ways to make trials more efficient and flexible. The Statistical Working Group of the ACTG is also working to broaden entry criteria for clinical trials and to speed their progress. Scientists writing new protocols have been encouraged to reduce requirements for laboratory tests and to shorten reporting forms.

But there are limits to these approaches. Some research questions require a high level of technological expertise. On the other hand, the academic medical centers that possess this expertise may not have the facilities to provide care for the full spectrum of HIV-infected patients. (Chapter 7 explores the limitations of some traditional clinical trial sites in providing care for women and people of color.) The establishment of the Community Programs for Clinical Research on AIDS (CPCRA), described in Chapter 1, is based on the concept that HIV infection raises many different types of research questions. Some are best answered within the confines of a traditional clinical trial; others are more appropriate for large, simple randomized trials in which the bulk of the patient population is treated in the community. "Low-technology" randomized trials, combined with expanded access programs, offer an opportunity to learn something from all segments of the population infected with HIV.

PREFERENCE TRIALS

Before addressing the positive features of the large, low-technology trial, it is important to examine the pros and cons of one other experimental design, the preference trial. The preference trial is based on the concept that when treatments are tested only on select subsets of patients and a treatment effect is observed, doubt remains about how the treatment will work for most patients under less controlled circumstances. Therefore, proponents of preference trials argue that studies of broad ranges of patients under varying conditions are necessary to discover how well treatments really work.

Patients may also have very different "utilities" with regard to the risks and benefits of experimental therapies. For example, an HIV-infected patient may feel that the reduced energy level associated with one investigational drug is preferable to the nausea and vomiting associated with another. Alternatively, on a more serious plane, patients may feel that the risk of a very severe adverse reaction in the present is worth the potential benefits of a decade or more of disease-free survival. Supporters of preference trials believe that ethical research should take account of patients' values, a factor that randomized drug trials generally fail to consider.

These supporters propose trials in which all patients who might benefit from an experimental therapy are given an opportunity to choose between the new therapy and other treatment options. The investigator's role would be to provide patients with as much information as possible about the potential risks and benefits of each option, and then to collect data about the patient's health status and quality of life as the trial progresses. The underlying assumption is that individual values would lead patients with almost identical characteristics at the beginning of a trial to choose different treatment options. At the end of the study, comparisons of the outcomes associated with each choice would enable scientists to estimate the relative safety and efficacy of the investigational drug.

Supporters of such trials say they have many potential advantages: (1) patients would be more likely to comply with treatment regimens that they have selected themselves; (2) patient accrual would be rapid because no patients would be turned away; (3) the subject population could reflect the broad spectrum of HIV-infected patients; and (4) the process of informing patients about potential risks and benefits would mirror events in the "real world" of clinical practice.

Critics argue that previous experience in drug investigation indicates that nonrandomized trials do not give reliable results. Too many factors can influence drug choice and clinical outcome. For example, rapid shifts in the popularity of certain underground drug therapies among HIV-infected persons demonstrate the power of a social network in influencing patient decision making. In addition, when patients choose their own treatment options, there may be important differences among the treatment groups that influence outcome. Even very sophisticated statistical techniques cannot control for all such effects; experience indicates, in fact, that many important factors are unknown or unquantifiable.

Scientists opposed to preference trials say it would be deceptive and unethical to tell patients in a nonrandomized study that they are contributing to advances in drug therapy because the data collected in such trials do not provide definitive answers to basic questions about drug efficacy. But scientists who are currently experimenting with preference trials answer that blind insistence on randomized controlled trials as the only appropriate method for evaluating drugs has limited our ability to discover the true value of most of the treatments available today—because such trials are costly, difficult to complete, and, when completed, apply only to the particular subset of patients who met eligibility criteria. They believe that there are "good" and "bad" studies of all kinds and that alternatives to RCTs must be judged by how well they answer important questions and by the quality of their execution.

LARGE, SIMPLE RANDOMIZED TRIALS

Some of the positive features of the preference trial, such as broad patient participation, could also be achieved through large-scale, "low-technology" randomized trials similar to those developed in Europe to study cardiovascular diseases. These trials have involved endpoints that are easy to measure (such as survival or stroke) and limited data collection (the minimum possible to achieve satisfactory results). For example, in the International Studies of Infarct Survival (ISIS), tens of thousands of patients in many different health care settings were randomly assigned to groups to explore ways to increase survival after heart attacks. The second ISIS trial, ISIS-2, demonstrated that streptokinase and aspirin were both highly effective (compared with placebo) in reducing cardiovascular mortality after an acute myocardial infarction, and that the two agents together were significantly better than either agent alone. These effects were recognized despite the fact that patients had a wide range of background treatments (beta blockers, nitrates, and calcium channel

blockers) and prognostic variables. The large size of the study ensured comparability of the patient groups.

Most of the European trials have involved drugs with known toxicities administered on a one-time basis (so compliance was not an issue), but some scientists believe that the format could be adapted to study HIV-related disorders. Large-scale trials among AIDS patients with broad eligibility requirements and streamlined data collection might be appropriate for answering questions about the optimal dosage (quantity and schedule) of an antiviral drug, drug combinations, drug interactions (especially with regard to prophylactic agents and treatments for opportunistic infections), and drug resistance.

With careful planning that emphasizes a factorial design,[1] virtually any HIV-infected patient who was willing to consent to randomization and who had access to a skilled primary care physician could be included in a trial of some kind. The idea would be to have an available trial for every AIDS patient. Data collection would focus primarily on such clinical endpoints as opportunistic infections, fevers, intractable diarrhea, HIV wasting syndrome, changes in stage of disease, important adverse reactions, and survival.

Registration could take place by telephone. A physician would call a central registration number and provide some initial data on the patient's medical history. The registrar would assign the patient to a protocol and, within 24 hours, send out patient consent forms, details of the protocol, drugs, and reporting forms.

Physician Participation

Large-scale AIDS trials would require the cooperation of many different segments of the health care community. Designated members of CPCRA and other community-based research groups would be logical sources of health care providers for these trials, but the ultimate goal would be to include independent physicians and their nursing and laboratory support staffs. One scientist suggests creating a roster of community physicians who have demonstrated their interest in the research process by attending special AIDS workshops or seminars. Workshop topics might include available protocols, patient

[1] A factorial experiment is one in which several factors are evaluated at the same time. For example, the effects of a drug may be evaluated by simultaneously varying doses and schedules; this is an example of a two-factor experiment. Factorial designs promote efficiency by addressing multiple questions simultaneously, including questions of drug-drug interactions.

consent, the collection of a core data set, staging, and ways to increase patient compliance.

For maximum efficiency, the link between specialists and primary care physicians could be maintained through a specialized computer network. The capability exists to develop extensive computer networks consisting of educational programs, bulletin boards with up-to-date information about ongoing trials (including special alerts about unexpected side effects), and electronic mail for direct access to medical consultants, nursing consultants, and data collection specialists.

Quality Control

One of the biggest challenges for the designers of large-scale AIDS trials would be to develop mechanisms for monitoring the quality of data. In addition to the usual data management strategies, some observers have suggested establishing auditing teams to visit participating physicians at random (primarily to compare patient records with information submitted to data collection centers).

DATA FROM THE PARALLEL TRACK

It is difficult to predict the ultimate importance of data collected through the parallel track and treatment INDs. Rapid implementation of large-scale randomized studies could greatly reduce the need for programs designed solely to increase access because most patients who could not qualify for current clinical trials would be eligible for trials with broadened eligibility requirements.

Efficacy Data

Whatever their size, parallel track programs are unlikely to provide substantial information about the efficacy of drug candidates. The value of data on efficacy depends on the existence of an adequate comparison or control group. The parallel track, as it is defined in the proposed PHS policy statement, does not make provisions for control groups of any kind. Although some researchers believe that important information on efficacy could be obtained using historical controls, many others feel that this method is flawed because of the dramatic changes in the treatment and prophylaxis of HIV-related

disorders, in the proportions of patients from different risk groups, and in disease manifestations within risk behavior groups.

Safety Data and Related Information

The situation is quite different with regard to safety data. If early parallel track and treatment IND programs remain the only alternatives to conventional clinical trials, they could play a vital role in the identification of important adverse reactions. Some believe that they also could provide some information about "real-world" drug interactions and drug resistance.

The value of data from an individual parallel track protocol would depend on the provisions made for data collection and for monitoring data quality. There are two basic types of data collection: event driven and regular reporting (according to a predetermined schedule). In event-driven reporting, physicians fill out reports only when they observe an outcome of interest, such as an unexpected adverse event. Event-driven reporting places the least possible burden on the practicing physician (because most patients proceed through treatment without experiencing a reportable event); however, the method does not provide any basis for determining the accuracy of estimated event rates. Lack of reports could mean either that no reportable events occurred or that physicians failed to comply with reporting procedures. Requiring physicians to make regular reports substantially reduces the problem of underreporting (although it does not eliminate it entirely). Regular reporting may be crucial for situations in which thousands of patients receive very early access to an experimental agent.

The quantity of data required would depend on the drug candidate. Expanded access programs involving drugs in the final stages of the evaluation process (such as the former treatment IND for AZT), or drugs that had been tested in other contexts, might require less data from participating physicians. Reporting requirements would be more stringent for drugs that did not have an established safety record.

Monitoring the quality of data from the parallel track as a whole could be very difficult, even with regard to reporting of adverse events. A possible strategy might be to use selected subgroups of parallel track participants (such as those described in Chapter 3) to make comparisons between safety data from the parallel track and safety data from corresponding clinical trials.

Expectations

Government scientists and others caution against unrealistic expectations about the types of questions that could be answered through the parallel track. Some have expressed concern that excitement over nonrandomized expanded access protocols could detract from efforts to revitalize and improve randomized clinical trials. For example, the "safety valve" represented by the parallel track might relieve pressure to modify exclusion criteria or to take other actions that would make conventional trials more effective.

Widespread distribution of a drug through early expanded access programs also could lead to inordinate pressures to approve drugs for marketing before scientists have gathered adequate clinical evidence of safety and efficacy. The simple presence of a drug in the patient population could lead to a presumption of effectiveness that might be very hard to dispel. Such pressures might result in approval of a drug for a tightly defined patient group, such as patients intolerant to or failing standard therapies. Experience indicates, however, that once a drug is in the marketplace some physicians will use it in ways that are not supported by any data in the hope that it will have greater benefits (with acceptable toxicity) than standard treatments.

5

DRUG INNOVATION AND THE PHARMACEUTICAL INDUSTRY

Treatment INDs for ddI and several non-AIDS drugs demonstrate that some large pharmaceutical companies have the resources to distribute investigational drugs to thousands of patients across the country, but new expanded access programs could test the limits of these resources. Industry spokespersons have expressed concern that expectations created by parallel track and other expanded access programs could begin to affect the way in which companies make decisions about product development. In the most troublesome scenario, companies would weigh expenses associated with expanded access against future profits and decide that AIDS drugs simply did not represent a good investment. As a result, some potentially successful AIDS therapies would not be developed.

The effects of adverse incentives created by expanded access would be evident first in smaller companies, particularly the fledgling biotechnology firms. These companies have the expertise to make major strides in the new field of rational drug design, but they may not have the resources to sustain premarket drug distribution.

Ultimately, the impact of expanded access on drug innovation in AIDS will depend on three issues: (1) the possibility that expanded access programs might delay commercialization of target drugs or of other drug candidates, either by raising safety concerns or by creating an environment in which controlled trials cannot be carried out; (2) the extent to which expanded access programs increase the direct costs of drug development; and (3) the perception of risk associated with expanded access, particularly with regard to product liability.

This chapter is based on the presentations of Patrick Gage, Stephen Sherwin, Jerome Birnbaum, Paul De Stefano, Lawrence Corey, and James Eigo.

Treatment IND regulations stipulate that under some circumstances a manufacturer may charge for an experimental drug, but solely to recover costs. The proposed policy statement for the parallel track contains a brief reference to the treatment IND ruling but does not explore further the issue of drug costs. The policy of the Pharmaceutical Manufacturers Association is that the drug sponsor should bear the cost of any drug administered before market approval—in clinical trials or through expanded access protocols. So far, only one sponsor of an AIDS drug has sought payment under existing IND regulations.

TIME TO COMMERCIALIZATION

Previous chapters have emphasized the importance of making sure that expanded access programs do not delay FDA approval of effective drugs by slowing patient accrual in randomized clinical trials. After all, access to a drug is greatest when the drug is on the pharmacist's shelf. Pharmaceutical manufacturers also are concerned about the possible loss of income. In most cases, manufacturers do not begin to make a return on their investment in a drug until the FDA has reviewed all safety and efficacy data and approved the drug for marketing. Thus, the perception that a government agency might request an expanded access protocol for a drug and that such a protocol could delay the time to commercialization might lead a manufacturer to forgo development of that drug.

A spokesman for Bristol-Myers Squibb notes that time and energy invested in the expanded access protocols for ddI have caused delays in market approval for two other drugs, both antibiotics in the late stages of clinical development. He says that the opportunity cost associated with these delays—the nonrecoverable loss of future sales resulting from reductions in useful patent life—might emerge as the largest single cost factor of the expanded access effort.

DIRECT COSTS OF EXPANDED ACCESS

A brief recounting of Bristol-Myers Squibb's experience with ddI demonstrates the full range of expenses associated with an effective expanded access program. At the request of the FDA, the company submitted a treatment IND application for ddI on August 15, 1989.

Manpower Needs

A company spokesperson recalled the coordination required to provide physicians and potential recipients of ddI with necessary information, to evaluate patient eligibility, and to manage the vast quantities of data generated by the expanded access program.

> In July of 1989 we had decided to locate our ddI (trade named Videx) product information center for expanded access at our U.S. Pharmaceutical Division at Evansville, Indiana. The objective was to be operational by early September.
>
> We immediately assembled a project team. Our Medical Department gathered and organized the information necessary to manage the expanded access project and worked with our Research Division and the FDA to develop and process the ddI protocols.
>
> Our Operations Group had the task of finding a building to house the information center and equipping it. Customer service representatives and other personnel were hired and trained. The staff at MIS [Management Information Systems] designed the computer system needed to handle physician and patient data. Our Marketing Group coordinated the information and communications elements. The Clinical Supply Group in the Research Division made preparations for the actual distribution of the drug.
>
> Just 35 days after the project started, the Videx Information Center was a reality. To date, our ddI hotline has handled over 30,000 calls from physicians and patients. We have sent out 3,566 ddI binders and enrolled 7,545 patients [as of March 11, 1990].
>
> The system works as follows: The physician calls our AIDS hotline. A data package and enrollment forms are sent the same day. The physician returns the completed forms, and the Center's medical staff evaluates the forms for patient eligibility. Within 72 hours of receiving the application, a month's supply of ddI is shipped or the physician is advised of patient ineligibility. Follow-up information from day 15 is provided to Bristol-Myers Squibb by day 30. Drug supplies for the second month are shipped upon receipt of this information.

In short, Bristol-Myers Squibb renovated a building, established warehouse space and shipping facilities, installed a comprehensive communications system, developed a computer system for data storage

and retrieval, and set up hard-copy record storage. In addition, they produced a four-part ddI registration kit that included study protocols, patient eligibility information, the necessary registration documents, and the ddI investigator's brochure.

Additional manpower costs (primarily medical and regulatory affairs personnel) have been devoted to monitoring the expanded access program. For example, the company has established a system of onsite protocol audits to gauge reporting of adverse effects. Professional staff also make a concerted effort to keep clinical investigators in the ACTG, government scientists, and AIDS patients and their representatives informed about any new developments in the various clinical trials and expanded access protocols.

Drug Costs

The drug itself is a major cost factor. Early in development, the unit cost of a drug is high because the manufacturer has not had an opportunity to optimize strategies for formulation, packaging, labeling, quality control, and shipping. Also, the volume of production may be relatively low, so the manufacturer cannot take advantage of economies of scale.

Drug costs in expanded access programs for AIDS drugs may be particularly high because thousands of patients require long-term treatment. The need to formulate drugs in different dosage strengths also adds to the cost. Bristol-Myers Squibb has produced ddI in three different dosages to accommodate patients of different weights.

The Small Manufacturer

Large pharmaceutical companies, such as Bristol-Myers Squibb and Burroughs Wellcome (the manufacturer of AZT), appear to have the manpower and financial resources to manage expanded access protocols, at least in the short term; this may not be true for smaller firms. A spokesman for Genentech (the largest of the new biotechnology companies) noted that most small companies would have difficulty marshaling the manpower required to provide administrative support for the parallel track.

Companies like Genentech often have to seek outside funding (for example, R&D [research and development] limited partnerships) to finance basic clinical trials and to support the documentation tasks required for FDA approval. The demand created by expanded access

protocols would be a further drain on resources. Biotechnology companies would have to begin the difficult process of scaling up production of recombinant proteins long before they had any chance of generating revenues. In some cases, they might have difficulty producing sufficient quantities of a drug for both randomized trials and expanded access.

These concerns have led one biotechnology executive to suggest a cost-recovery program in which companies would be permitted to charge for expanded access drugs. The arrangement would be similar to that described in the treatment IND and medical device regulations. This kind of program, however, would be effective only if patients had some mechanism to pay for the drugs, either through government sponsorship or through expansion of private health care coverage (see Chapter 6).

Patient advocates and some scientists involved in the drug development process are uncomfortable with this proposal. They say that most administrative costs associated with expanded access could be recaptured when a candidate drug receives market approval; for example, physician and patient education programs and drug distribution mechanisms in the parallel track could become the core of the commercial marketing program.

Critics also express concern about the potential of expanded access to distort the clinical trials process. If manufacturers could recoup costs prior to market approval, wide distribution under a treatment IND or parallel track might become a goal in itself. Companies might have less incentive to complete randomized trials to collect definitive evidence about the safety and efficacy of a drug.

For now, the latter concern is primarily theoretical. The basic cost issues, however, represent a practical barrier that may have to be addressed more fully by the architects of the expanded access concept.

PRODUCT LIABILITY

Smaller companies also are exceedingly sensitive to the potential for expensive legal actions. In the past, almost all drug-related product liability cases have involved agents already on the market. The expectation has been that subjects in clinical trials would not bring suit against drug manufacturers because the subjects had decided to participate in a research protocol knowing that there were risks involved in taking experimental drugs. Recently, however, suits brought against some manufacturers for adverse reactions sustained

during drug trials have created an air of uncertainty for manufacturers. The law is unsettled with regard to liability for investigational drugs, and this uncertainty creates a perception of liability that may deter innovation.

Pharmaceutical manufacturers incorporate liability concerns into decisions about which agents to develop and bring to market. Representatives of small and medium-sized companies suggest that the push for expanded access could increase the perception of liability for some drug candidates, thereby making them less attractive to potential sponsors.

Concerns Specific to the Parallel Track

Three features of the parallel track heighten concern about product liability. The first is timing. Parallel track protocols are slated to begin very early in the drug development process—long before the sponsor has definitive information about the potential severity of adverse effects.

The second feature is the large number of participants. Administering a relatively unknown drug to 150 persons in a phase 2 trial is very different, in terms of potential lawsuits, from administering the drug to 5,000 patients in an expanded access protocol.

The third issue is the diversity of health care providers. In a traditional drug trial, the pharmaceutical manufacturer depends on skilled clinical investigators to provide the highest level of medical care. These clinical researchers have access to sophisticated technology to help them monitor patients and to recognize the onset of adverse reactions. Many physician participants in expanded access protocols will not have research experience. Also, some physicians will see only a few patients on a parallel track protocol; they might have more trouble spotting the side effects of an investigational drug than someone who has 50 patients on the same protocol.

Potential Solutions

Observers have suggested several mechanisms to diminish the impact of liability concerns on decisions related to AIDS drugs.

- In *Brown* v. *Superior Court*, the California Supreme Court recently eliminated strict liability (liability without fault) for pharmaceutical products. Instead, plaintiffs must prove actual negligence on

the part of the companies. Some other states have similar tort rules, but in general, inconsistency is the rule on the issue among the states. If this doctrine could be extended to apply to investigational drugs, companies might be reassured.

- Another reform would be to implement the so-called government standards defense. Under this theory, a company that has complied with the FDA requirements for approval has a legal defense to a negligence claim. This mechanism would prevent judges or juries from second-guessing the conclusions of the regulatory agency. However, it might be difficult to extend this form of legal protection to products not yet approved by the FDA.
- Product liability decisions are made by state courts. If the federal government stepped in to standardize these rules nationally, manufacturers would consider this action a large step forward.
- A final mechanism would be to amend existing FDA regulations to make it possible for pharmaceutical manufacturers to negotiate directly with prospective subjects in clinical trials, who would then waive their right to sue. The FDA usually does not permit this type of one-on-one negotiation, but an industry lawyer suggests that it might be appropriate in the context of expanded access programs for AIDS drugs because patients and their physicians assume greater responsibility for the decision to proceed with treatment than do participants in traditional clinical trials.

6

THIRD-PARTY PAYERS

Most expanded access drugs have been provided "free of charge" to patients, but this term can be misleading. For example, Bristol-Myers Squibb has not charged patients for ddI under the treatment IND or parallel track protocols, but patients cannot participate in these protocols unless their physicians send monthly follow-up reports to the company about their health status. These reports must include the results of laboratory tests that cost between $100 and $300. Neither the company nor, in many cases, third-party payers will reimburse patients for these charges. Thus, even though the drug is free, either the patient or the health care system must absorb a substantial amount of drug-related charges.

The parallel track concept has arisen at a time of considerable turmoil in the U.S. health care system. Widespread concern over the high cost of medical care in the United States has placed great pressure on both public and private third-party payers to minimize expenditures. At the same time, government policymakers have been bombarded by studies showing a severe shortage of basic health care services for major segments of the population, particularly low-income minorities in urban centers.

This environment provides a particularly difficult setting in which to resolve questions about payment for health care services related to investigational drugs. Traditionally, third-party payers have covered services that are reasonable and necessary for the treatment of illness or injury. With respect to drugs, this has meant drugs recognized by the FDA as safe and effective—in other words, drugs that are

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This chapter is based on the presentations of David Higbee, Susan Gleeson, Steven Peskin, Lee Mortenson, and Daniel Hoth.

considered part of standard medical practice. Most third-party contracts specifically exclude coverage of investigational drugs.

Although such policies seem straightforward, they leave considerable room for interpretation. For example, when a severely ill patient receives an investigational drug, how much of that patient's care is attributable to the investigational protocol and how much would have been required in any case? Also, how should one handle costs for a disease such as AIDS, in which the appropriate and medically required treatment for a patient may be investigational in nature? Finally, how should third-party payers assess coverage for FDA-approved drugs used in ways that are not specified on the drug's FDA-approved label?

Some patient advocates claim that worsening economic conditions in health care have caused third-party payers to become increasingly restrictive in their reimbursement policies. In certain situations, they say, a patient's decision to enter a clinical trial has led insurers to refuse reimbursement for hospitalization, physician fees, and patient care costs that would have been required even if the patient had not been involved in a research protocol. They worry that such behavior will have a negative effect on drug innovation; physicians and institutions that become wary about reimbursement policies might stop entering their patients in clinical trials.

Patient advocates also express concern about the emphasis on drug labels; they say that they have seen a growing tendency to restrict reimbursement for FDA-approved drugs to indications specified on the drug label. They suggest that this practice, and the related practice of requiring prior approval for reimbursement of unlabeled indications, interfere with the physician's ability to provide good medical care. For example, a representative of the Association of Community Cancer Centers reports that there are 12 indications for interferon specified in the *U.S. Pharmacopoeia* (USP), but only 3 are listed on the FDA label.

Third-party payers, on the other hand, say that they have responded as quickly as possible to a series of very rapid shifts in medical practice, especially with regard to new therapies. A spokeswoman for Blue Cross and Blue Shield uses recent changes in the treatment IND program to illustrate this situation. From the perspective of third-party payers, she says, the treatment IND was supposed to act as a bridge from phase 3 trials to FDA approval. Suddenly, however, the FDA approved a treatment IND for ddI, which had not even entered phase 2 trials.

Blue Cross and Blue Shield, the Health Insurance Association of America (which represents about 320 independent insurance companies

in the United States), and the Health Care Financing Administration (HCFA; which administers Medicare and Medicaid) have all begun to reexamine their policies with regard to reimbursement for clinical trials and off-label uses of FDA-approved drugs.

BLUE CROSS AND BLUE SHIELD

Among Blue Cross and Blue Shield plans, 89 percent pay hospital and physician charges for patients in clinical trials when the hospitalization is medically necessary, independent of the investigational treatment. Eleven percent do not pay these standard patient care costs.

A representative of the Blue Cross and Blue Shield Association explains that each of the 74 plans nationwide makes its own decisions about coverage. Often, however, the decisions are based on recommendations made by the association's nationally recognized technology assessment programs. Recently, the association began a study of reimbursement for patient care costs, with special emphasis on clinical trials. The study will look at coverage issues that arise when one or both arms of a trial involve standard therapies. Staff members hope to develop a classification system that will help Blue Cross and Blue Shield plans assess future research protocols.

Last year, the association and plans adopted a new position on FDA labeling. In the past, reimbursement was limited to labeled indications; now, most Blue Cross and Blue Shield plans will reimburse for off-label indications if there is specific evidence of efficacy. Such evidence may come from one of the major drug compendia or from a plan's own assessment of existing research. In addition to efficacy and safety data, a plan may look for evidence that the desired drug is at least as beneficial as existing therapies. (Some patient advocates say that this new position is actually a retreat because many plans paid for off-label indication as part of standard patient care costs in the absence of an official policy.)

The Blue Cross and Blue Shield Association has a mixed record with respect to expanded access programs for investigational drugs. Last year, after considerable debate, the association advised plans that it would continue to view Group C cancer drugs as investigational, largely because plan contracts say that a drug must have final approval from the FDA to be payable. However, the plans did pay for the AIDS-related drug aerosolized pentamidine when it was distributed under a treatment IND (this may have been related to the fact that pentamidine already was approved by the FDA for intravenous administration).

The association's overall policy on HIV infection is that it should be treated just like any other disease. At the beginning of the epidemic, the central question was how to manage benefits in the absence of effective therapies. A large Blue Cross and Blue Shield task force recommended that plans adopt the case management approach, a strategy for assessing the circumstances of individual patient cases and making exceptions to standard contracts in an organized fashion.

Services that may be reimbursed under the case management approach include counseling, home care, and hospice care. Blue Shield of California has used the case management approach to supplement services provided by local community groups. Blue Cross and Blue Shield of Massachusetts is exploring the use of case management (under a cost-sharing agreement with participating teaching hospitals) to cover investigational treatments for life-threatening diseases that lack alternative remedies. A representative of Blue Cross and Blue Shield says that case management probably will remain the primary strategy for accommodating the special needs of patients with AIDS and other life-threatening diseases. She does not anticipate any specific contract changes.

Some patient advocates greet such news with concern. They believe that it is illogical to treat vast numbers of patients by exception. In addition, they fear that uncertainties about coverage and delays in reimbursement will discourage physicians from treating AIDS patients. Case management will become more difficult, they say, as more patients progress to the later stages of HIV infection.

HEALTH INSURANCE ASSOCIATION OF AMERICA

The Health Insurance Association of America (HIAA) is the largest trade association for the commercial insurance industry. The companies it represents underwrite about 85 percent of all commercial health insurance in the United States. Recently, HIAA convened a task force to make recommendations to member companies about off-label uses of approved drugs, treatment IND drugs, Group C drugs, and related issues. The recommendations encourage companies to be flexible, especially with regard to drugs for immediately life-threatening conditions.

For example, the task force suggested that member companies refer to three national compendia in assessing reimbursement for off-label uses of FDA-approved drugs. They are the *American Hospital Formulary Service Drug Information*, the *American Medical Association Drug Evaluations*, and the *U.S. Pharmacopoeia Drug Information*. In addition, the task force recommended that insurers study the peer-reviewed literature and seek guidance directly from the research community. For immediately life-threatening conditions—patients with no other hope—the task force encouraged consideration of novel approaches that might not have received full peer review.

With regard to investigational drugs, the task force recommended that drugs for immediately life-threatening or serious conditions be considered for coverage—or at least not categorically denied—by health insurers. This includes treatment IND drugs and Group C cancer drugs. The task force also advised member companies to reimburse for costs associated with hospitalization for multidrug regimens involving a combination of approved and investigational drugs. (The experimental drugs themselves would not be covered; typically, these drugs are paid for by the pharmaceutical company or through research grants.) The task force did not recommend reimbursement for hospitalizations associated with single-drug clinical investigations. (Again, however, exceptions might be made for drugs for immediately life-threatening conditions.)

A spokesman for the task force said that the industry would welcome greater input from the FDA in evaluating the efficacy of investigational drugs. He also recommended the development of an alternative to tort remedy for fair, equitable, and expedient adjudication of disputes over drug coverage denials.

Patient advocates applaud HIAA's recognition of the three major compendia for assessing off-label uses of approved drugs and the recommendations concerning payment of hospital and patient care costs for multidrug clinical trials. They add, however, that it is too early to judge the impact of the recommendations because it is not clear whether member companies will follow them. Moreover, evidence from several studies indicates that the proportion of AIDS patients who are covered by private health insurance has declined over time. This trend probably will continue as the demographics of the epidemic continue to change. In addition, a 1988 survey by the congressional Office of Technology Assessment (OTA) found that commercial insurance companies, along with Blue Cross and Blue Shield plans and health maintenance organizations, were planning to reduce their exposure to the financial impact of AIDS. (Possible strategies included reducing sales to individuals and small group markets through tighter underwriting guidelines, expanding the use of HIV and other testing, adding AIDS-related questions to enrollment applications, and denying coverage to applicants with a history of sexually transmitted diseases.) Some commercial carriers have placed

dollar limits on AIDS coverage in new policies and others have introduced waiting periods for AIDS benefits. In this environment, the positive effects of HIAA's new policies on drug coverage might be relatively limited with respect to HIV-related disorders.

HEALTH CARE FINANCING ADMINISTRATION

Three years ago, the Health Care Financing Administration of the Department of Health and Human Services estimated that 40 percent of all patients with AIDS were served under Medicaid. This figure probably has increased substantially as a result of the growing proportion of cases associated with intravenous drug abuse. In some areas, such as New York and New Jersey, the proportion of patients covered by Medicaid may be as high as 70 percent. Medicare, in contrast, covers fewer than 2 percent of AIDS patients.

Medicaid

Drug coverage under Medicaid varies tremendously among states because it is considered an optional service; the only statutory guideline is that states may not receive federal payment for drugs that have not been determined effective by the FDA. Coverage of investigational drugs and of unlabeled indications of approved drugs is usually at the discretion of the state.[1]

[1]In a 1989 decision, the U.S. Court of Appeals, Eighth Circuit, placed a limit on state discretion with respect to the coverage of unlabeled indications of FDA-approved drugs. The case challenged a Missouri Medicaid rule precluding certain Medicaid recipients with AIDS from receiving reimbursement for AZT. The Missouri regulations limited coverage for AZT to patients who had a history of cytologically confirmed *Pneumocystis carinii* pneumonia (PCP) or an absolute CD4 lymphocyte count of less than 200 per cubic millimeter in the peripheral blood before therapy (limitations stipulated in the FDA approval statement for the drug). The court concluded, "the fact that FDA has not approved labeling of a drug for a particular use does not necessarily bear on those uses of the drug that are established within the medical and scientific community as medically appropriate. It would be improper for the State of Missouri to interfere with a physician's judgment of medical necessity by limiting coverage of AZT based on criteria that admittedly do not reflect current medical knowledge or practice." The court found that Missouri Medicaid's approach to its coverage of the drug AZT was "unreasonable and inconsistent with the objectives of the Medicaid Act" (*Weaver* v. *Reagen*, 886 F.2d 194, 8th Cir., 1989).

State Discretion

A recent informal survey of 12 states conducted by HCFA staff members revealed that 7 (Colorado, Florida, Idaho, Massachusetts, Michigan, Texas, and Utah) did not allow any coverage of investigational drugs. The other 5 states—Illinois, New York, California, Iowa, and Virginia—allowed limited coverage on a case-by-case basis. For example, Medicaid coverage of an investigational drug in Illinois depends on three conditions: (1) the drug must be for the treatment of AIDS or an AIDS-related condition; (2) the drug must have official treatment IND status from the FDA; and (3) the recipient or program must be officially charged for the drug by the drug sponsor.

New York has a policy against payment for experimental medical care or services through Medicaid; however, the state will make an exception for an investigational drug if the FDA provides guidelines for the safe administration of the drug and if the guidelines meet the approval of the New York State Department of Health. When these criteria are met, determinations are made on a prior-approval basis for each individual. As of March 1990, the only drug approved for coverage in this fashion was aerosolized pentamidine.

In California, a patient's physician may request authorization for reimbursement for an investigational drug before treatment. Again, determination is made on a case-by-case basis.

Patient Care Costs

Such variation among the states raises the issue of fairness to beneficiaries of the different plans. The fairness issue becomes even more acute, however, in relation to patient care costs associated with investigational drugs. Recently, scientists have noticed that the probability of dying from AIDS increases in those patients who are on their second year of AZT therapy. This observation leads many to believe that the positive effects of AZT may begin to "wear off" in many AIDS patients after 12 to 18 months. For thousands of patients, the only remaining therapeutic alternative is an investigational drug.

Drug sponsors or research grants usually pay drug-related patient care costs for individuals enrolled in traditional clinical trials, but there are no similar arrangements for patients receiving drugs through treatment IND or parallel track protocols. Decisions by individual states about how to handle these costs through Medicaid will influence physician participation in expanded access protocols; such

decisions could determine the level of care provided for impoverished AIDS patients across the country.

Medicare

At present, Medicare does not cover investigational drugs other than Group C cancer drugs, although there is some possibility that this situation may change in the near future. HCFA is in the process of establishing regulations to govern the Medicare coverage process. A HCFA spokesman says that when the notice of proposed rulemaking was published in the *Federal Register*, the agency received numerous letters from the public urging Medicare coverage of treatment INDs. The impact of these letters will not be known until the final rule has been published.

RESOURCES FOR CLINICAL INVESTIGATION

In 1988, the National Institutes of Health (NIH) asked the Institute of Medicine to convene a committee to study issues pertaining to support for clinical investigation. Several of the committee's recommendations dealt specifically with the role of third-party payers in the clinical trials process. For example, the committee concluded:

> . . . it is wholly inappropriate for third party payers to deny reimbursement for all appropriate and necessary patient care costs (not marginal costs owing to investigational intervention) that would have been incurred in any case simply because a patient is on an investigational protocol. Such denial would be tantamount to an abrogation of a contractual obligation. Medicare regulations already will not pay for care of Medicare beneficiaries for investigational therapies that may be the best available treatment. These policies interfere with the patient-doctor relationship and patient free choice.[2]

The committee also recognized that there are diseases for which appropriate and required care involves investigational protocols. In

[2]Institute of Medicine, *Resources for Clinical Investigation* (Washington, D.C.: National Academy Press, 1988, p. 7).

these cases, the committee said, third-party payers should pay the standard patient care costs while costs related to investigational conclusions should be borne by the drug sponsor—a pharmaceutical company, NIH, or a foundation.

7

IMPROVING ACCESS TO CARE

The previous chapters in this report focused on mechanisms for expanding access to investigational drugs. This chapter addresses a related but slightly different issue: the role of clinical trials and expanded access programs in improving access to health care for the disenfranchised populations that make up the fastest-growing segment of the AIDS epidemic.

By the end of the 1980s it became clear that the demography of the AIDS epidemic was shifting: the rate of new HIV infections among homosexual and bisexual men in major urban centers appears to have dropped. A comparison of AIDS cases reported to the Centers for Disease Control before 1985 and those reported during the first six months of 1989 shows an 11 percent decrease in the proportion attributed to homosexual behavior. In contrast, the proportion attributed to intravenous drug abuse increased by 28 percent. The largest percentage increase—100 percent—occurred among the heterosexual partners and children of intravenous drug abusers.

The men, women, and children at greatest risk of acquiring HIV infection through intravenous drug abuse are among the most disadvantaged members of society. The socioeconomic factors associated with high rates of drug abuse in minority populations are also associated with high rates of HIV infection. Blacks, who make up only 11.6 percent of the U.S. population, account for 27 percent of adult and 52 percent of pediatric AIDS cases. Hispanics, who represent 6.5 percent of Americans, account for 15 percent of adult and 23 percent of pediatric AIDS cases. More than 70 percent of all women with AIDS are black or Hispanic.

This chapter is based on the presentations of Gerald Friedland, Lawrence S. Brown, Jr., Mark Smith, Deborah Cotton, Philip Pizzo, and Harvey Makadon.

Very few of these patients have a regular relationship with a health care provider; as a result, they often lack access to the life-prolonging drugs and services that have become the mainstay of treatment for HIV infection. Some advocates argue that clinical trials and expanded access protocols could be a major avenue for bringing state-of-the-art medical care to this population. (In the past, white males have predominated in almost all clinical trials.) They suggest that including these patients in drug trials would meet several goals: (1) improved medical care for a population that traditionally has been underserved; (2) a more equitable distribution of health care resources; and (3) collection of vital scientific information about the ways in which people of different backgrounds respond to specific investigational drugs.

Other scientists, some with a great deal of experience in providing care to AIDS patients, say that it is not realistic to expect clinical trials or other drug protocols to solve the problem of access to health care. They, too, would like to accomplish the above goals but believe that economic, ethical, and social barriers limit what can be accomplished through drug research.

In fact, some health care providers are concerned that parallel track and other expanded access mechanisms will actually widen the gap in access to medical care between wealthy and indigent populations. Patients who have private physicians with the time and resources to fill out data forms and comply with other requirements of the parallel track will have access to new drugs at the earliest possible moment; patients who do not have primary care providers or who must depend on the overworked staffs of large inner-city hospitals, and those without insurance or other means to pay the costs associated with drug delivery, will be much less likely to gain entry into an expanded access system.

To redress this imbalance, efforts to increase access to investigational drugs must be accompanied by broader measures to improve health care for the entire spectrum of AIDS patients. Ideally, such measures would be incorporated into efforts to improve access to care for all indigent populations in the United States. In the short term, however, AIDS-specific actions must be taken to help states and cities whose health care systems are faltering under the medical and financial burdens of the epidemic.

PEOPLE OF COLOR

Physicians who care for minority AIDS patients list three major barriers to the use of clinical trials as a means of improving access to care for people of color. First, many of the institutions that serve low-income minority patients are already overburdened; they simply are not prepared to follow substantial numbers of patients on new investigational drugs. Second, many people of color view the research establishment and the institutions behind it with suspicion; they may not be willing to participate in programs based at these institutions. Third, the lack of options for impoverished patients raises strong ethical concerns about their ability to give genuine informed consent.

Resource Considerations

Advocates for people with AIDS, government scientists, and physicians all agree that clinical trials should include a more balanced sampling of the population infected with HIV. In the early years of the AIDS epidemic, almost all trials of prospective AIDS drugs involved white gay men. Then scientists became concerned that the results of such trials might not be applicable to the growing population of individuals infected with HIV through intravenous drug abuse, many of whom were people of color. The latter tended to have more concurrent infections, poorer nutrition, and a different natural history of disease—for example, a lower incidence of Kaposi's sarcoma—all of which may alter how drugs work to fight HIV infection. Moreover, clinical trials represented the only access to potentially life-saving drugs; basic considerations of equity argued that they should not be restricted to one patient group.

Increased access for minorities was one rationale behind the Community Programs for Clinical Research on AIDS. In addition, NIAID created a program to support minority medical institutions in developing the necessary operational capabilities for an AIDS clinical trials unit (ACTU) and provided increased funding for existing ACTUs to help them recruit and retain previously underserved populations. The situation is improving. In 1987, only 6.5 percent of the subjects in protocols being run by the NIAID AIDS Clinical Trials Group were black, and 10.6 percent were Hispanic. By 1989, 13.9 percent were black, and 14.1 percent were Hispanic.

Some health care providers say, however, that it may be difficult to progress much beyond these levels. Most of the public hospitals

and clinics that serve indigent patients are understaffed and overcrowded. Providing them with funds to conduct clinical trials enables them to hire special research staff, but it does not solve the space problem. In the absence of capital improvements, these institutions might have trouble meeting new expectations.

One of the common goals of community-based trials and expanded access protocols is to enable patients to receive investigational drugs through their own physicians. But many of these physicians are not equipped to determine eligibility for drug trials, to follow and monitor patients on new therapies, and to report on laboratory parameters and adverse reactions. For example, the director of the Boston AIDS Consortium reports that physicians from the city's neighborhood health centers are beginning to attend meetings of the consortium's Clinical Providers Group but that at this time they are more concerned with how to provide basic primary care than with the design and implementation of sophisticated clinical trials. He says:

> Their concerns are about how to keep records confidential; where to get CD4 testing done reliably and at a reasonable cost; how to administer, bill, and get reimbursed for aerosolized pentamidine treatments; and how to get their neighborhood pharmacies to carry AZT.
>
> I hope it is clear that if we are to be realistic, the issue of expanding access must be viewed from a broader perspective and has to be considered in the context of our capability to provide primary care generally, our preparedness to provide this for people with HIV infection, and the fact that even when we are doing this, unfortunately, to a great extent, we must weigh competing demands, offering detection, counseling, and initiation of standard antiretroviral therapy versus expanding access to clinical trials.

Programs to place clinical trials in primary care settings often fail to deal effectively with reimbursement issues. New York State has developed enhanced reimbursements for physicians seeing patients with AIDS in designated centers, but this is by no means universal. In most cases, time spent on clinical investigations is added to time spent doing routine care and, often, finding appropriate treatment for patients with drug abuse problems. All of these tasks together may be reimbursed at the same level as a routine office visit. Whatever the means that are finally adopted, government planners must deal effectively with these resource issues to enhance access to investigational drugs through the primary care providers that serve low-income minority patients.

Suspicion

Increasing minority enrollment in clinical trials also depends on greater understanding of the deep ambivalence that exists among people of color with regard to the premier academic research institutions in this country. An AIDS physician from Johns Hopkins University reports that he was greeted with hostility and suspicion when he first attempted to make contact with members of the black community in Baltimore. He discovered that some people growing up in the neighborhoods around the medical center had been told as children that scientists from the medical school snatched black people off the streets at night and put them in the basement to experiment on them. It was clear that the people who told these stories did not believe them in a literal sense, but the fact that they repeated them indicated a general level of unease with the medical establishment.

Individuals in the community also were extremely familiar with the details of the infamous Tuskegee study, in which members of the Public Health Service followed hundreds of poor black men with syphilis for four decades (1932–1972) without offering them treatment. The subjects neither knew nor consented to their role in this "scientifically controlled experiment."

Fears associated with both real and imagined abuses by the research community, combined with persistent memories of segregated care, will continue to hamper recruitment efforts for clinical trials unless they are discussed openly. Too often, there is a tendency to respond with a joke when a patient says, "So you mean I'm going to be a guinea pig, doc?" For people of color—as well as other patients—the question could mask a serious plea for reassurance.

Informed Consent

Reassurance takes on even greater importance for patients who feel they have no alternative to participation in a clinical trial. Chapter 2 explores the difficulties of obtaining genuine informed consent in AIDS-related drug trials. Poor patients may not have the option of forgoing randomization and obtaining a desired drug through some other mechanism.

Some patients also may be at a disadvantage because they do not have the educational skills necessary to understand the complex details of a research protocol. One way to make protocols more responsive to the needs of such patients is to broaden membership on local institutional review boards (another option discussed in Chapter 2). This would provide a forum for members of the community to educate clinical investigators about the best ways to present new treatment options.

WOMEN

An experienced research nurse at a major academic medical center recently told the principal investigator at her institution that she would much rather see a 40-year-old male engineer in her clinical trials than a young woman with two children who has forgotten the baby's bottle and diapers. This sentiment illustrates just one of the problems with the expectation that clinical trials could be a major avenue for increasing access to care for women with HIV infection. In most hospitals, the clinics that monitor AIDS drug trials do not have the resources or facilities—in terms of transportation, babysitting services, and staff members knowledgeable about women's health care issues—to meet the needs of women.

The Gender Perspective

In fact, the problems go much deeper than resource issues. The AIDS epidemic among women differs in almost every respect from the AIDS epidemic among men. For example, the growth of the epidemic among women is very different. One scientist suggests that the majority of men who will develop HIV-related illnesses in the next 10 to 20 years are already infected; moreover, a significant proportion have progressed to the symptomatic stages of disease. In contrast, most HIV-infected women are in the early stages of disease and there is a large population of high-risk women who have yet to become infected. (This situation has arisen because of the transmission patterns in the United States; early in the epidemic, most transmission occurred through male homosexual activity and intravenous drug abuse—about 70 percent of IV drug abusers are men. Heterosexual transmission did not become a major factor until later.) Physicians who provide health care to women are concerned that too much emphasis on enrolling women in clinical trials could overshadow the tremendous opportunities that still exist for prevention.

Risk Factors

Prevention education and recruitment for clinical trials both require identification of a target population, which raises another difference between men and women with respect to HIV infection. Almost all HIV infection in men is associated with their own personal behavior—either homosexual sex or IV drug abuse. Recent decreases in new infections among gay men and IV drug abusers indicate that educators can reach out to these populations and help them alter the behaviors that place them at risk (for example, by practicing safer sex or "AIDS-safer" injection).

Among women, however, a relatively large percentage of cases occur in individuals with undetermined risk. Many women are infected by sexual partners who have not been truthful about previous high-risk experiences. These women may be completely surprised when they develop symptoms of HIV-related disease or bear an HIV-infected infant.

It is extremely difficult to direct educational efforts toward a population whose members do not realize they are at risk. It is even more difficult to incorporate this population into clinical trials.

Protocol Development

Several drug protocols have been developed recently to study the safety and efficacy of anti-HIV therapy in pregnant women. Although the need for such therapy is clear, protocol development has been problematic for many reasons. First, scientists know very little about the natural history of HIV infection in women in general, and even less about the natural history of the disease in pregnant women. Uncertainty about transmission rates also presents a problem. Several years ago, HIV-infected women were told that they had a 60 percent chance of transmitting the virus to their fetus and that all infected children would die within one to two years. Today, scientists believe that the transmission rate is in the range of 25 to 30 percent and that some infected children will live well beyond their toddler years. But the scientific community still has not determined when in gestation a woman transmits the virus to her fetus. Given these

uncertainties, it may be very difficult for a woman to decide whether or not to participate in a clinical trial.

The second problem with recent drug protocols is that they do not take account of the realities of the health care setting. The low-income women who are at greatest risk of HIV infection often have poor prenatal care, late prenatal care, or no prenatal care at all. The expectation that many of them will be identified and enrolled in clinical trials during the first trimester of pregnancy is probably unrealistic.

Women as Vectors

The dominant problem with the protocols for pregnant women, however, is that their major focus is on interrupting perinatal transmission. This reflects a tendency in society to consider women with AIDS only in relation to their ability to transmit infection to their male sex partners or their infants.

One arm of a protocol now in the planning stages would identify HIV-infected women early in pregnancy but not treat them until the onset of labor. Studies in men have shown that early treatment with antiviral agents can delay AIDS-related symptoms, but no one knows the effects of these agents on the developing fetus. Thus, the decision to delay therapy raises very complex issues about the rights of the mother versus the rights of the child.

A New Approach

Efforts to increase access to clinical trials for women will be most successful if they are part of a new gender-specific approach to HIV education and therapy. Such an approach might include greater support for research on the natural history of HIV infection in women, a commitment to include physicians who are knowledgeable about women's health issues in the design of clinical trials, and a unified approach to the scientific, medical, and ethical issues surrounding clinical trials in pregnancy. Women should be viewed as primary recipients of care, and every effort should be made to repudiate the characterization of HIV-infected women as vectors, transmitters, or vessels of disease.

Today, an HIV-infected woman with an infected child is often required to broker her care among four different providers: her routine provider, her clinical trial site, her child's routine provider,

and her child's clinical trial site. Even a woman with extraordinary financial and emotional resources would find such a task difficult. For the average woman with HIV infection, who must worry about feeding, clothing, and housing her healthy children as well as her sick children, it is almost impossible. Future efforts to increase access to investigational drugs for women will be most effective in centers that integrate clinical trials with routine medical care for both women and children.

THE PEDIATRIC POPULATION

The AIDS epidemic has produced a dramatic change in the way the scientific community approaches clinical trials in children. In the past, clinical trials were generally not begun in children until safety, and perhaps even efficacy, had been established in adults. The rationale for the delay was that it protected children from exposure to unnecessary experimentation. But the severity of HIV infection and the steady increase in infected children (government officials estimate that the number of HIV-infected children in the United States is between 6,000 and 20,000) have created incentives for change.

Government scientists now recognize the need to begin phase 1 trials in children concurrently with or just slightly after the start of adult trials, which should help avoid the types of problems that arose with zidovudine (AZT). Zidovudine was approved for adults in 1987, but children did not have access to the drug outside of traditional clinical studies until October 1989, when the FDA approved a treatment IND for the pediatric population. Parents and physicians of children with HIV continued to have difficulty obtaining the drug until May 1990, when the FDA waived rules for separate efficacy studies in children and approved the drug for anyone above three months of age.

Over the next few years, clinical trials may play a greater role in pediatric AIDS therapy than in adult therapy, in part because the total number of recognized cases remains relatively small. Also, clinical trials provide a controlled environment in which to begin addressing the scientific and social problems that now impede the delivery of care to children with AIDS.

Scientific Issues

The scientific problems result primarily from lack of experience in conducting clinical trials in newborns and young children and from the paucity of information about the natural history of HIV infection in this age group. In fact, three-quarters of the drugs that are now part of standard formularies were never tested in children; they are simply used by extension. Because pharmaceutical companies have very little incentive to produce formulations specifically for the pediatric population, the pace of future clinical trials in children will depend in part on developing such incentives and increasing the availability of appropriate substances.

Scientists also need more information about the progression of HIV-related diseases in children with perinatal infection. As noted earlier, more HIV-infected children survive infancy than was previously expected, and some children do not develop symptomatic disease until well after their fifth birthday. Investigators cannot completely assess the efficacy of drug candidates until they understand the factors that determine the onset and pace of disease in the absence of drugs.

Social Issues

Earlier sections have alluded to the fact that most children with perinatal HIV infection come from severely impaired families. In some cases, the day-to-day demands of poverty and drug abuse may prevent parents from taking an active role in their children's care; in other cases, parents may be severely ill themselves. Pediatric clinical trials among this population must offer much more than investigational drugs and research-related medical care. Compliance with trial regimens depends on the availability of a broad range of services to provide physical and emotional support for the entire family. The multidisciplinary teams developed for pediatric clinical trials could become a model for pediatric AIDS care in other settings.

HIV-infected children who have no family support usually enter the foster care system, a circumstance that raises additional issues. Foster care agencies vary from city to city in their policies on investigational therapies. The implementation of AIDS-related clinical trials may be difficult in areas where the foster care system does not recognize the importance of access to experimental drugs.

In addition to infants born to high-risk women, one other pediatric population is at great risk of HIV infection: adolescent runaways (officials estimate that there are about a million teenage

runaways across the United States). In large cities, such as New York and San Francisco, runaways often use sex as a way of earning a living, which places them at enormous risk of infection from all types of venereal diseases. Providing regular health care for these homeless children is extremely difficult; the potential for including them in clinical trials is limited. The most urgent task with regard to teenage runaways is AIDS prevention education; communications skills developed to help adolescents avoid HIV infection might be used later to promote long-term care for this very challenging target group.

INSTITUTE OF MEDICINE

Conference Summary

Developing Effective Therapies for AIDS-Related Infections

1992



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DEVELOPING EFFECTIVE THERAPIES FOR AIDS-RELATED INFECTIONS

Conference Summary
April 9–10, 1991

Roundtable for the Development of Drugs
and Vaccines Against AIDS

Institute of Medicine

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The report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The image adopted as a logotype by the Institute of Medicine is based on a relief carving from ancient Greece, now held by the Staatlichemuseen in Berlin.

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PREFACE

The Roundtable for the Development of Drugs and Vaccines Against AIDS was established in 1988 by the Institute of Medicine. Composed of leaders from government, the pharmaceutical industry, academia, and patient advocacy, its mission is to identify and help resolve impediments to the rapid availability of safe, effective drugs and vaccines for human immunodeficiency virus (HIV) infection and acquired immune deficiency syndrome (AIDS). The Roundtable accomplishes its mission through regular meetings of its membership, during which urgent issues are identified and discussed, as well as through public conferences and workshops that explore scientific and policy matters central to the development of AIDS therapeutics. This publication is the report of a conference held April 9 and 10, 1991, in Washington, D.C.

The apparent lag in opportunistic infection (OI) drug research relative to antiretroviral research has generated substantial debate about the appropriate balance between efforts to develop antiretroviral drugs and those to develop OI therapies. The biomedical research community and pharmaceutical industry are investing heavily in the development of antiretroviral therapy for HIV infection, and some critics have asserted that this emphasis may have slowed or diverted attention from basic and clinical research related to opportunistic infections. Other factors, however, may also be important—in particular, gaps in scientific knowledge that impede OI research and drug development. The purpose of the Roundtable's April 1991 conference was to review what is known about the epidemiology, basic biology, and treatment of the major opportunistic infections and to examine obstacles to the development of effective OI therapies. Various perspectives on these issues, including those of the biomedical and clinical research communities, the pharmaceutical industry, health care providers, and patient advocates, were presented.

This report is not a consensus document but rather a synthesis of selected scientific and public policy aspects of the conference presentations. It contains no recommendations or conclusions, and the Roundtable has neither altered nor commented on the views and opinions expressed by the speakers, except for purposes of clarity. The Roundtable and staff wish to thank our consultant, Margie Patlak, for her assistance in preparing this summary. Thanks are also due to Richard Hafner, chief of the Opportunistic Infections Treatment Research Section, Division of AIDS, National Institute of Allergy and Infectious Diseases, for his valuable contributions in updating the table in Appendix B. We also thank, once again, the conference speakers for their thoughtful presentations and all the participants for the lively, provocative discussions that occurred throughout this event.

CONTENTS

Introduction 1

Epidemiological Trends in AIDS-Related Infections 3

Scientific Impediments to OI Drug Development and Drug Trials 7

Setting OI Research Priorities 9

Impediments to Industry's OI Drug Development 10

Dissemination of New OI Therapies 14

Conclusion 19

Appendix A: Conference Program 21

Appendix B: Commonly Encountered AIDS-Related Opportunistic Infections and Their Treatments 26

Acronyms and Abbreviations 32

DEVELOPING EFFECTIVE THERAPIES FOR AIDS-RELATED INFECTIONS

INTRODUCTION

As of 1990, there were an estimated 1 million people in the United States who were infected with the human immunodeficiency virus (HIV). In the absence of a cure for HIV infection, the majority of these individuals will eventually succumb to one or more of the opportunistic infections (OIs) associated with acquired immune deficiency syndrome (AIDS)—the final stage of HIV disease—or various forms of cancer. Although HIV causes AIDS and is responsible for the progressive immunologic deterioration that increases susceptibility to opportunistic infections, it is these infections that account for much of the morbidity and mortality associated with AIDS, as well as the diminishing quality of life that frequently occurs. (It must be noted, however, that other conditions—such as wasting, dementia, peripheral neuropathy, nephropathy, myocardiopathy, lymphoma, and Kaposi's sarcoma [KS]—also contribute to overall HIV-related morbidity and mortality.) The frequency and types of opportunistic infections seen among persons with AIDS are changing largely because of current OI prophylaxis and treatment regimens, as well as antiretroviral therapy (e.g., zidovudine [AZT]). Relatively uncommon infections, for example, are becoming more prevalent. New and as yet unrecognized infections may appear in the future.

Although drugs are available to treat a number of the most common AIDS-related opportunistic infections (see Appendix B), problems exist with many of these current therapies. For some such infections, therapy is highly toxic; in addition, it may be inconvenient to administer, expensive, and not entirely effective. For others, therapy may be initially effective, but long-term use (often required to prevent recurrence of infection) may lead to patient intolerance or pathogen drug resistance, which may necessitate dose alterations or discontinuation of treatment. For still other opportunistic infections, no effective therapy presently exists. People in the late stages of AIDS are particularly vulnerable to drug side effects, in part

because of their severe immunologic impairment, and to drug interactions among the multiple therapeutic agents required simultaneously for treatment of primary HIV infection and concomitant opportunistic infections. The emergence of an increasing number of drug-resistant OI pathogens further limits the usefulness of current therapies.

Effective prophylaxis and treatment of opportunistic infections is critical to the work of clinicians who care for AIDS patients, yet a limited number of new OI therapies are in the development pipeline. A number of obstacles face researchers in developing effective OI treatments. Among them are gaps in our basic scientific understanding and knowledge of specific pathogens, as well as some inadequacies in the current experimental systems used to acquire that knowledge. From the pharmaceutical industry's perspective, the pursuit of new OI drugs frequently involves substantial research and development costs, as well as market risks. There are also multiple research priorities competing for limited resources. Efforts to develop new antiretroviral agents have often taken precedence, given that inhibition of HIV is essential if the host is to optimally combat opportunistic infections. Yet it is necessary to strike an appropriate balance between such research efforts and those to develop OI therapies.

Additional hurdles are sometimes encountered in disseminating timely information to health care providers about therapeutic developments and scientific advances in AIDS treatment. When an OI drug receives marketing approval from the Food and Drug Administration (FDA) or becomes available through an expanded access program, care providers must gain information rapidly about the new drug's availability and appropriate use. It is possible to overcome the time lag inherent in publication of research findings in the peer-reviewed medical literature by disseminating important treatment information and therapeutic trial results through alternative channels—for example, clinical announcements issued by the National Institutes of Health (NIH) or state-of-the-art AIDS treatment conferences.

Patient access to OI therapies may be hindered by a lack of third-party reimbursement for unlabeled indications of approved drugs (i.e., indications not specified on the drug label). In some cases, drugs that are currently being used to prevent and treat opportunistic infections have been approved by the FDA for other indications or conditions, which means that such treatments may not be covered by third-party payers because they are considered "off-label uses." Additionally, there may be a limit to the number of prescription drugs that will be paid for during a given time period (e.g., 1 month), as is the case in some state Medicaid programs.

The following sections examine current epidemiological trends in AIDS-associated opportunistic infections and many of the obstacles that impede development and marketing of effective OI therapies and patient access to treatment. The sections also present a number of suggestions by conference participants regarding measures that might help overcome these impediments. It must be emphasized, however, that these suggestions do not represent consensus, nor do they necessarily reflect the views of the Roundtable.

EPIDEMIOLOGICAL TRENDS IN AIDS-RELATED INFECTIONS[1]

By the end of 1990, the Centers for Disease Control (CDC) had received reports on more than 160,000 cases of AIDS involving 234,000 AIDS-defining conditions, 175,000 of which were opportunistic infections. Of the AIDS-defining conditions diagnosed in 1988 and 1989 among individuals 13 years of age or older in the United States, *Pneumocystis carinii* pneumonia (PCP), wasting, and esophageal candidiasis constituted well over 60 percent of such conditions reported to the CDC through 1990. Despite the availability of effective prophylaxis for PCP, it continues to rank as the leading AIDS-defining diagnosis among all adolescents and adults.

CDC surveillance data on opportunistic infections provide a minimum estimate of the burden of AIDS-related morbidity across population groups and geographic regions, as well as an opportunity to examine general trends in the frequency and distribution of AIDS-defining conditions over time. These data, however, do not generally distinguish between those conditions reported at the time of an AIDS diagnosis and those that occurred subsequently; they also do not capture the full spectrum of HIV-related conditions that occur before or following the initial AIDS diagnosis. In addition, these data are not directly linked to the therapies that are used in treating various AIDS-related infections; therefore, it is difficult to discern the specific effects of treatment and the long-term prognosis for these conditions. A CDC representative pointed out that these data, nevertheless, may indirectly offer some insight into the overall impact of OI prophylaxis and treatment on the prevalence of AIDS-associated infections.

When the AIDS-defining conditions reported to the CDC are examined by demographic category, several notable differences are apparent. Among homosexual and bisexual men, Kaposi's sarcoma remains a predominant cause of morbidity. *Mycobacterium avium intracellulare* (MAI) and

[1]This section is based on material presented by Patricia Fleming, Richard Chaisson, Charles Carpenter, Philip Pizzo, and Edward Connor.

cytomegalovirus (CMV) infections are also more common in this group. A CDC representative explained that this pattern may stem from the prevailing use among homosexual men of antiretroviral therapies, which may in turn lead to AIDS being diagnosed at a later stage in the HIV disease process when immune dysfunction is likely to be more pronounced.

Extrapulmonary tuberculosis (TB) appears more frequently among heterosexual men and women than among homosexual men. This pattern can be largely explained by the fact that about 80 percent of the heterosexual men and about 50 percent of the women who have been so diagnosed are injection drug users, among whom TB has become increasingly prevalent.

Over the past decade, tuberculosis has continued its resurgence worldwide and in the United States, in part as a result of the widening HIV epidemic. Of particular concern is the increasing concentration of TB among the urban poor and racial and ethnic minorities with HIV infection in the United States. Although effective treatments exist for *Mycobacterium tuberculosis* (MTB) infection, adverse reactions to such therapies are more common among HIV-infected than among non-HIV-infected individuals; such reactions frequently require alteration or discontinuation of therapy. Another problem in TB treatment is the continuing emergence of multidrug-resistant strains of MTB (i.e., strains that are unresponsive to standard therapies). The combination of these factors limits the effectiveness of currently available drug regimens in treating tuberculosis.[2]

There are also varying patterns of AIDS-defining conditions among different racial and ethnic groups. For example, extrapulmonary TB, cryptococcosis, and esophageal candidiasis are more common among blacks, and toxoplasmosis is more prevalent among Hispanics. MAI and CMV infections appear to be more prevalent among whites, which is consistent with the trends observed among homosexual and bisexual men who constitute approximately 75 percent of AIDS cases in this group.

Although the natural history of HIV infection in women is not yet fully understood, investigators have identified some notable gender-specific differences in the prevalence of AIDS-defining diagnoses. For instance, esophageal candidiasis and chronic ulcerative herpes simplex virus infections seem to be more prevalent among women. One study, conducted at Brown University, of an ethnically diverse group of 200 HIV-positive women revealed that the most frequent initial clinical manifestation of HIV infection was recurrent *Candida* vaginitis with increased frequency and

[2]The potential for multidrug-resistant TB transmission, particularly in the health care setting, to other patients and care providers has engendered considerable concern among public health officials and medical personnel.

persistence.[3] There is also some evidence that human papillomavirus infection in women with HIV infection may enhance the development of squamous intraepithelial lesions of the cervix. Such lesions appear to be more frequent among HIV-seropositive women than among seronegative women.

HIV-infected children often exhibit strikingly different clinical manifestations and opportunistic infections than those experienced by adults. Nevertheless, PCP remains the most prevalent AIDS-defining diagnosis among both children and adults, generally occurring among children within the first year of life. *Pneumocystis* pneumonia can be particularly devastating in young children; it leads to death in roughly 40 to 60 percent of cases.

Opportunistic infections (e.g., PCP) in young pediatric patients often occur as primary infections rather than as the reactivation of disease or infection, a pattern commonly seen in adults. For children diagnosed with AIDS in 1988 and 1989 and reported to the CDC through 1990, PCP, lymphoid interstitial pneumonitis (LIP), and bacterial infections accounted for about 50 percent of the reported AIDS-defining conditions.

Recurrent bacterial infections are a significant cause of morbidity among children infected with HIV. (Serious bacterial infections are also prevalent among HIV-infected adults, especially pneumococcal pneumonia, sinusitis, and bacterial sepsis.) Infections that are particularly common among HIV-infected children include those resulting from encapsulated organisms (e.g., *Streptococcus pneumoniae*, *Hemophilus influenzae*, and *Staphylococcus aureus*) and from enteric organisms. Congenital syphilis is emerging as a problem in these patients as it increases among HIV-infected adults, especially women. As the survival time of children with HIV infection lengthens, mycobacterial disease, particularly MAI, has also become more common.

In addition to HIV-related infections, HIV-infected children are prone to infection with the common respiratory viruses of childhood, such as respiratory syncytial virus, parainfluenza viruses, adenoviruses, and measles. However, these children, unlike their non-HIV-infected counterparts, continue to shed these viral agents and frequently suffer from secondary bacterial infections.

Several studies have demonstrated that normal CD4+ cell counts in young non-HIV-infected children are substantially higher than such counts

[3]C. C. J. Carpenter, K. H. Mayer, M. D. Stein, et al., "Human Immunodeficiency Virus Infection in North American Women: Experience with 200 Cases and a Review of the Literature," *Medicine* 70(1991):307-325.

in non-HIV-infected adults.[4] This recognition of age-related variations in normal CD4+ cell counts has raised questions about the appropriate CD4+ cell threshold at which therapeutic intervention or prophylaxis, particularly for PCP, should be initiated in HIV-infected children. For HIV-infected adults with CD4+ cell counts of 200 or less, PCP prophylaxis is currently recommended. Yet if this same threshold is applied to children, many HIV-infected children at risk of PCP may miss the opportunity for early intervention. For example, several studies have found that a majority of HIV-infected children with PCP have CD4+ cell counts above 200.[5] Recognizing that the criteria for therapeutic intervention and prophylaxis need to vary for the pediatric population, an expert working group (convened by the National Pediatric Resource Center in New Jersey) issued, in 1991, separate, age-appropriate guidelines for PCP prophylaxis of HIV-infected children.[6]

PCP continues to stand out as the number one AIDS-defining condition among all groups; it is substantially more common than other AIDS-associated opportunistic infections. Since 1988, however, the number of AIDS-defining cases of PCP among homosexual and bisexual men appears to be leveling off, or increasing only slightly if adjustments are made for reporting delays. This trend may reflect the impact of wide use of PCP prophylaxis in this group. During the same time period, there appears to be no leveling off of PCP diagnoses among heterosexual male injection drug users or among women and children. (With the advent of new PCP prophylaxis guidelines for HIV-infected children, it is hoped that future trends in PCP diagnoses among these children may shift downward.) Other conditions, such as extrapulmonary TB, pulmonary candidiasis, toxoplasmosis, and cryptococcosis, are increasing among homosexual and bisexual men and heterosexual male injection drug users.

Bacterial infections appear to be declining among children diagnosed with AIDS through 1989. This decline of between 15 and 25 percent may

[4]Y. Yanase, T. Tango, K. Okumura, et al., "Lymphocyte Subsets Identified by Monoclonal Antibodies in Healthy Children," *Pediatric Research* 20(1986):1147-1151; T. N. Denny, P. Niven, C. Skuza, et al., "Age-related Changes of Lymphocyte Phenotypes in Healthy Children (Abstract 916)," *Pediatric Research* 27(1990):155A.

[5]E. Connor, M. Bagarazzi, G. McSherry, et al., "Clinical and Laboratory Correlates of *Pneumocystis carinii* Pneumonia in Children Infected with HIV," *Journal of the American Medical Association* 265(1991):1693-1697; E. Leibovitz, M. Rigaud, H. Pollack, et al., "*Pneumocystis carinii* Pneumonia in Infants Infected with the Human Immunodeficiency Virus with More Than 450 CD4 T Lymphocytes per Cubic Millimeter," *New England Journal of Medicine* 323(1990):531-533.

[6]Centers for Disease Control, "Guidelines for Prophylaxis Against *Pneumocystis carinii* Pneumonia for Children Infected with Human Immunodeficiency Virus," *Morbidity and Mortality Weekly Report* 40, RR-2(March 15, 1991):1-13.

reflect the impact of therapeutic interventions. These therapies include intravenous immunoglobulin (IVIG), zidovudine, and early antibiotic treatment of non-AIDS-defining bacterial infections in HIV-infected children. Data from a study sponsored by the National Institute of Child Health and Human Development indicate that for some HIV-infected children with CD4+ cell counts above 200, the incidence of bacterial infections, particularly streptococcal pneumonia, may be reduced when intravenous immunoglobulin is administered.[7] However, these children were not uniformly receiving zidovudine therapy. A recent nonrandomized study conducted at the National Cancer Institute suggests that antiretroviral therapy in pediatric HIV-infected patients may be tied to a significant reduction in some of the more common infections, particularly bacteremia and pneumonia.[8] The use of antiretroviral therapy and its potential impact on bacterial infections are undergoing further study to determine whether such therapy, either independently or concomitantly with IVIG, diminishes the occurrence of bacterial infections.

The epidemiological trends previously described suggest that effective preventive and therapeutic agents targeted against specific opportunistic infections can substantially affect morbidity. Better prevention and treatment of PCP and esophageal candidiasis could have a significant impact on overall morbidity among persons diagnosed with AIDS. In addition, prolonged survival of people with AIDS is likely to require not only continued advances in antiretroviral therapy but also early identification and treatment or prophylaxis of opportunistic infections. Continuing efforts are also needed to ensure that HIV-infected individuals have access to and receive timely and appropriate medical care.

SCIENTIFIC IMPEDIMENTS TO OI DRUG DEVELOPMENT AND DRUG TRIALS[9]

The preclinical discovery and subsequent development of new drugs require several scientific resources including in vitro culture systems and animal models, an understanding of the target organism's basic biology and

[7]National Institute of Child Health and Human Development Intravenous Immunoglobulin Study Group, "Intravenous Immune Globulin for the Prevention of Bacterial Infections in Children with Symptomatic Human Immunodeficiency Virus Infection," *New England Journal of Medicine* 325(1991):73-80.

[8]E. Roilides, D. Marshall, D. Venzon, et al., "Bacterial Infections in Human Immunodeficiency Virus Type 1-Infected Children: The Impact of Central Venous Catheters and Antiretroviral Agents," *Pediatric Infectious Disease Journal* 10(1991):813-819.

[9]This section is based on material presented by Fred Sattler, Margaret Johnston, and Daniel Hoth.

pathogenesis, a readily available source of reagents, and trained investigators to conduct the necessary preclinical (and clinical) studies. The currently inadequate pool of each of these critical resources poses several scientific obstacles to the development of new, more effective drugs to prevent or treat opportunistic infections.[10]

No suitable culture methods, which are necessary to understand the basic biology and life cycles of pathogens, are currently available for several OI organisms (e.g., *Pneumocystis carinii*, *Cryptosporidium*). There are also problems with existing culture systems—for example, cumbersome measurement methods, absence of correlation to the in vivo situation, and lack of standardization among laboratories. The latter makes comparisons of preclinical studies conducted at different laboratories exceedingly difficult. In part because of the limitations of current in vitro systems, the life cycles of most OI organisms are poorly understood. Consequently, few targets (e.g., enzymes, structural or regulatory proteins of specific organisms) for drugs have been identified; of those targets that have, few have been purified, cloned, and developed into usable assay systems. Scientific understanding of host defenses against some OI pathogens is also limited.

In addition to the paucity of satisfactory in vitro systems in which to design and test new OI drugs, there is also a lack of suitable animal models for some OI organisms. Moreover, many of the animal models that do exist often are not widely available. These models have several additional drawbacks, such as requiring cumbersome and expensive methods to quantify infection—and therefore the efficacy of a given compound—or the need of further development to ensure that they model human disease and its treatment. Of further concern in OI drug development is the need to make reagents more generally available and to augment the number of trained investigators capable of carrying out the necessary preclinical studies.

Another complicating factor in OI drug development is the changing spectrum of AIDS-related opportunistic infections (that is, the incidence and virulence of various infections shift over time). These changes add to the difficulties faced in establishing appropriate research priorities and in targeting drug development efforts.

[10]A more detailed discussion of the gaps in our understanding and treatment of major OI pathogens, as well as the research opportunities and priorities that should be pursued in developing effective OI therapies, appears in B. E. Laughon, H. S. Allaudeen, J. M. Becker, et al., "Summary of the Workshop on Future Directions in Discovery and Development of Therapeutic Agents for Opportunistic Infections Associated with AIDS," *Journal of Infectious Diseases* 164(1991):244-251.

Once promising agents are identified for specific infections, additional impediments to the clinical evaluation of these new drugs often arise. These obstacles stem largely from the complexity and problems inherent in conducting therapeutic OI drug trials. For example, the time and bureaucracy involved in developing research protocols and launching clinical studies may present difficulties. The identification and enrollment of trial subjects also can be particularly challenging, because patients with opportunistic infections often present with acute illness that may require hospitalization and immediate treatment. Even when such patients are successfully enrolled in clinical trials, managing the research protocols is frequently complicated by the patient's advanced HIV disease, possible intercurrent illnesses, multiple drug regimens (i.e., patients are often taking other drugs besides the one under investigation), and the numerous medical and ancillary services needed to care for these patients.

SETTING OI RESEARCH PRIORITIES[11]

There is no simple equation that relates the epidemiology of AIDS-related opportunistic infections to an appropriate research strategy. As noted previously, changing patterns of disease among people with AIDS compound this process. In targeting the development of therapies for particular opportunistic infections, factors to consider include the incidence and virulence of specific infections and the relative burden of disease attributed to them (i.e., their prevalence as well as impact on quality of life and on reduction in overall survival), variation in their distribution, current therapies available to treat or prevent various infections, and the relative effectiveness of such therapies.

It was suggested that increased research attention should be focused on the less common opportunistic infections, because the most common ones, such as *Pneumocystis*, herpes, and *Candida* infections, are currently the most readily treatable. In addition, the less prevalent infections have either very limited or no treatment options. Improved therapies for MAI and tuberculosis, in particular, are needed. Because the rarer conditions may be resistant to drug therapy and therefore intrinsically more difficult to treat, they pose substantial obstacles to the adequate treatment of AIDS patients. Moreover, the less common opportunistic infections produce significant morbidity and mortality. Their incidence and prevalence are also in flux, largely because the use of antiretroviral therapy and the prophylaxis or treatment of the most common conditions are altering the natural

[11]This section is based on material presented by Judith Feinberg.

history of advanced HIV disease. As a result, in the future, the less frequent infections may become more prevalent among persons with advanced disease.

From both a research and clinical care standpoint, there is an increasing need to develop improved, rapid diagnostic methods for those opportunistic infections—for example, PCP or toxoplasmosis—that currently entail invasive or quasi-invasive procedures for diagnosis. Another priority in OI research is the development of long-half-life parenteral or oral agents—that is, agents that are easily administered—to substitute for those OI drugs (e.g., ganciclovir) that require frequent—and expensive—intravenous administration. An overarching goal in developing therapies for these conditions is to expand the number of treatment options available to clinicians and thereby improve drug efficacy and decrease toxicity. Development of parenteral or orally administered therapies might not only increase available therapeutic options but also reduce toxicity and the overall cost of treatment, as well as improve patients' quality of life. In addition, the availability of oral agents might also enhance the feasibility of prophylaxis for various opportunistic infections, which is critical to reducing patient morbidity and mortality. Development of successful prophylactic OI therapies, however, generally depends on the demonstrated safety and effectiveness of these agents for acute infection.

Ultimately, the rational identification of strategies and priorities for OI prophylaxis and treatment will require a more complete understanding of the frequency of specific infections, the risk factors for them, and the effects of medical intervention on long-term prognosis. This information could be garnered through continuing natural history studies of HIV-infected individuals who are stratified by various categories—for example, HIV exposure and demographic characteristics, initial AIDS-defining diagnosis or presenting illness, or CD4+ cell counts.

IMPEDIMENTS TO INDUSTRY'S OI DRUG DEVELOPMENT[12]

A major impediment to the pharmaceutical industry's development of OI drugs is the high cost of new drug development in general, combined with the potentially limited market potential and short commercial lifetime for new OI drugs. This combination of drawbacks means that the return on a company's investment capital may be inadequate to cover the costs of OI drug research and development. Pharmaceutical companies may therefore be reluctant to invest heavily in such ventures as the development of new OI drugs, in which the financial risks are likely to be high and the return on investment relatively low.

[12]This section is based on material presented by Ronald Hansen, Sandra Lehrman, David Martin, Scott Hopkins, Margaret Johnston, and D. Bruce Burlington.

Over the past two decades, the expenditures of pharmaceutical firms on research and development have expanded dramatically. In 1970, such expenditures represented 11.5 percent of sales; by 1991, they had risen to an estimated 16.9 percent. Some of the costs involved in new drug development include any investment that is made in basic research and drug discovery, expenditures associated with clinical testing of drugs, and the interest paid on money borrowed to invest in drug development. If research and development is funded through company-retained earnings, the opportunity costs of this investment (i.e., alternative uses of these funds) must also be considered. An additional factor is the resources expended on investigating and evaluating drugs that ultimately never receive marketing approval.

To explore the cost of new drug development, researchers at the Tufts University Center for the Study of Drug Development compiled a data base from information provided by 12 U.S. pharmaceutical firms on new chemical entities that entered clinical trials between 1970 and 1982.[13] Based on their analysis, they estimate that fewer than 25 percent of all drugs that enter clinical trials eventually obtain marketing approval. Furthermore, these researchers estimate that on average, when all the costs described above are factored into the analysis, the research and development cost per new drug approved for marketing is approximately $231 million (in 1987 dollars).

Factors specific to opportunistic infections are likely to augment the costs and financial risks inherent in new drug development. For example, OI pathogens are intrinsically difficult to treat because they are often well adapted to their hosts. It is difficult, therefore, to find a unique feature in the metabolism of a particular organism to target in designing drugs that will be effective without producing serious adverse reactions. As noted earlier, limited basic science knowledge about many OI pathogens adds to the difficulty and expense of developing effective therapies. Paradoxically, although this knowledge base is expanding and may foster the development of new, more effective drugs, it may also lead to product obsolescence before a drug even reaches the market. That is, because the drug development process can span a decade or more, drugs currently under development may be superseded before or shortly after marketing by newer agents whose design is based on recent advances in OI research or on variations in the spectrum of opportunistic infections.

[13]J. A. DiMasi, R. W. Hansen, H. G. Grabowski, and L. Lasagna, "Cost of Innovation in the Pharmaceutical Industry," *Journal of Health Economics* 10(1991):107-142.

An additional difficulty that is a prominent feature of OI drug development is evaluating the safety of potential therapeutic agents. Patients who require treatment for opportunistic infections generally have advanced HIV disease. These patients seem to experience more drug side effects than individuals in earlier stages of HIV disease or with normal immune function. It is difficult to predict the safety and pharmacokinetics of an OI drug to be used in patients with advanced disease if the agent has been clinically evaluated in persons with early HIV disease. Yet if new drugs are tested in patients with advanced disease, many agents may be discarded as unsafe, even though they may be useful for prophylaxis or chronic suppression of opportunistic infections among people in earlier stages of disease.

Once a safe, effective new drug reaches the market, there are still uncertainties about its relative profitability for a company. Several studies[14] of returns on research and development in the pharmaceutical industry suggest that only a small percentage of the drugs that are marketed actually earn a rate of return that is sufficient to cover the average cost of development. Grabowski and Vernon (1990) estimated that only about 30 percent of the new drugs in their sample recovered the average cost of research and development. The profitability of new drug development as a whole, consequently, is heavily supported by a few "blockbuster" drugs (e.g., drugs that average $100 million in annual sales). Fewer than 10 percent of new drug introductions fall into the "blockbuster" category, which means that drug companies face a financial gamble when they develop and bring a new drug to market.

Several factors specifically influence a new OI drug's profitability, including the size of the market and the commercial lifetime of the drug. For example, because the overall prevalence of many opportunistic infections is relatively low, the market for any given OI therapeutic agent—particularly one developed for the less common infections—is likely to be limited. Drugs to treat the most prevalent infections, such as PCP, may have a larger market but an uncertain commercial life span. As noted earlier, the market lifetime of a particular product may be truncated as scientific advances spur the development of new and improved OI drugs. The changing frequency and distribution of opportunistic infections also add to the uncertainty about market potential and lifetime of individual OI therapies.

[14]H. Grabowski and J. Vernon, "A New Look at the Returns and Risks to Pharmaceutical R&D," *Management Science* 36(1990):804-821; P. Joglekar and M. L. Paterson, "A Closer Look at the Returns and Risks of Pharmaceutical R&D," *Journal of Health Economics* 5(1986):153-177.

Product liability may also be of concern, because many OI drugs will be administered as chronic, maintenance therapy to suppress or prevent recurrence of infection. The potential toxicities of such long-term use may be unknown at the time the drug is marketed. OI drugs are also likely to be given in combination with other medications, including antiretroviral therapy, which heightens the risk of unpredictable adverse effects from possible drug interactions.

What Can Be Done

To offset some of the long-term research costs and financial risk involved in OI drug development, an industry representative at the conference suggested that drug companies could exploit areas of overlap or research synergy in their own discovery and development programs. Several companies have developed a broad knowledge base in the antihypertensive area, for example, which may have some application to antiretroviral drug research and development. Companies could also develop analogs of existing compounds that are known to be effective (e.g., develop oral analogs of intravenous OI drugs rather than search for new agents that can be orally administered); such analogs may have improved properties or efficacy against a specific OI pathogen. Some companies are investigating new uses of drugs that were originally developed and evaluated for indications other than a particular opportunistic infection. In fact, most of the OI drugs currently in clinical trials fall into this category of development.

As described earlier, pharmaceutical companies may be more likely to develop existing agents than to invest in new OI drug development. An NIH representative observed that, in light of this reality, the federal government could take the lead in pursuing basic OI research, identifying molecular targets for drug development, and screening potential compounds for activity against specific OI pathogens.[15] The successful development of effective OI therapies will ultimately require cooperation between industry and government researchers.[16]

[15]Collaboration among clinical investigators in different disciplines (e.g., oncology, organ transplantation) who share a scientific interest in the same OI pathogens could also facilitate the advancement of OI research and drug development.

[16]The National Institute of Allergy and Infectious Diseases (NIAID) has launched the National Cooperative Drug Discovery Group program for the treatment of AIDS-associated opportunistic infections. This program is intended to bridge the gap between basic and applied research and to stimulate participation by the private sector in the earlier stages of OI drug discovery and development.

Another industry representative suggested shifting or redistributing the costs and risk associated with new OI drug development to relieve some of the financial burden shouldered by the private sector. For instance, the federal government could guarantee a market for a given OI drug by issuing a purchase order for a minimum amount of drug sales at a fair price over a specified number of years. This approach could diminish the inherent market uncertainty faced by drug companies in developing new OI drugs by spreading the financial risk across society rather than passing it directly to the consumer (in the form of high-priced drugs) or leaving it to be borne solely by the pharmaceutical industry.

Several conference participants indicated that shorter, simpler clinical drug testing requirements, as well as expedited FDA review of new drug applications (NDAs) and, ultimately (if appropriate), swift approval, could also reduce the pharmaceutical industry's drug development costs.[17] Such testing and reviews can be accelerated when representatives from all parties involved in new drug development—drug companies, NIH, or academic research centers—meet with representatives from the FDA early in the drug development process. This consultation can help ensure the soundness of preclinical data on a given agent, the rational basis for establishing appropriate dosing schedules, and the adequacy of the proposed clinical study design and methodology. This kind of interaction facilitates the collection of useful data on the drug's safety and effectiveness. The FDA should also have an opportunity to evaluate these data as soon as they emerge from clinical trials in order to address potential problems in analysis before the data are assembled and submitted in a formal new drug application for FDA review.

DISSEMINATION OF NEW OI THERAPIES[18]

Clinical Information Dissemination

For many areas of OI treatment, particularly those characterized by only a few alternative therapeutic agents, investigational therapies (i.e., therapies that are not yet approved for marketing by FDA) represent state-of-the-art care for many patients. Gaining access to such therapies can be

[17] An FDA representative emphasized that the agency has given priority to the expeditious review and approval of AIDS-related NDAs.

[18] This section is based on material presented by David Miller, Daniel Hoth, Lawrence Deyton, Donald Abrams, Calvin Cohen, Arnold Relman, Michael Friedman, Louis Lasagna, and David Barr.

difficult in some communities because of the absence of nearby clinical trial units or the existence of stringent enrollment criteria that restrict trial participation. In addition, health care providers may lack adequate information about existing therapeutic trials (e.g., clinical trial sites, current agents under investigation, patient enrollment or eligibility criteria), which limits their ability to refer their patients for participation in such trials.

Once new OI therapies are found to be safe and effective, their rapid introduction and incorporation into medical practice can be impeded by publication time lags of the research findings that support their therapeutic use. An additional obstacle is the plethora of AIDS research data that are currently published, from which clinically relevant information is sometimes difficult to abstract.

Third-Party Reimbursement

Securing third-party reimbursement for inpatient care and for other, ancillary costs associated with administration of an investigational agent can also be problematic. Many health insurers will not pay hospitalization costs for patients who are receiving an investigational therapy. Because patients who require OI drugs are often acutely ill and need hospitalization, such reimbursement restrictions can impede the use of investigational OI treatments, as well as complicate the conduct of therapeutic drug trials.

The use of approved OI drugs can also be limited by some states' Medicaid rules. Prescription drug coverage is an optional benefit in state Medicaid plans; hence, coverage varies widely across states. Some choose to restrict the number of prescription medicines that can be purchased monthly by Medicaid recipients. This limitation creates problems for many AIDS patients who require multiple medications simultaneously to treat both their primary HIV infection and opportunistic infections. In addition, third-party payers often do not pay for unlabeled indications of already approved (and marketed) drugs, which hinders their use in treating opportunistic infections. Furthermore, there is frequently a lack of consistency and uniformity across payers (and geographic regions) in reimbursement policy for various therapies that may be used in OI treatment.

What Can Be Done

Several measures could alleviate some of the problems involved in disseminating new OI therapies. One conference participant suggested that drug companies set up toll-free numbers so that health care providers

could contact a firm's medical personnel and ascertain quickly whether their patients qualified for participation in company-sponsored drug trials. The availability of investigational therapies through expanded access programs for those individuals who are ineligible to participate in clinical trials would also allow promising investigational OI drugs to reach patients who have exhausted other therapeutic alternatives.[19] Community-based trials could also aid this process, although such settings may not be appropriate for early phases (e.g., phase 1) of drug testing, which require close clinical and laboratory monitoring of pharmacokinetics and toxicity profiles. Community-based trials are particularly well suited to evaluations of OI prophylaxis regimens.

An FDA representative observed that the key to wider availability and broader patient access to any drug product is swift marketing approval. In the past, FDA has approved new drugs on the basis of their effect on a surrogate endpoint (i.e., a laboratory marker or measurement that reflects the status or progression of the disease or condition of interest) whose correlation with a significant clinical endpoint (e.g., survival or reduced morbidity) generally has been validated. The use of an established surrogate endpoint in drug trials permits earlier determination of drug effects in the course of clinical evaluation, which then facilitates swifter approval and more widespread availability of an effective therapy. One approach to expediting approval of AIDS-related NDAs, therefore, would be to use surrogate endpoints (e.g., CD4+ cell counts, p24 antigen levels) in evaluating drug effectiveness[20] and to shorten the drug development and review process by eliminating the requirement for phase 3 clinical trials. FDA announced in the October 21, 1988, *Federal Register* its new procedures to expedite the development and evaluation of drugs for life-threatening and severely debilitating diseases; these procedures would effectively eliminate phase 3 studies and permit marketing approval following well-designed phase 2 controlled clinical trials. The agency is currently exploring a proposal that would provide expedited approval—based

[19]The FDA has generally provided mechanisms for access to investigational therapies for critically ill patients (for example, under the compassionate use investigational new drug [IND] and Treatment IND programs). In addition, the Department of Health and Human Services announced the proposed parallel track program in the May 21, 1990, edition of the *Federal Register*. This program would allow HIV-infected patients to receive promising drugs that were still under investigation, following phase 1 trials, in parallel with their continued evaluation in controlled clinical trials.

[20]For example, didanosine (ddI) was approved for marketing in October 1991 primarily on the basis of its positive effect on patients' CD4+ cell counts rather than because of its impact on clinical endpoints. The clinical significance of this increase in CD4+ cells is still under study.

on surrogate endpoints—of promising new drugs for serious and life-threatening illnesses. Approval would be given as early as possible; however, it would also carry provisions for continued study of the drugs' clinical effects after approval, or would provide limitations on distribution.

Once a new OI therapy has been shown to be safe and effective, the investigators generally submit a manuscript, which describes and analyzes the clinical trial results, to a medical journal for publication. This information can be more rapidly disseminated if the authors make early contact with journal editors who can then tag the article as a priority for publication. If a manuscript submitted to a scientific journal is considered a priority, editors can often expedite the peer-review process to ensure that the article is published within a month or so after submission (always providing the research results and data analyses merit publication).

NIH can also inform physicians about new, life-saving OI therapies by issuing a clinical announcement, which condenses NIH-sponsored research results. A clinical announcement is a brief communication, made either through a large-scale mailing or by inclusion in a widely read medical journal, that summarizes the results of clinical studies considered crucial by the sponsoring NIH institute. The announcements usually include a background description of the disease setting, the study design, minimal details about the procedure, and some data on therapeutic efficacy and toxicity. These announcements are intended to bring new information quickly to the attention of clinicians to reduce the interval between identification of a safe, effective therapy and its widespread adoption. Only the important findings of studies that are well designed, methodologically sound, quality controlled, and likely to have significant clinical impact are generally considered for dissemination through clinical announcements. Prior to this early dissemination, the research data are rigorously reviewed by several different committees within the issuing institute to ensure the validity of the data and the appropriateness of the conclusions that have been drawn. A full report of the results is published later through the usual medical literature channels.

To assist clinicians in sifting through the volume of published AIDS-related information, a biomedical researcher noted that professional representatives of drug companies could communicate with physicians in an efficient, timely manner about currently approved therapies. An NIH representative suggested that another potentially useful means of informing care providers about state-of-the-art OI therapy is a computer data base system that provides updated information on HIV and OI treatments, as well as on current clinical trials. Such a data base could be patterned after the Physician Data Query (PDQ) cancer treatment reference system sponsored by the National Cancer Institute. Systems of this kind, however, would only be useful to those clinicians who have ready access to computer

technology and expertise. State-of-the-art HIV therapy conferences could also be conducted on a regular basis, during which treatment guidelines for HIV infection and opportunistic infections could be developed. Increased patient and provider education regarding AIDS treatment developments could be sponsored by AIDS service organizations, professional medical associations, and federal health agencies.[21]

The conference did not include detailed discussions of specific mechanisms to overcome some of the difficulties in obtaining third-party reimbursement for investigational AIDS drugs that are used for therapeutic purposes or reimbursement for unlabeled indications of approved drugs. Nevertheless, one conference participant pointed out that the National Committee to Review Current Procedures for Approval of New Drugs for Cancer and AIDS (also known as the Lasagna Committee) recommended that "insurance coverage of investigational drugs, and of marketed drugs prescribed for unlabeled indications, should rely primarily on their approval by expert government agencies for therapeutic use or their status in authoritative medical compendia."[22] For patients who cannot tolerate or are unresponsive to standard therapies, the committee recommended that "scientifically meritorious investigational drug therapy is the best available treatment and together with ancillary medical care should be covered by all health insurance agencies." Another conference participant suggested that the Health Care Financing Administration (HCFA) could expand its Medicare reimbursement policy to cover investigational drugs and unlabeled indications of approved drugs that are considered in the medical and scientific community to be state-of-the-art treatment. Although drug coverage policies under Medicaid vary across states, it was noted that changes in HCFA's Medicare reimbursement policy in this area might serve as a model for the modification of state Medicaid rules. HCFA is currently developing regulations to govern the Medicare coverage process and is expected to issue them in the near future.

[21]Although not specifically discussed at the conference, other mechanisms to disseminate AIDS treatment information include the AIDS regional education and training centers (ETCs) for health care professionals, sponsored by the Health Resources and Services Administration (HRSA), and the reporting of HIV and OI treatment guidelines in the CDC's *Morbidity and Mortality Weekly Report*.

[22]National Cancer Institute, *Final Report of the National Committee to Review Current Procedures for Approval of New Drugs for Cancer and AIDS* (Washington, D.C.: President's Cancer Panel, National Cancer Institute, August 15, 1990, pp. 13-14).

CONCLUSION

As the HIV epidemic continues into the 1990s, the development of alternative and improved treatments, as well as effective prophylaxis, for AIDS-related infections will continue as a research priority. For people with AIDS, such therapies represent hope for enhanced quality of life and prolonged survival. Yet numerous scientific obstacles often frustrate attempts to develop safe, effective OI drugs. Overcoming these hurdles will require a strong commitment to and investment in OI basic research. In addition, a variety of creative solutions will be needed to resolve some of the economic disincentives in new OI drug development; perhaps several viable alternatives may be found among the wide range of suggestions that surfaced at the conference. Finally, the quality of treatment offered to HIV-infected individuals will depend not only on the availability of safe, effective drugs but also on the timely dissemination of information to health care providers about new and improved therapies and on third-party reimbursement for medically necessary care.

APPENDIX A

CONFERENCE PROGRAM

Tuesday, April 9, 1991

8:20 **Welcome and Opening Remarks**
- Harold Ginsberg, Eugene Higgins Professor of Medicine and Microbiology, College of Physicians & Surgeons, Columbia University, and Roundtable Co-chair

8:25 **Epidemiological Trends in AIDS-Related Infections**
- Patricia Fleming, Epidemiologist, Surveillance Branch, Division of HIV/AIDS, Centers for Disease Control

8:50 **UNDERSTANDING THE MAJOR OPPORTUNISTIC INFECTIONS: PART I**

Moderator: Richard Hafner, Section Head for Research in Opportunistic Infections, Division of AIDS, National Institute of Allergy and Infectious Diseases

***Pneumocystis carinii* Pneumonia**
- Walter Hughes, Chairman, Department of Infectious Diseases, St. Jude's Children's Research Hospital

Mycobacterial Infections: MAI and TB
- Richard Chaisson, Director, AIDS Service, Johns Hopkins Hospital

Toxoplasmosis
- Benjamin Luft, Associate Professor of Medicine, State University of New York at Stony Brook

10:30 **UNDERSTANDING THE MAJOR OPPORTUNISTIC INFECTIONS: PART II**
Moderator: R. Gordon Douglas, President, Merck Vaccine Division, Merck & Co., Inc.

Cryptococcal Infections
– Robert Larsen, Chief, Communicable Diseases Inpatient Service, Los Angeles County-University of Southern California Medical Center

Cytomegaloviral Infections
– Mark Jacobson, Assistant Professor of Medicine in Residence, University of California, San Francisco

11:25 **General Discussion**

1:00 **AIDS-RELATED INFECTIONS AMONG WOMEN AND CHILDREN: CONSIDERATIONS FOR RESEARCH AND TREATMENT**
Moderator: Edward Connor, Associate Director, Division of Allergy, Immunology, and Infectious Diseases, Children's Hospital of New Jersey

– Charles Carpenter, Professor of Medicine, Brown University
– Philip Pizzo, Chief, Pediatric Branch, Clinical Oncology Program, National Cancer Institute

1:40 **General Discussion**

2:00 **OI DRUG RESEARCH: CURRENT OBSTACLES AND FUTURE DIRECTIONS**
Moderator: Fred Sattler, Associate Professor of Medicine, University of Southern California

Scientific Impediments to OI Drug Development
– Margaret Johnston, Chief, Developmental Therapeutics Branch, Division of AIDS, National Institute of Allergy and Infectious Diseases

Setting OI Research Priorities
– Judith Feinberg, Assistant Professor of Medicine, Division of Infectious Diseases, Johns Hopkins University School of Medicine

ACT UP's "Countdown 18 Months"
– Derek Link, Member, ACT UP/New York

Obstacles to OI Drug Trials
– Daniel Hoth, Director, Division of AIDS, National Institute of Allergy and Infectious Diseases

3:15 **General Discussion**

3:55 **WHICH DRUGS WORK BEST? USING THE COMMUNITY-BASED RESEARCH SYSTEM TO GET THE ANSWER**
Moderator: Bruce Chabner, Director, Division of Cancer Treatment, National Cancer Institute

Gathering Data on Therapeutic Effectiveness Through Community-Based Research
– Lawrence Deyton, Chief, Community Clinical Research Branch, Division of AIDS, National Institute of Allergy and Infectious Diseases

Community Consortium (An Association of Bay Area HIV Health Care Providers): The PCP Prophylaxis Experience
– Donald Abrams, Assistant Director, AIDS Activities, San Francisco General Hospital

Industry's Use of Community-Based Trials
– Calvin Cohen, Research Director, Community Research Initiative of New England

4:45 **General Discussion**

5:15 **Adjourn**

Wednesday, April 10, 1991

8:45 **Opening Remarks**
– Sheldon Wolff, Physician-in-Chief, New England Medical Center, and Roundtable Co-chair

8:50 **PHARMACEUTICAL INDUSTRY INVOLVEMENT IN OI DRUG DEVELOPMENT**
Moderator: David Martin, Executive Vice President, The Dupont Merck Pharmaceutical Company

Investing in High-Risk Ventures: What Does it Take?
- Ronald Hansen, Associate Dean for Academic Affairs, William E. Simon Graduate School of Business Administration, University of Rochester

Industry Discussants:
- David Martin, Executive Vice President, The Dupont Merck Pharmaceutical Company
- Sandra Lehrman, Head, Department of Infectious Diseases, Burroughs Wellcome Company
- Scott Hopkins, Senior Director, Clinical Research, Pfizer Central Research, Pfizer, Inc.

9:50 **General Discussion**

10:30 **DISSEMINATION OF CLINICAL INFORMATION TO PHYSICIANS**

Moderator: Kenneth Mayer, Director, Brown University AIDS Program

Clinical Announcements vs. Peer-Reviewed Articles
- Michael Friedman, Associate Director, Cancer Therapy Evaluation Program, National Cancer Institute
- Arnold Relman, Former Editor, *New England Journal of Medicine*

Getting the Word to Community Physicians
- David Miller, Chair, Nueces County Medical Society Committee on AIDS

11:20 **General Discussion**

11:40 **EXPANDING ACCESS TO INVESTIGATIONAL AND APPROVED OI THERAPIES**

Moderator: Peter Barton Hutt, Partner, Covington and Burling

- D. Bruce Burlington, Deputy Director for Scientific and Medical Affairs, Center for Drug Evaluation and Research, Food and Drug Administration
- Louis Lasagna, Dean, Sackler School of Graduate Biomedical Sciences, Tufts University
- David Barr, Assistant Director of Policy, Gay Men's Health Crisis

12:30 **General Discussion**

1:00 **Summary Remarks**
- Sheldon Wolff, Physician-in-Chief, New England Medical Center, and Roundtable Co-chair

1:10 **Adjourn**

APPENDIX B Commonly Encountered AIDS-Related Opportunistic Infections and Their Treatments

Infecting Agent	Manifestations	Treatment	Toxicities of Treatment	Comment
Pneumocystis carinii	Pneumonia (usually interstitial); rarely disseminated	Trimethoprim/sulfa-methoxazole, 15-20/75-100 mg/kg per day orally or intravenously (IV) in 3-4 divided doses for 3 weeks	Skin rash, neutropenia, abdominal pain, fever	Trimethoprim, 5 mg/kg every 8 hours, and dapsone, 100 mg per day, may be as effective as trimethoprim/sulfamethoxazole or primaquine, 30 mg per day, plus clindamycin, 450 mg every 6 hours for 21 days.
		or		
		Pentamidine isethionate, 3-4 mg/kg per day by slow IV; 2-3 weeks' duration of therapy	Hypoglycemia, hyperglycemia, hypocalcemia, azotemia, hepatic dysfunction, hypotension	For failure or intolerance to standard therapy, Atovaquone (BW566C80), 750 mg orally 3 times daily for 21 days; now in expanded access clinical trials for mild to moderate PCP. (For mild to moderate PCP, Atovaquone generally preferred over trimetrexate.) After episode of *P. carinii* pneumonia or in patients with CD4+ lymphocytes $<0.200 \times 10^9$/L (<200 cells/μL), prophylaxis recommended with aerosolized pentamidine isethionate, 300 mg monthly, or trimethoprim/sulfamethoxazole, 320/1600 mg per day, or dapsone, 50-100 mg per day.
		or		
		If intolerant or failing standard therapy, trimetrexate, 45 mg/m^2 per day IV, plus leukovorin, 20 mg/m^2 every 6 hours IV or orally. If (Alveolar-arterial) O_2 gradient >35 or PO_2 <70, then Prednisone, 40 mg twice daily for 5 days; then 20 mg twice daily for 5-10 days; then 20 mg per day for 11-21 days		
Cytomegalovirus	Retinitis, colitis, cerebritis, pneumonitis, esophagitis, adrenalitis	Ganciclovir [9-(1,3-dihydroxy-2 propoxymethyl) guanine (DHPG)], 5 mg/kg IV twice daily for 2-3 weeks; then 5 mg/kg IV daily maintenance	Anemia and neutropenia	Bone marrow toxicity of ganciclovir may be additive with that of zidovudine. Maintenance therapy should be continued indefinitely for retinitis and possibly for cerebritis; reinductions required often with both drugs.
		or		
		Foscarnet (phosphonoformate), 60 mg/kg 3 times daily for 2-3 weeks; then 90-120 mg/kg IV daily maintenance	Azotemia, seizures, hypomagnesemia	
Candida albicans	Oral thrush	Clotrimazole troches, 5 times daily	Generally free of toxicity	
		or		
		Nystatin suspension, 5 mL swish and swallow, 4 times daily	Generally free of toxicity	
		or		
		Ketoconazole, 200-400 mg per day orally	Hepatitis, adrenal insufficiency	
		or		
		Fluconazole, 50-100 mg per day		

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APPENDIX B *Continued*

Infecting Agent	Manifestations	Treatment	Toxicities of Treatment	Comment
	Esophagitis	**Mild**: Swallow nystatin suspension, sucking clotrimazole troches *or* Ketoconazole 200-400 mg per day orally	Hepatitis, adrenal insufficiency	
		Severe: Amphotericin B, 0.3 mg/kg per day IV for 5-10 days *or* Fluconazole 100-200 mg per day	Fever, chills, nausea, vomiting, thrombophlebitis, azotemia, hypokalemia, anemia, hypomagnesemia	
	Rarely disseminated	Amphotericin B, 0.4-0.5 mg/kg per day or as a double dose on alternate days for several weeks		
Mycobacterium avium-intracellulare	Disseminated, particularly in bone marrow, lung, lymph node, liver	No recognized therapy; 3 to 5 drugs chosen from among ethambutal, rifampin or rifabutin, ciprofloxacin, amikacin, clofazimine		In clinical trials: clarithromycin, 500-1000 mg twice daily; Azithromycin, 600-900 mg per day
Mycobacterium tuberculosis	Pulmonary; disseminated (frequent)	3 or 4 drugs chosen from among isoniazid, rifampin, ethambutol, pyrazinamide (streptomycin–not yet available in U.S.), and others		Short-course regimens not recommended. Treatment should be a minimum of 9-12 months with at least 2 drugs active in vitro. Initial response to therapy generally good. Role for long-term maintenance therapy remains unclear. In clinical trials: ciprofloxacin and ofloxacin.
Cryptococcus neoformans	Meningitis; pulmonary; disseminated	Amphotericin B, 0.5-0.6 mg/kg per day IV when used alone or 0.3-0.5 mg/kg per day when used in combination with 5-fluorocytosine (5FC, flucytosine) ***or in combination with*** 5-Fluorocytosine, 100 mg/kg per day in 4 divided doses every 6 hours orally *or* Fluconazole, 400 mg per day	See above for *Candida albicans* treatment Rash, myelosuppression, hepatitis	Requires indefinite maintenance therapy; fluconazole, 200 mg per day, or amphotericin, 1 mg/kg per week

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APPENDIX B *Continued*

Infecting Agent	Manifestations	Treatment	Toxicities of Treatment	Comment
Toxoplasma gondii	Encephalitis; intracerebral mass; ocular disease (rare)	Pyrimethamine, loading dose of 100-200 mg orally in 2 divided doses for 2 days; then 50-75 mg per day for 6 weeks; then maintenance dose of 25-50 mg per day in single dose	Anemia, neutropenia, thrombocytopenia, rash	Initial response in patients who recover usually occurs within 2 to 3 weeks.
		plus		
		Sulfadiazine loading dose of 50-75 mg/kg orally; then 75-100 mg/kg per day in 4 divided doses every 6 hours orally	Usual for sulfonamides, especially crystalluria, hematuria, rash	For maintenance therapy, pyrimethamine, 25-50 mg per day, plus clindamycin, 450 mg every 6 hours
		plus		
		Folinic acid, 10 mg per day orally in single dose; alternative: pyrimethamine plus clindamycin, 600 mg every 6 hours		
Herpes simplex virus	Severe mucocutaneous disease including perianal skin	Acyclovir, 5 mg/kg every 8 hours for 7 days IV or 200 mg orally, 5 times daily for 10 days	Generally free of toxicity	May recur, but maintenance therapy usually not indicated; for acyclovir-resistant herpes simplex virus, foscarnet, 40 mg/kg every 8 hours
	Esophagitis; pneumonia; disseminated (rare)	Acyclovir, 10 mg/kg every 8 hours for 10 days IV	Azotemia, central nervous system (CNS) changes, rash, mild hepatitis	
Herpes zoster	Severe cutaneous disease; dissemination (rare)	Acyclovir, 500 mg/m^2 every 8 hours IV for 7 days; if dermatomal, acyclovir, 800 mg/m^2 orally 5 times daily for 7-10 days or 30 mg/kg daily for 7 days IV	Azotemia, CNS changes, rash, mild hepatitis	
Cryptosporidium	Prolonged, severe diarrhea; malnutrition, wasting	None proven; paramomycin in clinical trials; supportive care including antimotility agents		Protracted diarrhea, unresponsive to therapy, may lead to inanition.
Isospora belli	Severe diarrhea; may be indistinguishable from cryptosporidiosis	Trimethoprim/sulfamethoxazole, 160/800 mg 4 times daily orally for 10 days; then twice daily for 3 weeks	See above for *Pneumocystis carinii*	Prophylaxis using trimethoprim/sulfamethoxazole, 160/800 mg 3 times weekly, or sulfadoxine/pyramethamine, 500/25 mg once per week, has been effective.
Salmonella sp.	Septicemia, diarrhea	Ampicillin, trimethoprim/sulfamethoxazole, quinolones, or chloramphenicol, depending on microbial sensitivities		Ciprofloxacin may also be effective.

Adapted from A.S. Fauci and H.C. Lane, "The Acquired Immunodeficiency Syndrome (AIDS)," *Harrison's Principles of Internal Medicine*, ed. J.D. Wilson, E. Braunwald, K.J. Isselbacher, R.G. Petersdorf, J.B. Martin, A.S. Fauci, and R.K. Root, 12th ed. (New York: McGraw-Hill, 1991).

ACRONYMS AND ABBREVIATIONS

AIDS	Acquired immune deficiency syndrome
AZT	Zidovudine
CDC	Centers for Disease Control
CMV	Cytomegalovirus
ddI	Didanosine
ETC	Education and training center
FDA	Food and Drug Administration
HCFA	Health Care Financing Administration
HIV	Human immunodeficiency virus
HRSA	Health Resources and Services Administration
IND	Investigational new drug
IVIG	Intravenous immunoglobulin
KS	Kaposi's sarcoma
LIP	Lymphoid interstitial pneumonitis
MAI	*Mycobacterium avium intracellulare*
MTB	*Mycobacterium tuberculosis*
NDA	New drug application
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OI	Opportunistic infection
PCP	*Pneumocystis carinii* pneumonia
PDQ	Physician Data Query
TB	Tuberculosis