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Conference Summary

Developing Effective Therapies for AIDS-Related Infections

1992

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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This conference summary was prepared by the Institute of Medicine's Roundtable for the Development of Drugs and Vaccines Against AIDS, chaired by Howard Temin and Paul Volberding and directed by Leslie Hardy. 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.

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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

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, 75,000 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. F. 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 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.

[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.

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**

<u>Wednesday, April 10, 1991</u>

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