DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Institute of Allergy
and Infectious Diseases
Bethesda, Maryland 20892

May 16, 1990

Dear Colleague:

The AIDS Clinical Trials Group is a nationwide network of medical centers established by the National Institute of Allergy and Infectious Diseases to evaluate promising therapies against the human immunodeficiency virus (HIV) and the opportunistic infections and cancers that characterize AIDS. Clinical trials conducted by the ACTG have contributed significantly to the understanding and the treatment of HIV disease.

For some time the ACTG has been singled out for intense criticism by the AIDS Coalition to Unleash Power (ACT UP), an activist organization. We welcome constructive comments and suggestions from all groups; however, ACT UP has widely circulated documents containing a number of allegations and inaccurate information about the policies and accomplishments of the ACTG.

A great deal of information is available from the Institute that addresses these concerns and other issues. We have prepared the enclosed package of information to provide you with specific facts about the ACTG as well as the philosophical and scientific principles undergirding the ACTG's research approach. Enclosed you will find:

1. A list of allegations and demands by ACT UP, with responses by NIAID;
2. ACTG Highlights, including accomplishments, priorities for future research, publications, and discussion of issues of special interest;
3. Three documents (a summary and two detailed Backgrounders) on NIAID's preclinical and clinical research on AIDS-related opportunistic infections.

I hope these materials will be helpful to your understanding of the issues. For additional information, please call the NIAID Office of Communications at (301) 496-5717.

Sincerely,

Anthony S. Fauci, M.D.
Director
National Institute of Allergy
and Infectious Diseases

Enclosures

NIAID RESPONDS TO ACT UP ALLEGATIONS AND DEMANDS

The AIDS Clinical Trials Group (ACTG) of the National Institute of Allergy and Infectious Diseases (NIAID) was established to evaluate promising therapies for use against the human immunodeficiency virus (HIV), the cause of AIDS, and the opportunistic infections (OIs) and cancers that characterize AIDS. The ACTG's goals are to conduct studies that will (1) provide timely information to guide physicians in the selection of appropriate therapies for their patients and (2) lead to the approval of new drugs.

The AIDS Coalition to Unleash Power (ACT UP) has distributed documents containing a number of inaccurate statements, allegations and demands concerning the activities of the ACTG to which the NIAID has made the following responses.

ACT UP ALLEGES
The ACTG has produced no new drugs for people with human immunodeficiency virus (HIV) infection.

THE FACTS
Clinical trials of virtually all antiretroviral drugs with significant promise have been or will be conducted by the ACTG. The fact is that, except for AZT and a few related compounds, very few promising antiretroviral drugs have yet emerged from preclinical research; thus few are available for testing. The antiretroviral drugs ddI and ddC are now in ACTG efficacy studies; other antiretroviral drugs are in earlier phases of ACTG research, to provide information on toxicity, appropriate dose, and indications of possible efficacy.

ACT UP ALLEGES
The ACTG has added only incremental knowledge about existing treatments such as AZT.

THE FACTS
On the contrary, because of clear evidence gained through ACTG clinical trials, 400,000 Americans with early or asymptomatic HIV disease can now receive AZT and thus slow the progression of their disease. ACTG studies proved AZT's effectiveness in delaying the development of HIV symptoms in persons with asymptomatic and early HIV disease. In addition, the ACTG demonstrated the effectiveness of AZT for patients at all stages of disease at a dose level half that specified at the time of the drug's approval. This research has already had a dramatic impact on the lives of persons infected with HIV.

ACT UP ALLEGES
Even when the ACTG has found information useful to people with AIDS, months have passed before these findings (AZT for early intervention, lower dose AZT) were translated into clinical practice.

THE FACTS
This is inaccurate. When clinical trials have been halted early by a Data and Safety Monitoring Board (DSMB), NIAID has promptly disseminated information widely to physicians and other health care professionals, constituency groups, and the scientific and medical press.

Within 2 weeks of the halt of the ACTG clinical trial of AZT in asymptomatic HIV-infected persons (ACTG 019), NIAID issued a Note to Physicians to thousands of doctors and professional medical organizations. The note summarized the results of 019, including the finding that AZT at lower doses was equally effective and less toxic than the drug given at higher doses. In addition, a clinical trials alert described the results of 019

and ACTG 016, a study of AZT in persons with early HIV symptoms that also had been stopped because the drug was found to delay disease progression.

Recently, a DSMB stopped a study because early results showed that oral fluconazole was as effective and less toxic than the standard therapy, intravenous amphotericin B, in preventing recurrences of cryptococcal meningitis in AIDS patients. NIAID immediately issued a Note to Physicians to some 18,000 doctors and followed up with a press release a week later.

All of these materials have been made available to patients and the general public through the Public Health Service toll-free clinical trials information service (1-800-TRIALS-A).

ACT UP ALLEGES
The ACTG has failed to conduct research on therapies for the prevention or treatment of OIs and cancers.

THE FACTS
Untrue. Up to May 1, 1990, the ACTG has studied 28 agents for the prevention or treatment of OIs and 12 cancer therapies. Of the 33 new ACTG studies approved thus far for initiation in 1990, 12 are studies of OI therapies or prophylaxis and 3 are for HIV-associated malignancies.

ACT UP ALLEGES
The ACTG produces data for drug companies rather than finding treatments that would be helpful to people with AIDS.

THE FACTS
ACTG studies identify the safest and best therapies, including combination therapies, that physicians can use in treating their patients with HIV-related disease. Some, but not all, ACTG studies lead to FDA approval and, therefore, general availability of new, efficacious AIDS drugs--a result that is squarely in the public interest.

ACT UP ALLEGES
The decision-making of some ACTG researchers is influenced by their receipt of subsidies from pharmaceutical companies.

THE FACTS
The success of applied biomedical research in the United States and in other countries is due largely to collaboration between government, academia, and industry. Concerns about the potential appearance of conflict of interest, given this collaboration and the prevailing reality of consulting arrangements between investigators and industry, are being addressed by the entire National Institutes of Health. NIAID and the ACTG will, of course, work within the NIH policies that are developed. In any case, individual investigators do not have the authority to direct or dictate ACTG research priorities.

ACT UP ALLEGES
ACTG trials have denied participants life-saving therapy or prophylaxis.

THE FACTS
Untrue. Therapy or prophylaxis proven to be effective is permitted in ACTG trials.

ACT UP ALLEGES
The ACTG has failed to provide children with AIDS with any treatments whatsoever.

THE FACTS
Untrue. ACTG Phase I and II trials of AZT in children formed the basis for the recent approval of AZT for children 3 months and older. In addition, ACTG studies determined the safety of AZT for children from 1 day to 3 months old. Enrollment has been completed for a Phase I ddI trial in children and another Phase I trial of soluble CD4 in children has been initiated.

Eight pediatric clinical trials are scheduled to begin in 1990, including Phase II studies of ddC and ddI, an evaluation of oral AZT in infants with perinatal exposure and a study of the use of AZT to block transmission from HIV-infected pregnant women to fetuses; Phase I studies of CD4-IgG in pregnant women and infants, and a dose deposition study of aerosolized pentamidine are also planned.

ACT UP ALLEGES
ACTG trials routinely exclude present and former drug users, people of color, and women.

THE FACTS
Untrue. Exclusion criteria in ACTG studies exist for medical indications only.

ACT UP ALLEGES
The ACTG has researched only one immune-enhancing drug, interleukin-2 (IL-2), and has used the failure of this drug to block research on other immune boosters.

THE FACTS
Untrue. The ACTG has studied, or will study in 1990, many immune modulators, including interferon alpha, interferon beta, interferon gamma, granulocyte macrophage colony-stimulating factor (GM-CSF), tumor necrosis factor, ampligen, intravenous gamma globulin, AS-101, HIV immunoglobulin (HIVIG), recombinant HIV gp160 antigen, and IL-2 augmented CD8 cells.

ACT UP ALLEGES
The ACTG has not allowed people with AIDS and their advocates to participate in selecting research priorities and designing clinical trials.

THE FACTS
NIAID values the perspective of patients and their advocates. They serve on many Institute advisory and review groups, including the NIAID Advisory Council, the AIDS Research Advisory Committee, and the AIDS Clinical Drug Development Committee. These groups advise NIAID on a broad range of scientific activities and research priorities. The ACTG has established a Patient Constituency Working Group, including 22 individuals representing those constituencies most affected by the HIV epidemic, which is drawing up specific recommendations for constituent involvement in the ACTG process.

ACT UP ALLEGES
Less than 1 percent of the American population with AIDS have had the opportunity to participate in ACTG clinical trials.

THE FACTS
The purpose of clinical trials is to identify effective therapies, not to provide treatment for large numbers of people. Studies involving no more than a few hundred patients can yield results that benefit many thousands;

e.g., 281 patients participated in the clinical trial on which FDA approval of AZT was based. Close to 11,000 persons, including asymptomatic and symptomatic HIV-infected individuals, have participated in ACTG clinical trials.

ACT UP ALLEGES
Only 17 percent of ACTG study participants have been in clinical trials of AIDS-related OIs and cancers.

THE FACTS
Since July 1989, there has been a 300 percent increase in the actual numbers of patients in ACTG studies of OIs (from 703 to 2065) and the percentage of ACTG participants who have been in OI studies has more than doubled (from 10% to 22%). 5.3% of ACTG participants have been enrolled in cancer studies.

ACT UP ALLEGES
A slow-down has occurred in the initiation of new studies because of the change-over of data analysis centers from Research Triangle Institute to the Statistical and Data Analysis Center, based at Harvard School of Public Health.

THE FACTS
Untrue. The rate of initiation of new ACTG studies has remained constant throughout the period of the change-over, which began in September 1989 and is expected to be completed in June of this year. Approximately 40 new studies were added in 1989. In 1990, approximately 40 new studies are anticipated to open and 9 studies have already begun.

ACT UP ALLEGES
From one-third to one-half of the ACTG grants are paid to the sites whether or not they enroll a single patient.

THE FACTS
All NIH grants and contracts include funds for overhead costs at awardee institutions. These indirect costs are linked to the amounts awarded for the costs of conducting studies. It is absolutely untrue that ACTG institutions are paid even if they fail to enroll a single subject. ATCG funding for direct costs is being linked to performance.

ACT UP DEMANDS
The ACTG must conduct small, quick clinical studies of new drugs, rather than large, long-term studies of existing drugs such as AZT.

THE FACTS
Both small, Phase I studies that primarily measure drug safety and dosage and large efficacy trials are important. Since its inception, the ACTG has conducted Phase I trials and will continue to do so as promising new agents emerge from preclinical research. Phase I studies of ddI, ddC and soluble CD4 were completed and these agents are now being further studied within the ACTG. Phase I studies of soluble CD4-IgG and N-butyl DNJ are under way. In addition, studies of ribavirin, dextran sulfate, ampligen, and AL-721 yielded negative results and, therefore, these drugs are not being pursued.

ACTG clinical trials now in progress include 36 Phase I or Phase I/II studies.

ACT UP DEMANDS
New ACTG sites must be established in underserviced areas such as Brooklyn, Newark, and Texas.

THE FACTS
The ACTG was established to conduct AIDS clinical trials; it is not meant to be a health care delivery system for the entire country. Nonetheless, NIAID is providing access to AIDS studies to a broad spectrum of HIV-infected populations located in various geographic areas. NIAID funds ACTG units or Community Programs for Clinical Research on AIDS, a new clinical research initiative, that are accessible to HIV-infected people in all the major epicenters, including Brooklyn, N.Y., and Newark, N.J. A pediatric unit is located in Houston, Texas.

ACT UP DEMANDS
The ACTG must conduct research on new approaches to anti-HIV therapy such as protease inhibitors, TIBO derivatives, and ribozymes.

THE FACTS
None of these agents is yet ready for clinical trials. NIAID is actively supporting or is collaborating with investigators who are working on these and a number of other promising agents. This preclinical research is being conducted by NIAID's 28 National Cooperative Drug Discovery Groups-AIDS and by other institutions. NIAID will evaluate clinically those agents showing adequate promise.

ACT UP DEMANDS
The ACTG must conduct clinical trials on 30 new drugs each year.

THE FACTS
Setting an arbitrary quota for drugs to be studied, rather than making such decisions on the basis of relative merit, is scientifically indefensible as well as highly wasteful of resources. The ACTG has completed, is now conducting, or has protocols in preparation for virtually every promising AIDS or AIDS-related therapy. These include studies of 70 drugs or drug combinations.

ACT UP DEMANDS
Open enrollment treatment trials for all AIDS complications must be available to all who, because of exclusion criteria, cannot enroll in an ACTG trial.

THE FACTS
NIAID recognizes the need to provide therapy options for patients who cannot participate in clinical trials, and has supported a proposed "parallel track" system for expanded availability of experimental drugs.

NIAID's efforts have made it possible for several experimental drugs to be available to various HIV-infected populations, prior to FDA approval, through the Treatment IND mechanism. Thousands of HIV-infected persons have benefitted from distribution of AZT (for adults in 1986, for children in early 1990), ddI, aerosolized pentamidine, ganciclovir, and trimetrexate through a Treatment IND.

ACT UP DEMANDS
The ACTG must actively encourage enrollment of underrepresented groups.

THE FACTS
Substantial efforts have been made by NIAID to enroll more minorities, women, IVDUs, and children in clinical trials. Between 1987 and 1989, the percentage of minorities (Hispanics and blacks) increased from 18

18 to 28%; the percentage of women rose from 5 to 11%; and the percentage of IVDUs remained fairly stable at 11%. 417 infants and children have been enrolled in ACTG studies.

NIAID has committed a total of $9 million in FY 1990 for three initiatives to make AIDS clinical trials more accessible to all of these groups: (1) through the AIDS Clinical Trial Infrastructure for Minority Institutions, cooperative agreement awards will be made to minority institutions not currently involved in the ACTG; (2) supplements will be awarded to some existing ACTG sites to expand the enrollment of currently underserved populations; this initiative is a collaboration with the National Institute on Drug Abuse, which is adding an additional $2 million for sites focusing on intravenous drug users; and (3) supplements will be awarded to some existing ACTG sites to increase the enrollment of children and pregnant women.

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AIDS Clinical Trials Group
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Public Health Service

ACTG HIGHLIGHTS

May 1990

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AIDS CLINICAL TRIALS GROUP
National Institute of Allergy and Infectious Diseases

The AIDS Clinical Trials Group (ACTG) is a cooperative clinical trials network established by the National Institute of Allergy and Infectious Diseases (NIAID) to evaluate promising therapies for use against the human immunodeficiency virus (HIV), the cause of AIDS, and the opportunistic infections and cancers that characterize AIDS. The ACTG consists of 47 AIDS Clinical Trials Units located at universities and medical centers throughout the United States, NIAID, and a Statistical and Data Analysis Center.

The goals of the ACTG are to conduct clinical trials that will (1) provide timely information to guide physicians in the selection of appropriate therapies for their patients, and (2) lead to the approval of new drugs.

The ACTG evaluates therapies for all aspects of HIV disease in adults and children, and conducts the full range of clinical trials, from early safety studies to large-scale, multicenter efficacy studies. The ACTG is built upon the concept of investigator-initiated research, fostered by National Institutes of Health, in which the best research ideas compete for support. Because the ACTG is independent of economic forces that largely determine the research priorities of industry, it is uniquely able to pursue research questions that are of critical importance to patients and physicians alike but may not lead to the approval of drugs for marketing.

SELECTED RESEARCH ACCOMPLISHMENTS

Antiretroviral Research

AZT was shown in 1986, in a Burroughs Wellcome Co.-sponsored study, to prolong the lives of persons with AIDS and was licensed for this use in 1987. Still, many questions remained about how best it should be used, and about its effectiveness in other HIV-infected adults and children. NIAID-supported studies of AZT have resulted in longer, healthier lives for hundreds of thousands of HIV-infected adults and children, by providing vital information about how best to use AZT alone and in combination with other drugs. NIAID is currently supporting both efficacy studies and phase I studies of several other promising antiretroviral agents.

AZT: Demonstrated that both high and low dose AZT are effective in delaying progression to more advanced disease in asymptomatic individuals.

Demonstrated that the previous standard dose of AZT is effective in preventing progression of disease in patients with early ARC.

Demonstrated that low dose AZT (600 mg/day) is at least as effective as standard dose and is less toxic.

Demonstrated that at even lower doses of AZT (300 mg/day), p24 antigen decreases and CD4 cell counts increase.

Demonstrated good tolerance of AZT in HIV-infected persons with hemophilia.

Demonstrated that probenecid prolongs the half life of AZT, permitting lower daily AZT doses (and therefore lower cost) with equal effect.

Demonstrated no synergistic or additive effects of the combination of acyclovir and AZT.

Demonstrated that high dose IL-2 in combination with AZT improves immunological parameters.

Preliminary analysis suggests that the combination of AZT and ddC has the same effect on p24 antigen and CD4 cell counts but is less toxic than continuous therapy with AZT.

Demonstrated no pharmacokinetic interaction between AZT and high or low dose trimethoprim/sulfamethoxazole.

Completed phase I and phase II trials of AZT in children; studies were the basis for approval by FDA.

Implemented the Treatment IND of AZT for children in collaboration with Burroughs Wellcome.

Determined the pharmacokinetics and safety profile of AZT for children between 1 day and 3 months.

ddC: Identified safety and tolerance of ddC and its effects on viral/immunologic parameters.

ddI: Identified safety and tolerance of ddI and its effects on viral/immunologic parameters.

Completed accrual for a phase I trial of ddI in children.

d4T: Established that d4T appears to be well tolerated and has a positive effect on CD4 cell counts and p24 antigen.

rsCD4: Demonstrated that recombinant soluble CD4 is well tolerated; efficacy has yet to be determined.

Initiated a phase I trial of recombinant soluble CD4 in children.

NIAID has also demonstrated the lack of efficacy of several drugs being widely used in the community, providing information of great importance to physicians caring for HIV-infected patients.

Ribavirin: Demonstrated that ribavirin fails to elicit an antiviral effect and seems to be lymphocytotoxic, particularly at high doses.

Dextran sulfate:
Demonstrated the lack of efficacy and bioavailability of oral dextran sulfate.

AL 721: Demonstrated no positive effect of AL 721 on p24 antigen or CD4 cell counts even at doses higher than those used in the community.

Opportunistic Infections

The urgent need to develop new and improved treatments for the myriad opportunistic infections that characterize AIDS and are the most frequent causes of death in AIDS patients will become even more pressing in the 1990s as the large number of asymptomatic HIV-infected persons progress to more advanced disease. These diseases are caused by a wide variety of viruses, bacteria, fungi, and parasites. ACTG studies of opportunistic infections have contributed important information that is useful to the practicing physicians who treat persons with HIV infection. The accomplishments below are listed by disease.

Pneumocystis carinii pneumonia (PCP):

Demonstrated a slower response to aerosolized pentamidine (AP) compared with trimethoprim/sulfamethoxazole (TMP/S) in patients with mild-moderate PCP.

Demonstrated the usefulness of a new combination, clindamycin plus oral primaquine in mild-moderate PCP, providing the basis for a pending comparative study of these two drugs in patients with mild "ambulatory" PCP.

Established and continuing to manage the Treatment IND for trimetrexate for patients intolerant to standard therapies.

Established and continue to manage an open protocol for trimetrexate for patients refractory to standard therapies.

In less than 1 year, completed accrual for a 600-patient primary PCP prophylaxis study of AP vs. dapsone vs. TMP/S.

CMV Retinitis

Developed an intermittent dosing schedule for foscarnet, previously administered only by continuous IV infusion.

Established the appropriate range of maintenance doses of foscarnet for use in further trials.

Established ganciclovir Treatment IND for patients with newly-diagnosed CMV retinitis, yielding supporting evidence for the ganciclovir NDA.

Produced preliminary evidence that GM-CSF may be useful in limiting the number of episodes of ganciclovir-induced neutropenia.

Initiated a dose-ranging study of FIAC in patients who shed CMV in order to examine its antiviral effect, pharmacokinetics and tolerance.

Histoplasmosis

Demonstrated the feasibility of using itraconazole for suppression of relapse of disseminated histoplasmosis in AIDS patients.

Cryptococcal Meningitis

Contributed pivotal data to support the licensing of fluconazole for acute treatment.

Demonstrated that fluconazole is better tolerated and at least as effective as the standard therapy, amphotericin B, for maintenance treatment of cryptococcal meningitis.

Oncology

Demonstrated that low dose multidrug chemotherapy (mBACOD) is as effective as, and less toxic than, a high dose regimen in patients with non-Hodgkins lymphoma.

Defined safety, maximal tolerated dose, and drug interactions of AZT and alpha interferon for Kaposi's sarcoma (KS) therapy, ensuring safe concomitant administration of the two compounds.

Defined tolerance of single agent doxorubicin in AIDS patients with KS.

Neurology

Preliminary analysis suggests a possible dose effect of AZT, with the higher dose (400 mg q4H) being more effective than the lower dose (200 mg q4H) for AIDS Dementia Complex.

CURRENT PUBLICATION RECORD OF THE ACTG

The following list refers only to research results directly related to specific protocols conducted by the ACTG.

PUBLICATIONS:	17
MANUSCRIPTS (in press)	9
MANUSCRIPTS (submitted for publication)	5
MANUSCRIPTS (in preparation)	5
ABSTRACTS (published from major meetings)	52
ABSTRACTS (to be presented at VI Int. Conference)	26

MAJOR STRATEGIES AND PLANS FOR 1990

Research Priorities for New Studies

Early in 1990, 30 new ACTG studies were approved for implementation. Since then, an additional 3 have been added. The eventual target for the year is 40 studies; the additional 7 are being defined as scientific opportunities emerge.

Of these, 12 are in opportunistic infections, 8 in pediatrics, 6 in HIV, 3 in immune-based therapies, 3 in oncology and 1 in AIDS dementia complex. This list clearly reflects the enhanced emphasis directed at the pediatric and opportunistic infections effort.

Antiretroviral Therapy

NIAID's research strategy for antiretroviral therapy focuses on 4 major areas:

(1) new drug evaluation;
(2) optimizing effective antiretroviral therapy;
(3) developing combination therapy;
(4) early intervention.

New Studies Planned for 1990

AZT vs ddC in long-term AZT AIDS/ARC patients
Phase II study of rsCD4 and AZT for AIDS/ARC patients
Soluble CD4-IgG plus AZT in AIDS/ARC
Pilot study of AZT vs AZT/ddI combination
AZT plus interferon-alpha plus CD4 combination
Pharmacokinetics of AZT and oxazepam.

Immune-Based Therapeutics

New Studies Planned for 1990

Two phase I studies of gp160 in asymptomatic and symptomatic HIV+ patients by intradermal and intramuscular routes.

A phase I/II trial of PEG-IL2 in asymptomatic and symptomatic HIV+ persons.

Pediatrics

New Studies Planned for 1990

Oral AZT in infants with perinatal exposure.

Phase II comparison of AZT and ddI.

Phase II trial of ddC.

Phase II trial of ddI.

A phase I/II trial of hyperimmune IVIG vs AZT for proven infected infants under three months of age.

Phase I trial of CD4-IgG in pregnant women and their newborns.

Phase I trials of CD4-IgG in HIV-infected infants and children.

Dose deposition study of aerosolized pentamidine.

Opportunistic Infections

The research strategy for opportunistic infections focuses on:

(1) expansion of the number of active agents or combinations available to clinicians, including validation of licensed agents for new indications;

(2) substitution of oral agents or parenteral agents with long half-lives for those requiring frequent intravenous dosing;

(3) developing prophylactic approaches.

New Studies Planned for 1990

Compare 3 all-oral regimens for the outpatient management of mild PCP.

Dose-ranging study of oral ganciclovir in patients shedding CMV.

Study of Schering 39304 for cryptococcal meningitis.

Clindamycin/pyrimethamine vs sulfadiazine/pyrimethamine for acute toxoplasmic encephalitis.

Clindamycin/pyramethamine vs sulfadiazine/pyramethamine maintenance for toxoplasmic encephalitis.

Phase I study of recombinant human interferon gamma plus pyrimethamine and sulfadiazine for toxoplasmic encephatitis.

Randomized, comparative study of rifampin, ciprofloxacin, clofazamine, ethambutol with and without amikacin for the treament of disseminated M.A.I.

Itraconazole for acute disseminated histoplasmosis.

Foscarnet vs ganciclovir for CMV retinitis.

Pharmacokinetics of foscarnet.

Intravitreal ganciclovir for salvage therapy of CMV retinitis.

Comparison of ceftriaxone versus penicillin for neurosyphilis in HIV-infected patients.

Oncology

New Studies Planned for 1990

Non-Hodgkins lymphoma: A multicenter phase II trial comparing low dose mBACODD with full dose mBACODD supported with GM-CSF will build on the results of ACTG protocols 008 and 074.

Hodgkins lymphoma: A single arm phase I/II study of ABVD with GM-CSF for HIV-associated Hodgkins disease will define the use of this therapy in an uncommon but difficult to treat HIV-associated malignancy.

Kaposi's sarcoma: phase I pharmacokinetic and toxicity study of oral VP-16.

Neurology

Neurological research nested within ACTG treatment studies is the basic research strategy for study of AIDS dementia complex.

New Studies Planned for 1990

Neurological effects of ddI compared to AZT.

ACTG MANAGEMENT PRIORITIES
Established January 1990

1. The process for determining overall scientific priorities is being further systematized and improved.

2. Strategies are being developed and implemented to increase participation of the ACTG in opportunistic infection research.

3. Protocols designated highest priority are being completed expeditiously.

   (1) ACTG 116: ddI vs. AZT
   (2) ACTG 117: ddI vs. AZT
   (3) ACTG 076: AZT in infants with perinatal exposure
   (4) ACTG 021: PCP secondary prophylaxis
   (5) ACTG 081: PCP primary prophylaxis

4. Protocols are being developed, implemented and completed more efficiently.

   - In order to conduct more studies with available resources, a special committee is streamlining ACTG protocols to ensure that only data required to achieve the goals of the study are collected.

   - Laboratory testing is being conducted more efficiently.

5. Short and long-term plans for the management of the Operations Office contract are addressing the current needs of the ACTG.

6. The Statistical and Data Analysis Center (SDAC) will be fully operational by the target date of June 1990.

   The NIAID's requirements for a data center changed dramatically after the award of the first contract in September 1986, due to the need for large-scale randomized multicenter studies. Given the change in workscope and budget, it was necessary to recompete the contract early.

   No slowdown has resulted from the shift to the new SDAC. The rate at which new protocols have been and will continue to be initiated during the course of the transition is the same as the rate for the two prior years.

7. A plan is being developed for the recompetition of the ACTUs that addresses the issues of incentive-based funding and increasing the participation of underrepresented populations. (For details on initiatives to increase participation of minorities, IVDUs, women, and children, see separate section.)

8. An institutional performance evaluation system is being developed that ensures better linkage between performance and funding.

ISSUES AND ANSWERS

What is Being Done to Increase Enrollment of Underrepresented Populations in ACTG Clinical Trials?

The ACTG has made substantial efforts to increase the numbers of minorities, women, intravenous drug users (IVDUs), and children enrolled in ACTG clinical trials. Between 1987 and 1989, the percentage of minorities (Hispanics and blacks) in ACTG trials increased from 18 to 28 percent; the percentage of women rose from 5 to 11 percent; and the percentage of IVDUs has remained fairly stable at 11 percent.

A total of 417 infants and children have been enrolled in ACTG studies. During the past 18 months, NIAID increased from 2 to 15 the number of ACTUs devoted exclusively to pediatric research. In addition, supplemental support is being provided to existing ACTUs to allow for increased enrollment of children in ACTG studies. A collaborative arrangement with the National Institute of Child Health and Human Development (NICHD) enables NICHD clinical trials sites and investigators to participate fully in ACTG studies. Current research priorities also include greater emphasis on pediatric studies.

New initiatives will make AIDS clinical trials even more accessible to all of these groups. NIAID has budgeted a total of $9 million to be awarded in FY 1990 for the following:

(1) minority institutions not currently involved in the ACTG will receive cooperative agreement awards through the the AIDS Clinical Trials Infrastructure for Minority Institutions;

(2) competitive supplements will be awarded to some existing ACTG sites to expand the enrollment of currently underserved populations; this initiative is a collaboration with the National Institute on Drug Abuse, which is providing an additional $2 million for sites making a major effort to recruit IVDUs. This collaborative effort will also establish linkages between ACTUs and NIDA-funded Treatment Research Units and Centers to combine their respective efforts to reach the IVDU population.

(3) supplemental funds will be awarded to existing ACTG units to increase enrollment of children and pregnant women.

What is NIAID's Position on the Use of Placebos in Clinical Trials?

The purpose of placebo controls in clinical trials is to allow direct estimation of the effects of the experimental treatment on the natural history of the disease. With potentially fatal conditions, placebos are appropriate only when there is no known effective treatment. Even then, the appropriateness of placebo controls depends on many other factors such as the seriousness of the condition and standard community practice. When there is a known effective treatment for a serious condition, that agent is used as the control arm--e.g., AZT is the control arm for ongoing evaluations of ddI. Placebo controls may be appropriate and optimal in studies of prophylaxis of some OIs where only a small proportion of the patients are likely to develop the OI during the course of the investigation.

Does the ACTG Use Standard-of-Care Prophylaxis?

Prophylaxis that has been demonstrated to be effective in reliable studies is permitted in ACTG studies. At this time, the only OI for which this is the case is PCP. Prophylaxis for other OIs has not been demonstrated to be effective, although NIAID recognizes that in some selected communities some agents may be used frequently. NIAID does not believe it is in the patient's best interests to encourage the use of multiple prophylactic regimens, the toxicities of which are likely to adversely affect quality of life, unless there is evidence that such regimens are effective.

What is the Purpose of the ACTG's Strict Eligibility Criteria for its Studies and the Restrictions on Participants' Taking Other Medications Concomitantly?

Certain patients must be excluded from studies on the basis of their health status, or because they are taking medications that may interfere with the action of the treatment under study. Exclusion criteria for clinical trials exist for medical purposes only. These exclusions ensure that the results are as clear and unequivocal as possible, and can be used by physicians when making decisions about treating their patients.

Realizing that some research questions may lend themselves to less strict protocol requirements, the ACTG has recently designed some protocols with less strict eligibility criteria and fewer restrictions on concomitant medications.

It is important to note that clinical trials are designed to identify effective and safe therapies, not to provide treatment for large numbers of people. Studies involving only a few hundred patients can, and often do, yield results that benefit many thousands.

What is the Relationship Between the ACTG and the AIDS Clinical Drug Development Committee (ACDDC)?

The ACDDC was established in December 1986 to advise the NIAID on the scientific merit and relative importance of agents proposed for clinical trials. It is completely independent of the ACTG, although its membership includes some ACTG investigators, as well as some Community Programs for Clinical Research on AIDS (CPCRA) investigators. The independent advice and recommendations of the ACDDC are important factors in the decision on whether an agent will enter clinical development under NIAID sponsorship. The actual development plan and specific studies are formulated by ACTG or CPCRA investigators and NIAID staff.

How Does NIAID Ensure that ACTG Investigators' Decisions On What Drugs to Study Are Made Objectively?

Collaboration between government, academia, and industry has contributed significantly to the success of applied biomedical research in the United States. Given this collaboration, and the prevailing reality of consulting arrangements between researchers and industry, the National Institutes of Health is addressing concerns about the potential appearance of conflict of interest. NIAID and the ACTG will, of course, work within the NIH policies that are developed.

In any case, individual investigators do not have the authority to direct or dictate ACTG research priorities. The ACTG Executive Committee, which guides the ACTG, is composed of one NIAID representative, one SDAC representative, and 8 ACTG investigators. Three of the

ACTG investigators are virologists. Other specialty areas represented on the ACTG Executive Committee include infectious diseases, oncology, internal medicine, and pediatrics.

How are Constituents Involved in the Clinical Trials Process?

NIAID values the perspective of HIV-infected persons and their advocates. Representatives serve on the NIAID Advisory Council and the NIAID AIDS Research Advisory Committee, as well as on many other Institute advisory committees and review boards. For example, Ramon Torres, M.D., a medical consultant to Gay Men's Health Crisis and a member of several patient constituency organizations, is a member of the AIDS Clinical Drug Development Committee (ACDDC). Dr. Torres is on the staff of St. Vincent's Hospital and Medical Center in New York. The ACDDC reviews information on promising compounds submitted by investigators and drug developers and helps establish priorities for further testing. In 1989, several constituents served on the committee that reviewed applications for the Community Programs for Clinical Research on AIDS (CPCRA), an innovative NIAID program that brings clinical trials to patients and their physicians in community settings. In addition, many HIV-infected persons and their advocates serve on advisory boards for the funded CPCRA sites.

In January 1990, the AIDS Clinical Trials Group (ACTG) established a Patient Constituency Working Group, including 22 individuals representing a broad spectrum of constituencies most affected by the HIV epidemic. This group is drawing up specific recommendations for constituent involvement in the ACTG process. Their proposal will be presented to the ACTG Executive Committee in May.

What is the ACTG Position on Parallel Track/Expanded Access to Experimental Therapies?

The ACTG Executive Committee, at its meeting in January 1990, fully endorsed the concept of parallel track, as contained in a draft version of the final PHS proposal. Although some individual ACTG investigators have voiced concerns about potential adverse effects of parallel track on ACTG clinical trials, the group as a whole is supportive of the concept.

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OI Backgrounder

Opportunistic Infections Research - National Institute of Allergy and Infectious Diseases

HIV-ASSOCIATED OPPORTUNISTIC INFECTIONS:

NIAID-SUPPORTED PRECLINICAL AND CLINICAL RESEARCH

The urgent need to develop effective treatments for opportunistic infections (OI) that take advantage of the weakened immune system will become even more pressing in the 1990s as thousands of asymptomatic HIV-infected people become ill.

The first cases of AIDS were brought to light by the observation of increasing frequencies of such illnesses as *Pneumocystis carinii* pneumonia (PCP) and ulcerative herpes among homosexual men. Since then, the range of HIV-associated OIs has continued to expand.

The National Institute of Allergy and Infectious Diseases (NIAID), under the leadership of its director, Anthony S. Fauci, M.D., has designated the understanding and treatment of HIV-associated OIs as high priority research areas. One-third of both the active clinical trials sponsored by NIAID's nationwide AIDS Clinical Trials Group (ACTG) and the clinical trials being conducted by NIAID intramural staff in Bethesda, Md., are evaluating agents to treat OIs.

Preclinical Research

The Developmental Therapeutics Branch (DTB), part of DAIDS, coordinates the major share of NIAID-supported preclinical investigations of HIV-associated OIs. DTB serves as a national resource for any individual or group of scientists interested in developing drugs against such OIs.

Traditionally, most drugs for infectious diseases have been discovered through random drug screening. Random screening of drugs for anti-HIV activity continues under a National Cancer Institute program. DTB, on the other hand, focuses on a newer approach to finding anti-HIV and anti-OI agents. This approach is called targeted drug discovery: that is, learning as much about the microbe as possible, and designing drugs that hone in on vulnerable targets of that microbe.

To facilitate the discovery and development of promising anti-OI agents, DTB has in place specific programs that foster collaborations between government, academic, and

industry scientists. DTB staff coordinate a five-arm, structured OI program consisting of: (1) the National Cooperative Drug Discovery Groups for Opportunistic Infections; (2) investigator-initiated basic research grants; (3) contracts to identify agents active against opportunistic pathogens; (4) contracts to analyze the efficacy and toxicity of single and combination therapies in animal models; and (5) resources to conduct chemical formulation and synthesis studies. DTB staff work closely with the staff of the DAIDS Treatment Research Program (TRP) to ensure that the best anti-OI drugs reach the clinic quickly.

In addition to the DTB effort, a smaller effort focused on viral OIs is integrated into the longstanding program of the Antiviral Research Branch (ARB) of the Institute's Division of Microbiology and Infectious Diseases. ARB oversees programs of drug discovery and development and provides animal models of important viral diseases in which promising compounds can be tested.

In September 1989, the Institute brought together a diverse group of infectious disease experts to address future directions in OI research. This workshop, cosponsored by DAIDS and ARB, drew more than 150 investigators from university, government, and industry laboratories. Current knowledge about specific pathogens was discussed and a recommended strategy to accelerate the development of OI therapies was developed.

Buttressing the Institute's newer programs is its 42-year history of commitment to funding basic research on infectious organisms, including bacteria, viruses, fungi, and parasites. NIAID's strong support of immunology research complements this ongoing effort by illuminating how these pathogens destroy or disrupt the body's immune system to allow diseases to develop.

Clinical Research

The majority of NIAID-supported clinical OI research is carried out by ACTG investigators, who are funded through the TRP. The ACTG is a network of 47 university-based adult and pediatric AIDS clinical trials units around the country. The rapidity with which such a large-scale clinical trials effort was established is extraordinary in the history of modern medicine.

Through the ACTG, TRP staff, and the ACTG's Harvard-based Statistical and Data Analysis Center, NIAID provides national leadership in (1) fostering and conducting clinical research to identify optimal therapies for HIV disease and OIs, (2) broadly disseminating the results of this clinical research, and (3) facilitating the application of such results to medical practice. The ACTG's ability to perform large, multicenter trials has positioned it at the vanguard of the HIV clinical trials movement, with several advances in anti-HIV clinical research to its credit. In the area of OIs, the ACTG has also made major contributions to the prevention and treatment of PCP, cytomegalovirus (CMV) retinitis, histoplasmosis, and cryptococcal meningitis.

Clinical research on OIs is enhanced by the new Community Programs for Clinical Research on AIDS (CPCRA). DAIDS established CPCRA to involve more primary care

practitioners in the clinical research effort and to reach large, traditionally underserved populations--blacks, Hispanics, women, and intravenous drug users. CPCRA investigators have identified treatment and prevention of OIs as their top priority.

The staff of NIAID's Division of Intramural Research conduct their own clinical investigation program at the National Institutes of Health's Clinical Center in Bethesda, Md. Intramural investigators have performed several important OI clinical trials, particularly for PCP and CMV retinitis. They also continue to characterize the disease processes underlying OIs. They pioneered studies that have led to a greater understanding of PCP and to the T4 cell count guidelines necessary for Food and Drug Administration licensing of pentamidine as prophylactic therapy for this disease.

In addition, intramural and extramural investigators supported by the Institute's Division of Microbiology and Infectious Diseases continue clinical research on infectious pathogens. Two special clinical programs contribute to this effort. The NIAID Collaborative Antiviral Study Group is a multicenter effort of 55 clinical investigators focused on rare herpesvirus infections, such as herpes encephalitis. The Mycoses Study Group is a similar NIAID-sponsored nationwide network of 28 medical centers dedicated to clinical research on serious fungal diseases. NIAID staff heading these programs work closely with AIDS clinical researchers and DAIDS staff to ensure that promising OI drugs are developed as quickly as possible.

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OI Backgrounder

Opportunistic Infections Research - National Institute of Allergy and Infectious Diseases

HIV-ASSOCIATED OPPORTUNISTIC INFECTIONS:

NIAID-SUPPORTED PRECLINICAL RESEARCH

The National Institute of Allergy and Infectious Diseases (NIAID) plays a major role in fostering the discovery of promising therapeutic agents directed against HIV-associated opportunistic infections (OIs). The largest part of this effort is coordinated by the Developmental Therapeutics Branch (DTB) of NIAID's Division of AIDS (DAIDS). In addition, a smaller effort focused on viral opportunistic infections is integrated into the longstanding program of the Antiviral Research Branch (ARB) of the Institute's Division of Microbiology and Infectious Diseases (DMID). Undergirding this effort is the Institute's commitment since its inception to the support of basic research in infectious diseases.

Reflecting the Institute's consideration of HIV-associated OIs as a high priority research area, DAIDS and DMID jointly sponsored a workshop in September 1989 on future directions in the search for OI therapies. More than 150 academic, industry, and government scientists attended.

Developmental Therapeutics Branch, NIAID Division of AIDS

To date, nearly all licensed drugs used to fight infections were discovered through random screening of synthetic and naturally occurring compounds. A newer approach and one being vigorously pursued by AIDS researchers is targeted drug discovery. In this second approach, researchers target vulnerable aspects of a microbe, learn as much as posssible about those targets, and design drugs to attack them. Targeted drug discovery is the primary emphasis of NIAID-supported programs to develop new therapies for HIV and HIV-associated OIs.

Basic research on infectious agents has always been supported by NIAID. The approach being used by DTB is novel in that through specific programs researchers are strongly encouraged to take their basic research findings one step further and specifically exploit that knowledge to design new drugs. DTB fosters this approach by building bridges between scientists working in academic and government laboratories, whose main focus is basic research, and scientists working in the private sector, whose expertise has traditionally been strongest in the later stages of drug development such as scale-up synthesis and formulation. The rationale for encouraging these collaborations is to assure a

smooth and rapid transition of promising agents from the laboratory through preclinical development to human clinical trials.

DTB, headed by Margaret Johnston, Ph.D., is a national resource for any individual or group of scientists interested in developing drugs against HIV and its associated OIs. DTB staff members assist scientists in obtaining necessary resources, facilitate their efforts to meet Food and Drug Administration guidelines for Investigational New Drug applications, and offer guidance on the potential clinical utility of novel agents. DTB also works closely with the DAIDS Treatment Research Program to assure that the best drugs reach the clinic quickly.

In addition, DTB coordinates a structured program on OIs comprising the following five efforts:

1. The National Cooperative Drug Discovery Groups for Opportunistic Infections (NCDDG-OI) program.
2. Investigator-initiated basic research grants.
3. Contracts to identify agents active against opportunistic pathogens.
4. Contracts to analyze the efficacy and toxicity of single and combination therapies in animal models.
5. Resources to conduct chemical formulation and synthesis studies.

National Cooperative Drug Discovery Groups for Opportunistic Infections

NIAID has set aside $3 million in Fiscal Year 1990 to fund first-year research for several new NCDDGs established specifically to develop treatments for HIV-related OIs. Twenty-four applications for research on major opportunistic pathogens such as *Pneumocystis carinii*, *Cryptosporidium*, *Toxoplasma gondii*, *Candida*, *Cryptococcus neoformans*, *Mycobacterium avium*, and cytomegalovirus were received by the December 8, 1989, deadline; awards are expected to be made in June. Each group will be funded for between 3 and 5 years.

The NCDDG-OI initiative, under the direction of H. S. Allaudeen, Ph.D., is modeled on the NCDDG-AIDS program. This latter program, now comprising 28 groups, has been extremely successful in fostering teams of industry, academia, and government scientists to develop new anti-HIV drugs.

The Request for Applications (RFA) for the existing NCDDG-AIDS program did not preclude research on OIs, but no OI applications were ever received. Therefore, it was decided that a separate RFA under the NCDDG mechanism should be issued to attract OI proposals.

DAIDS believes that a separate drug discovery program for OIs will stimulate the field and help find better ways to treat these diseases. Treatment of OIs is vitally important since it is one of the key areas where treatment may actually help prolong patients' lives.

Like the NCDDG-AIDS groups, each NCDDG-OI will be assembled by a principal investigator. The principal investigator is responsible for forming a multidisciplinary consortium representing the various skills needed to design, synthesize, and evaluate, at the preclinical level, potential therapies for HIV-associated OIs. Consortium members may be associated with academic, nonprofit, or commercial research organizations. A scientific coordinator from NIAID will be affiliated with each NCDDG-OI.

Basic Research Grants

Several important accomplishments have resulted from ongoing basic research projects supported by DTB. Investigators have:

- Developed novel methods for the efficient delivery of drugs to organs affected by OIs. These include inhalation therapy for *Pneumocystis carinii* pneumonia (PCP) and the development of liposomal-encapsulated amikacin, an antibiotic, for *Mycobacterium avium* infections.
- Identified new classes of anti-OI agents that are produced naturally in the body. Proteins named defensins, produced by scavenging white blood cells, have been found to possess antifungal activity *in vitro*, and natural salivary proteins called histatins have been discovered to have anti-*Candida* activity.
- Identified immunomodulators important in protecting against human toxoplasmosis.
- Identified bovine colostrum (the first postpartum milk from lactating cows) containing antibodies against *Cryptosporidium* as a potential protective therapy for this infection.
- Conducted basic research on the life cycle of *Pneumocystis carinii*. This information is useful for understanding how *Pneumocystis carinii* multiplies so rapidly within the body.
- Identified a novel anti-*Pneumocystis* compound now under development by a major pharmaceutical manufacturer.

Fifteen investigator-initiated (R01) grants for research on opportunistic infections were funded in Fiscal Year 1989. Another seven grants are expected to be funded by the summer of 1990.

Drug Screening and Animal Model Contracts

DAIDS is presently funding nine contracts for *in vitro* screening of potential therapies for non-viral OIs. Eight of these contracts, under the direction of Barbara Laughon, Ph.D., and Mohamed Nasr, Ph.D., include evaluations of promising therapies in animal models. Program staff regularly interact with basic scientists, other government agencies, and pharmaceutical firms to acquire novel compounds for evaluation.

Among their accomplishments, contractors have:

- Screened more than 800 compounds and plant extracts last year for *in vitro* activity against organisms causing OIs. These evaluations included both confirmatory and primary screens.
- Identified potent inhibitors of the folate metabolizing enzymes of *Pneumocystis carinii* and *Toxoplasma gondii*.
- Identified and developed the combination of clindamycin and primaquine as treatment and prophylaxis for PCP. These drugs appear to have fewer adverse reactions than the present standard-of-care regimens.
- Identified additional anti-malarial analogs of primaquine that have more potent anti-*Pneumocystis* activity than primaquine.
- Developed a standardized method of infecting immunosuppressed rats with *Pneumocystis carinii* for drug evaluations, allowing for more reliable and reproducible experiments.
- Confirmed the similarity of *Pneumocystis carinii* to fungi. This has led to the development of a method for laboratory culture of the organism using fungal media. This will contribute to the study of the organism's metabolism and sensitivity to antimicrobials, which will enable the design of more effective and specific therapies.
- Identified the potential of severe combined immunodeficiency (SCID) mice as models of *Pneumocystis* infections in AIDS patients.
- Synthesized, evaluated, and developed a pentamidine analog that is less toxic and more efficacious in animals and can be administered orally for treating PCP. Further development and testing of this compound in rats is necessary before human clinical trials can be considered.
- Developed less toxic amphotericin B delivery systems for treatment of fungal infections.
- Identified thiacetazone (an anti-tuberculosis drug) and azithromycin as potential treatments for *Mycobacterium avium* infections.
- Identified plant extracts with anti-*Candida* activity to serve as prototypes for future drug development.

Other Preclinical Resources

NIAID and the National Cancer Institute reached an agreement last year that NIAID would assume primary responsibility for discovery and preclinical development of therapies for HIV-associated OIs. To carry out this mission, DAIDS has established resources to conduct chemical synthesis and formulation studies. DAIDS is planning to expand these resources, contingent upon the availability of funds, to include all studies required in an Investigational New Drug application.

Antiviral Research Branch, NIAID Division of Microbiology and Infectious Diseases

Seven herpesviruses are known to infect humans: herpes simplex viruses (HSV) 1 and 2, varicella zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), and the more recently discovered human herpesviruses (HHV) 6 and 7. Active opportunistic infections caused by herpesviruses have been detected in up to 50 percent of people with AIDS at autopsy. The most serious of these infections is CMV retinitis, which can lead to blindness and has been found to occur in 5 to 38 percent of persons with AIDS. Chronic HSV ulceration (in the mouth or genital area) as well as shingles caused by reactivation of VZV (the chickenpox virus) also affect a small but significant percent of people infected with HIV. Hairy leukoplakia, the result of oral EBV infection, is considered predictive of the development of AIDS in HIV-infected persons. Besides the herpesvirus family of diseases, genital warts, caused by specific human papillomaviruses, are another significant viral opportunistic infection in people with AIDS.

NIAID's Antiviral Substances Program was created 20 years ago to identify and develop new agents to treat human viral infections. In 1989, it was expanded into the Antiviral Research Branch (ARB), now headed by Catherine Laughlin, Ph.D. The ARB does not support research on drugs against HIV itself but does support research on drugs against viral OIs associated with HIV disease.

This preclinical research falls into two broad categories: drug discovery and development, and animal model development.

Drug Discovery and Development

Drug discovery efforts are funded through grants, contracts, and cooperative agreements. Currently, the ARB supports eight cooperative agreements for research on designing drugs specific for molecular targets of several viruses, including HSV and CMV. Recent progress includes:

- Using antiviral, drug-resistant mutants to identify targets for the design of new antiviral agents.
- Identifying HSV viral sequences that may serve as targets for antiviral drug design.
- Synthesizing a new type of antiviral drug, anti-sense oligonucleotides, that have the potential to specifically interfere with virus replication without causing toxicity to the cell.
- Generated human monoclonal antibodies to CMV that will be used as a component of ganciclovir-containing drug delivery systems called immunoliposomes.

Because almost all currently licensed antiviral therapies were discovered by screening of natural products or existing drugs, the Branch also supports two *in vitro* screening facilities through contracts. These facilities evaluate compounds submitted by academic, industrial, and government investigators for activity against a panel of herpes and respiratory viruses, including the opportunistic viruses HSV, CMV, VZV, and EBV. More than 100 compounds have been evaluated in both primary and conformatory tests. Ten of

the most active compounds have progressed into animal model evaluation. This service is available to any scientist who has a potential antiviral compound and is unable to test it.

Currently, the ARB also manages a separate DAIDS-supported program of five contracts, now in their third year, for the development of antivirals for treating CMV infection in people with HIV disease or those who are otherwise immunosuppressed. Although the FDA approved the use of ganciclovir for treatment of CMV retinitis in June 1989, problems with the drug exist (for example, toxicity and lack of oral delivery), and thus, the search for better therapies continues. Several promising anti-CMV compounds developed by these contractors are now being evaluated in animal models.

Animal Model Contracts

Seven research contracts support 11 animal models of human viral infections. Experimental compounds provided by investigators can be evaluated in these models to determine the compound's toxicity and efficacy. These models include a guinea pig model of genital herpes; an African green monkey model for simian varicella; guinea pig and mouse models for CMV infections; and rabbit and nude mouse models for papillomavirus infections. Several compounds have shown promising effectiveness in the mouse model of CMV infection. The most thoroughly evaluated of these, HPMPC, was significantly more effective than ganciclovir. Furthermore, it was equally effective whether given with intermittent (every 3 to 7 days) dosing or with the more traditional daily dosing. This may be an important advantage if the drug will be given in combination with other therapeutic agents. In a related development, a topical form of PMEG, a compound similar to HPMPC, showed efficacy against papillomavirus-induced warts in the cottontail rabbit.

Basic Research in Immunology and Infectious Diseases

Since NIAID's beginnings in 1948, the Institute has directed a major portion of its efforts to illuminating the molecular mechanisms underlying infectious diseases. The scope of the Institute's research has continually expanded to accomodate the growing recognition of disease-causing parasites, bacteria, fungi, and viruses. This ongoing effort now has increased urgency because of HIV disease and its attendant OIs. In the last few years, basic research has provided an increasingly sophisticated understanding of infectious agents and of the immune system's remarkable capacity to produce powerful, appropriate, and self-limiting responses to infection. NIAID-supported scientists have pioneered many areas of infectious disease research.

Joint Workshop on Opportunistic Infections

In September 1989, DTB, ARB, and the Medical Branch of DAIDS held a joint workshop titled "Future Directions in Discovery and Development of Therapeutic Agents

for Opportunistic Infections Associated with AIDS." This 2-day workshop was attended by 150 investigators from academia, industry, the FDA, and the National Institutes of Health.

The major goals of the workshop were to identify research and resource needs, to reach a consensus on recommended research priorities, and to facilitate communication among investigators working with the diverse opportunistic pathogens.

Review presentations in the plenary session addressed issues of clinical care, epidemiology, and drug design. In these talks, the need for OI treatments was presented in the context of the worldwide AIDS epidemic, and the magnitude of the problem was thus defined. It was noted how much is known about *Pneumocystis* compared with other organisms, but how little still is known about its life cycle and pathogenesis. The participants then divided into six working groups, each focused on a specific pathogen(s) (*Pneumocystis*, *Toxoplasma*, enteric parasites, fungi, *Mycobacterium*, and CMV). The working groups: (1) identified problems with drugs in clinical use, (2) discussed the current understanding of each pathogen and its mode of infection, (3) set priorities for research needs and resources, and (4) defined the role of NIAID in the drug discovery and development process.

Key points that emerged from the working group discussions are as follows:

1. The need for more effective, less toxic antimicrobials.
2. The need for more knowledge of the basic biology and pathophysiology of these organisms.
3. The need to identify new chemotherapeutic targets through more basic research on the biology and biochemistry of these organisms.
4. The need to improve and standardize test-tube culture systems and animal models for testing potential therapeutic agents.
5. The need for a national repository of standardized reagents such as monoclonal antibodies, gene libraries, and selected strains of certain pathogens.
6. The recommendation that more such meetings be held to coordinate and expedite drug discovery and development.

Summaries are being prepared, to be published in a scientific journal, that will include the specific recommendations from the individual working groups.

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Backgrounder

Opportunistic Infections Research - National Institute of Allergy and Infectious Diseases

HIV-ASSOCIATED OPPORTUNISTIC INFECTIONS:

NIAID-SUPPORTED CLINICAL RESEARCH

The major NIAID-supported effort directed toward clinical research on HIV-associated opportunistic infections (OIs) is coordinated by the Treatment Research Program (TRP) of NIAID's Division of AIDS (DAIDS). TRP coordinates two major clinical trials initiatives, the AIDS Clinical Trials Group (ACTG) and the Community Programs for Clinical Research on AIDS (CPCRA). ACTG is a collaborative network of 47 university medical centers across the country that carry out AIDS clinical research. CPCRA, a community-based clinical research program, currently includes 18 clinical units at the front line of the AIDS epidemic. At the National Institutes of Health (NIH) campus in Bethesda, NIAID researchers conduct AIDS clinical research through the Institute's Division of Intramural Research (DIR). In addition, NIAID's Division of Microbiology and Infectious Diseases (DMID) supports clinical research on viral and fungal diseases that occur as HIV-associated OIs through two special programs, the Collaborative Antiviral Study Group (CASG) and the Mycoses Study Group (MSG).

Clinicians who care for people infected with HIV face a challenging situation. HIV-associated OIs are rarely curable. At best, they can be controlled during an acute episode and usually require long-term suppressive therapy. Concurrent or consecutive infections with different organisms are common, and this can affect the clinical response to treatment. Moreover, infections associated with HIV are often severe. They commonly occur in disseminated forms and are characterized by a high density of organisms in the affected tissues.

Many current therapies for OIs are toxic, or must be given intravenously and thus are difficult to administer for long periods. Some OI organisms have or will become resistant to standard therapies. New and improved agents to treat and prevent most HIV-associated OIs are urgently needed.

Clinical trials of experimental agents pose several difficulties. Potential enrollees usually have a sudden, acute OI that must be treated immediately. To ensure that such patients have the opportunity to enroll in a clinical trial of a promising new agent, the research center must maintain effective working relationships with primary care and emergency room physicians and with health care workers of clinics where the patients will first seek treatment. Round-the-clock staffing by the research team--including physicians,

nurses, and pharmacists--is necessary so potential study participants can be entered immediately into the study.

Clinical protocols for HIV-related OIs are unusually complex. Many potential participants are gravely ill, have multiple infections, and may already be taking other therapeutic drugs, including zidovudine (AZT). OI studies can also be expensive because patients frequently must be hospitalized for several weeks and often require services of specialists and laboratories beyond those provided by the research grant. In many cases, these expenses may not be reimbursed through third-party payments. Because of the complexities of care for these patients and the need for attentive, long-term monitoring, the research team must work closely with hospital staff and home health care providers.

NIAID Division of AIDS

AIDS Clinical Trials Group

Led by DAIDS Director Daniel F. Hoth, M.D., and Associate Director of TRP, Peter Gamatos, M.D., Ph.D., TRP spearheads the national effort to develop safe and effective therapies for HIV disease and its associated OIs and cancers. The nucleus of TRP-sponsored clinical research is the AIDS Clinical Trials Group (ACTG), a national network of clinical research units that conduct HIV-related clinical trials. The ACTG was established in December 1987 by merging two smaller nationwide NIAID clinical efforts begun in 1986 and 1987.

The ACTG initiative laid the foundation for a comprehensive program of AIDS clinical research in the United States. The rapidity with which this was done was extraordinary in the history of modern medicine.

The cooperative group model embodies the concept of investigator-initiated research and has several advantages over the more traditional private industry sponsorship of clinical trials. Specifically, the ACTG can establish research priorities independent of the economic forces that influence private sector research. The ACTG's focus is to establish the best therapies and the best ways to use them for a given condition, rather than to license a particular agent. A second major advantage is the ACTG's ability to conduct large, multicenter efficacy trials, thereby expediting the licensure of promising agents.

Clinical trials are currently being conducted by the ACTG's 47 ACTUs involving more than 100 clinical sites located throughout the country. Fifteen of the ACTUs are devoted exclusively to pediatric AIDS clinical trials research, and seven of the adult ACTUs also perform pediatric studies.

DAIDS strategy for research on OIs focuses on four main areas:

- Expand the number of active agents or combinations available to clinicians, including validating already licensed agents for new indications.

- o Substitute oral agents or parenteral agents with long half-lives for those requiring frequent intravenous dosing.
- o Where suitable treatments are available, document their efficacy for prophylaxis.
- o Achieve the ultimate goal of preventing OIs by supplanting therapy with prophylaxis.

As of May 1, 1990, the total number of active ACTG protocols was 86. One-third of these trials addressed HIV-associated OIs. Approximately 12 new protocols for OIs are in development. The highest priority has been assigned to the following protocols and diseases:

1. *Pneumocystis carinii* pneumonia prophylaxis studies.
2. Treatment studies for *Pneumocystis carinii* pneumonia (PCP), including aerosolized pentamidine, clindamycin plus primaquine, and dapsone plus trimethoprim.
3. Cryptococcal meningitis treatment and prophylaxis studies, including fluconazole and SCH39304.
4. Cytomegalovirus retinitis treatment studies, including foscarnet and oral agents such as ganciclovir and FIAC.
5. Toxoplasmosis treatment studies.
6. Acute treatment for symptomatic, disseminated *Mycobacterium avium intracellulare*.

TRP has developed a comprehensive framework of action for developing clinical trials for PCP and CMV, two particularly important OIs. Studies have been designed to answer specific questions that make possible a logical progression of trials that address both acute therapy, initial and salvage, and prophylactic therapy. The following accomplishments for PCP acute initial treatment studies illustrate this strategy. The ACTG has:

- Completed and published the findings of a dose-ranging study of trimetrexate that establlished the dose to be used in the phase III comparative trial.
- Demonstrated a slower response to aerosolized pentamidine compared with trimethoprim/sulfamethoxazole in patients with mild to moderate PCP.
- Completed the first phase of a pilot study of a new combination--intravenous clindamycin plus oral primaquine--for use in patients with mild to moderate PCP. Twenty-one of 24 patients responded by day 7.
- Completed 75 percent accrual for the extension of the oral clindamycin plus primaquine trial. These data will support the use of oral clindamycin plus primaquine as one arm in a comparative study for patients with mild, "ambulatory" PCP who can be treated from the outset on an outpatient basis.

In developing salvage therapies for PCP, the ACTG has:

- Established and continues to manage the Treatment Investigational New Drug (IND) for trimetrexate for patients intolerant to standard therapies for PCP.
- Established and continues to manage an open protocol for trimetrexate for patients refractory to standard therapies.

Prophylaxis studies are the other major focus of ACTG PCP efforts. In this area, the ACTG has:

- In less than 1 year, completed accrual for a 600-patient primary PCP prophylaxis study of aerosolized pentamidine *vs.* dapsone *vs.* trimethoprim/sulfamethoxazole.
- Nearly completed accrual for a secondary PCP prophylaxis study of aerosolized pentamidine *vs.* trimethoprim/sulfamethoxazole.

Initial and salvage acute therapies for CMV are also being comprehensively developed through the ACTG. In the area of acute, initial CMV therapies, the ACTG has:

- Established the ganciclovir Treatment IND for newly diagnosed CMV retinitis, yielding evidence that supported the ganciclovir New Drug application.
- Developed an intermittent dosing schedule for intravenous foscarnet to treat patients with CMV retinitis. Foscarnet was previously administered only by continuous intravenous infusion.
- Completed 75 percent of accrual for a study of ganciclovir alone *vs.* ganciclovir plus GMCSF, with GMCSF appearing to be useful in limiting the number of episodes of neutropenia.
- Initiated a dose-ranging study of FIAC in certain people infected with CMV to examine the drug's antiviral effect, pharmacokinetics, and toxicity.

Studies on salvage therapies for CMV performed by the ACTG include:

- Ongoing study of intravitreal ganciclovir for patients intolerant systemic ganciclovir.
- Nearly complete accrual for a dose-comparison study of foscarnet maintenance, including individuals who cannot be treated with ganciclovir.

The ACTG plans to evaluate prophylactic treatments for CMV infections in high-risk individuals as soon as a dose and schedule of appropriate oral or long half-life parenteral agent are identified.

Other important contributions to new and improved OI therapies made by the ACTG include:

- Demonstrated that fluconazole is better tolerated and at least as effective as standard therapy, amphotericin B, for maintenance treatment of cryptococcal meningitis.
- Contributed critical data to support the licensing of fluconazole for acute treatment of cryptococcal meningitis.
- Demonstrated the feasibility of using itraconazole to suppress relapse of disseminated histoplasmosis in people with AIDS.

Community Programs for Clinical Research on AIDS

The Community Programs for Clinical Research on AIDS (CPCRA), established in October 1989 under the direction of Lawrence Deyton, M.D., was initiated by DAIDS to

broaden the base of NIAID's HIV treatment research programs and to tap the expertise of community clinicians who care for persons with HIV disease. The 18 CPCRA units represent the front line of the AIDS epidemic and a cross-section of primary care providers serving large populations of those who have been underrepresented in existing HIV clinical research--blacks, Hispanics, women, and intravenous drug users. The CPCRA will be especially valuable for answering many important treatment questions that require neither the technologically sophisticated facilities of the ACTG nor the complex data collection necessary for most ACTG clinical trials.

CPCRA clinicians have identified OI treatment and prevention as their highest priority. OI studies require large numbers of patients who can be followed over a long period of time. CPCRA physicians together care for more than 30,000 persons with HIV disease. The large patient population served by CPCRA will facilitate the goals of their OI studies.

The serious brain infection caused by *Toxoplasma gondii* has been identified by CPCRA physicians as the first OI project they hope to undertake. The clinical trial will compare the efficacy of two commonly used treatment for *Toxoplasma gondii* infection, pyrimethamine and clindamycin, as possible prophylactics for this OI. The protocol is in the final stages of development, and the first patients are expected to enroll during the summer. Other projects under consideration are treatment and prophylaxis studies for *Mycobacterium avium-intracellularae* infection, tuberculosis, fungal diseases, and PCP.

NIAID Division of Intramural Research

Under the direction of Anthony S. Fauci, M.D., NIAID Director, NIAID intramural scientists became involved in AIDS clinical research in 1982 when the disease first came to light. Intramural clinical trials are conducted at the NIH Clinical Center (CC) in Bethesda, which is recognized worldwide as a model facility for clinical research. Its physical layout--parallel corridors of patient care rooms and laboratories on most floors--reflects its intent to bridge the frontiers of medical science and patient care.

H. Clifford Lane, M.D., NIAID Deputy Clinical Director, and his colleagues have conducted clinical trials on a number of anti-HIV therapies, including AZT, alpha interferon, interleukin-2, AZDU, recombinant soluble CD4, CD4-IgG, AS-101, and bone marrow transplants. In addition to their research on anti-HIV therapies, NIAID staff work closely with their colleagues in the CC's Critical Care Medicine (CCM) Department and the National Eye Institute to characterize HIV-associated OIs as well as to conduct clinical trials of promising therapeutic agents. Studies have been conducted on treatments for PCP, toxoplasmosis, and CMV infections.

Since 1982, approximately 36 clinical protocols have been conducted by NIAID/CCM staff, of which about one-third have addressed OI treatments. There are currently two OI protocols open and two pending.

A central mission of DIR is to develop new treatments. Dr. Lane and his colleagues pioneered the clinical studies of ganciclovir for CMV retinitis, and recently completed the first controlled clinical trial of foscarnet for the same disease, a trial that clearly documents the drug's efficacy. Other NIAID DIR clinical researchers continue their long-term studies of fungal, bacterial, viral, and parasitic diseases in patients not infected with HIV. The progress made by these investigators augments the work being done by those working with HIV-associated OIs.

In addition to conducting clinical trials for OIs, Dr. Lane and his colleagues have led efforts to understand how one of the most important of these opportunistic infections, PCP develops. In one study, published in the *Annals of Internal Medicine* in 1988, they found no evidence that *Pneumocystis* organisms set up a latent infection in the lungs. In another study, also published in the *Annals of Internal Medicine* but one year later, they found that CD4 cell counts of HIV-infected persons are predictive of who will develop opportunistic pneumonias. They demonstrated that patients do not usually develop PCP unless their T4 cell counts drop below 200. This information was used by the PCP Task Force to develop guidelines that the Food and Drug Administration used to decide who could benefit by using prophylactic aerosolized pentamidine. Dr. Lane and his colleagues continue to characterize the disease processes underlying pulmonary problems in HIV-infected persons.

Division of Microbiology and Infectious Diseases

Because of the rarity of certain viral and fungal diseases, DMID several years ago established two networks of clinical groups to conduct trials in these areas.

Antiviral Research Branch

Besides supporting preclinical research on viral opportunistic infections associated with HIV, the Antiviral Research Branch (ARB) of NIAID's DMID also supports clinical trials of experimental therapies for severe herpesvirus and papillomavirus infections. Some diseases caused by these viruses--such as shingles, genital warts, and disseminated CMV--are opportunistic infections seen in persons with AIDS.

Herpesvirus clinical trials are conducted by the Collaborative Antiviral Study Group (CASG), directed by Richard J. Whitley, M.D., at the University of Alabama at Birmingham. This multicenter group of 55 clinical investigators focuses on rare herpesvirus infections that may not provide sufficient economic incentive for aggressive industrial investment. The CASG interacts closely with the Food and Drug Administration (FDA) and industrial drug sponsors in the planning and execution of the clinical trials. This close communication helps ensure that the resultant data are both scientifically significant and acceptable to the FDA for licensing purposes.

ARB also expects to award five cooperative agreements this fiscal year to develop and improve diagnostic tests for several opportunistic and sexually transmitted viral infections, including CMV, HSV, VZV, and EBV, and non-viral infections, including gonorrhea, syphilis, and chlamydia.

The ARB interacts closely with DAIDS staff to ensure that therapies with clinical potential for people with AIDS are identified and evaluated expeditiously.

Mycoses Study Group

Clinical trials for fungal diseases differ from those for most bacterial and viral diseases in three principal ways. In general, therapy of most systemic mycoses must be administered over months to years, in contrast to viral or bacterial infections where duration of treatment ranges from a few days to a maximum of 2 months. Similarly, post-therapy evaluations in systemic mycotic diseases must be extended up to one year, much longer than for bacterial or viral infections, to adequately assess for relapse. Finally, because of the lower incidence of systemic mycoses in the population, fewer patients are available for recruitment and evaluation.

The Mycoses Study Group (MSG) is an NIAID-sponsored nationwide network of medical centers dedicated to clinical research on serious fungal diseases. William E. Dismukes, M.D., of the University of Alabama at Birmingham, serves as its director. During its initial contract period, from 1978 to 1984, the MSG focused on clinical trials in non-AIDS patients with systemic mycoses. During the second contract period, from 1985 to 1990, the MSG expanded its activities to include both non-AIDS and AIDS populations.

Over the past 11 1/2 years, the MSG has completed 8 clinical trials. Another 13 are currently ongoing. The MSG has carried out five studies exclusively in AIDS patients; four of these studies were run jointly by the ACTG and the MSG. Active participation by the MSG has been key to adequate patient enrollment in several of these studies.

Of the five studies that include only AIDS patients, three that are now closed tested fluconazole as a treatment for crytococcal meningitis. Based on preliminary results of one of these studies, NIAID issued in May 1990 a recommendation that fluconazole replace amphotericin B as the treatment of choice for preventing recurrences of cryptococcal meningitis. Fluconazole proved to be just as effective as amphotericin B and less toxic. The two other studies, currently open, are testing SCH39304 for cryptococcal meningitis and itraconazole for histoplasmosis.

In addition to these studies conducted exclusively in AIDS patients, the MSG has also conducted three studies for coccidioidomycosis involving both AIDS and non-AIDS patients. Future plans include studies of blastomycosis, sporotrichosis, aspergillosis, and candidemia.

# # #

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Los Angeles County-University of Southern California
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